Dental Implications of Inherited Connective Tissue Disorders in South Africa

by

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"Pulchriores oculi eius vino et dentes lacte candidiores"

Genesis 49:12

'His eyes are more beautiful than wine, and his teeth whiter than milk.'

In Osteogenesis imperfecta type III the sclerae and teeth are normal

DECLARATION

I, Manogari Chetty, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Introduction

The prevalence of Osteogenesis imperfecta type III (OI III) as a category of the inherited connective tissue disorders in South Africa is of paramount importance. Although worldwide, autosomal recessive (AR) OI is rare, it had emerged that the frequency of OI III is relatively high in the indigenous Black African population of South Africa. A review of the literature revealed a paucity of information regarding the dental and craniofacial manifestations of the disorder in this ethnic group. For these reasons, the central theme of this thesis is the identification, documentation and analysis of these features in individuals with OI III in the Black African population of SA.

Osteogenesis imperfecta type III (OMIM 259420) is a severe autosomal recessive disorder in which frequent fractures and progressive limb and spinal deformity result in profound physical disability. The condition is heterogeneous and dentinogenesis imperfecta (DI) is an important syndromic component of some types of OI III. Other maxillofacial and dental manifestations also have significant implications in terms of management.

Methodology

A total of 64 Black African affected persons were assessed. In addition 5 persons of Cape Mixed Ancestry (CMA) and 3 Indian individuals were investigated.

With the support and co-operation of clinical colleagues in Pietermaritzburg, Durban and the Free State, patients with OI III who were under their care, were accessible to the author.

This study had predominantly clinical and imaging components in which dental and craniofacial abnormalities in affected persons were documented. Although radiographic resources were limited, 15 CBCT images, 20 panorex and 20 cephalometric radiographs were obtained. Where relevant, data generated by routine molecular genetic studies undertaken by the Division of Human Genetics (DHG) at the University of Cape Town (UCT) at the request of the clinicians, were utilized to elucidate genotype-phenotype correlations.

Results

In terms of genotype-phenotype correlations in the Black African population group, 23 persons with the homozygous mutation, *FKBP10*_HOM_c.[831dupC][831dupC], 3 persons with the compound heterozygous mutation, *FKBP10*_CHET_c.[831dupC][831delC] and 1 person with the compound heterozygous mutation, *FKBP10*_CHET_c.[831dupC][1400-4C>G] were identified. The primary teeth of these 27 persons was normal. Their permanent teeth was clinically normal, but radiographic images confirmed the presence of mild DI.

Dentinogenesis imperfecta, in terms of clinical discolouration of teeth, was present in the primary dentition of 35 Black African persons with the unknown molecular status. Of these 35 persons, 23 also had clinical DI in their permanent teeth. Two persons with a history of DI in their primary teeth had clinically normal permanent teeth. In 10 young patients with no permanent teeth and DI in their primary teeth, it was impossible to predict if the condition would manifest in their secondary dentition.

The 5 CMA patients had the phenotypic features of classical OI III, specifically severe fracturing, stunted stature, white sclerae and moderate to severe DI. Their general health was reasonably good and longevity was a major factor. One person, the prototypic OI III patient described in SA, was now 61 years of age. Each of these individuals had massive mandibular prognathism with dental and skeletal Class III malocclusions.

Two Indian patients had a common ancestral background from the state of Gujerat, bone fragility, moderate DI as well as ocular involvement of uncertain aetiology. The question of their disorder being related to the Osteoporosis pseudoglioma syndrome is under investigation.

A Class III dental malocclusion was present in 70% of all individuals with OI III. A skeletal Class III malocclusion was evident in 18 persons out of 20 in whom cephalometric radiographs were obtained. The patients posture and spinal malalignment are possible contributing factors to their malocclusion. This high incidence of class III malocclusion and DI indicates the need for orthodontic, orthognathic and aesthetic dental management.

By reason of their similarity to OI, three very rare autonomous genetic thin bone disorders, Pyle Disease, Osteolysis (Torg-Winchester Syndrome) and Osteoporosis-pseudoglioma Syndrome were also investigated and documented in this project. The dental aspects of these disorders had not previously been reported. The patients with Pyle disease and Osteolysis had ostensibly normal teeth, but radiographic features of dysplastic dentine were present. There was also a delay in the eruption

and exfoliation of teeth by approximately 28 months. The mandibular condyles of each of the three patients were asymmetrical and there was a loss of surface cortical bone.

Conclusion

Osteogenesis imperfecta type III is relatively common in the Black African population of South Africa.

Dentinogenesis imperfecta is subclinical in patients with the homozygous and compound heterozygous mutations in exon 5 of *FKBP10.* The clinical manifestation of DI in the primary dentition was not a predictive indicator that the permanent dentition would also be affected.

In South Africa, a developing country, the allocation of resources in terms of specialized dental facilities is limited. Socio-economic barriers also exist with patient access to dental care.

The previously neglected dental and craniofacial abnormalities documented in this study emphasizes the importance of a raised level of awareness in terms of dental management and the possible challenges that may be encountered.

DEDICATION

In memory of my Grandmother

Mrs Subbamma Chetty.

You left fingerprints of love and grace on my life.

You will not be forgotten.

'நான் உங்களை மிஸ்'

'I miss you'

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I am grateful for the opportunity of working with Professor Peter Beighton as my supervisor. His understanding of where I am in my professional development, his generosity with his time, his helpful comments and suggestions and his commitment to my project is deeply appreciated. He enabled me to make new academic contacts, expand my network into a society of like-minded individuals and navigate the administrative issues encountered as a postgraduate student.

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Thanks are also due the members of the Division of Human Genetics, UCT, especially Ms Alvera Vorster who, under the auspices of Prof R Ramesar (Head of Division of Human Genetics) was pivotal in the accomplishment of the molecular diagnostic testing of biological samples from affected individuals.

The involvement of Dr Karen Fieggen, Dr D Thompson, Dr Henderson and Dr Ganie who facilitated access to affected individuals in Cape Town, Pietermaritzburg, Bloemfontein and Durban respectively, is greatly valued.

To my colleague and friend, Dr Tina Roberts, I am most indebted to you for your encouragement and support, but most of all for introducing me to the world of Human Genetics.

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A special thank you to my family; your continued love and support in every aspect of my life empowered me to grow and achieve academic success.

Finally, to Devin, my son, thank you for your unconditional love.

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LIST OF ABBREVIATIONS

IDCT: Inherited disorders of connective tissue

OI: Osteogenesis imperfecta

OI III: Osteogenesis imperfecta type III

BS: Bruck syndrome

SA: South Africa

CT: Cape Town

UCT: University of Cape Town

DHG: Division of Human Genetics

UWC: University of the Western Cape

RXH: Red Cross Children's Hospital

CMA: Cape Mixed Ancestry

MOI: Mode of inheritance

AR: Autosomal recessive

AD: Autosomal dominant

DI: Dentinogenesis imperfecta

DD: Dentine dysplasia

HDD: Heritable dentine disorders

HOM: Homozygous

CHET: Compound heterozygous

WT: Wild type

CBCT: Cone beam computed or computerized tomography

TMJ: Temporomandibular joint

GLOSSARY

Genetic Terminology

Apoptosis: Programmed involution or cell death of a developing tissue or organ of the body

Autosomal dominant: A gene on one of the non-sex chromosomes that manifests in the heterozygous state

Autosomal recessive: A gene located on one of the non-sex chromosomes that manifests in the homozygous state

Codon: A sequence of three adjacent nucleotides that codes for one amino acid or chain termination

Compound heterozygote: An individual who is affected with an autosomal recessive disorder having two different mutations in homologous genes

Consanguinity: Relationship between blood relatives

Epigenetic: Heritable changes to gene expression that is not due to differences in the genetic code

Gene: A part of the DNA molecule of a chromosome that directs the synthesis of a specific polypeptide chain

Genetic counselling: The process of providing information about a genetic disorder that includes details about the diagnosis, cause, risk of recurrence, and options available for prevention

Genetic heterogeneity: The phenomenon that a disorder can be caused by different allelic or non-allelic mutations

Genotype: The genetic constitution of an individual

Genotype-phenotype correlation: Correlation of certain mutations with particular phenotypic features

Heterozygous: The state of having different alleles at a locus on homologous chromosomes

Homozygous: Having identical alleles at one locus

Mutation: A change in genetic material, either of a single gene or in the number or structure of the chromosome. A mutation that occurs in the gametes is inherited; a mutation in the somatic cells (somatic mutation) is not inherited

Phenotype: The appearance (physical, biochemical, and physiological) of an individual that results from the interaction of the environment and the genotype

Proband: An affected (irrespective of sex) through whom a family comes to the attention of an investigator

Syndrome: The complex of symptoms and signs that occur together in any particular disorder

Dental Terminology

Anatomic Crown: The part of the tooth that is covered in enamel

Alveolar Bone: The tooth bearing area of the mandible and maxilla and forms the tooth sockets

Calculus: Hard concretion which has formed on the surface of a tooth

Clinical Crown: The part of the tooth that is visible in the oral cavity

Deciduous dentition: Primary teeth that function during the first 8 years of life, then exfoliate providing space for the eruption of the permanent dentition

Dental crossbite: One or more of the upper teeth biting on the inside of the lower teeth. A crossbite can be in the back of the mouth, termed a posterior crossbite or in the front of the mouth, termed an anterior crossbite

Dental openbite: Defined as a condition where the upper crowns fail to overlap the crowns of the lower teeth when the mandible is brought into full occlusion. Most often in the anterior region of the mouth

Dental lamina: Horse-shoe shaped epithelial bands on the surface of the developing upper and lower jaws and which gives rise to enamel of the tooth

Dental papilla: The mesenchymal component of the developing tooth germ which gives rise to dentin and the pulp

Dentin: Hard tissue that surrounds the pulp of teeth and composed of mineralized and organic substances

Dentition: Refers to the teeth in both the maxilla and the mandible

Dentinogenesis: The process of dentin formation during the development of teeth

Enamel: Mineralized tissue covering dentin in the crowns of teeth

Enamel organ: Originates from the dental lamina and is composed of 4 layers

Impaction: Position of a tooth in the bone that prevents eruption

Lamina dura: Thin layer of compact bone lining the tooth sockets

Mandibular condyle: The rounded projections of the mandible that articulate with the temporomandibular fossa of the temporal bone

Mixed dentition: Simultaneous possession of both primary and permanent teeth

Odontoblast: Columnar cells arranged in a layer surrounding the pulp and function in dentin formation

Periodontium: The tissue surrounding and supporting the teeth

Plaque: A deposit of organic substance on the surface of the tooth

Pulp: Soft tissue within the tooth consisting of connective tissue

Pulp stones: Calcified masses of dentin-like substance within the pulp chamber

Root canal: The extension of the pulp from the coronal pulp to the root apex

Root sheath of Hertwig: The merged inner and outer enamel epithelium of the enamel organ which extends beyond the crown to enable the development of the root

Sella turcica: Transverse depression in the midline of the sphenoid bone that contains the hypophysis

Temporomandibular joint: Joint between the mandibular condyle and the temporomandibular fossa of the temporal bone

SECTION I: Project Overview and Literature Review

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CHAPTER 1: Introduction and Overview of the Thesis

1.1 Introduction and Background

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Preamble

This chapter introduces the thesis and describes the manner in which the study evolved to focus on Osteogenesis Type III (OI III) in the Black African population of South Africa. During the course of the investigations, three other rare genetic thin bone disorders, which closely resembled OI III were investigated and documented. These conditions were Pyle Disease, Osteolysis (Torg-Winchester Syndrome) and Osteoporosis-pseudoglioma Syndrome.

1.1 Introduction and Background

The Inherited Disorders of Connective Tissue (IDCT) are a heterogeneous group of genetic conditions in which involvement of the bones, joints and skin predominate. Numerous autonomous variable entities in this general category have been delineated, and although individually rare, they are collectively not uncommon.

The clinical manifestations in various IDCTs may include stunted stature, limb malalignment and bone fragility. Likewise, disturbance of structure or mechanical properties of tendons, ligaments and joint capsules can be expressed clinically as articular laxity resulting in orthopaedic problems.

Although the craniofacial tissues and the teeth are involved in many of the IDCTs, these abnormalities are often overshadowed by other severe syndromic components. Consequently, the dental and craniofacial features of these conditions have received little attention.

1.1.1 Inherited Disorders of Connective Tissue in South Africa

The Division of Human Genetics (DHG) at the University of Cape Town (UCT) has had a special interest in the IDCTs for more than 4 decades. During this period several hundred affected persons with diverse conditions of this type have been examined, investigated and documented. The establishment of a Medical Research Council unit for the investigation of the IDCTs in the DHG during the 1980s and 1990s gave impetus to these endeavours. Affected persons and their families were seen at genetic clinics in Cape Town (CT), and in special facilities for the physically disabled at various centres in South Africa (SA). The clinical and genealogical studies were underpinned by biochemical and molecular investigations in the DHG. Pertinent data were archived and remained available. During the course of these investigations, other important IDCTs which presented in SA, were delineated. These investigations facilitated diagnostic precision and accurate genetic counselling and they had an important translational component. Provision of these services continues through the DHG.

1.1.2 Dental Genetics in Cape Town

Links between the DHG, UCT and the Faculty of Dentistry, University of the Western Cape (UWC) commenced in the 1990s when Dr Lawrence Stephen of UWC undertook a PhD project at UCT.

In 2002, a weekly collaborative UWC-UCT Special Dental Genetic clinic was established at the Red Cross Children's Hospital (RXH). This clinic has provided the basis for on-going dental research in genetic disorders and contributed to career development of dental postgraduates.

1.2 Development of the Project

This study had a predominant clinical component in which dental and craniofacial abnormalities in affected persons were documented. The physicians caring for the patients had requested routine molecular genetic investigations which were undertaken by DHG at UCT. Where appropriate, these findings were made available to the author.

During the identification and recruitment of affected individuals for the purpose of this project, it emerged that OI III was relatively common in the Black African population of South Africa. A review of the literature revealed a paucity of information regarding the dental and craniofacial manifestations of the disorder in this ethnic group.

The central tenet of this thesis is to identify and document these features in individuals with OI III in the Black African population of SA for the purpose of alerting the dental fraternity to possible complications and appropriate management.

During the active phase of this project, the author was introduced to 5 individuals of Cape Mixed Ancestry (CMA) heritage who presented with an OI III phenotype and significant dental and craniofacial abnormalities. Three affected Indian persons with a putative autosomal recessive (AR) form of OI were also encountered by the author at clinics in KwaZulu Natal. Both these groups of individuals are included in this study but are documented separately.

Three rare genetic thin bone disorders, Pyle Disease, Osteolysis (Torg-Winchester Syndrome), and Osteoporosis-pseudoglioma Syndrome, were also recognized in patients at clinics in KwaZulu Natal and RXH. In view of their clinical overlap with OI III, and the fact that all three disorders were initially diagnosed as OI, the inclusion of these rare genetic conditions in this study was warranted. Comprehensive dental and craniofacial investigations were executed and the observations have been documented and discussed.

1.3 Aims of the Study

The aim of this study was to document and elucidate the dental and craniofacial manifestations in persons with OI III and other related genetic thin bone disorders in SA.

1.4 Objectives

- To identify the dental needs of the affected persons
- To facilitate the formulation of appropriate protocols for dental management

1.5 Structure of Thesis

The formatter includes the title page, declaration, dedication, acknowledgements, the abstract and the table of contents. Dental terminology used in this project is presented in a glossary. A list of abbreviations, figures and tables are also submitted. The manuscript was assessed for plagiarism using the 'turnitin' software and a favourable result was obtained.

Following an introduction and background, the evolution of the thesis and the eventual focus on OI III in the Black African ethnic group, in South Africa is outlined.

This thesis is divided into 6 sections and 20 chapters. Each chapter begins with a short preamble outlining the contents and relevant background information. The appendix includes 13 appendices. Dental concepts relevant to this study, tooth numbering, tooth anomalies, occlusion and a brief description of cephalometrics are also included also in the appendix *(Appendices 2, 3, 4 and 6).* Teeth are numbered and referred to according to the system proposed by the FDI (Féderation Dentaire Internationale) *(Appendix 2).* References are listed at the end of each chapter and organized as a cumulative list as a bibliography *(Appendix 1).*

Section I: Literature Review

This section has 4 chapters and provides background information and a review of the literature on OI regarding the classification and nosology. The specific form of OI III in the Black African population of South Africa is described comprehensively with regard to phenotypic features, molecular background and pathogenesis. The *FKBP10* gene is discussed in depth as mutations in this gene are responsible for the molecular pathogenesis in some persons with OI III in SA.

Section II: Investigation Methodology

The research design and methodology is described in this section together with the inclusion criteria for individuals documented in this study. The various components of the investigative process, notably clinical, dental and craniofacial assessment, imaging techniques employed and biological specimen collection for routine molecular investigation are documented. It must be emphasized that the routine

molecular investigations were not an inherent component of this dental project. These laboratory studies were undertaken by Alvera Voster in the DHG, UCT, as a service for diagnostic confirmation, at the request of the patients' physician and under the auspices of Prof R Ramesar (Head of Division of Human Genetics).

Section III: OI III: Results and Comments

Dental, craniofacial and molecular findings in the OI III affected individuals are presented in this section. Brief comments and discussion of findings are presented where relevant. Clinical and radiographic images are provided throughout the thesis for the purpose of clarity and to augment the understanding of the observations. At a phenotypic and molecular level, distinctions were evident between the different population groups of persons with OI III. Consequently, the author has elected to discuss the Black African persons in Chapters 8, 9 and 10 and the general phenotypic, dental and molecular data of the CMA persons are described and discussed in Chapter 11. The craniofacial features of the CMA group are described and commented on in Chapter 12. The dental and craniofacial observations of the Indian individuals are presented and discussed in Chapter 13.

Section IV: Discussion

This section encompasses Chapters 14, 15 and 16. A review and a detailed discussion of 3 significant concepts in dentistry are rendered.

Bisphosphonate Therapy (Chapter 14)

The management of OI III with bisphosphonate therapy is relevant to the dental and craniofacial management of the affected individuals due to possible orodental complications notably osteonecrosis of the jaws.

Dentinogenesis imperfecta (Chapter 15)

Abnormality of the dentition in terms of colour of the teeth is an important orodental feature of several forms of OI. In this context it was considered relevant to review the current literature, provide an update on the classification and discuss hereditary dentine disorders (HDD) in detail.

Taurodontism (Chapter 16) is a manifestation of dysplastic dentin. This feature was identified radiographically in 2 individuals with OI III and the boys affected with Pyle disease and Osteolysis.

Section V: Rare Genetic Thin Bone Disorders in SA

The project provided a unique opportunity for the investigation and discussion of three rare genetic thin bone skeletal disorders which can mimic OI III, specifically Pyle Disease, Osteolysis (Torg-Winchester Syndrome) and Osteoporosis-pseudoglioma Syndrome. The craniofacial and dental findings are detailed and discussed in Chapters 17, 18 and 19 respectively.

Section VI: Conclusion

Chapter 20, the final chapter, encompasses concluding remarks, comments, recommendations and suggestions made by the author with the emphasis on OI III in SA. Updates on therapeutic approaches are also presented in this chapter.

The bibliography and appendices are attached at the conclusion of the thesis.

1.6 Ethical Considerations Relevant to this Study

All investigations were undertaken in complete accordance with the Declaration of Helsinki, the Hippocratic Oath and the Singapore Statement on Research Integrity. The active phase of the study began only after formal ethical approval (HREC reference number: 203/2013) was obtained from the University of Cape Town's ethics committee *(Appendices 11, 12, and 13).*

Further ethical approval was sort and acquired from the Universities of the Free State and KwaZulu Natal prior to assessment of the affected persons at these centres.

Written informed consent was attained from all participants on standardized forms which were available in English, Afrikaans, Xhosa and if necessary other indigenous languages. When minors were involved, consent was obtained from their parents and where possible, assent was acquired from the children themselves (*Appendix 10).*

All information was secured in password protected computers. Written information was concealed in a locked office. Personal identifiers were altered when the data was presented. Photographs were obtained and used in this thesis with signed informed consent. There was no risk of physical harm to any individuals during this study. No other genes or genetic information, other than that related to the persons condition were analysed. Participation in the study was on a voluntary basis and all participants were informed that they had the option to discontinue their involvement at any time

should they so wish. Contact details of the researcher and the supervisors were supplied on an information sheet *(Appendix 9).*

After communication and guidance from the editor of the South African Medical Journal and the ethics office at UCT, the author has elected to adhere to the nomenclature used by the current South African government in their profiling of the various ethnic groups within the population (census 2011). The terms 'Black African', 'Coloured', 'White' and 'Indian' were used.

In the Black African population the term 'linguistic' is applied to specific groups, in accordance with current accepted convention.

South Africans described as being of 'Cape Mixed Ancestry' heritage are a people of mixed lineage descended from the indigenous Khoisan who lived in the Cape, individuals from Angola and Mozambique, Javanese from the former Dutch East India Company and European Whites.

The majority of South Africa's Asian population is Indian in origin, many of them descended from indentured workers brought to work on the sugar plantations of what was then Natal in the 19th century.

These identities are based on ethno-cultural factors and not socio-political differences; therefore, there are no implied negative connotations at any point in this dissertation.

Reference

1. Census 2011: Census in brief. Pretoria: Statistics South Africa. 2012. ISBN 9780621413885. Retrieved 12 January 2013.

CHAPTER 2: Review of Osteogenesis Imperfecta

Preamble

The history and evolution of the classification of OI is outlined and discussed in this chapter. The expansion of the nosology based on molecular concepts is also highlighted as these factors are crucial in the identification of genotype-phenotype correlations of craniofacial and dental manifestations.

2.1 Introduction

The historical evolution of knowledge concerning Osteogenesis Imperfecta (OI) has been chronicled in successive editions of Victor McKusick's magisterial book 'Heritable Disorders of Connective Tissue' (Beighton, 1993).

In the mid nineteenth century, Lobstein (Fig 2.1) documented the adult form of OI while Vrolik (Fig 2.2) described the lethal infantile type. At the beginning of the 20th century, Looser of Heidelberg introduced the terms 'OI tarda' and 'OI congenita'. These designations have remained in use in clinical medicine.

Fig 2.1 Jean Frederick Lobstein 1777 – 1835

Google: https://commons.wikimedia.org (July 2015)

Fig 2.2 Willem Vrolik 1801 – 1863

Google: https://commons.wikimedia.org (July 2015)

With the onset of clinical genetics in the 1960's, the autosomal dominant (AD) mode of inheritance of OI-tarda was well established. In OI-congenita, the consistent normality of the parents and the occasional recurrence in siblings was suggestive of autosomal recessive (AR) inheritance. By the late 1980's, however, discoveries in collagen biochemistry and later in molecular biology conclusively indicated that OI-congenita resulted from new dominant mutations. The occurrence in siblings was explained on the basis of gonadal mosaicism.

2.2 Nosology of Osteogenesis Imperfecta

Impetus to the understanding of OI was afforded by Sillence et al. (1979) when four main types were proposed. This classification is based upon an analysis of clinical manifestations and the mode of inheritance (Table II.1).

Table II.1 Classification of OI (Sillence et al., 1979)

Type	Clinical Features	Mode of Inheritance
I	Blue sclera, moderate bone fragility	AD
II	Lethal in the perinatal period	AR
III	White sclera, severe with progressive deformity	AR
IV	White sclera, variable bone fragility	AD

This classification does not reflect the true heterogeneity of the syndrome, but it remains useful in terms of genetic counselling, predicting the evolution of the disorder and for decisions on therapeutic measures.

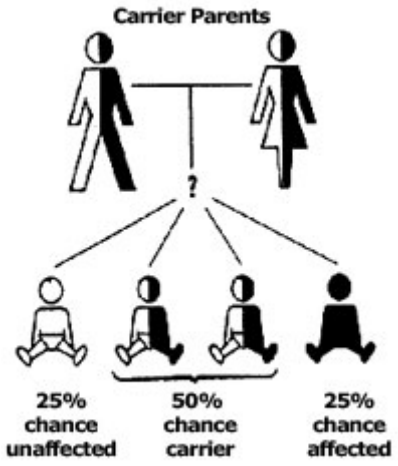

Fig 2.3 A basic example of a genetic chart used by a counsellor

Google: http://www.tbdhu.com/Clinics/Genetics (November 2015)

Persons who receive details regarding testing, treatment and available choices are empowered to make decisions which are most suitable for them, their pregnancy, or their child's health.

A genetic cause of OI, a deletion in a collagen gene (COL1A1) was discovered in 1983 (Chu et al., 1983) and an expanded Sillence classification was published in 2004 (Rauch and Glorieux, 2004). These authors added OI Types V – VII which had unknown genetic defects. Thereafter, following radiographic, bone morphologic and comprehensive molecular genetic analyses, an expanded classification was established. This is presented in Table II.2 (Steiner et al., 2005).

Table II.2 Expanded Classification of OI (Steiner et al., 2005)

Type	MOI	Severity	Fractures	Bone Deformity	Stature	DI	Sclerae	Hearing Loss
I	AD	Mild	Few to 100	common	Normal or slightly short for family	+/-	Blue	Present in +/- 50%
II	AD	Perinatal lethal	Multiple fractures of ribs, minimal calvarial mineralization platyspondyly, marked compression of long bones	Severe	Severely short stature	+	Dark blue	-
III	AR	Severe	Thin ribs, platyspondyly, thin fragile bones with many fractures, 'popcorn' epiphyses common	Moderate to severe	Very short	+	Blue	Frequent
IV	AD	Moderate to mild	Multiple	Mild to moderate	Variably short stature	+/-	Normal to grey	Some
V	AD	Moderate	Multiple with hypertrophic callous	Moderate	Variable	-	N	No
VI	?	Moderate	Multiple	Rhizomelic shortening	Mild short stature	-	N	No
VII	AR	Moderate	Multiple	Yes	Mild short stature	-	N	No

?: uncertain

With the discovery of each new genetic determinant and revisions of the nomenclature, the types of OI increased to OI XIV. The categories OI I – OI IV were defined according the radiological and clinical

presentation of the disorder, whereas OI V – OI XIV were defined according to the molecular findings. Nevertheless, there was overlap in the clinical presentation of OI I – OI IV and OI V – OI XIV (van Dijk et al., 2010; Forlino et al., 2011).

In recent years, OI has been the subject of extensive molecular investigations and it has emerged that the molecular determinants are complex.

In August 2009, the Nosology Committee of the International Skeletal Dysplasia Society identified 456 conditions and placed them into 40 groups which were defined by molecular, biochemical and /or radiographic criteria (Warman et al., 2011). Osteogenesis imperfecta was placed in group 25 and was given special attention at this meeting (Table II.3).

Table II.3 Category 25: Osteogenesis imperfecta and Decreased Bone Density Group (Warman et al., 2011) (modified by the author to only include conditions relevant to this study)

Name of Disorder	MOI	MIM No.	Locus	Gene	Protein
OI, non-deforming (OI 1)	AD	166200		*COL1A1, COL1A2*	*COL1A1*: Collagen 1 alpha 1 chain *COL1A2*: Collagen 1 alpha 2 chain
OI, perinatal lethal form (OI 2)	AD, AR	166210		*COL1A1, COL1A2, CRTAP, LEPRE1, PPIP*	*CRTAP*: cartilage associated protein *LEPRE1*: leucine proline enriched proteoglycan (leprecan) *PPIP*: peptidylprolyl isomeraseB (cyclophilin B)
OI, progressively deforming type (OI 3)	AD, AR	259420		*COL1A1, COL1A2, CRTAP, LEPRE1, PPIP, FKBP10, SERPINH1*	*FKBP10:* FK506 binding protein 10 *SERPINH1*: serpin peptidase inhibitor, clade H, member 1
OI, moderate form (OI 4)	AD, AR	166220		*COL1A1, COL1A2, CRTAP, FKBP10, SP7*	*SP7*: SP7 transcription factor (Osterix)
OI: with calcification of the interosseous membranes and/ or hypertrophic callus (OI 5)	AD	610967		Not identified	Not identified

Table II.3 Continued

Name of Disorder *OI: Other Types*	MOI	MIM No.	Locus	Gene	Protein
Bruck syndrome type I	AR	259450	17q21	*FKBP10*	FK506 binding protein 10
Bruck syndrome type II	AR	609220	3q23-24	*PLOD2*	Procollagen lysyl hydroxylase 2
Osteoporosis-pseudoglioma syndrome	AR	259770	11q12-13	*LRP5*	LDL-receptor related protein 5

The Nosology Committee suggested that the Sillence classification which defined and classified OI according to clinical characteristics and inheritance pattern and not molecular findings should be retained in clinical practice (Warman et al., 2011). This recommended 'Working Nosology' is presented in Table II.4 and Arabic numerals are used instead of Roman numerals.

Table II.4 Recommended Nomenclature of OI Syndromes in order of Severity (Nosology Committee of the International Skeletal Dysplasia Society (ISDS) Warman et al., 2011)

Name of Syndrome	Equivalent Numerical Types
Classic non-deforming OI with blue sclerae (OI type 1)	**I**
Common variable OI with normal sclerae (OI type 4)	**IV**
OI with calcification in interosseous membranes (OI type 5)	**V**
Progressive deforming OI with normal sclerae (OI type 3)	**III**
Perinatally lethal OI (OI type 2)	**II**

The 9th edition of the nosology lists 436 disorders in 42 groups and 364 genes (Bonafe et al., 2015). OI remains in group 25 and the phenotypically based Sillence classification is maintained. OI type 5 has

been included since it is radiologically distinct from other OI types. The nomenclature used in terms of OI is that recommended in 2011 and presented in Table II.4 (above).

The number of genes documented in OI type 1 and OI type 2 remains the same as those noted in 2011. However, the number of genes involved in OI type 3 has increased from 7 in 2011 to 15 and in OI type 4 the number of genes listed is currently 8. The gene and the associated protein for OI type 5 have been identified by Semlar et al. (2012) and presented in Table II.5.

Table II.5 Category 25: Osteogenesis imperfecta and Decreased Bone Density Group (Bonafe et al., 2015), (modified by the author to only include conditions relevant to this study)

Name of Disorder	MOI	MIM No.	Gene	Protein
OI type 3	AD, AR	259420	*COL1A1, COL1A2, CRTAP, LEPRE1, PPIP, FKBP10, SERPINH1* *BMP1, PLOD2, SERPINF1, SP7, WNT1, TMEM38B, CREB3L1, SEC24D*	*Refer to OI type 3 (Table II.III)* *BMP:* Bone morphogenetic protein 1 *PLOD:* Procollagen lysyl hydroxylase 2 *SERPINF1:* serpin peptidase inhibitor, clade F, member 1 *SP7:* SP7 transcription factor (Osterix) *WNT1:* Wingless-type MMTV integration site family, member 1 *TMEM38B:* Transmembrane protein 38B *CREB3L1:* OASIS *SEC24D:* SEC24-related gene family, member D
OI type 4	AD, AR	166220	*COL1A1, COL1A2, CRTAP, FKBP10, SP7* *WNT1, SERPINF1, PPIB*	Refer to OI type 3 above *PPIP*: peptidylprolyl isomeraseB (cyclophilin B)
OI type 5	AD	610967	*IFITM5*	Interferon induced transmembrane protein 5

The genes highlighted in red are the latest additions to the 2015 nosology list.

Bruck syndrome (BS) type 1, BS type 2 and Osteoporosis-pseudoglioma syndrome are currently listed as autonomous disorders in group 25 (Bonafe et al., 2015) and not as 'OI, Other types' (Warman et al., 2011).

The Nosology Committee concluded that OI is a classic skeletal disorder whereby molecular diagnosis depends on next generation sequencing yet the prognosis is centred on phenotypic observations accumulated over the last 40 years (Van Dijk and Sillence, 2014).

2.3 Molecular Genetics of Osteogenesis Imperfecta

Most instances of AD OI are caused by mutations in the *COL1A1* and *COL1A2* genes. These genes are located on chromosome 17 and 7 respectively and encode the polypeptide chains of type I collagen. Until 2006, these were the only mutations known to cause OI (Eyre, 2013). More than 90% of affected persons display the phenotypic consequence of this dominant mutation that alters the primary sequence of alpha1 (1) and alpha2 (1) collagen chains. In 2012, the molecular abnormality was identified in the rare AD OI type 5 in which *IFITM5* encodes Interferon induced transmembrane protein 5 (Semler et al., 2012).

The further 10% of AR instances has been shown to be caused by a growing list of mutant genes. They include *LEPRE 1, PPIB, PLOD2, FKBP10, SERPINH1, SERPINF1, BMP1, SP7, CRTAP* and *TMEM38B* (Cabral et al., 2012; Caparros-Martin, 2013; Eyre, 2013; Volodarsky et al., 2013; Rubinato et al., 2014). Mutations in *WNT1* which encodes a signalling molecule in osteoblast differentiation and proliferation have been identified (Keupp et al., 2013). Most recently a homozygous deletion of *CREB3L1* was identified in a family with the progressively deforming OI phenotype (Symoens et al., 2013).

In the Black African population in SA, mutations in the *FKBP10* gene are a frequent molecular finding *(see Chapters 4 and 8)*.

2.4 Biosynthesis of Collagen Type I

The AR mutations in OI involve genes that encode proteins involved in collagen type I biosynthesis.

Collagen type I consists of two α1-chains and one α2-chain. After translation, pro-α1-chains and pro-α2 chains are processed in the rough endoplasmic reticulum. The three chains are then aligned in order to commence folding into a triple helical structure. During this folding process, genetically determined post-translational modification by specific proteins takes place. After transport of procollagen type I to the Golgi complex and following exocytosis into the extracellular matrix, cleavage of the C-and N-propeptides results in formation of collagen type I. Thereafter, cross-linking of collagen type I molecules, results in fibril formation. Multiple collagen type I fibrils form collagen fibres which are important constituents of bone (van Dijk and Sillence, 2014).

The molecular pathology of OI type III is further described in Chapters 3 and 4.

2.5 Conclusion

Osteogenesis imperfecta has displayed marked genotypic variability, but the phenotypes remain classified according to Sillence. In instances of autosomal recessive inheritance, genotypic investigations are recommended to augment genetic councelling (Valadares et al., 2014).

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CHAPTER 3: Osteogenesis Imperfecta Type III

3.1 Historical Background

3.2 General Phenotypic Features

3.3 Molecular Findings

3.4 Bruck Syndrome

Preamble

Osteogenesis type III is well recognized in the indigenous Black African population of SA. This disorder is the focus of the project and it is discussed in detail in terms of history, phenotypic features and molecular findings. Bruck Syndrome and its association with OI III are also briefly discussed in this chapter. The molecular findings of the determinant gene, FKBP10, are reviewed in Chapter 4.

3.1 Historical Background

Osteogenesis imperfecta type III (OI III) is a rare, well defined entity characterized by AR inheritance and severe physical deformity. In a review of 345 pedigrees of families with OI in Australia only seven kindred had criteria suggestive of OI III namely, white sclerae, normal teeth and fractures or deformity present since birth (Sillence et al., 1986).

In South Africa and Zimbabwe OI III was found to be fairly common in the indigenous Black African population (Beighton and Versfeld, 1985). The affected individuals originated from the Sotho, Pedi, Swazi, Zulu and Tswana linguistic groups among others and a ratio of OI I to OI III as 1 to 6 was estimated in this population group (Viljoen and Beighton, 1987). It was suggested that the reason for this high prevalence is that the unaffected heterozygote may have a biological advantage in the African environment and that the mutation for OI III in Africa occurred more than 2000 years ago in West or Central Africa prior to migration to present day Southern Africa (Beighton and Viljoen, 1987).

3.2 Phenotypic Features of OI III

At birth, affected individuals present with multiple fractures and limb deformities. The fractures continue into childhood with a disturbance of growth and stunted stature. The neck and trunk are relatively short and a discrepancy in the ratio of arm span to height is consistently found, namely, the arm span is more extensive than the height. Kyphoscoliosis is a frequent presentation and is age-related with the majority of adults having severe spinal deformity (Fig 3.1). The colour of the sclerae may be blue at birth and infancy, but this fades by I year of age and is then described as normal (Sillence et al., 1986). Some affected persons survive into adulthood but experience progressing physical disability and bone deformity even in the absence of fractures (Beighton et al., 1983). The bitemporal diameter may be wide, creating the appearance of a disproportionately large head (Beighton and Versveld, 1985). Intellect is normal. Death usually occurs during the first and second decades of life due to pulmonary hypertension and cardiopulmonary failure arising from spinal malalignment (Sillence et al., 1986).

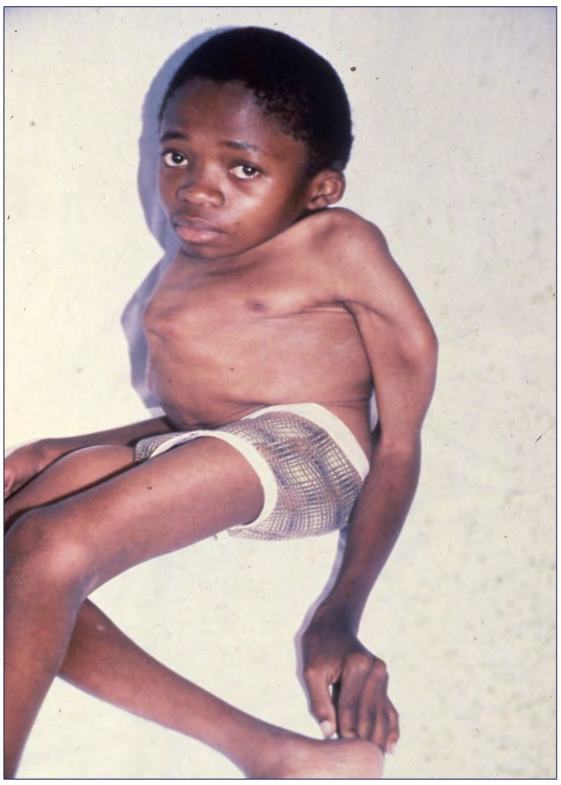

Fig 3.1 A Black African child with OI III. Marked skeletal deformity is evident (Courtesy of Prof P Beighton).

Radiographic features are a porotic skeleton and the consequences of multiple fractures. The long bones are usually bowed and wormian bones are evident in the cranium. Vertebral biconcavity, protusio acetabulae and elongation of the pedicles of the lumbar vertebrae are important diagnostic criteria (Beighton and Versfeld, 1985).

Orodental abnormalities, both radiographic and morphological evaluation of the teeth have only been reported in a few OI III patients. In an analysis of the clinical features of an individual with OI III, the teeth were reported as being normal (Nicholls et al., 1984). Conversely, Lund et al. (1998) found that 81% of a series of OI III patients showed features of DI. This discrepancy probably reflects the molecular heterogeneity in OI III. Further orodental abnormalities were described in 22 OI III affected persons in a survey undertaken by the Heritable Disorders Branch of the National Institute of Child Health and Human Development at the National Institutes of Health in the USA (O'Connel and Marini, 1999). These authors found that the incidence of DI was greater than 80% in the primary dentition. Caries, attrition and tooth discolouration did not feature to the same extent in the permanent dentition as in the primary dentition. Class III dental malocclusion was present in 80% of these individuals. There was also a high incidence of anterior and posterior cross bites and open bites. A

delay in dental development was observed in 21% of persons in this survey (O'Connel and Marini, 1999).

Prior to the present investigations no craniofacial and orodental evaluations had been undertaken and documented in persons with OI III in the indigenous Black African population of South Africa.

3.3 Molecular Findings in OI III

In the routine investigation of OI, biochemical analysis of type I collagen in fibroblasts may serve as the first diagnostic step before screening for mutations of involved genes.

During the early 1980's, molecular and biochemical investigations were reported in only one person with OI III. The individual was a boy aged 21 months with unaffected consanguineous parents. He had a mutation affecting the translation of collagen α2(1) polypeptide. Type I procollagen produced by cultured fibroblasts from this child did not contain collagen α2(1) chains and consequently resulted in under-calcified and fragile bone (Nicholls et al., 1984).

Four years later, ten affected persons with OI III from three families were analysed using COL1A1 and COL1A2 associated restriction fragment length polymorphisms (RFLPs) (Beighton et al., 1988). Two of these families were Black South African individuals. Type I procollagen molecules produced by skin fibroblasts of 7 affected black indigenous individuals migrated normally as did those of the control persons,

suggesting that mutations within or near the type I collagen structural gene were not responsible for this form of OI III (Beighton et al., 1988).

Further linkage studies were performed in 8 black indigenous OI III families, previously identified by Beighton and Versfeld (1985), using RFLPs associated with the *COL1A1* and *COL1A2* loci to determine if mutations in the type I collagen genes were responsible for this particular type of OI (Wallis et al., 1993). No evidence was subsequently found for defects in the synthesis, structure, secretion or post-translational modification of the procollagen type I chains produced by any family members. These results further highlighted the fact that mutations near or within the collagen type I structural genes were not responsible for OI III in the affected SA families (Wallis et al., 1993).

During the next decade, the only mutations known to cause OI III were the two genes coding for type I collagen chains. Since 2006 a growing list of mutant genes causing the 5–10 % of AR OI III has emerged. They include *CRTAP, LEPRE1, PPIB, PLOD2, SERPINH1, SERPINF1, BMP1, TMEM38B, SP7,*

WNT1, CREB3L1 and *FKBP10.* These genes are responsible for the multistep process that involves a number of post-translational modifications in the processing, assembly and transportation of procollagen chains during the biosynthesis of collagen type I.

Currently 13 genes have been listed as determinants in OI III (Bonafe et al., 2015). These genes and their disease causing mechanisms are summarized in Table III.1.

Table III.1 Brief description of the molecular pathogenesis and the genes involved in AR OI III

Genes Involved	Consequence of Mutation	Reference
CRTAP, LEPRE1, PPIB	Collagen 3-hydroxylation defect	Pyott et al., 2011
SERPINH1, FKBP10	Chaperone defect	Van Dijk et al., 2012
PLOD2, ***BMP1***	Late processing of folded collagen type 1 chain Defective collagen processing	Martinez-Glez et al., 2012
CREB3L1	CREB3L1 encodes OASIS, an endoplasmic reticulum-stress transducer	Symoens et al., 2013
SEC24D	Defective vesicle trafficking from the ER	Bonafe et al., 2015
TMEM38B	Defective intracellular calcium release	Volodarsky et al., 2013
SP7	Impaired osteoblast differentiation	Eyre, 2013; Harrington et al., 2014
SERPINF1	Mineralization defect	Caparros-Martin, 2013; Harrington et al., 2014
WNT1	Impaired osteoblast function	Keupp et al., 2013

In the context of this thesis, it is relevant that overseas researchers initially identified a specific mutation in the *FKBP10* gene in a South African family with OI-III (Kelly et al., 2011). The molecular biology of *FKBP10* as well as its relevance to OI III in SA is discussed in Chapter 4.

3.4 Bruck Syndrome (OMIM 259450 and 609220)

Bruck syndrome (BS) is an autosomal recessive disorder characterized by the combination of OI III and pterygium formation across large joints with marked reduction in mobility (Viljoen et al., 1989). This syndrome was further characterized by McPherson and Clemens (1997) when they described a North American infant with congenital contractures with pterygia, early onset of fractures, short stature, severe limb deformity and progressive scoliosis.

The condition is genetically heterogeneous with BS type 1 caused by mutations in *FKBP10* and BS type 2, which is rare, caused by a mutation in *PLOD2.*

During the review of the *FKBP10* gene (*see Chapter 4*), it was observed that individuals with OI III and BS were documented with mutations in this gene (Schwarze et al., 2013). To the best of the author's knowledge, 21 persons with BS type 1 have been reported in the literature.

There were 6 affected persons (Fig 3.2) with the BS type 1 phenotype in this cohort of patients. Five of them had a homozygous mutation in the *FKBP10* gene. For this purpose a brief review of BS type 1 was undertaken and described below.

Fig 3.2 Affected girl (PMB1) with phenotypic features of BS type 1. She is approximately 97cm in length with marked limb deformities with contractures evident in her knees and ankle joints

Viljoen et al. (1989) initially documented OI III and congenital joint contractures in a South African girl, of Tswana heritage and termed the condition 'Bruck Syndrome'. This prototype patient was also included in another publication by Mokete et al. (2005). Biological material from this South African girl and other affected persons was subjected to molecular genetic analysis and the findings were published by Kelley et al. (2011).

Thereafter, other reports of *FKBP10* mutations which cause AR OI included 11 independent mutations (Alanay et al., 2010; Kelley et al., 2011; Shaheen et al., 2010, 2011; Steinlein et al., 2011; Setijowati et al., 2012; Venturi et al., 2012) (*see Table IV.I, Chapter 4*). The phenotypic spectrum of the affected individuals included AR OI III and BS type I, suggesting that OI III and BS type I are disorders within a phenotypic range of severity that may be manifestations of intragenetic heterogeneity within the *FKBP10* gene. The BS phenotype has widened to also include conditions with minimal fracturing and joint rigidity being a major feature. Further discussion of this complex and evolving nosological situation is outside the scope of this thesis.

Since large joints develop in utero in a flexion position, any limitation in movement will result in a lack of differentiation in the tissues developing around the joint (Barnes et al., 2013). It can be hypothesized that the putative BS might be a secondary manifestation of OI III, produced by environmental factors and possible epigenetic factors.

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CHAPTER 4: The *FKBP 10* gene

4.1 Introduction

4.2 Location and Molecular Biology

4.3 Mutations Identified in the *FKBP10* gene

Preamble

Documentation of the dental and craniofacial phenotype and the correlation with the genotype in affected persons is a major objective of this study. During this project specific mutations in the FKBP10 gene were detected in 27 Black African persons of the total 72 individuals with OI III. These observations are relevant to this project and mutations in this gene are reported and briefly discussed in order to clarify the molecular pathogenesis of OI III and BS in SA.

Most of the literature, in terms of FKBP10 has centred on Bruck Syndrome, which has been variously regarded as either an autonomous entity or a secondary manifestation of OI III.

4.1 Introduction

There have been substantial advances in the understanding of the genetic basis of AR OI III in recent years. Consanguinity and small founder populations are factors in the geographic distribution of the various forms of OI III. Examples include mutations in the *FKBP10* gene identified in Samoa, Turkey and southern Africa (Alanay et al., 2010; Kelly et al., 2011).

Autosomal recessive OI III in the Black African population of SA has been shown to be caused by mutations in the *FKBP10* gene that encode the collagen chaperone-like protein FKBP65. *FKBP10* is one of the newer members of an expanding list of AR OI genes and was first described in OI III by Alanay et al. (2010).

4.2 Location and Molecular Biology of the *FKBP10* gene

The gene map locus of *FKBP10* is 17q21.2 (Fig 4.1). This gene encodes an extracellular matrix protein FKBP65.

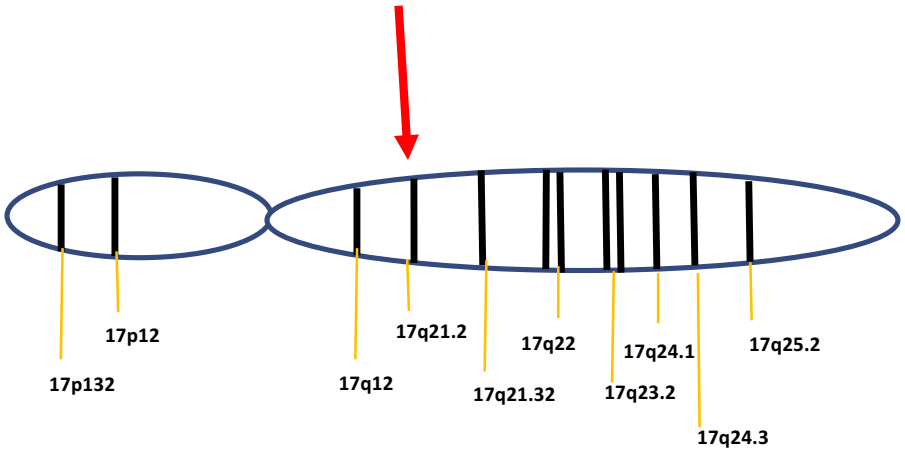

Fig 4.1 The molecular location of *FKBP10* on the long arm of chromosome 17 at position 21.2

The *FKBP10* gene is located on chromosome 17 from base pair 41,812,261 to base pair 41,823,216. This gene encodes the FK506-binding protein 65 (FKBP65) found in the endoplasmic reticulum. FKBP65 is a chaperone protein which is important for the processing of collagen and elastin which are components of the extracellular matrix (ECM). In the ECM, FKBP65 binds to the collagen molecule through a hydroxylation reaction which modifies a particular region of the molecule and enables the

correct folding. It also promotes thermal stability of the collagen triple helix, and cross link formation between collagen molecules to form fibrils (Alanay et al., 2010). These modifications to the collagen molecule need to take place in an orderly and timely sequence and chaperone proteins such as FKBP65 regulate this process (Cundy, 2012). In this context, FKBP65 encoded by *FKBP10* acts as a molecular chaperone for type I procollagen (van Dijk et al., 2012).

4.3 Mutations Identified in the *FKBP10* gene

Mutations in the *FKBP10* gene have been identified in biological specimens from persons with AR OI III in several parts of the world. To date, 28 unique DNA variants have been reported in the *FKBP10* gene on the Leiden Open Variation Database (LOVD).

In SA, individuals with the phenotypic features of AR OI III and BS were listed by Mokete et al. (2005) prior to genotypic investigations. Reported individuals with BS type 1 in SA up to 2005 included a male belonging to the Pedi linguistic group and a female of Tswana heritage with short stature, with joint contractures and normal teeth. They were previously described by Viljoen et al. (1986). Two siblings, a brother and sister, of Venda origin were also described by Mokete et al. (2005). The brother had joint contractures while the sister presented with the classic OI III phenotype. Both siblings had short stature and normal teeth.

From 2007, molecular investigations commenced in patients documented as having BS and AR OI III. The molecular findings of the brother and sister of Venda origin described by Mokete et al. (2005) was reported by Kelley et al. (2011).

Biological material from a German individual described by Brenner et al. (1993) was also subjected to genetic evaluation and the molecular results were published by Steinlein et al. (2011). These affected persons, their mutations and their dental phenotype as described in the literature, are listed in Table IV.1.

Another autosomal recessive congenital contracture disorder similar to BS is Kuskokwim syndrome which was described in isolated consanguineous groups of Yup'ik Inuits in southwest Alaska. Individuals with Kuskokwim syndrome have normal teeth. A homozygous three-nucleotide deletion was identified in *FKBP10* and it was proposed that the identification of this mutation extends the phenotypic spectrum to include this congenital contracture condition which lacks significant skeletal fragility (Barnes et al., 2013).

The outcomes of molecular studies revealed that the same *FKBP10* mutation may cause OI III alone or OI III with contractures in unrelated individuals or in siblings. This led to the conclusion that contractures are a variable manifestation of the *FKBP10* mutations (Barnes et al., 2013).

Table IV.1 Reported *FKBP10* mutations in persons with AR OI and BS since 2010

Affected persons in a single family are highlighted in black, red and blue.

Ref	No. of AP	C of O	Cons	Aff Sibs	Dental and Craniofacial	Genotype: Mutation in the *FKBP10* gene
1	5 1 F 1 M 1 M	Turkish Mexican-American	Y N	 Y (3)	Normal Normal	HOM: (c.321_353del) HOM: (c.831_832insC)
7	1 F 1 F 1 F 1F 1 M 1 F	Turkish Punjabi Caucasian Twsana (SA) Venda (SA) Venda (SA)	Y Y N N Y Y	N N N N Y Y	Not Described Not Described Normal Normal Normal Normal	HOM:(c.831dup) HOM:(c.122_156del) CHET:(c.831dup)+(c.344>A) Insertion in exon 5 p.(Gly278Argfs_95) single-nucleotide duplication c.1276dup HOM:(c.831dup) **BS** HOM:(c.831dup)
13	1 F 1 F 1 M 1 M 1 M	Saudi Saudi Saudi Saudi Saudi	Y Y Y Y Y	Y (2) Y (2) Y (2)	Not Described Not Described Not Described Not Described Not Described	HOM: (c.743dupC) 1 base pair duplication HOM: (c.743dupC) 1 base pair duplication HOM: (c.831dupC) 1 base pair duplication **BS**
14	1 M 1 M 1 M	German/ Bavarian	N	Y (3)	Dentinogenesis imperfecta in PD and SD	(FKBP65-p.Arg403X) homozygous C-terminal premature stop codon in the *FKBP10* gene
16	1 M	Italian	Y	N	Normal teeth with mild mandibular prognathism	HOM: (c.1399+1G>A) splicing mutation
2	1 F	Palestinian	Y	N	Normal	HOM: (c.1271_1272delCCinsA)
10*	1 M	Egyptian	Y	N	*	HOM: c.1271_1272delCCinsA

Table IV.1 Continued

Ref	No. of AP	C of O	Cons	Aff Sibs	Dental and Craniofacial	Genotype: Mutation in the *FKBP10* gene
12	1 M	Indonesian	Y	Y (3)	Normal	HOM:(c.600-604del) in Exon 4
11 ** 	17 17 4	Samoa Middle East USA			Normal Normal Normal	9 separate mutations were identified: HOM: [c.14delG] HOM: [c.288dupG] HOM: [c.337G . A] HOM: [c.344G . A] HOM: [c.407C . T] HOM: [c.743dupC] HOM: [c.831dupC] CHET: [c.831dupC] + [c.948dupT] HOM: [c.948dupT] HOM: [c.1330C . T]
4 *** 	1F 1F 1M	Egyptian Lebanon Sudanese	Y Y y	Y (1)	Teeth not described	HOM:(c.21dupC) HOM:(c.689T>C) HOM:(c.831dupC) **BS**
9	1F	Iranian	Y	N	Normal	HOM: c.204delCinsAAA
18	1M	Chinese	?	N	Normal	CHET: c.764_772dupACGTCCTCC in exon 5 and c.1405G.T in exon 9

Abbreviations: Table IV.1

Ref: The number of the reference from the list below

No of AP: Number of affected persons in a family

Cons: Consanguinity

BS: Individuals with OI III phenotype and contractures

Aff sibs: Affected siblings

PD: Primary dentition **SD:** Secondary dentition

*The craniofacial and oral features described in the Egyptian male person were a high arched palate and a deep overbite. There was no mention of his teeth (Puig-Hervas et al., 2012).

**These authors reported on 38 affected persons belonging to 21 families with mutations in the *FKBP10* gene. Eighteen of these persons had the BS 1 phenotype.(Schwarze et al., 2014)

***The Egyptian individual was described as having a round face, low anterior hair line, hairy forehead, wide eyes, long eye lashes, long philtrum, small mouth and bow shaped thick lips. These authors also described a Lebanese person with a round flat face and a broad forehead, bitemporal narrowing, mid-facial hypoplasia and micrognathia, tongue tie and a large haemangioma on the left side of her face. The craniofacial features of the Sudanese individual were a round face, broad forehead, wide palpebral fissures and low set cupped ears (Caparros-Martin et al., 2013).

It is uncertain whether the craniofacial features described in the Egyptian, Lebanese and Sudanese individuals are components of the disorder or chance concomitant traits within the normal range.

From this table it is evident that there is paucity of available information in the literature regarding the craniofacial and dental abnormalities in individuals identified with mutations in the *FKBP10* gene. In order to facilitate genotype-phenotype correlations in terms of dental and craniofacial abnormalities further studies are necessary.

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SECTION II: OI III – Investigation Methodology

CHAPTER 5: Case Ascertainment and Access

CHAPTER 6: Clinical, Radiographical and Molecular Investigations

CHAPTER 5: Case Ascertainment and Access

5.1 Study Design

5.2 Inclusion Criteria

5.3 Cape Town

5.3.1 Archived Notes of the Division of Human Genetics (UCT)

5.3.2 Red Cross Children's Hospital

5.3.3 University of the Western Cape: Faculty of Dentistry

5.4 Other Centres in South Africa

5.4.1 Durban: University of Kwa-Zulu Natal: Inkosi Albert Luthuli Central Hospital

5.4.2 Pietermaritzburg: Metabolic Bone Clinic: Grey's Hospital

5.4.3 Pretoria: University of Pretoria: Steve Biko Academic Hospital

5.4.4 Free State: University of the Free State Outreach Clinics: Qua Qua and Bethlehem

5.4.5 Umtata: Ikwezi Lokuza School for the Physically Disabled

5.1 Study Design

This study had a predominant clinical component in which dental and craniofacial abnormalities in affected persons were documented on standardized forms *(Appendix 10).*

Clinical photographs were obtained in order to clearly depict the phenotype. When possible, craniofacial radiographic evaluation was also undertaken. Saliva was collected from affected individuals for routine molecular genetic studies which had been formally requested by the clinician caring for the patient. Informed consent was obtained for all relevant investigations *(Appendix 9).*

5.2 Inclusion criteria

All patients that were invited to participate in the study had been seen by a medical specialist and had a confirmed diagnosis of OI III. The focus of the study was to investigate and document the orodental features in affected Black African persons in SA. Five individuals of CMA heritage who presented with the phenotypic characteristics of OI III and three Indian persons with an unusual form of autosomal recessive OI were also investigated. A total of 72 individuals with the OI III phenotype were assessed.

5.3 Cape Town

5.3.1 Archived notes of the Division of Human Genetics (University of Cape Town)

The archived case notes from the DHG since 1972 were reviewed and where possible, persons with OI III were contacted and invited for a dental evaluation.

5.3.2 Red Cross Children's Hospital (RXH)

The weekly collaborative UWC-UCT Special Dental Genetic clinic provides the basis for dental research in individuals with genetic conditions. The author participated in this clinic and appropriate patients were dentally assessed and provided with any essential management.

5.3.3 UWC: Faculty of Dentistry

Affected individuals with special needs from various dental clinics throughout the Western Cape are referred to the Faculty of Dentistry for assessment and treatment. Persons with skeletal dysplasias were evaluated by the author and individuals that met the inclusion criteria were invited to participate in this study.

5.4 Other Centres in South Africa (Fig 5.1)

During the initial reconnaissance period of this study, the author, networked widely with dental and medical colleagues throughout SA in order to arrange access to individuals with OI III and to organise provisional clinical, imaging and other relevant investigative studies.

In April 2013 the active phase of the study began at centres in SA including Grey's Hospital in Pietermaritzburg, Inkosi Albert Luthuli Central Hospital in Durban, University of the Free State outreach clinics in Qua Qua and Bethlehem, Steve Biko Academic Hospital in Pretoria and Ikhwezi Lokusa School for the physically handicapped in Mthata (Umtata).

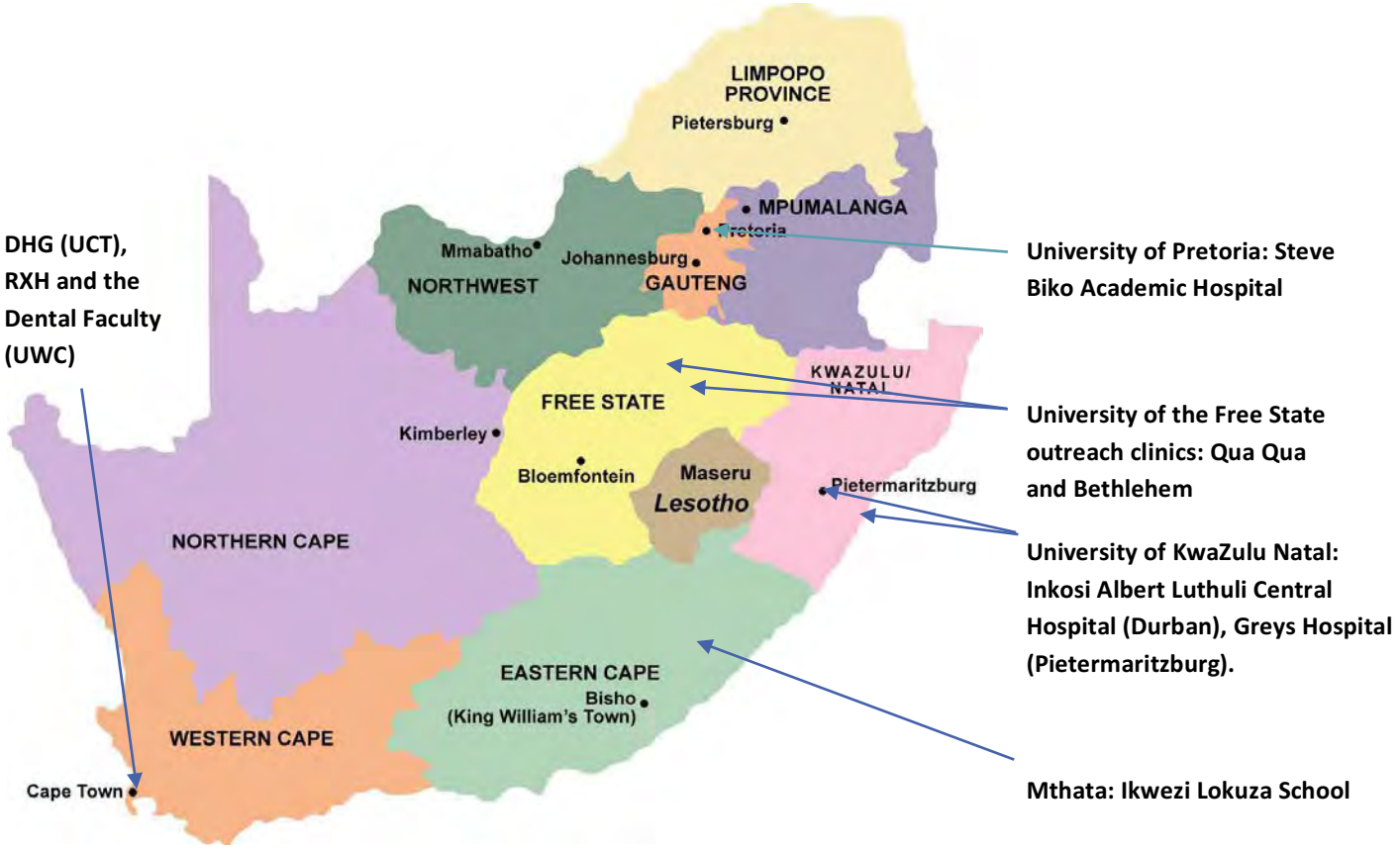

Fig 5.1 Map of SA showing the 9 provinces. Cities and towns where affected individuals were assessed are indicated with arrows (www.whereig.com/south-africa/map-political.html).

5.4.1 Durban: University of Kwa-Zulu Natal: Inkosi Albert Luthuli Central Hospital

The head of the Department of Human Genetics, Dr Thirona Naicker, at the University of Kwa-Zulu Natal was contacted with a request from the author to assess patients with OI III.

The author was invited to attend three clinics that were organized by Dr Ganie, the endocrinologist, for OI III patients who were to receive bisphosphonate infusions. During these visits affected persons were assessed dentally and their findings documented.

5.4.2 Pietermaritzburg: Metabolic Bone Clinic: Grey's Hospital

The Department of Orthopaedics at Grey's hospital, headed by Dr D Thompson and assisted by Dr Piet Mare organises a metabolic bone clinic twice a year. The affected persons have skeletal dysplasias consequent to metabolic bone disorders. The author attended these clinics for two years and appropriate individuals were referred for a dental appraisal.

5.4.3 Pretoria: University of Pretoria: Steve Biko Academic Hospital

Dr Engela Honey invited the author to attend two clinics at Steve Biko Academic Hospital in Pretoria in which OI III affected individuals received their bisphosphonate infusions. These persons were dentally assessed.

5.4.4 Free State: University of the Free State: Qua Qua, Bethlehem

Dr Bertram Henderson, a consultant paediatrician in the Department of Human Genetics at the University of the Free State is involved in several outreach clinics within the Free State. Arrangements were made for the author to attend clinics in Bethlehem and Qua Qua for access to individuals with OI III.

5.4.5 Mthata (Formally Umtata): Ikwezi Lokuza School for the Physically Disabled (Fig 5.2)

During perusal of the archived notes at the Department of Human Genetics (UCT), the author became aware of the Ikwezi Lokusa School for the physically disabled in Mthata. After receiving permission from the principal, Mr Gulwa, the school governing body and the department of health in the Eastern Cape, arrangements were in place for a three day visit. At the request of the principal, all 300 children were screened and their dental needs documented and reported to the principal.

Six individuals with OI III were identified by Dr Piet Mare, the orthopaedic surgeon, and dentally assessed. No radiographic facilities were available.

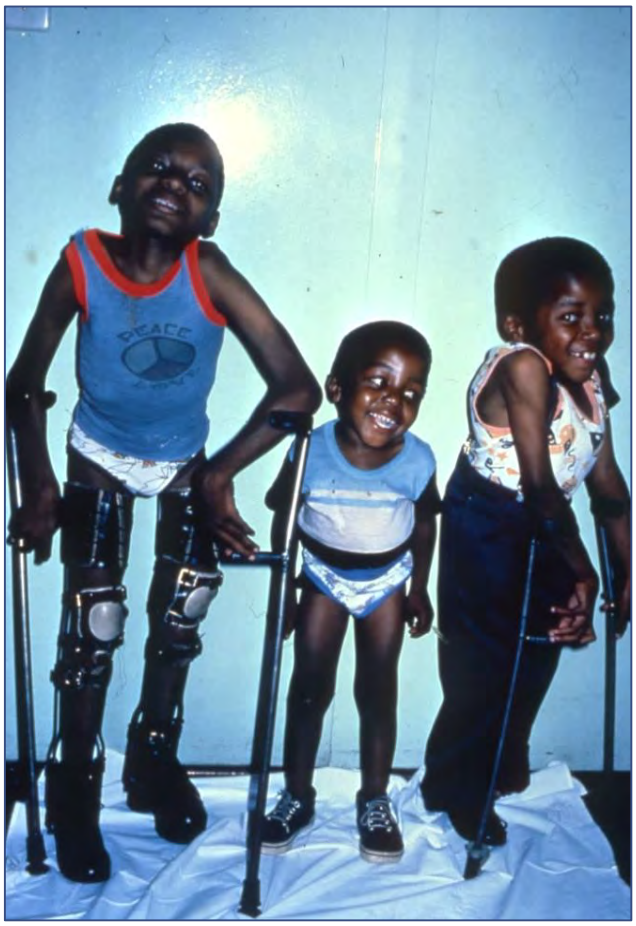

Fig 5.2 Affected children at Ikwezi Lokusa School for the Physically Disabled in Mthata

(Courtesy of Prof P Beighton)

All affected persons that required dental management were identified and referred to colleagues practicing in or close to their areas for appropriate dental therapy. Provision for transport was prearranged for individuals that required this facility. Prior to the author's departure, effective strategies were in place for the children to receive current and future dental care at the dental unit at the Nelson Mandela Hospital in Umtata.

CHAPTER 6: Clinical, Radiographical and Laboratory Investigations

6.1 Clinical and Dental Evaluation of Affected Persons

6.2 Imaging Techniques

6.2.1 Panorex

6.2.2 Cephalometric Radiography

6.2.3 Cone Beam Commuted Tomography

6.3 Molecular Investigations

6.4 Biochemical investigations and Ultrastructural studies

Preamble

Once individuals had met the inclusion criteria of the study, they were dentally and clinically evaluated. Radiographical investigations were undertaken if these resources were available. When requested by the attending physician, affected persons were invited to contribute a saliva sample for routine DNA analysis as a diagnostic service.

6.1 Clinical and Dental Evaluation of Affected Persons

This component of the study involved a craniofacial and dental examination of the affected persons. A detailed family history of the condition was obtained when possible and pedigrees were recorded on a standardized data capture form which was designed to facilitate information recording *(Appendix 10).* Medical records were reviewed and clinicians provided clarity on medical details that were difficult to obtain from the patient or their caregivers. Written permission for clinical photographs of the affected individual were obtained from the patient or their caregiver.

Radiographic evaluation of an individual is an important facet of a comprehensive dental and craniofacial appraisal. Dental radiographs are obtained by dentists and dental specialists for many reasons including assessment of dental structures, malignant or benign masses, bone loss and dental cavities.

6.2 Imaging Techniques

Craniofacial imaging was undertaken when this resource was locally available. Panorex and cephalometric radiographs were obtained and cone beam CT imaging was also carried out when appropriate. The attainment of radiographic images were dependant on the necessity of these investigations in terms of clinical management and availability of these facilities. Radiographic images that had previously been obtained by the patient's physician, for instance, lateral views of the skull, were also available to the author.

The imaging facilities used were only available at specific dental centres. The structure of the apparatus used is described and depicted in detail *(Appendix 5)* in order to highlight the difficulties encountered when attempting to position an individual with short stature and severe physical deformity. It is relevant that several affected persons in this project were unable to stand or adopt the appropriate posture for an acceptable image to be obtained. Although radiographic resources were limited, 15 CBCT images, 20 panorex and 20 cephalometric radiographs were obtained.

All radiographic findings were confirmed by two consultant radiologists from the universities of the Western Cape and Stellenbosch.

6.*2.1 Panorex*

In a general dental practice, these radiographs are used for the diagnosis of dental caries, detection of periodontal disease and assessment of the integrity of the temporomandibular joint. They are also routinely used for craniofacial assessments by dental specialists including orthodontists, maxillofacial surgeons and prosthodontists. This two-dimensional dental radiograph, often digital, displays the maxilla, mandible and teeth in the same film (Fig 6.1).

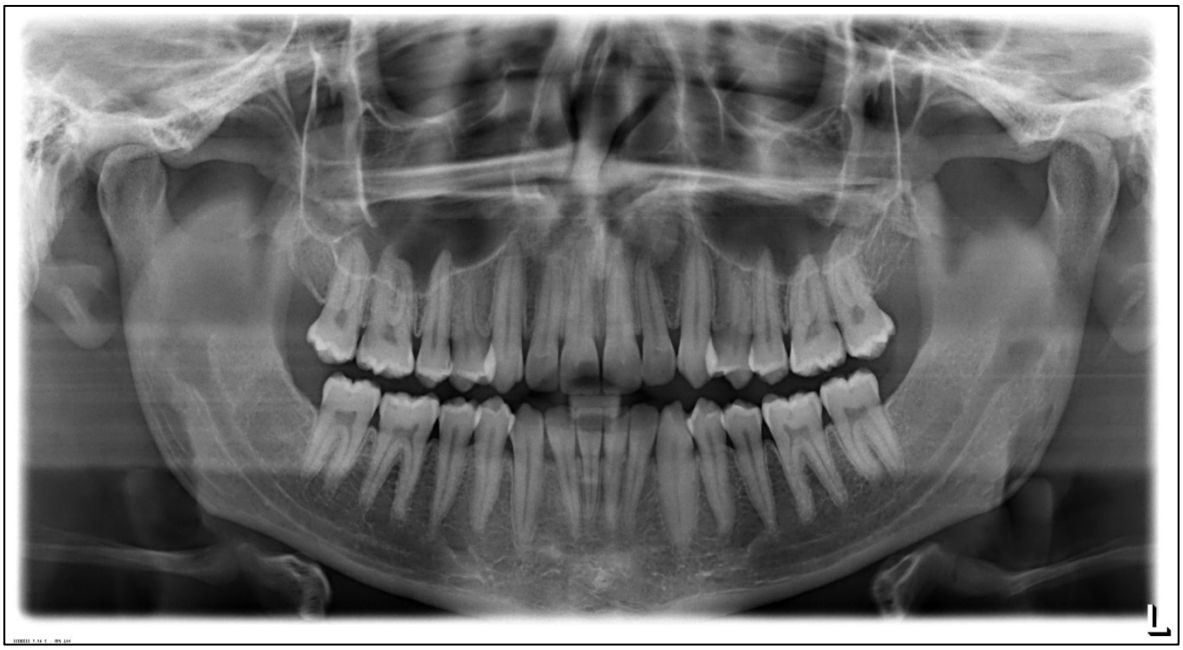

Fig 6.1 Panorex image of the entire upper and lower jaw, temporomandibular joint, nasal sinuses and the mandibular nerve canal (Courtesy of Dr Devin Chetty)

6.*2.2 Cephalometric Radiography*

In view of the importance of cephalometric radiographs in the assessment of the occlusion and cranial base structures, a detailed account of the relevance and interpretation of cephalometrics is provided in Appendix 6.

This profile radiograph of the skull and soft tissues is used to assess the relative positions of the teeth in the jaws, the relationship of the jaws to the skull and the relation of the soft tissue to the teeth and jaws. The film is traced and various standard landmarks, lines and angles are recorded (Fig 6.2). In normal children, these values can be used to predict the growth of craniofacial structures (Profitt et al., 2013).

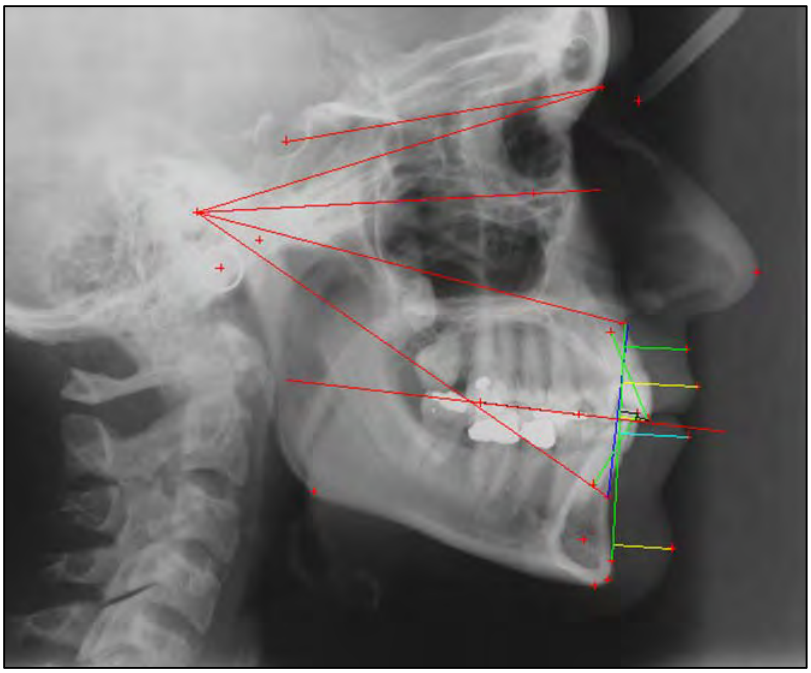

Fig 6.2 Cephalometric image showing profile of the skull and soft tissues (Courtesy of Dr A Hudson)

Computerised cephalometrics is the process of entering cephalometric data in digital format into a computer for cephalometric analysis. This approach permits the automatic measurement of landmark relationships. Computerized cephalometrics offers the advantage of instant analyses, readily available ethnic, sex and age related norms for comparison and facilitates the prediction of soft tissue changes and surgical outcome.

6*.2.3 Cone Beam Computed/ Computerized Tomography (CBCT)*

CBCTs have been in use in South Africa for the past decade, but in the last 5 years this technology has been frequently employed for the planning of specific craniofacial procedures. An optimal image is dependent on correct patient positioning. A three dimensional image of dental structures, soft tissues, nerve pathways and bone in the craniofacial and cervical region is generated in a single scan (Fig 6.3).

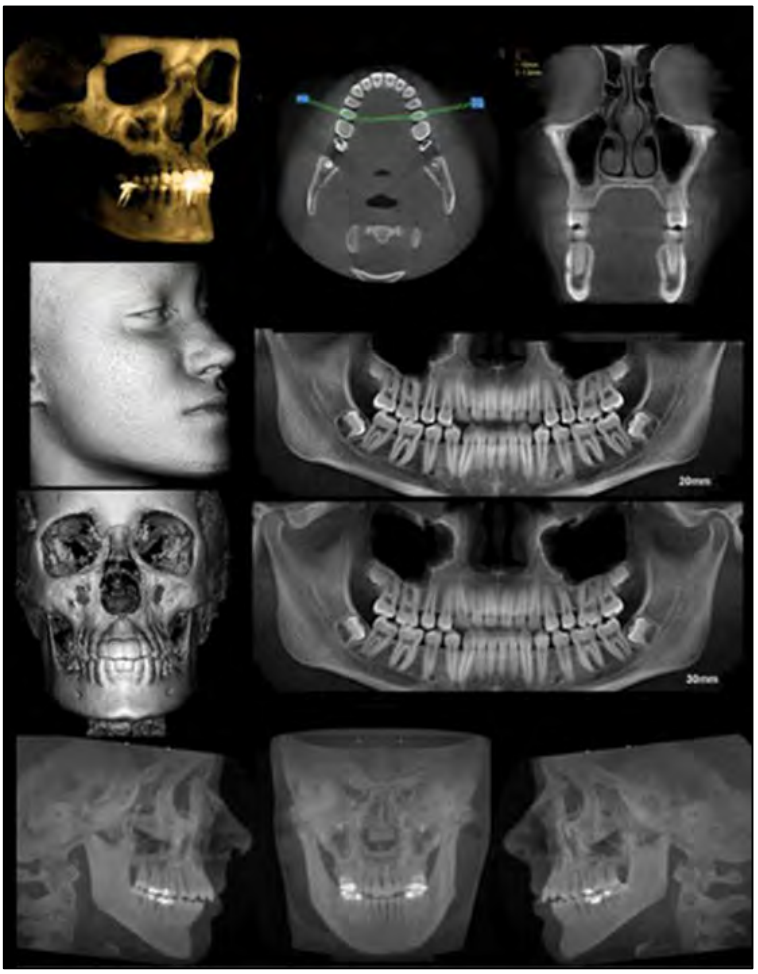

Fig 6.3 Examples of 3D images obtained from a CBCT scan of an individual

(https://www.schickbysirona.com)

All CBCT scans that were acquired in this study were obtained with the full consent of the patient or the parent of a minor child. The patient's prior medical imaging history was reviewed before imaging. The risks and benefits of the procedure were fully explained to the patient or parent of the child. These images were obtained only to provide clinical information which other imaging modalities could not. No further dental radiographs were acquired once a CBCT scan had been attained. Exposure settings for the dental CBCT examination were optimized to provide the lowest radiation dose that would yield an image quality that was adequate for accurate diagnostic purposes.

6.3 Molecular Investigations

Physicians caring for the persons with OI III routinely requested diagnostic molecular studies from the DHG, UCT. In every instance standardized laboratory request forms were completed and signed by the clinician and affected persons or their legal guardian.

Saliva samples were obtained for DNA extraction and molecular investigation in the DHG laboratory, UCT. The Oragene saliva collection kits were used and DNA was extracted according to the laboratory operating protocol. DNA was extracted from epithelial cells in saliva collected from affected individuals and analysed for a mutation in the *FKBP10* gene which has the cytogenetic location 17q21.2.
Although molecular investigations were not an inherent component of this dental project, these results facilitated appropriate genetic counselling and management of the affected families in the genetics clinic of DHG, UCT and other centres.

As OI III is genetically heterogeneous, the results of the molecular investigation enabled possible genotype-phenotype correlations at the craniofacial and dental level in the context of this project.

6.4 Biochemical Investigations and Ultrastructural Studies

The electron microscopic findings in dental tissue from affected persons would have greatly contributed to the understanding of the changes that occur in dentin. The author hoped to correlate the ultrastructural alterations in the dentin to the molecular findings.

Due to the difficulty in obtaining teeth for imaging purposes, this process was only carried out on a tooth from the individual with Pyle Disease *(see Chapter 17).*

At the conclusion of this project, a few teeth became available. These were stored appropriately and will be the subject of further research in term of ultrastructure of the teeth in OI III affected persons in SA. The author hopes to correlate these findings with the molecular status of the individuals.

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Section III – OI III: Results and Comments

CHAPTER 7: General Population Data

7.1 Affected Persons

7.1.1 Number, Gender, Age and Ethnic Groups of Individuals

7.2 Basic Clinical and Molecular Data

7.3 Comments on:

7.3.1 Fractures

7.3.2 General Physical Condition

7.3.3 Molecular Status

7.3.4 Bisphosphonate Therapy in OI III: Radiological Observations

7.3.5 Age-Related Phenotypic Manifestations

Preamble

The general information obtained from the clinical assessment of all 72 of the OI III affected persons is captured in appropriate tables and analysed in this chapter. Individuals are represented by alphabetical-numerical designations pertaining to the investigation centre and the chronological order in which they were assessed.

Specific research results obtained for each population group are documented in separate chapters which follow.

7.1 Affected Persons

7.1.1 Number, Gender and Age of Affected Persons

Of the 72 affected individuals with OI III who were investigated, 39 were female and 33 were male. Sixty four were of Black African stock, 5 were of CMA heritage and 3 were South Africans of Indian decent.

In the context of OI III being a progressively deforming disorder and an autosomal recessive condition, the age of each individual and the number of affected siblings were recorded. The parents of the affected persons were normal and there was no direct evidence of consanguinity.

The general data pertaining to the Black African persons are displayed in Table VII.1.

Information with regard to the CMA and Indian affected persons are presented in Tables VII.2 and VII.3 respectively since they present with a different phenotype and genotype when compared with affected individuals of Black African heritage.

For ethical reasons, patient identifiers were not mentioned and affected persons were given an alphabetic-numeric designation based on the investigation centre and the chronological order in which they were examined.

Since the CMA and Indian persons have been removed from Table VII.1, the numbers may not follow logically.

Siblings, QQ 1, QQ 2 and QQ 3 are highlighted in red.

Table VII.1 Details of Affected Black African Individuals: Date of Birth, Age when examined, Gender, Linguistic group and Investigation centre

Affected Individual	Date of Birth	Age (Years)	Gender	Affected Siblings	Linguistic Group	Investigation Centre
BTHM 1	22/01/1988	25	F	1	Zulu	UOFS:BTHM
BTHM 2	19/11/2008	6	M	1	Sesotho	UOFS:BTHM
BTHM 3	26/9/2004	8	F	0	Sesotho	UOFS:BTHM
BTHM 4	13/06/2008	6	M	0	Sesotho	UOFS:BTHM
CPT 1	11/12/1994	19	F	0	Xhosa	UCT:GSH:CPT
CPT 7	26/07/1984	30	F	0	Xhosa	UCT:GSH:CPT
DBN 2	08/08/1994	19	M	0	Zulu	OAS:Dbn
DBN 3	12/06/1994	19	M	1	Zulu	OAS:Dbn
DBN 4	01/01/1995	18	M	0	Zulu	OAS: Dbn
DBN 5	08/08/1994	19	M	0	Zulu	OAS: DBN
DBN 7	4/01/2012	3	M	0	Zulu	IALCH: Dbn
DBN 8	31/07/2012	3	F	0	Zulu	IALCH: Dbn
DBN 10	13/05/2013	2	F	0	Zulu	IALCH: Dbn
DBN 11	07/04/2010	4	M	2	Zulu	IALCH: Dbn
DBN 12	05/04/2011	3	F	1	Zulu	IALCH: Dbn
DBN 13	31/12/2009	5	F	0	Zulu	IALCH: Dbn
DBN 14	22/01/2002	12	F	1	Zulu	IALCH: Dbn
DBN 15	20/01/2003	11	M	0	Zulu	IALCH: Dbn
DBN 16	26/09/2000	14	F	1	Zulu	IALCH: Dbn
DBN 17	25/05/2008	6	M	0	Zulu	IALCH: Dbn
DBN 18	18/06/1992	20	F	0	Zulu	IALCH: Dbn
DBN 19	04/06/2013	2	M	1	Zulu	IALCH: Dbn
DBN 20	27/10/2012	3	M	0	Zulu	IALCH: Dbn
DBN 21	31/07/2002	12	F	0	Zulu	IALCH: Dbn
DBN 22	11/10/2001	13	F	1	Sesothu	IALCH: Dbn
MTH 1	19/03/1997	17	M	0	Xhosa	ILS
MTH 2	16/09/2000	14	M	0	Xhosa	ILS
MTH 3	20/01/1993	19	M	0	Xhosa	ILS
MTH 4	28/07/2003	10	F	0	Xhosa	ILS
MTH 5	13/04/1994	20	F	0	Xhosa	ILS

Table VII.1 continued

PMB 1	18/03/1998	16	F	0	Zulu	GH: Pmb
PMB 2	16/06/2003	11	F	0	Zulu	GH: Pmb
PMB 3	04/05/2007	7	M	0	Zulu	GH: Pmb
PMB 4	04/11/2010	4	F	0	Zulu	GH: Pmb
PMB 5	24/03/2008	6	M	2	Zulu	GH: Pmb
PMB 6	26/10/2010	4	M	0	Zulu	GH: Pmb
PMB 7	16/05/2005	9	F	1	Zulu	GH: Pmb
PMB 8	05/05/2000	14	M	0	Zulu	GH: Pmb
PMB 9	22/06/2008	6	F	0	Zulu	GH: Pmb
PMB 10	02/05/2011	4	M	0	Zulu	GH: Pmb
PMB 11	17/10/2001	13	F	2	Zulu	GH: Pmb
PMB 12	09/10/1999	15	M	2	Zulu	GH: Pmb
PMB 13	06/05/2008	6	M	1	Zulu	GH: Pmb
PMB 15	02/01/1995	19	F	0	Zulu	GH: Pmb
PMB 16	04/05/2010	4	F	0	Zulu	GH: Pmb
PMB 17	03/06/2010	4	M	1	Zulu	GH: Pmb
PMB 18	10/11/2010	4	F	0	Zulu	GH: Pmb
PMB 19	01/01/2005	8	F	0	Zulu	GH: Pmb
PMB 21	25/10/2011	2	F	0	Zulu	GH: Pmb
PMB 22	07/03/2011	2	F	0	Zulu	GH: Pmb
PMB 23	28/08/2003	10	F	0	Zulu	GH: Pmb
PMB 24	12/01/2003	11	F	2	Mpondo	GH: Pmb
PMB 25	16/12/1997	17	M	0	Zulu	GH: Pmb
PRET 1	13/03/2010	4	M	2	Shangan	SBAH: Pretoria
PRET 2	13/05/2011	3	M	0	Sesotho	SBAH: Pretoria
PRET 3	29/01/2007	7	F	1	Sepedi	SBAH: Pretoria
PRET 4	15/07/2003	10	M	0	Shona	SBAH: Pretoria
PRET 5	22/10/2005	8	F	0	Zulu	SBAH: Pretoria
PRET 6	13/02/2013	1	M	0	Sesotho	SBAH: Pretoria
PRET 7	13/08/2012	2	M	1	Zulu	SBAH: Pretoria
QQ 1	29/02/1988	25	F	2	Sesotho	UOFS: Qua Qua
QQ 2	13/09/1984	29	M	2	Sesotho	UOFS: Qua Qua
QQ 3	16/06/2003	10	F	2	Sesotho	UOFS: Qua Qua
QQ 4	04/05/2003	10	M	0	Sesotho	UOFS: Qua Qua

Table VII.2 Details of Affected Individuals of CMA Heritage

Affected Individual	Date of Birth	Age (Years)	Gender	Affected Relatives	Investigation Centre
CPT 2	20/04/1952	62	F	0	UWC: Tyg: CPT
CPT3	02/05/1993	19	F	0	UWC: Tyg: CPT
CPT 4	30/05/1986	26	F	0	UWC: Tyg: CPT
CPT 5	30/05/1986	26	F	0	UWC: Tyg: CPT
CPT 6	20/12/2001	13	F	0	UWC: Tyg: CPT

Table VII.3 Details of Affected Individuals of Indian decent

Affected Individual	Date of Birth	Age (Years)	Gender	Affected Relatives	Investigation Centre
DBN 6	11/08/1995	17	F	0	IALCH: Dbn
DBN 9	22/11/2012	2	F	0	IALCH: Dbn
PMB 20	11/03/1999	15	F	0	GH: Pmb

Abbreviations from Tables VII.1, VII.2 and VII.3

UOFS: University of the Free State

- **BTHM:** Bethlehem
- **QQ:** Qua Qua

CPT: Cape Town

- **UCT:** University of Cape Town and **GSH:** Groote Schuur Hospital
- **UWC:** University of the Western Cape (Faculty of Dentistry) and **TYG**: Tygerberg Hospital

DBN: Durban

- **OAS:** Open Air School
- **IALCH:** Inkosi Albert Luthuli Central Hospital

PMB: Pietermaritzburg

- **GH:** Greys Hospital

PRET: Pretoria

- **SBAH:** Steve Biko Academic Hospital

MTH: Mthatha (Umtata)

- **ILS:** Ikwezi Locusa School for the Physically Disabled

A summary of the data from Tables VII.1, VII.2 and VII.3 is presented in Table VII.4.

Table VII.4 Number of Individuals in Various Age Ranges in each Population Group

Age (years)	Black African Total: 64	Cape Mixed Ancestry Total: 5	Indian Total: 3
0 – 5	20	-	1
6 – 10	16	-	-
11 – 15	14	1	-
16 – 20	9	1	2
21 – 25	3	-	-
26 – 30	2	2	-
>50	-	1	-

The majority of the affected individuals (77%) were less than 15 years. This age range was influenced by the fact that many of the OI III affected individuals were children receiving bisphosphonate therapy at the various clinics that the author attended.

The basic clinical and molecular information of each Black African affected individual is recorded in Table VII.5 and data pertaining to the CMA and Indian individuals are presented in Table VII.6 and Table VII.7 respectively.

7.2 Clinical and Molecular Data (*Tables VII.5, VII.6 and VII.7*)

The colour of the sclerae of all the affected persons was within normal limits.

The **fractures** sustained by an affected individual are a major contributing factor to the progressive deformity experienced by persons with OI III and to their physical condition in terms of **mobility**.

Since stunted stature is an important phenotypic feature of the condition, the **height** of the affected persons was also recorded.

The management of the disorder with the use of **bisphosphonate therapy** is relevant to the dental management due to possible orodental complications. All of the affected persons received or were currently receiving bisphosphonate therapy except 14 individuals namely DBN 2, DBN 3, DBN 4 and

DBN 5, the 5 individuals of CMA heritage and the 5 persons from Umtata. It is suggested that the administration of bisphosphonates impacts on the progression of the disorder; hence it was also documented. A review of the literature and discussion in this regard is presented in Chapter 14.

DNA was extracted from oral epithelial cells from all 72 affected individuals and analysed by the DHG (UCT) for a mutation in exon 5 of the *FKBP10* gene. These **molecular findings** are also presented.
In this context, the homozygous mutation in exon 5 is a duplication designated as *FKBP10*_HOM_c.[831dupC][831dupC].
A few affected persons who were identified with a compound heterozygous mutation; the mutation is designated *FKBP10*_HET_c.[831dupC][831delC] and *FKBP10*_HET_c.[831dupC][1400-4C>G] and are highlighted in yellow.
The term 'wild type' is used to designate a molecular finding that was negative for the mutation which has been identified in exon 5 in the *FKBP10* gene.

Affected persons with the Bruck Syndrome phenotype are designated 'BS' *(see Chapters 3 and 4).*

DI was recorded based on the presence or absence of clinical discolouration of the teeth. When individuals had only secondary teeth, an account of their primary teeth was obtained from the individual, his parent/caregiver or from medical records.

In terms of bisphosphonate therapy (Bis.), 'Y' indicates that the individual is currently receiving or has completed therapy. The 14 affected persons have never received bisphosphonate therapy and these individuals are annotated as 'N'.

The abbreviations 'DI PT' and 'DI ST' represent clinically discoloured primary teeth and secondary teeth respectively. This information is relevant to the results and discussed in Chapters 10, 11 and 13 in order to document possible phenotype-genoptype correlations in terms of DI.

It must be emphasized that general phenotype-genotype correlations are outside the scope of this thesis. Phenotypic details have been included in order to give a perspective of the severity of the condition and to facilitate correlation with dental and craniofacial features *(see Chapters 9, 12 and 13).* Similarly, molecular data was used in the analyses of the oro-facial manifestations.

The data are presented in Tables VII.5, VII.6 and VII.7 and commented on following the tables.

Table VII.5 Disability Status and Molecular Findings of Black African Affected Individuals

Affected Individual	No. of #s	Age (years)	Height (cm)	General Physical Condition in terms of Mobility	Bis	Molecular Findings	DI PT	DI ST
BTHM 1	>5	25	92	Walks with an aid	Y	WT	Y	Y
BTHM 2	4	6	81	Walks with an aid	Y	WT	Y	Y
BTHM 3	>5	8	96	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
BTHM 4	>30	6	79	Cannot walk or crawl	Y	WT	Y	Y
CPT 1	>10	19	119	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
CPT 7	>50	30	105	Chairbound	N	FKBP10_HET_c.[831dupC][1400-4C>G]	N	N
DBN 2	>20	19	107	Chairbound	N	WT	Y	Y
DBN 3	>10	19	102	Walks with an aid	N	WT	Y	Y
DBN 4	8	18	103	Walks with an aid	N	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
DBN 5	>10	19	108	Chairbound	N	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
DBN 7	>10	3	60	Cannot crawl	Y	WT	Y	?
DBN 8	3	3	61	Crawls	Y	WT	Y	?
DBN 10	3	2	50	Cannot crawl	Y	WT	Y	?
DBN 11	4	4	64	Crawls	Y	WT	Y	?
DBN 12	2	3	55	Crawls	Y	WT	N	?
DBN 13	>5	5	59	Chairbound	Y	WT	Y	Y
DBN 14	>10	12	90	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
DBN 15	>20	11	92	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
DBN 16	>5	14	97	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
DBN 17	>5	6	80	Walks with an aid	Y	WT	Y	Y
DBN 18	>20	20	114	Chairbound	Y	WT	Y	Y
DBN 19	1	2	51	Cannot walk or crawl	Y	WT	N	?
DBN 20	2	3	50	Crawls	Y	WT	Y	?
DBN 21	>30	12	75	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
DBN 22	>10	13	80	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
MTH 1	>10	17	100	Chairbound	N	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
MTH 2 (BS)	>20	14	101	Chairbound	N	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
MTH 3	>20	19	100	Chairbound	N	WT	Y	Y
MTH 4 (BS)	>10	10	101	Chairbound	N	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
MTH 5	>20	20	105	Chairbound	N	WT	Y	Y

Table VII.5 continued

PMB 1 (BS)	>20	16	97	Chairbound	Y	WT	Y	Y
PMB 2	>5	11	117	Chairbound	Y	WT	Y	Y
PMB 3	>10	7	98	Chairbound	Y	WT	Y	Y
PMB 4	3	4	68	Crawls	Y	WT	Y	?
PMB 5	>5	6	59	Walks with an aid	Y	WT	Y	Y
PMB 6	3	4	71	Crawls	Y	WT	Y	?
PMB 7	>10	9	90	Cannot walk	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
PMB 8	>10	14	118	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
PMB 9	>5	6	68	Walks with an aid	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
PMB 10	2	4	79	Crawls	Y	WT	N	?
PMB 11	3	13	100	Walks with an aid	Y	WT	Y	Y
PMB 12	>10	15	106	Chairbound	Y	WT	Y	Y
PMB 13	>10	6	69	Chairbound	Y	WT	Y	Y
PMB 15	>20	19	120	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
PMB16 (BS)	>5	4	89	Cannot walk	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	?
PMB 17	>5	4	94	Crawls	Y	WT	Y	?
PMB 18	>5	4	92	Cannot walk	Y	WT	Y	?
PMB 19	>5	8	99	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
PMB 21	3	2	76	Cannot Crawl	Y	WT	Y	?
PMB 22	>5	2	86	Cannot Crawl	Y	WT	Y	?
PMB 23	>5	10	100	Chairbound	Y	WT	Y	Y
PMB 24	>10	11	99	Chairbound	Y	WT	Y	Y
PMB 25	>5	17	118	Chairbound	Y	WT	Y	Y
PRET 1	>5	4	85	Cannot walk or crawl	Y	WT	Y	?
PRET 2	>5	3	80	Cannot walk or crawl	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	?
PRET 3	>10	7	82	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
PRET 4 (BS)	>10	10	93	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
PRET 5 (BS)	>10	8	95	Chairbound	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	N
PRET 6	3	1	76	Cannot walk or crawl	Y	FKBP10_HOM_c.[831dupC][(831dupC)]	N	?
PRET 7	3	2	84	Cannot walk or crawl	Y	WT	Y	?
QQ 1	>20	25	119	Chairbound	Y	FKBP10_HET_c.[831dupC];[831delC]	N	N
QQ 2	>20	29	115	Chairbound	Y	FKBP10_HET_c.[831dupC];[831delC]	N	N
QQ 3	>10	10	118	Walks with an aid	Y	FKBP10_HET_c.[831dupC];[831delC]	N	N
QQ 4	>10	10	95	Walks with an aid	Y	WT	Y	Y

Table VII.6 Disability Status and Molecular Findings of CMA Affected Individuals

Affected Individual	No. of #s	Age (Years)	Height (cm)	General Physical Condition in terms of Mobility	Bis. Therapy	Molecular Findings	DI PT	DI ST
CPT 2	>50	62	96	Chairbound	N	WT	Y	y
CPT 3	>30	19	93	Chairbound	N	WT	Y	Y
CPT 4	>50	26	95	Chairbound	N	WT	Y	Y
CPT 5	>50	26	95	Chairbound	N	WT	Y	Y
CPT 6	>20	13	80	Chairbound	N	WT	y	Y

Table VII.7 Disability Status and Molecular Findings of Indian Affected Individuals

Affected Individual	No. of #s	Age (Years)	Height (cm)	General Physical Condition in terms of Mobility	Bis. Therapy	Molecular Findings	DI PT	DI ST
DBN 6	>15	17	115	Walks with an aid	Y	WT	Y	Y
DBN 9	>5	2	45	Cannot walk or crawl	Y	WT	Y	?
PMB 20	>10	15	114	Walks with an aid	Y	WT	Y	Y

Abbreviations:

Bis: Bisphosphonate therapy

No. of #s: Number of fractures

Y: Yes

?: Absence of permanent teeth

7.3 Comments on:

7.3.1 Fractures

The number of fractures encountered from birth until dental assessment was documented. When the affected individuals were unable to provide this information, clarity was obtained from their parents, clinicians or their clinical notes. The type of fracture recorded was that which necessitated medical or orthopaedic management. Several individuals reported the occurrence of multiple hairline fractures that essentially required pain control; these were not recorded. The quantity of fracturing in an individual provided a perspective on the severity of the disorder. In turn, severity of the disorder in the various population groups could be related to the dental and craniofacial features and to the presence or absence of DI.

Fracturing in OI III is a continual complication, therefore, the number of fractures recorded is influenced by age. Given that 34 individuals were between 0 – 10 years, a record of the number of fractures in these individuals may not be an accurate representation of the severity of the disorder. Longevity impacts on the clinical, craniofacial and dental features.

Further analyses are outside the scope of this dentally orientated project but overall severity is highlighted by details presented in Tables VII.5, VII.6 and VII.7.

The 5 individuals of CMA heritage whom sustained more than 30 fractures were adults aged between 26 and 62 years and had severe DI. It is relevant that none of these persons had received bisphosphonate therapy.

The Black African and CMA affected individuals of 18 years and older achieved a final adult height of 1.2 m or less. The CMA adult persons achieved a maximum height of 98cm. The 2 adult Indian affected persons, DBN 6 and PMB 20, had an average height of 1.15m. All the affected infants aged between birth and 36 months and individuals between 3 and 18 years displayed a marked compromise in height with centile values of 50% and less.

The final height and general physical condition of the affected individuals are dependent on the number of fractures endured as well the malalignment of the limbs due to the malleability of the bones in the absence of fracturing. An accumulation of these features contribute to the overall physical compromise of the affected persons.

7.3.2 General Physical Condition as determined by Mobility

The extent of compromise in terms of mobility serves as an additional indicator of the severity of the disorder. In this series, no affected individual was able to walk unaided and 76% of persons aged between 5 and 62 years were chairbound.

This information was ascertained during the dental examination and where necessary, the parent or clinician provided relevant details. The mobility status was recorded in all individuals, divided into two age ranges, summarized and presented in Table VII.8.

Table VII.8 General Physical Condition as determined by the Mobility of the Affected Persons

Age Range: 1 month – 4 years	Age Range: 5 - 30 years
Walks unaided: 0 Crawls: 7 Unable to crawl or walk: 10	Walks Unaided: 0 Walks with an Aid: 12 Chairbound: 39

The height, the general physical deformity and mobility of affected persons impacts on and poses several challenges in terms of the dental and craniofacial management of these individuals.

7.3.3 Molecular Findings

In exon 5 of *FKBP10,* three DNA variations were identified in this cohort of affected individuals.

The **homozygous** mutation was identified in **23 affected persons**. All of these individuals belonged to the Black African ethnic group of SA. This homozygous mutation, **c.[831dupC];[(831dupC)]**, a frameshift DNA variant which is predicted to alter the protein sequence by substituting a Glycine residue with an Arginine at position 278 of the 65 kDa FK506 Binding protein 10. This is achieved by introducing a shift in the reading frame which results in the introduction of a premature termination codon, 95 residues from the substitution point (NM_021939.3(FKBP10_i001):p.(Gly278Argfs*95)). The introduction of this premature termination codon results in the loss of 211 amino acid residues.

A **compound heterozygous** mutation, **c. [831delC]; [831dupC]** was identified in **3 Black African** siblings with OI III. This is a frameshift DNA variant in exon 5 of *FKBP10* which is predicted to alter the protein sequence by substituting a Glycine residue with an Alanine at position 278 of the 65 kDa FK506 Binding protein 10. A consequent shift in the reading frame results in the introduction of a premature

termination codon, 20 residues from the substitution point (NM_021939.3(FKBP10_i001):p.(Gly278Alafs*20)). The premature termination codon results in the loss of 286 amino acid residues.

Both these frameshift variations result in the loss of two peptidylprolyl isomerase domains (PPIase 3 and PPIase 4) and both EF-hand (EF-hand 1 and EF-hand 2) domains which are essential for localisation to the endoplasmic reticulum (Boudko et al., 2014).

Another **compound heterozygous mutation, c.[831dupC][1400-4C>G]** was identified in a **29 year Black African** female belonging to the Xhosa linguistic group. The designation 'c.1400-4c>g', means that a single nucleotide has been substituted 4 bases from the intron-exon junction. Although this mutation does not change the protein coding sequence directly, it might alter the splicing of the exon that it precedes.

The DNA of the **45 affected individuals** which includes the CMA and Indian affected persons in whom no disease causing mutations have been identified in exon 5, will be utilized for ongoing mutation screening of the remaining coding regions of FKBP10 in an attempt to account for all the genetic determinants in this patient cohort. These persons were given the molecular status **'Wild Type' (WT).**

The homozygous mutation, c.[831dupC];[(831dupC)] has been reported 19 times on the Leiden Open Variation Database.

However, to the best of the author's knowledge, 9 individuals with this homozygous mutation were documented in published reports *(listed in Table IV.1, Chapter 4).* The phenotypic features of these 9 persons ranged from progressively deforming OI to BS. These reports were orientated to the discussion of BS and 8 of these affected persons had contractures *(see Chapter 3).* The teeth were described as normal in each of the 9 affected persons.

7.3.4 Bisphosphonate Therapy in OI III: Radiological Observations

The dental literature on bisphosphonate therapy, osteonecrosis of the jaw (ONJ) and treatment protocols have been reviewed and discussed in detail in Chapter 14.

In this project there was no clinical evidence of ONJ and no history of this complication was obtained from any affected person or their clinician.

A radiological observation in 2 affected persons is presented below.

Radiographical differences in the jaws of 2 affected persons in this project was observed by the author. One individual, CPT 1, had received bisphosphonate therapy and the other had not (DBN 5). In order to illustrate this disparity, panoramic radiographs of CPT 1 (Fig 7.1) and DBN 5 (Fig 7.2) are presented.

Affected person CPT 1 was a Black African female, aged 19 years who has received bisphosphonate therapy for the last 5 years. She had recent extractions of 2 molar teeth with no subsequent complications despite a history of a difficult and traumatic procedure.
Affected person DBN 5 was a Black African male, aged 19 years who had never received bisphosphonate therapy. He had a molar tooth extracted a year ago with no complications.
Both individuals have the same homozygous mutation, c.[831dupC];[(831dupC)].

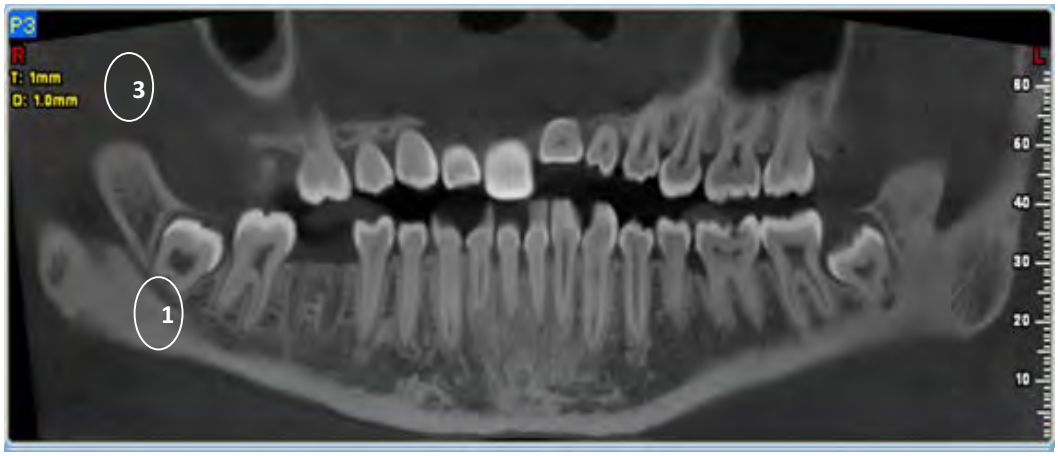

Fig 7.1 CPT 1. Panoramic image of CPT 1 from her CBCT. It is distorted due to difficulty in positioning the patient. Her marked mandibular prognathism precluded the maxilla and mandible from being in focus simultaneously. The mandibular cortex (1) is radiodense and sclerosed throughout to a thickness of approximately 3 mm. There is mild rarefication of the cancellous bone of the mandible (2). The lamina dura is sclerosed (3).

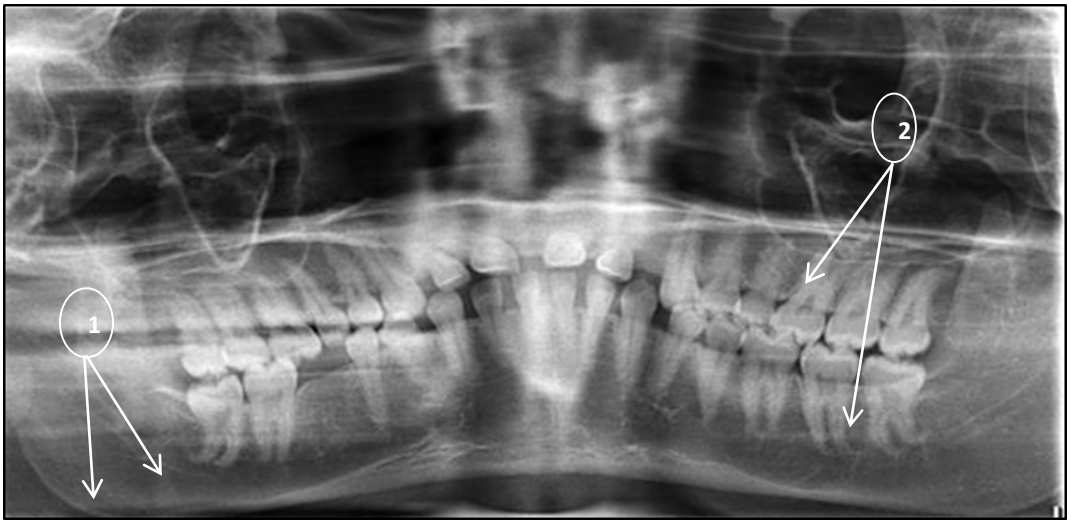

Fig 7.2 Panoramic radiograph of DBN 5. Image is distorted due to difficulty in positioning DBN 5. Hypomineralization of the cortical and cancellous bone of the jaws is evident (1). The lamina dura is absent in both mandible and maxilla (2).

Bisphosphonates have an increased affinity for hydroxyapatite crystals which is the inorganic constituent of bone and teeth (Fleisch, 1998). Longitudinal studies are required in order to evaluate the beginning of bisphosphonate therapy at a very young age and the natural history of DI in the primary and secondary dentition. Bisphosphonate therapy, theoretically, may increase the amount of dentin as it does bone (Brown et al., 2008). Even if the quality of dentin does not change, the resistance and the colour of the teeth may change. Future studies in this regard will confirm or negate this hypothesis.

Longitudinal studies may also prove valuable in determining the incidence of ONJ in children and adults with OI III receiving bisphosphonate therapy.

7.3.5 Age-Related Phenotypic Manifestations

Osteogenesis imperfecta type III is usually not lethal in the neonatal period but growth is impaired and short stature is usual (Beighton et al., 1983).

In the past, death often occurred in persons with OI III during the first two decades of life. Management of OI III with bisphosphonate therapy has now resulted in numerous affected individuals living into adulthood (Sillence et al., 1986).

Prolonged life resulting from bisphosphonate therapy may influence the dental and craniofacial manifestations as these features are age related (O'Connell and Marini, 1999).

In the current investigation, the relative longevity is corroborated by the example of siblings QQ3, aged 10 years (Fig 7.3) and QQ2, aged 29 years (Fig 7.4). Their parents are normal and there is no history of the disorder in any of their relatives. They belong to the Sesotho linguistic group and are 95 cm and 99 cm in height respectively. QQ3 has sustained 8 fractures and QQ2 has had approximately 20 fractures as well as eight orthopaedic operations with consequent severe physical compromise. He has been chairbound for the last 15 years.

Both individuals received bisphosphonate infusions and their molecular findings confirm that they have the same compound heterozygous mutation, c.[831dupC];[831delC] in exon 5 of the *FKBP10* gene.

The spectrum of their orodental changes are age related and may present initially as an edge to edge bite and a bilateral posterior open bite in QQ3 (Fig 7.3) and progress to an anterior open bite with marked splaying of the anterior teeth, a posterior crossbite, a flattened palate and moderate deposits of plaque and calculus observed in QQ2 (Fig 7.4). An edge to edge bite in a preadolescent person is highly suggestive of an eventual adult Class III malocclusion (Profitt et al., 2013).

The age-related progressively deforming nature of OI III is evident in the images of siblings QQ 2 and QQ 3.

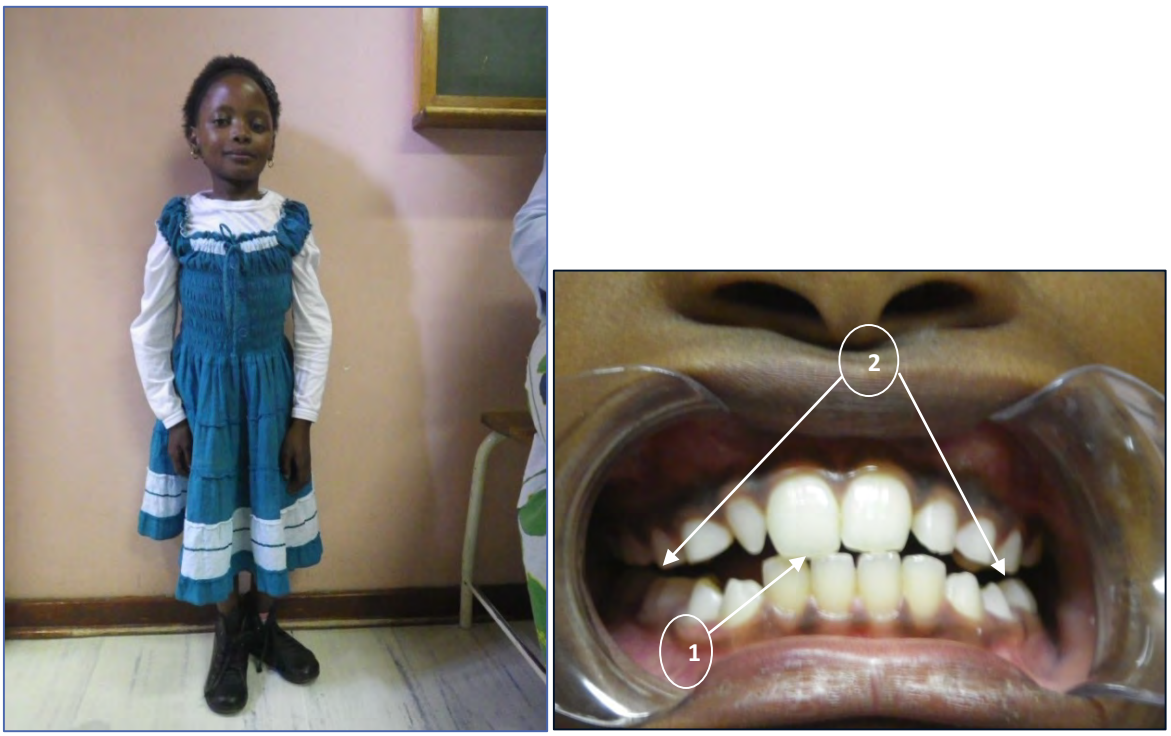

Fig 7.3 QQ 3 aged 10 years, walked with an aid**.** She had an anterior edge to edge bite (1) and a bilateral posterior open bite (2). Her lower jaw could not be positioned more posteriorly.

Fig 7.4 QQ 2 aged 29 years is a sibling of QQ 3. He was chairbound with marked physical disability. An anterior open bite (1) and splayed (proclined) anterior teeth were evident. He also had a bilateral posterior crossbite (2). Moderate deposits of plaque and calculus were visible in the cervical region of his lower anterior incisors (3). He had difficulty incising food and he had limited opening of his mouth.

As previously stated, skeletal deformity is an important factor in dental care in terms of seating and imaging. In some developing countries, skeletal deformity in OI may be a consequence of suboptimal care due to a lack of primary medical care services for managing fractures. Several affected individuals in the current investigation lived out in rural areas and had to travel long distances in order to access medical care. As suggested by Van Dijk and Sillence (2014), skeletal deformity may not be the only basis of the progressive deformity intrinsic to the disorder.

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Chapter 8: OI III: Black African Population Group: General Data and Dental Observations

8.1 Summary of Data

8.1.1 Age Range of Individuals

8.1.2 General Physical Condition

8.1.3 Molecular Findings regarding FKBP10

8.2 Dental Observations

8.2.1 Size of Teeth

8.2.2 Shape of Teeth

8.2.3 Missing Teeth

8.2.4 Impacted Teeth

8.2.5 Occlusal Anatomy

8.2.6 Delayed Eruption of Teeth

8.2.7 Dental Caries

8.3 Conclusion

Preamble

The clinical findings and a comprehensive account of the dental observations in the Black African population group of affected individuals are documented in this chapter. The craniofacial observations are presented and commented on in Chapter 9.

The description and comment on the dentition in this chapter excludes the features of Hereditary Dentin Dysplasia, particularly DI. These features are reviewed, documented and commented on in detail in Chapters 10 and 15.

8.1 Summary of Data

Detailed clinical and molecular findings were presented in Chapter 7 (Tables VII.1, VII.2, VII.3 and VII.5). The tables displayed in this chapter represent a summary of data of only the Black African affected persons. Each finding is recorded and where relevant followed by a comment. This approach has been taken for sake of clarity.

8.1.1 Age Range of Individuals

Table VIII.1 A summary of the data captured in Table VII.1 indicating the number of affected individuals examined in the various age groups

Age (years)	Black African affected persons: Total 64
0 – 5	20
6 – 10	16
11 – 15	14
16 – 20	9
21 – 25	3
26 – 30	2
>50	-

Comment:

A total of 64 Black African affected individuals were assessed. Fifty-five were evaluated by the author at clinics where they received their bisphosphonate infusions. A further 9 affected persons were seen at the Open Air School in Durban and ILS in Mthata. These persons lived out in remote rural areas that were far removed from appropriate medical facilities and services. None of these 9 individuals had received bisphosphonate therapy.

8.1.2 General physical condition

Table VIII.2 Number of Fractures

Number of Fractures	Number of Individuals
0 – 10	38
11 – 20	13
21 – 30	10
31 – 40	2

Table VIII.3 General Physical Condition as determined by Mobility and Age

Age Range: 6 month – 48 month	Age Range: 5 - 30 years
Walks unaided: 0 Crawls: 10 Unable to crawl or walk: 10	Walks Unaided: 0 Walks with an Aid: 10 Chairbound: 33

Comment:

The general physical condition of the affected individuals is the consequence of several fractures and the general malleability of the bones. Their general physical condition in terms of mobility also emphasizes the progressively deforming nature of the disorder. It is also apparent that an increasing proportion of these persons now survive into the second and third decade of life.

8.1.3 Molecular Findings regarding FKBP10

Molecular findings documented in Table VII.4 *(see Chapter 7)* are summarized and presented in Table VIII.4.

The *FKBP10* gene is discussed in detail in Chapter 4 and a brief report on the molecular pathogenesis of the homozygous and compound heterozygous mutations identified in *FKBP10* in this cohort of individuals is provided in Chapter 7 *(Page 63).*

A total number of 64 saliva samples were analysed and the results are presented in Table VIII.4

Table VIII:4 Numbers of Individuals in the various Linguistic Groups with the *FKBP10* mutation in exon 5 and others in whom a mutation has not as yet been Identified (Wild Type)

Black African Linguistic Groups	HOM c.[831dupC][831dupC]	C HET c.[831dupC][831delC]	C HET c.[831dupC][1400-4C>G]	Wild Type (WT)
Zulu	12	0	0	26
Xhosa	4	0	1	3
Sesotho	4	3	0	3
Sepedi	2	0	0	2
Shona	1	0	0	2
Shangan	0	0	0	1
TOTAL	***23***	***3***	***1***	***37***

Six affected individuals, MTH 2, MTH 4, PMB 1, PMB 16, PRET 4 and PRET 5 had the phenotypic features of Bruck Syndrome *(see Chapters 3 & 4).* Five of these persons had the homozygous mutation, *FKBP10*_HOM_c.[831dupC][831dupC].

Affected person, PMB1, had the clinical features of BS but did not have the mutation in exon 5 of *FKBP10*.

Comment:

The phenotypic spectrum of the 64 Black African affected persons include progressive deforming OI III (58 persons) and BS type I. The clinical and molecular findings confirm the variable expression and genetic heterogeneity of OI III in this population and are suggestive of the possible influence of epigenetic factors on the phenotypic expression of the disorder.

8.2 Dental Observations

These dental observations were recorded mainly from an intraoral clinical examination of the affected individual. In addition, when radiographic resources were available, dental radiographs were obtained.

The Black African affected persons had many anomalies in their dentition. These findings are presented together with the molecular data in Table VIII.5.

Table VIII:5 Abnormalities in the Dentition of Affected Persons in the various *FKBP10* Molecular Categories

DENTITION	*FKBP10* HOM: n=20	*FKBP10*_C HET: n=4	WILD TYPE: n=36
Abnormal size	0	2	2
Abnormal shape	6	2	5
Missing teeth	2	0	4
Impacted teeth	5	0	10
Occlusal irregularity	14	1	19
Delayed eruption: >10 months	10	0	14

The definition, classification and features of the Hereditary Dentin Dysplasias are discussed in Chapter 15. The DI findings in the Black African persons in the various molecular categories are presented in Chapter 10.

Comments**:** *(Definitions and details of the anomalies of the dentition are described in Appendix 3)*

8.2.1 Size of Teeth

Abnormal size of teeth was a subjective finding of generalized or localized teeth which were larger or smaller than normal. In the 4 instances the abnormal teeth were peg shaped permanent upper lateral incisors, representative of localized microdontia. "Peg-shaped" upper lateral incisors and small third molars are seen regularly by the practicing dentist. Peg-shaped incisors tend to be familial .

8.2.2 Shape of Teeth

In terms of the shape of teeth, the morphology of the crown of the tooth was assessed and when possible, periapical radiographs were obtained in order to view the morphology of the roots. Of the 13 individuals with abnormally shaped crowns or roots, 8 had features of abnormal roots such as *dilacerations* and *flexion* and 2 affected persons, CPT 1 and DBN 4, had features suggestive of *taurodontism.* The 3 remaining individuals in this category had abnormally shaped crowns, notably of their anterior teeth.

Dilaceration is a severe bend in the long axis of the tooth (Fig 8.1) and usually results from trauma to the unfinished tooth when development is in progress.

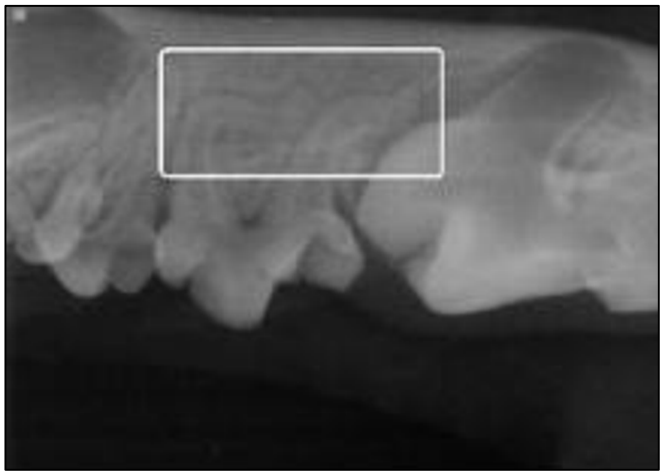

Fig 8.1 Radiographic image of dilacerated roots

Flexion is a deviation or bend restricted just to the root portion of the tooth and may be a result of trauma to the developing tooth (Fig 8.2).

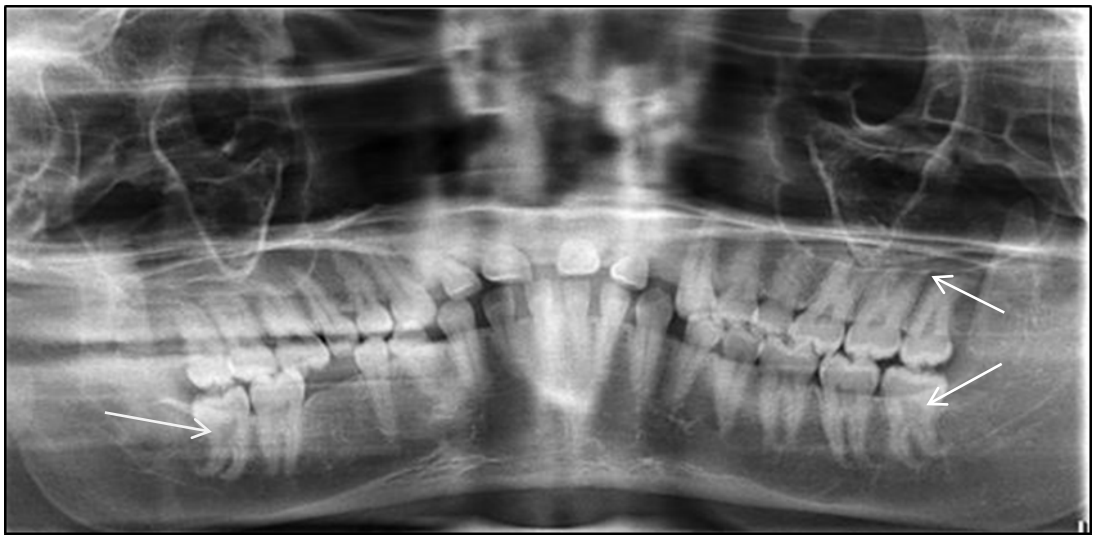

Fig 8.2 Panorex of DBN 5. There is flexion of the roots of 28, 38 and 48 (arrows)

Taurodontism means 'bull-like teeth'. (*see Chapter 16. A review and discussion of Taurodontism*)

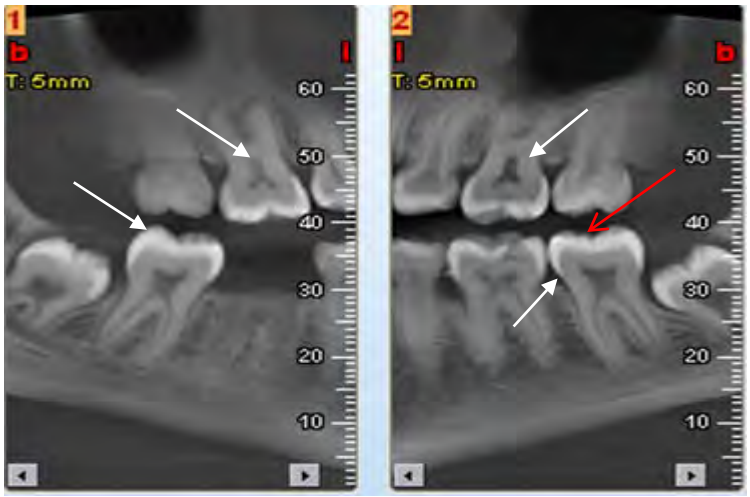

Fig 8.3 Cropped CBCT image of Individual CPT 1 with features of hypotaurodontism evident in the 17, 27 37 and 47 (white arrows). Radiographic evidence of an atypical occlusal anatomy (red arrow) of the molar.

The most important clinical challenges of dilaceration, flexion and taurodontism are encountered when root canal therapy or an extraction is necessary. Due prudence is warranted.

8.2.3 Missing Teeth

Missing teeth or congenitally absent teeth could only be recognized with the aid of radiographs. Four individuals had missing 8th molars (wisdom teeth), one had missing upper lateral incisors and another had a missing lower premolar, representative of partial anodontia. The prevalence of missing permanent teeth in Sweden and Denmark ranged from 6.1% to 7.8% (Rolling, 1980). After the analysis of panoramic radiographs of 49 persons with OI, congenitally missing teeth was observed in 11 individuals (Malmgren and Norgren, 2002).

8.2.4 Impacted Teeth

Of the 15 individuals with impacted teeth, 10 had impacted upper wisdom teeth, 2 had impacted first molars, 1 had an impacted upper second molar and another had an impacted upper canine. Possible aetiological factors include the angulation of the occlusal plane and the posterior position of the maxilla. It has been suggested that impactions of this type are independent of the presence or absence of DI and the malocclusion that affected persons frequently present (Malmgren & Norgren, 2002).

8.2.5 Occlusal Anatomy

The occlusal anatomy of the permanent molars was examined clinically and more than 50% of the affected individuals displayed abnormalities in this regard (Figs 8.3 and 8.4).

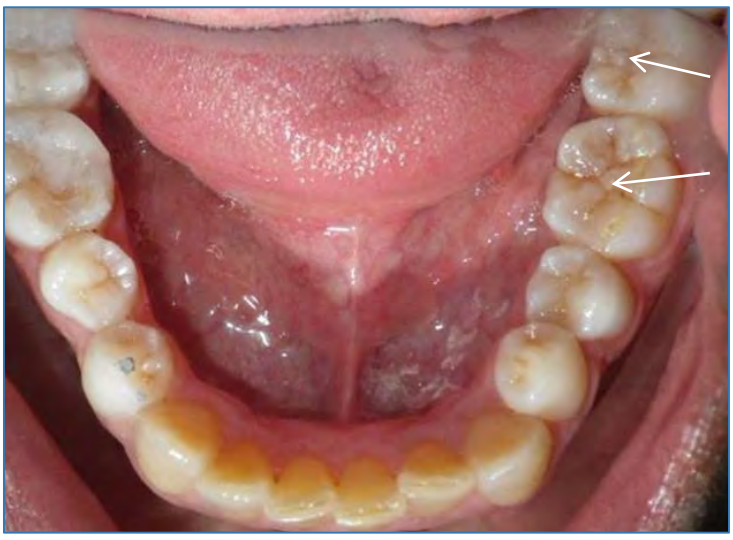

Fig 8.4 Irregularities in the occlusal anatomy of the molar teeth of DBN 2 (arrows)

Teeth form within the bony matrix of the mandible and the maxilla; hence an abnormality in the connective tissue of the bone can affect the developing teeth. During odontogenesis, an interaction

between the mesenchymal and ectodermal tissues takes place. This suggests that a mesenchymal defect may influence the incremental secretion and mineralization of the enamel organic matrix. Morphological deviations can result and insufficient dentine matrix may lead to bending of the overlying epithelial enamel organ and consequent occlusal irregularity (Ruch et al., 1983).

8.2.6 Delayed Eruption of Teeth

The lack of adequate radiographic facilities in some centres precluded that accurate verification of eruption dates. In these circumstances, these values were obtained from a subjective clinical intraoral examination. Twenty four (38%) affected individuals demonstrated a delay in the eruption of either their primary or permanent teeth and all these individuals were receiving bisphosphonate infusions (*see Chapter 14 for a detailed summary and discussion of bisphosphonate therapy and the possible dental complications*). In a study involving 33 children with OI that received bisphosphonate therapy, a 1.67 year delay in tooth eruption was recorded in all 33 children (Kamoun-Goldrat et al., 2008). Bisphosphonates increase bone mass density primarily by decreasing osteoclastic activity (Zeitlin et al., 2003). Osteoclasts have a role during craniofacial development since they are necessary for the resorption and subsequent exfoliation of the primary teeth and creating a pathway for the eruption of the permanent teeth.

8.2.7 Dental Caries

Dental caries was not found to be more common in this cohort of individuals and tooth eruption and dental maturity were age appropriate in 62% of affected persons. This was an expected observation since the enamel is normal. However, if carious lesions develop, they are expected to progress at a faster rate because of the abnormal dentin. Regular dental visits are important with a view to prevention of caries and maintenance of the dentition.

8.3 Conclusion

The prevalence of dental aberrations in OI III highlights the importance of clinical and radiographic early dental examination, particularly radiographic investigations.

References

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Chapter 9: Black African Population Group: Craniofacial and Periodontal Observations

Preamble

The craniofacial and periodontal observations of affected persons in the Black African population are presented and commented on in this chapter.

Affected individuals with OI III often exhibit characteristic craniofacial deformities encompassing abnormalities of the head and neck. There is frequent disharmony between the mandible and the maxilla which eventually results in functional and aesthetic concerns for the affected person.

The author is cognisant that within the Black African population each linguistic group may have genetically determined craniofacial features, but the identification of such inherent features were not pursued in this project.

The craniofacial results are presented in each molecular category. This approach enabled possible phenotype-genotype correlations to be identified and highlighted.

9.1 Occlusion *(see Appendix 4 for the definition and types of occlusion and malocclusion)*

In this project, occlusion was determined from a clinical oro-dental examination of the affected persons. When possible, cephalometric radiographs were obtained in order to confirm a skeletal-jaw relationship. Cephalometrics is the interpretation of lateral skull radiographs taken under standardized conditions*. (see Appendix 5 for a summary of practical cephalometrics and the interpretation of cephalometric values)*

Abnormalities in the occlusion and skeletal relationship of the upper and lower jaws are presented and summarized for each molecular group of Black African affected persons in Table XI.1. The occlusion was assessed and classified from a craniofacial and dental clinical examination and when available, an interpretation of a cephalometric radiograph. These malocclusions were classified according to those presented and described in Appendix 4.

Other clinical factors that influence the occlusion of an individual such as open, cross, edge to edge bites and splayed (proclined) teeth were also recorded in Table IX.1.

An edge to edge bite in this instance was only identified in children with only their deciduous dentition and in those in the mixed dentition period.

Table IX.1 Summary of Occlusal Findings

***FKBP10*_HOM c.[831dupC][831dupC] : 23 Affected Persons**								
Class I	**Class II**	**Class III**	**Open Bites**		**Cross Bites**		**Edge-edge bite**	**Proclined teeth**
			Ant	**Post**	**Ant**	**Post**		
1	0	11	6	2	4	10	10	8
***FKBP10*_C HET_c.[831dupC][831delC] : 3 Affected Persons**								
Class I	**Class II**	**Class III**	**Open Bites**		**Cross Bites**		**Edge-edge bite**	**Proclined teeth**
			Ant	**Post**	**Ant**	**Post**		
1	0	2	1	1	0	2	1	2
***FKBP10*_CHET_c.[831dupC][1400-4C>G] : 1 Affected Persons**								
Class I	**Class II**	**Class III**	**Open Bites**		**Cross Bites**		**Edge-edge bite**	**Proclined teeth**
			Ant	**Post**	**Ant**	**Post**		
0	0	1	0	1	0	1	0	1
Wild Type : 37 Affected Persons								
Class I	**Class II**	**Class III**	**Open Bites**		**Cross Bites**		**Edge-edge bite**	**Proclined teeth**
			Ant	**Post**	**Ant**	**Post**		
8	0	12	4	1	3	5	8	3

Clinical images of CPT 1 (Fig 9.1) and PRET 3 (Fig 9.4) are presented in order to depict the occlusal abnormalities observed.

Several anomalies in terms of malocclusion are illustrated in Fig 9.1 of CPT 1 whose molecular status is *FKBP10* HOM c.[831dupC][831dupC]. A cephalometric radiograph (Fig 9.2) and tracing thereof (Fig 9.3), obtained prior to the commencement of orthodontic treatment, confirms the presence of a dental Class III and skeletal Class III malocclusion in CPT 1.

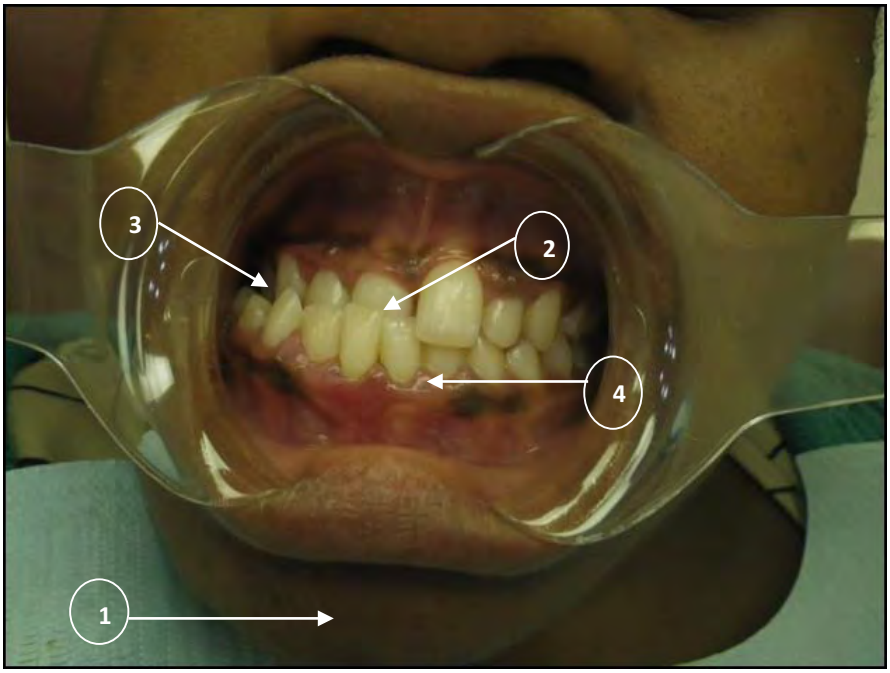


Fig 9.1 Intraoral photograph of CPT 1 with molecular defect *FKBP10* HOM c.[831dupC][831dupC]. She has a Skeletal Class III malocclusion with a prognathic mandible (1) and an anterior crossbite (2). A posterior crossbite (3) and swollen, inflamed gingiva (4) are evident.

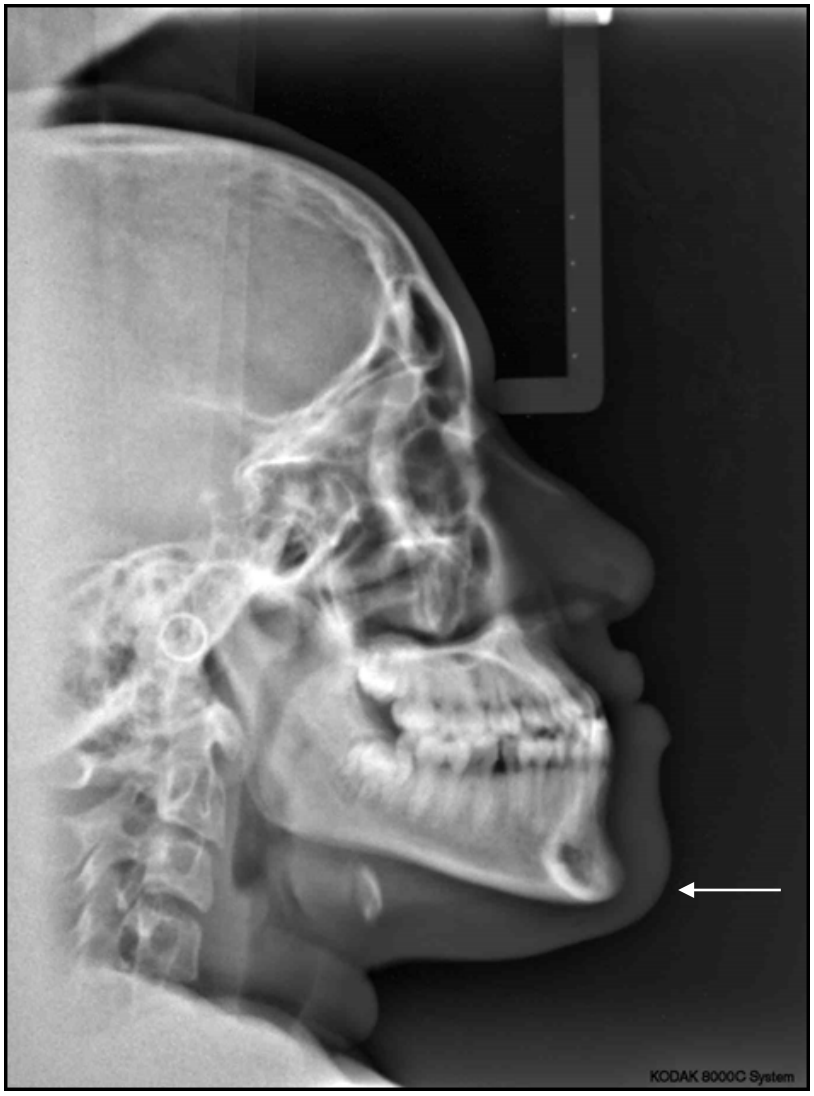
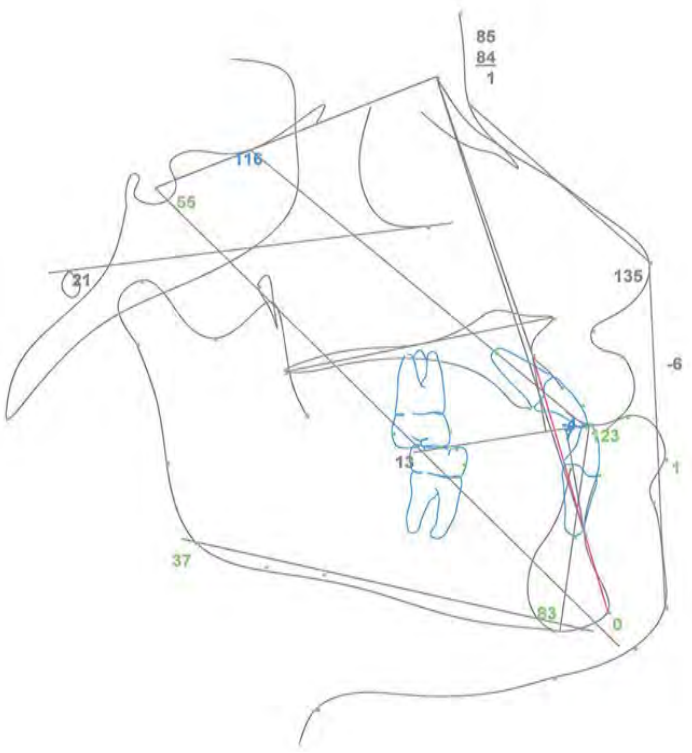


Fig 9.2 Cephalometric radiograph of affected person CPT 1 confirming a skeletal Class III malocclusion. Her mandible is prognathic (arrow).



	Value	Norm	Std Dev	Dev Nor	
Interincisal Angle (U1-L1) (°)	123.5	130.0	6.0	-1.1	*
IMPA (L1-MP) (°)	83.0	95.0	7.0	-1.7	*
ANB (°)	1.0	1.6	1.5	-0.4	
Lower Lip to E-Plane (mm)	1.2	-2.0	2.0	1.6	*
Upper Lip to E-Plane (mm)	-6.2	-6.0	2.0	-0.1	
MP - SN (°)	37.5	33.0	6.0	0.7	
SNA (°)	85.3	82.0	3.5	0.9	
SNB (°)	84.2	80.9	3.4	1.0	
U1 - SN (°)	116.0	102.8	5.5	2.4	**
L1 - NB (mm)	7.4	4.0	1.8	1.9	*
U1 - NA (mm)	5.1	4.3	2.7	0.3	
U1 (labial surface) to NA (mm)	5.7	4.3	2.7	0.5	
Pog - NB (mm)	-0.4	2.4	1.7	-1.6	*
Soft Tissue Convexity (°)	135.3	132.4	4.0	0.7	
SN - GoGn (°)	36.2	32.0	5.0	0.8	
Facial Angle (FH-NPo) (°)	99.3	88.6	3.0	3.6	***
Wits Appraisal (mm)	-3.9	-1.0	1.0	-2.9	**
FMA (R4 Version) (°)	20.8	23.9	4.5	-0.7	
L1 Protrusion (L1-APo) (mm)	6.8	2.7	1.7	2.4	**
S - A (mm)	78.7	90.8	-13%		
Mandibular Length (Jarabak G - Me	71.3	82.0	5.0	-2.1	**
Maxillary length (ANS-PNS) (mm)	51.7	51.6	4.3	0.0	
Y-Axis -- Downs (SGn-FH) (°)	55.2	60.3	3.4	-1.5	*
Nasolabial Angle (Col-Sn-UL) (°)	83.0	102.0	8.0	-2.4	**
Overjet (mm)	-0.8	2.5	2.5	-1.3	*
Overbite (mm)	0.4	2.5	2.0	-1.1	*

SUMMARY ANALYSIS
Anterior Crossbite

Fig 9.3 Cephalomteric tracing and results of CPT 1 confirming a skeletal Class III profile and a Class III dental relationship

An edge to edge bite can be observed in children who have only their primary dentition (Fig 9.4). This occlusal observation is significant as it often tends to progress to an adult Class III dental malocclusion and a potential skeletal Class III malocclusion.

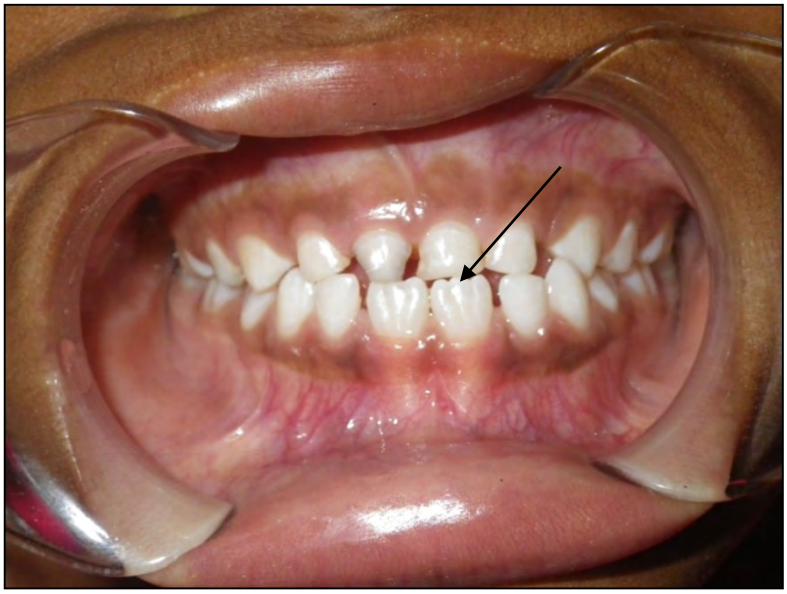


Fig 9.4 Intraoral picture of 6 year old PRET 3 with molecular defect *FKBP10* HOM c.[831dupC][831dupC] showing an edge to edge bite (arrow)

9.2 Palatal Anatomy

The anatomy of the palate is clinically relevant since it is a contributing factor to the development of cross bites and open bites and in this manner impacts on the occlusal status of an affected person.

During the course of the clinical investigations, the author observed flattened palates in several young adult persons with OI III. Conversely, the palatal anatomy of most young children was within normal limits. In view of this disparity, the palatal anatomy of affected individuals was documented using subjective scores where 1 indicated a high arched palate, 2 suggested a palate within normal limits and 3 represented a flattened palate.

In the twenty three *FKBP10* HOM c.[831dupC][831dupC] individuals, 17 had flat palates (Fig 9.5) and 6 children had normal palates.

Three of the four adult individuals with the compound heterozygous mutations, *FKBP10*_C HET_c.[831dupC][831delC] and *FKBP10*_CHET_c.[831dupC][1400-4C>G] had flat palates while a child of ten years (QQ 3) presented with a normal palate.

Fifty percent of the affected persons with the unknown genetic mutation (WT) exhibited a flat palate while the other 50% had normal palates. The persons with the flattened palates were predominantly early adolescents and teenagers (Fig 9.5, Fig 9.6). The persons with normal palates were children aged 8 years and below.

Clinical images of DBN 5 and PMB 1 are presented below in order to depict a flat palate with consequent occlusal abnormalities (Fig 9.5, Fig 9.6 and Fig 9.7).

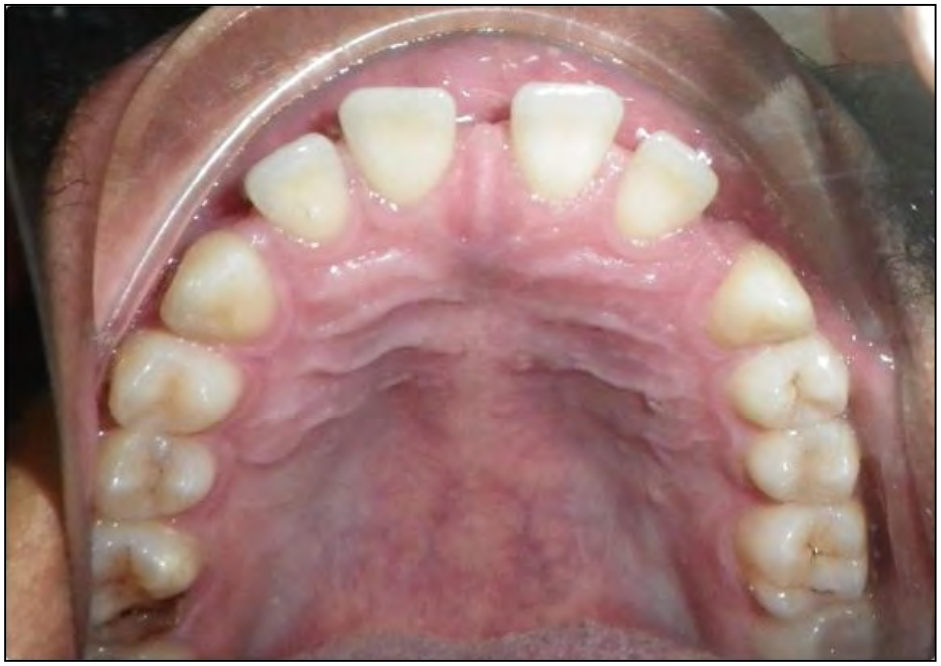


Fig 9.5 Flat palate of DBN 5 (*FKBP10* HOM c.[831dupC][831dupC]) at 19 years with resultant splaying of his anterior teeth (proclined upper anterior teeth)

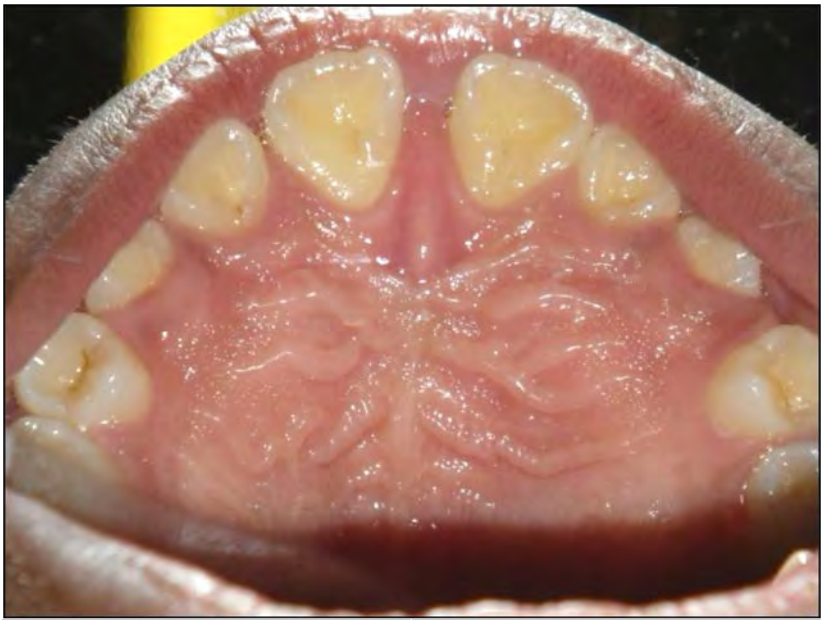


Fig 9.6 Flat palate of PMB 1 (WT) at 18 years. Her anterior teeth are splayed (proclined)

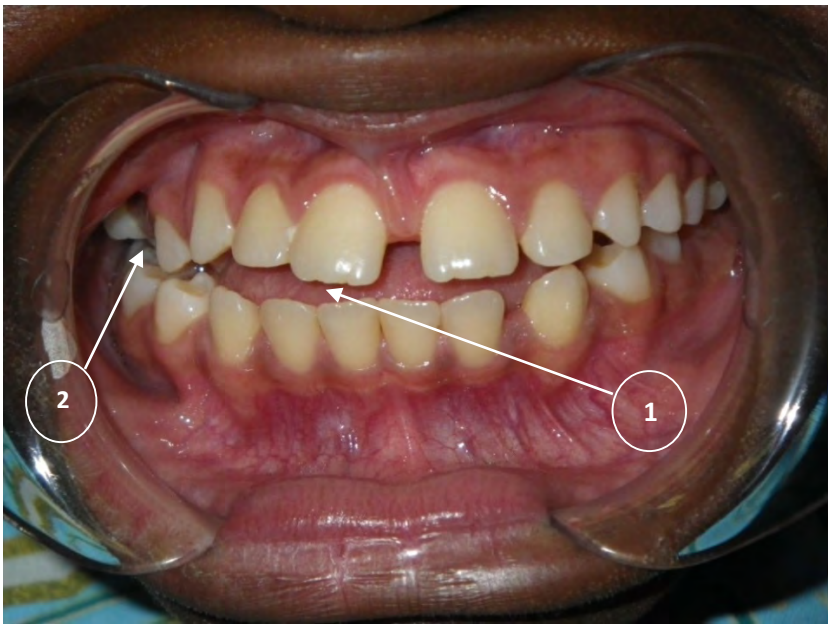


Fig 9.7 An intraoral picture of PMB 1. She has an anterior open bite (1) and a posterior cross bite (2).

Comment: Occlusion and Palatal Anatomy

Significant dental malocclusion, particularly Class III, was noted in OI III affected Black African persons.

The craniofacial abnormalities are related to the abnormal bone matrix and consequent skeletal malleability which leads to a deformed skull. The affected persons' posture, weight and size of the head are often abnormal and these variables may contribute to the development of the Skeletal Class III malocclusion. A mandibular overjet (prognathic mandible) in individuals with OI III has been previously documented (O'Connel and Marini, 1999). Cephalometric radiographs have revealed a flattened cranial base, a posteriorly reclined maxilla and a protrusive mandible, thereby creating a profile of midface hypoplasia. This process tends to occur in adolescence and early adulthood (Stenvik et al., 1985; Lund and Jensen, 1997).

Some forms of malocclusion are secondary and develop due to dental attrition and loss of vertical dimension of maxillofacial structures. Attrition may lead to the development of a deep bite or an anterior rotation of the mandible and a subsequent mandibular overjet (Bjork et al., 1983). An edge to edge bite in children (Fig 9.4) often develops into an adult Class III malocclusion (Profitt et al., 2013).

The increased incidence of anterior and posterior cross-bites and anterior and posterior open-bites is to be expected given the high incidence of Class III malocclusion. Posterior open-bites occurred in adolescence and young adults and were often bilateral. These posterior open bites can be explained by an abnormal vertical dento-alveolar development thus permitting an increased interdental space for the tongue. Posterior open-bites can also be caused by the absence of dental compensation for the protrusive mandible. Anterior open-bites do not allow the affected person to incise food adequately and posterior cross bites and open bites compromises an individual's ability to masticate.

During the oral phase of swallowing, food is moved against the hard palate and the tip of the tongue is placed on the palate behind the incisor teeth. Food is then moved posteriorly into the pharynx by the elevation and pressure of the anterior two thirds of the tongue against the palate. As the child gets older, this physiological process of swallowing and consequent tongue pressure against the palate may be an aetiological factor in the progressive development of a flattened palate. In turn, the flattening of the palate could also be a contributory factor to the development of cross bites and open bites.

The pressure of the tongue may also lead to changes in the axial inclination of the incisors and subsequent splaying of the teeth. Since the affected individuals had a decrease in the quantity and

quality of their bone, forces such as tongue positional pressures can result in a deformity of the palate and alveolar bone.

In order to identify the many factors that may contribute to the malocclusion, longitudinal studies would be necessary in OI III affected persons in SA.

9.3 Periodontal Status

Bitewing intraoral radiographs are ideal in the radiological assessment of the periodontium, but, it was imperative to minimize the radiation exposure levels in every instance. For this reason, available panorex and CBCT images were examined and periodontal findings were reported.

Affected individuals did not present with an unequivocal increase in susceptibility to periodontal disease even though a loss of their lamina dura was evident on dental radiographs. These findings are similar to those reported in the literature (O'Connell et al., 1999; Malmgren and Norgren, 2002).

Thirteen affected individuals between 16 and 30 years exhibited an elevated plaque and gingival index with an average pocket depth of 5mm. An estimate of 2mm of alveolar bone loss was detected in 5 individuals in whom radiographs were available.

Further longitudinal studies are necessary in OI III affected individuals in order to determine the incidence and progression of periodontal disease in SA.

9.4 Temporo-mandibular joint (TMJ)

No significant TMJ findings were observed in the majority of the project participants. Nevertheless, mild changes in the shape of the head of the mandibular condyle and a lack of cortical bone (Fig 9.8) on the joint surfaces were observed on CBCT images of 5 individuals between the ages of 15 and 20 years. TMJ problems may arise later in adulthood in these persons.

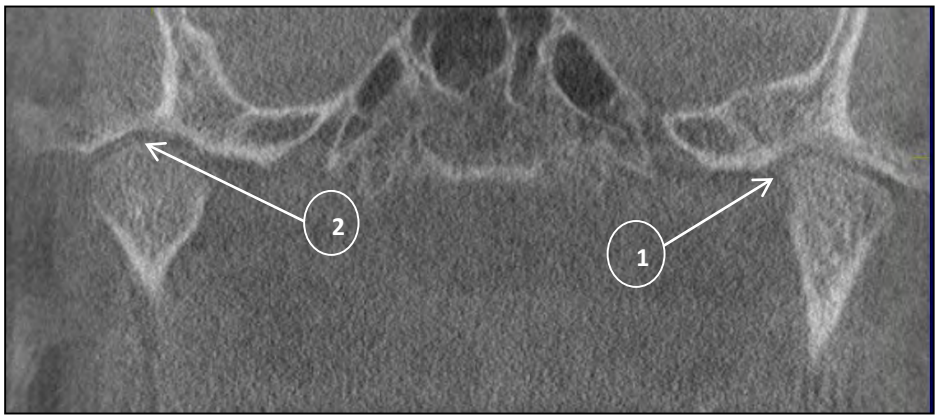


Fig 9.8 Coronal section through CBCT of DBN 4. The heads of the mandibular condyles are irregularly shaped (1) and there is loss of surface cortical bone (2).

Thirteen individuals between 15 and 20 years were clinically examined and all of them revealed a maximum oral cavity opening of less than 35mm. It is relevant that the normal range of opening is 50-60mm depending on the age and size of the individual.

Their maximum lateral movement of the mandible was between 5 - 6mm. The normal average range of lateral movement to the right or left is between 7mm and 12mm. The maximum protrusive movement of the affected persons was 5mm. The normal range of protrusive movement is between 8 and 11mm depending on the size of the individual and the skull morphology.

Their limited oral opening was most likely due to the irregularly shaped mandibular condyles.

To the best of the author's knowledge, there are no reports on the involvement of the TMJ in OI III in SA. Longitudinal studies would be necessary in OI III affected individuals in order to determine the possibility of further TMJ disorders developing.

9.5 Sinuses

In the 5 affected individuals in whom CBCT images were obtained, marked changes were evident in several paranasal sinuses, notably sinus hypoplasia and partial opacification (Fig 9.9). These 5 individuals also gave a history of repeated upper respiratory tract infections and they experienced mild to moderate difficulty in breathing through their nose.

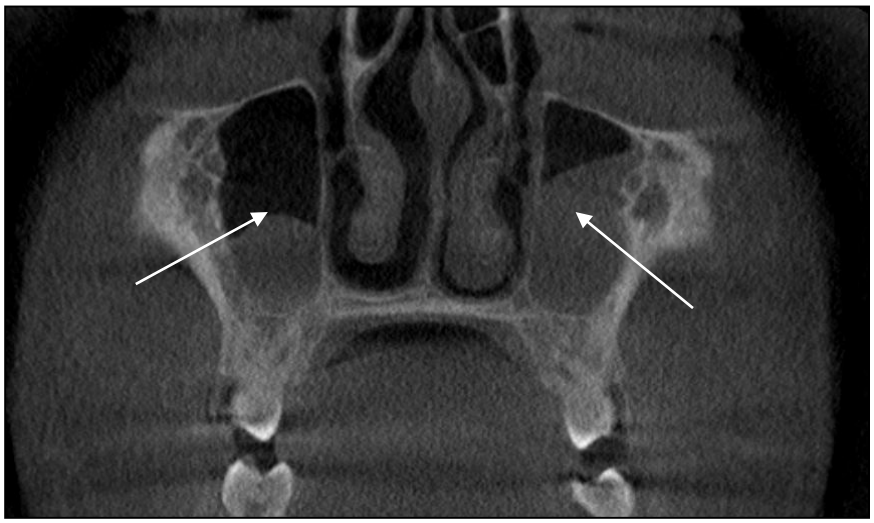


Fig 9.9 Partial opacification of the L and R maxillary sinuses (arrows) of DBN 4

To the best of the author's knowledge, there are no published reports on sinus changes or complications in persons with OI III and the significance of these sinus observations are uncertain.

9.6 Cranial Base Abnormalities

Several reports have documented cranial base anomalies in OI individuals (Arponen et al., 2012; Arponen et al., 2015; Rios-Rodenas et al., 2015). Since pathology in the craniocervical junction can be a cause of serious complications in OI affected individuals, irregularities in this area were noted when recognized in this project. Cranial base anomalies can be diagnosed from cephalometric radiographs and lateral skull radiographs. In each instance, a consultant radiologist identified and verified these findings.

In order to illustrate these observations a cephalometric radiograph of DBN 2 (Fig 9.10) was assessed. Features of platybasia and a 'J' shaped sella turcica were observed. The molecular status of DBN 2 was designated 'WT'.

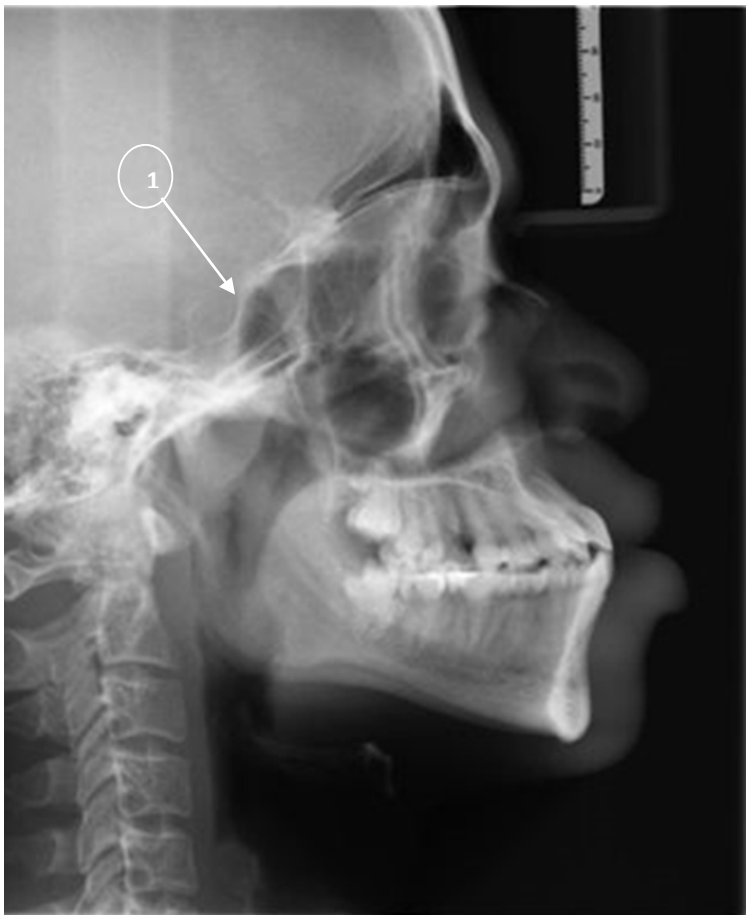


Fig 9.10 A cephalometric radiograph of DBN2. Platybasia and a 'J' shaped sella turcica is evident (1)

A further cephalometric radiograph of DBN 4 (Fig 9.11) was also assessed. His molecular status was *FKBP10* HOM c.[831dupC][831dupC]. He also presented with platybasia and a 'J' shaped sella turcica.

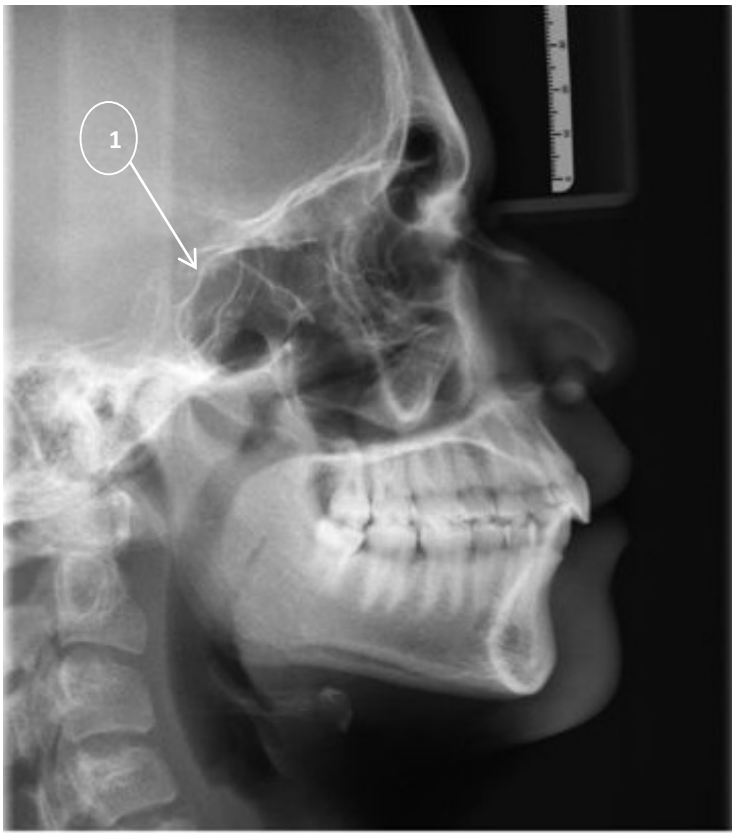


Fig 9.11 A cephalometric radiograph of DBN 4. Platybasia and a 'J' shaped sella turcica is distinguished (1)

Cephalometric radiographs of 5 Black African affected persons were obtained as requested by the orthodontist to whom they were referred and a further 6 individuals already had lateral skull radiographs available. The radiographs of these 11 Black African affected persons aged between 15 and 21 years were analysed.

Features of platybasia and a 'J' shaped sella turcica were noted in 8 individuals.

Comment: Cranial Base Abnormalities

In OI III, reports suggest that pathology of the craniocervical and base of skull region can be divided into platybasia, basilar invagination and basilar impression and it is suggested that these complications can occur separately or concurrently (Arponen et al., 2012; Arponen et al., 2015; Rios-Rodenas et al., 2015). Cranial base anomalies impact on dental therapy in that caution is warranted when a patient's head is manipulated in order to avoid atlanto-axial subluxation and spinal cord compression.

Arponen et al. (2012) documented the natural progression of cranial base anomalies in 150 persons with OI aged between 0 – 39 years and reported that 37% had abnormalities. These authors found that the severity of the condition and marked growth failure suggested the presence of cranial base anomalies. They subsequently recommended a radiological management strategy with regular follow-up. In their cohort of patients, the number of individuals on bisphosphonate therapy was low; hence, a further study was undertaken in order to resolve the issue of the effect of bisphosphonates in the development of cranial base anomalies (Arponen et al., 2015). They reported that although the early initiation of bisphosphonate treatment may defer the development of cranial base pathology, abnormalities also arise despite bisphosphonate therapy.

In severe forms of OI, Sillence (1994) advocated radiographic screening of the skull base every two or three years from the age of 5years onwards.

In addition to platybasia, a'J' shaped sella turcica was observed in 8 individuals in this survey in whom radiographic access was available. In cephalometric analyses of dentofacial morphology, the sella point constitutes an important reference point. This feature warrants awareness by the dental clinician in order to enable the distinction between pathology and normal developmental patterns.

An altered shape of the sella can be present in normal persons as well as in medically compromised individuals with spina bifida (Kjaer et al. 1998) and craniofacial deformities (Becktor et al., 2000; Kjaer, 2015).

The shape of the sella has been observed by researchers in 180 persons between the ages of 11 years and 26 years. A a significant difference was observed in the shape and diameter of the sella in persons with a skeletal Class I, Class II and Class III malocclusion (Alkofide, 2007; Vaishnav et al., 2015). Since the morphology of the sella turcica may vary from individual to individual, and the establishment of normal standards will aid in the process of eliminating any abnormality in such an important region. The sella shape and dimensions reported in this study (Alkofide, 2007) may be used as a reference standards for further investigations involving the sella turcica area in Saudi subjects.

To the best of the author's knowledge, there is no reported association between a 'J' shaped sella turcica and OI but the author considers this a noteworthy finding despite an asymptomatic presentation. It may be relevant that a 'J' shaped sella turcica has been reported in Hajdu-Cheney syndrome, another rare genetic disorder of the skeleton (Diren et al., 1990; Satyanarayana et al., 2013). This condition resembles OI by virtue of osteoporosis and craniofacial features of platybasia, micrognathia, premature loss of teeth, wormian bones and open cranial sutures.

9.7 Concluding Comments

Osteogenesis imperfecta type III is associated with craniofacial abnormalities irrespective of their molecular abnormality. These discrepancies impact on dentofacial appearance and masticatory function. A coordinated surgical and clinical approach by a maxillofacial surgeon and an orthodontist is necessary in order to achieve an optimal aesthetic and functional outcome.

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CHAPTER 10: Black African Population: Dentinogenesis imperfecta

Preamble

The findings with regard to dentinal abnormalities in affected Black African persons are documented in this chapter and further discussed.

Recommendations and suggestions for further investigations to unravel the semantic confusion in terms of DI are highlighted. The author proposes the use of appropriate, evidence based terminology, thereby, facilitating consistency within the dental fraternity.

Although the occurrence of abnormal dentine in some forms of OI is well documented, there is scant information on the association of OI type III with abnormal dentine in South Africa. In terms of AR OI III in SA, the teeth of some affected individuals were described as 'normal'. In this chapter the author highlights and provides an understanding of the dental findings in the affected Black African persons in the separate molecular categories.

The representative photographic and available radiographic images of individuals in each molecular category are presented in order to highlight the findings in terms of DI in an endeavour to elicit a possible genotype-phenotype correlation. Brief case reports are included in order to exemplify the appearance of the teeth in OI III and to provide an overview of the dental manifestations.

10.1 Affected persons with *FKBP10*_HOM_c.[831dupC][831dupC]

Twenty three Black African affected persons were identified with the homozygous mutation in *FKBP10.* No clinically obvious features of DI such as discoloured or translucent teeth were evident in the primary and secondary teeth of all twenty three individuals. These dental findings have been confirmed by means of intraoral clinical pictures and a detailed dental history.

In order to exemplify these outcomes brief case reports on CPT 1, DBN 4 and DBN5, with representative images, are provided below.

Case 1

CPT 1 (Fig 10.1) is a Black African female aged 16 years belonging to the Xhosa linguistic group. She presented at the UWC- UCT combined genetic clinic at the RXH, Cape Town. Her parents and siblings are normal and there is no history of the disorder in any member of her extended family. Her clinical history revealed the she was orthopaedically managed for 10 serious fractures and that she had received intravenous bisphosphonate therapy. She is 119cm in height, her limbs and spine are severely maligned and she has been chairbound since childhood.

She was referred to the dental faculty at Tygerberg Hospital for appropriate management.
A dental clinical examination of CPT 1 confirmed that the colour of her permanent teeth was normal and her mother gave a history of her primary teeth also being normal. Two teeth, the 24 and 36, were extracted with no consequent complications. She had a Class III skeletal relationship, anterior and posterior cross bites and moderate deposits of subgingival calculus.

Fig 10.1 CPT 1 in her wheelchair. An intraoral picture shows apparently normal teeth. She gave no history of discoloured primary teeth.

She required orthodontic management for her malocclusion and a CBCT and a cephalometric radiograph was requested by the orthodontist. Representative images of her radiographs highlighting abnormalities in terms of HDD, specifically mild DI, are presented in Fig 10.2.

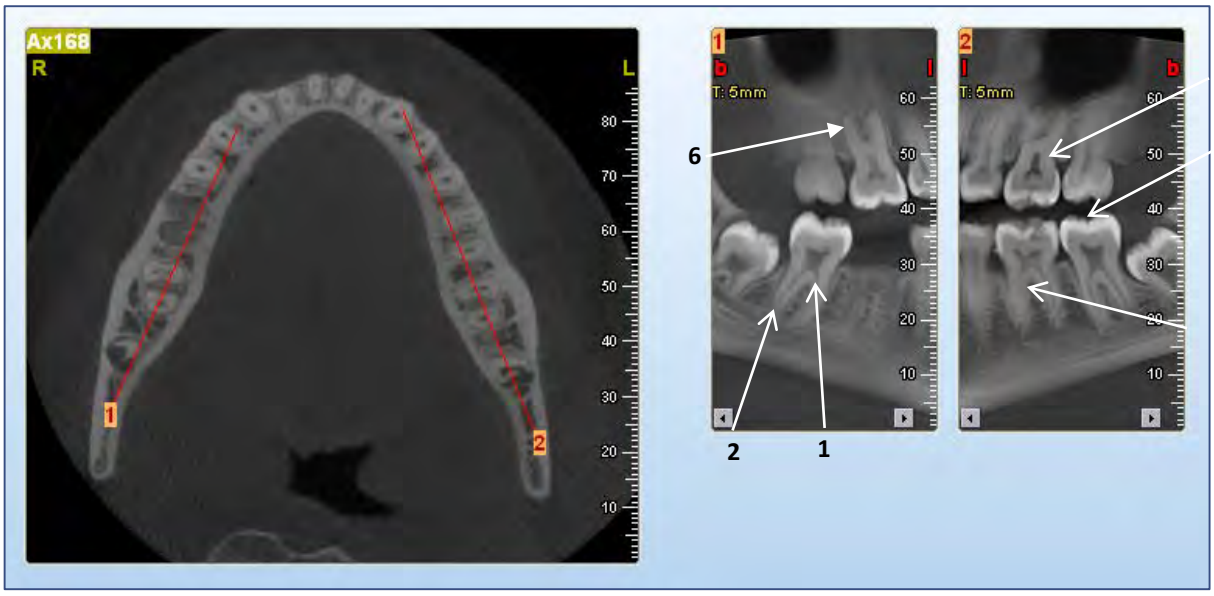

Fig 10.2 Cropped CBCT image of Individual CPT 1 with features of HDD including hypotaurodontism (1), thin short roots of molars (2), cervical constriction of crowns of molars (3) abnormal occlusal anatomy (4) and focal areas of narrowed and occluded root canals (5). Periapical radiolucencies involving teeth 17 and 27 (6).

Case 2

DBN 5 (Fig 10.3) is a Black African male aged 19 years belonging to the Zulu linguistic group. There was no history of OI III in any member of his family. He attended a school for the physically disabled in Durban from where he matriculated.

He was 108 cm in height, never received bisphosphonate therapy, and had more than 15 fractures. Currently he is able to stand with an aid but requires a chair for mobility. He experienced limited movement and sensation in his left arm and leg. His sclerae were white and the colour of his teeth was normal (Fig 10.3).

An intraoral examination revealed that the 46 had been extracted due to caries and there was unremarkable healing of the oral tissues. His palate was flat, his anterior teeth were proclined and he had a bilateral posterior crossbite (Fig 10.3).

He was referred to an orthodontist in Durban in order to address his functional occlusal concerns.

Fig 10.3 DBN 5. An intraoral picture shows that his teeth are not discoloured. Marked splaying of the anterior teeth and bilateral posterior cross bites are evident (arrows).

Several attempts at obtaining an optimal CBCT image proved unsuccessful due to his short stature which resulted in difficulty positioning him. A panorex and a cephalometric radiograph were then requested. The panorex image (Fig 10.4) is distorted due to difficulty in positioning of the patient. Radiographical abnormalities of his teeth suggestive of mild DI are highlighted.

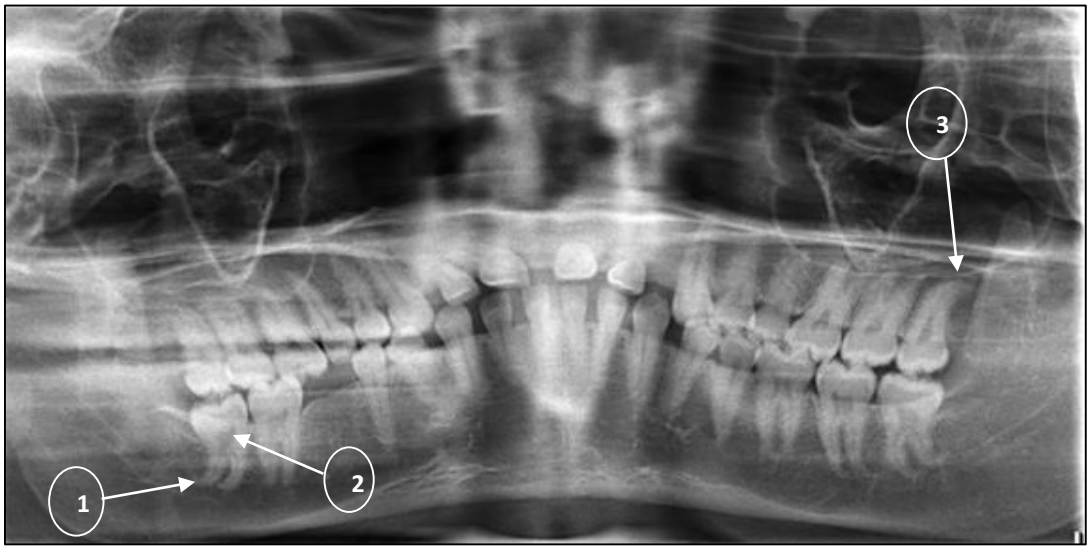

Fig 10.4 Suboptimal panorex of DBN 5. The roots of his molars are thin, short, and tapered (1). Pulp cavities show pulp stones and partial obliteration (2). There is flexion of the roots of the 28, 38 and 48 (3).

DBN 5 is currently being managed by an orthodontist and the outcome and challenges associated with his treatment are being recorded and will be published in the dental literature.

Case 3

DBN 4 aged 18 years (Fig 10.5), is a male Black African affected person belonging to the Zulu linguistic group and is the only affected family member. A year ago he matriculated from a school for the physically disabled in Durban.

He is 108cm in height, has experienced more than 10 fractures and has never received bisphosphonate therapy.

An orodental examination revealed normal permanent teeth and he had no history of discoloured primary teeth. He was concerned about his gums bleeding and was referred to a periodontist for further assessment and management. A CBCT was requested as a diagnostic aid in the evaluation of his craniofacial bones and dentition.

A panorex radiograph that was obtained in 2012 was made available to the author. Features of mild DI were evident on this panorex radiograph of DBN 4 (Fig 10.6) and the cropped CBCT image of his posterior molars (Fig 10.7). Features of hypotaurodontism were identified in the 17 and 27.

Fig 10.5 DBN4 is able to walk short distances with the use of an aid. He is otherwise confined to a wheelchair. His teeth are normal in colour. His labial gingiva is inflamed (1)

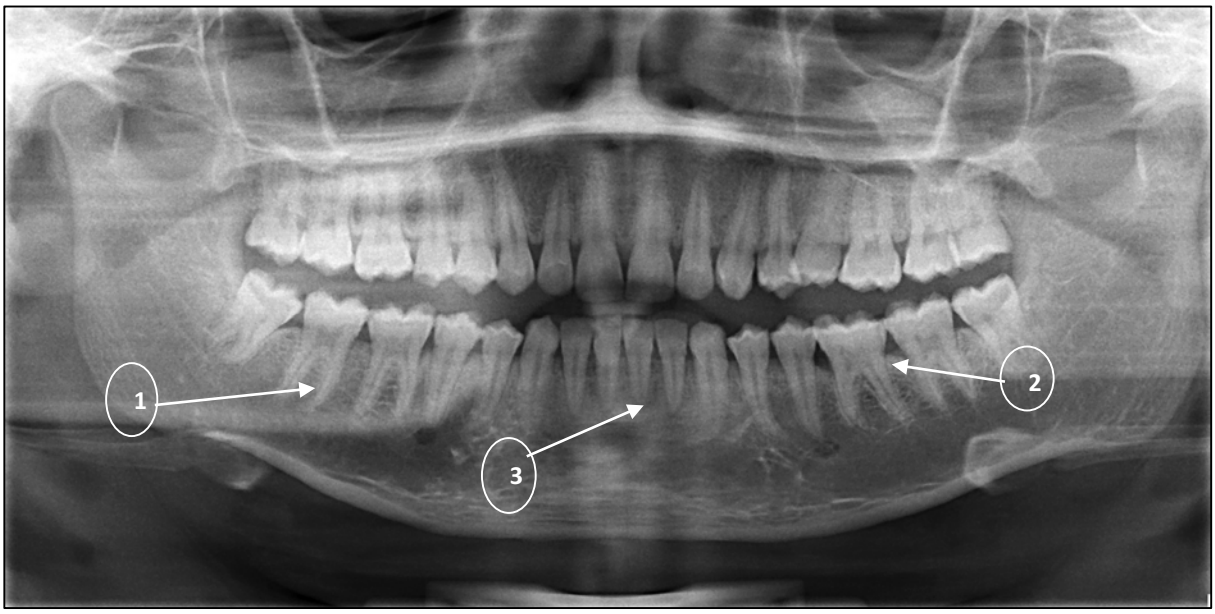

Fig 10.6 Panorex of DNB 4 showing thin shortened roots with focal areas of obliteration of root canals (1). Mild to moderate cervical constriction is present (2). Periapical radiolucencies are evident but there is no pulpal exposure (3)

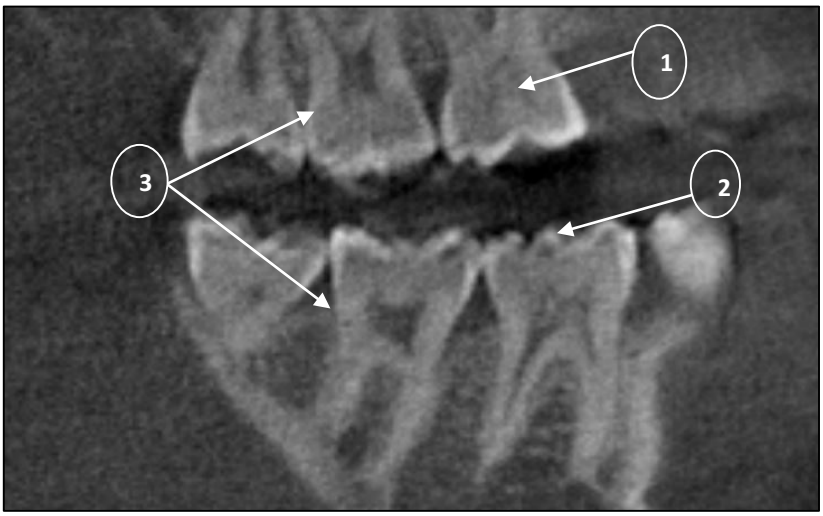

Fig 10.7 Cropped CBCT image of DBN 4 showing intrapulpal calcifications (1) as well as an unusual occlusal anatomy (2). Features of hypotaurodontism are evident in the 17 and 27 (3).

10.1.1 Comment on Findings

The author proposes that the term dentinogenesis imperfecta (DI) be used to denote clinically, radiologically and histologically aberrant teeth associated with OI *(see Chapter 15).*

The twenty three individuals of Black African stock with the F*KBP10* HOM c.[831dupC][831dupC] mutation showed no clinical features of DI in their primary and secondary dentition. The colour of their teeth was clinically normal.

Complex modifications of the collagen molecule are necessary for correct folding, thermal stability of the triple helix and cross-link formation between collagen molecules. These modifications need to take place in an orderly and timely sequence. Chaperone proteins such as FKBP65 help to regulate this process (Cundy, 2012). This implies that the abnormality in dentine is due to the abnormality in the collagen matrix.

Several studies indicate that DI at clinical, radiological and histological levels is more frequent in OI III and OI IV (Sillence et al., 1979; Lukinmaa et al., 1987; Vetter, 1992).

The clinical dental findings in this cohort of 23 individuals showed phenotypically normal teeth, but when subjected to radiological investigation, the contrary proved true. This is perhaps the reason for previous reports of 'normal teeth' documented in the South African persons with OI III (Beighton and Versveld, 1985). The dental findings in affected individuals in this study; although the teeth were clinically unaffected, exhibited a range of radiological manifestations of DI which range from severe to mild.

Several studies have shown that teeth with no apparent clinical DI in association with OI, do have radiological, histological and electron microscopic abnormalities of dentine (Lygidakis et al., 1996; Salvolini et al., 1999; Malmgren and Lindskog, 2003). Discolouration of teeth, should therefore, not be the minimal criterion for the diagnosis of DI.

The author concludes that the teeth in OI III affected individuals with the homozygous genotype, although not discoloured, show radiographical features consistent with mild DI. The author suggests that this diagnosis must include teeth that are clinically and/or radiologically aberrant, and should not exclude the presence of other, milder, dentinal aberrations associated with OI.

There was no correlation between the severity of DI and the severity of OI.

10.2 Affected persons with *FKBP10*_C HET_c.[831dupC][831delC]: 3 individuals

Affected persons QQ 1, QQ 2 and QQ 3 are siblings with an identical genotype (Fig 10.8, Fig 10.9 and Fig 10.10). QQ 2 has completed his course of bisphosphonate therapy while QQ 1 and QQ 3 are currently receiving bisphosphonate therapy. Their clinical history confirms that QQ 2 and QQ 1 had more than 20 fractures while QQ 3 had already had 10 fractures by the age of 10 years.

An intraoral examination revealed no clinically apparent DI features in their primary and secondary teeth of these affected individuals. Due to the lack of radiological facilities, the presence or absence of DI could not be confirmed or negated. Peg shaped lateral incisors were observed in 2 of the siblings (QQ 2 and QQ 3).

Fig 10.8 QQ 2 (brother of QQ 1 and QQ 3) in his wheelchair. An intraoral picture shows no abnormal discolouration of the teeth. The peg shaped lateral incisor (1) and an anterior open bite (2) is evident.

Fig 10.9 QQ 1 (sister of QQ 2 and QQ 3) in her wheelchair and an intraoral picture with teeth showing no abnormal discolouration

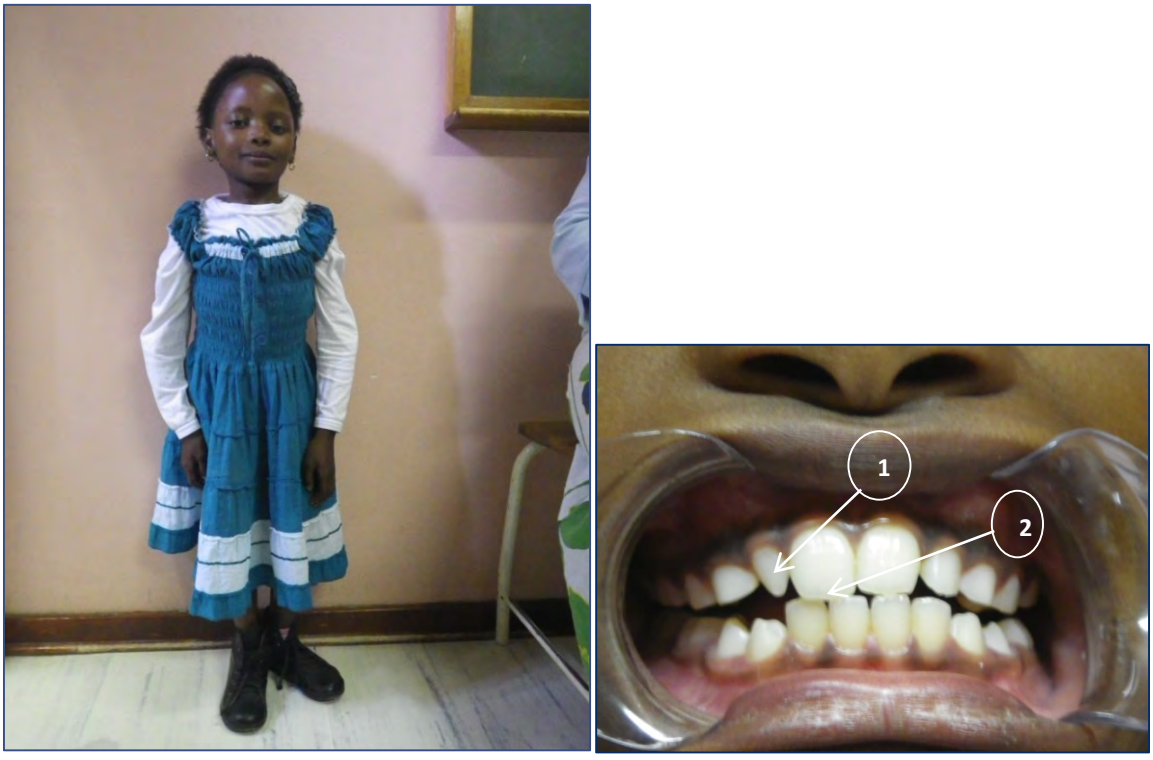

Fig 10.10 QQ 3 (sister of QQ 2 and QQ 1). The peg shaped lateral incisor (1) and the edge to edge bite (2) is evident. There is no abnormal discolouration of her teeth

10.3 *FKBP10* _C_HET_c.[831dupC][1400-4C>G]

Only a single person, CPT 7, had this particular compound heterozygous genotypic status.

Case 4

CPT 7 is a Black African female aged 30 years belong to the Xhosa linguistic group and is the only affected member in her family. Currently, she is chairbound and cannot recall being able to walk (Fig 10.11). She gave a history of having more than 50 fractures over the years despite completing a course of bisphosphonate therapy. She has experienced numbness in her legs for the last 2 years and she has limited movement of her right arm.

Two years ago she delivered a baby boy via a caesarean section from which she recovered with no complications. Her baby is unaffected.

Her orodental concerns were bleeding gums and pain in the lower right quadrant of her mouth. Her mandibular left molar was extracted 3 years ago with no complications.

Radiographs were necessary for a thorough orodental evaluation, but these proved impossible to obtain due to her physical deformity (Fig 10.11). She could not stand and a CBCT, a panorex or a cephalometric radiograph could not be obtained. Her maximum oral opening was 30mm and only bitewing radiographs were possible. Bitewing radiographs are obtained by inserting a film into the mouth and an image of the crowns of the upper and lower molar teeth can be viewed on a single film. These images were not optimal since it was difficult for CPT 7 to open her mouth wide enough for the film to be placed in her mouth with bending.

An intraoral examination revealed a flattened palate with mild proclination of her anterior teeth (Fig 10.11). The colour of her teeth was normal and a clinical periodontal assessment confirmed moderate deposits of subgingival plaque but no apparent bone loss. Given the challenges in terms of dental management of CPT 7, a treatment plan was subsequently formulated for her by a specialist periodontist.

Fig 10.11 CPT 7 is chairbound and the colour of her teeth is normal. Her anterior teeth are mildly proclined (arrows).

10.3.1 Comment on Findings

The 3 individuals of Black African stock with the *FKBP10*_CHET_c.[831dupC][831delC] mutation and the one female affected person (CPT 7) with the *FKBP10* _C_HET_c.[831dupC][1400-4C>G] molecular status had phenotypically normal teeth in terms of clinical colouration. The lack of radiological equipment at the centres where these individuals were examined and the difficulty in obtaining radiographic images for CPT 7, due to her physical dimensions, prevented any further diagnostic investigation.

Conclusion:

Black African individuals in SA with the homozygous and compound heterozygous mutation in the *FKBP10* gene have clinically unaffected teeth yet exhibited radiographic features of DI to varying degrees. This characterization is suggestive of a relationship between the genetic abnormality and the manifestation of DI. There was no correlation between severity of OI and DI in this cohort of individuals.

10.4 Wild Type: 37 Affected Persons

In this group of affected persons, the status of the teeth was recorded in terms of the presence or absence of clinical discolouration. In individuals with only secondary teeth, an account of their primary teeth was obtained from the individual, parent, and caregiver or from medical records.

A summary of these investigations are presented in Table X.1.

Table X.1 Summary of presence or absence of clinical DI

DI	Primary teeth	Secondary teeth
Clinical DI present in all teeth	34	29
Clinical DI present in some teeth	0	5
No clinical DI	3	3

Of the 34 persons with clinically discoloured primary teeth, 29 had discoloured secondary teeth. In affected persons with only some clinically discoloured teeth (Fig 10.12), dental radiographs were obtained and features of DI were confirmed in all teeth (Fig 10.13).

Affected person DBN 2 reported marked discolouration and attrition of all his primary teeth. His permanent teeth were less severely involved and there was mild discolouration in some teeth with a few normal appearing teeth (Fig 10.12). He was referred for an orthodontic evaluation of his malocclusion.

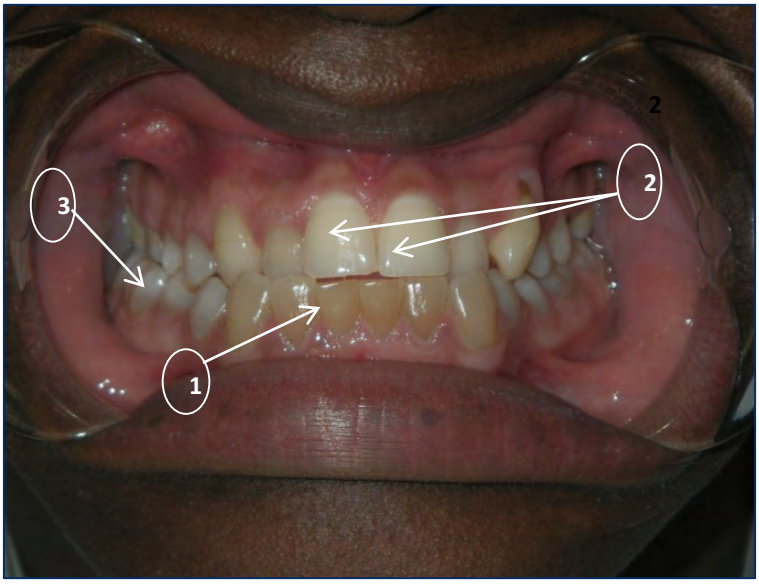

Fig 10.12 Intraoral picture of DBN 2. Amber translucent teeth are evident especially the lower incisors (1). The 11 and 21 appear clinically normal (2). The posterior molars are translucent in the cervical third (3).

Radiographs were obtained as a component of his diagnostic evaluation and abnormalities in terms DI were highlighted (Fig 10.13).

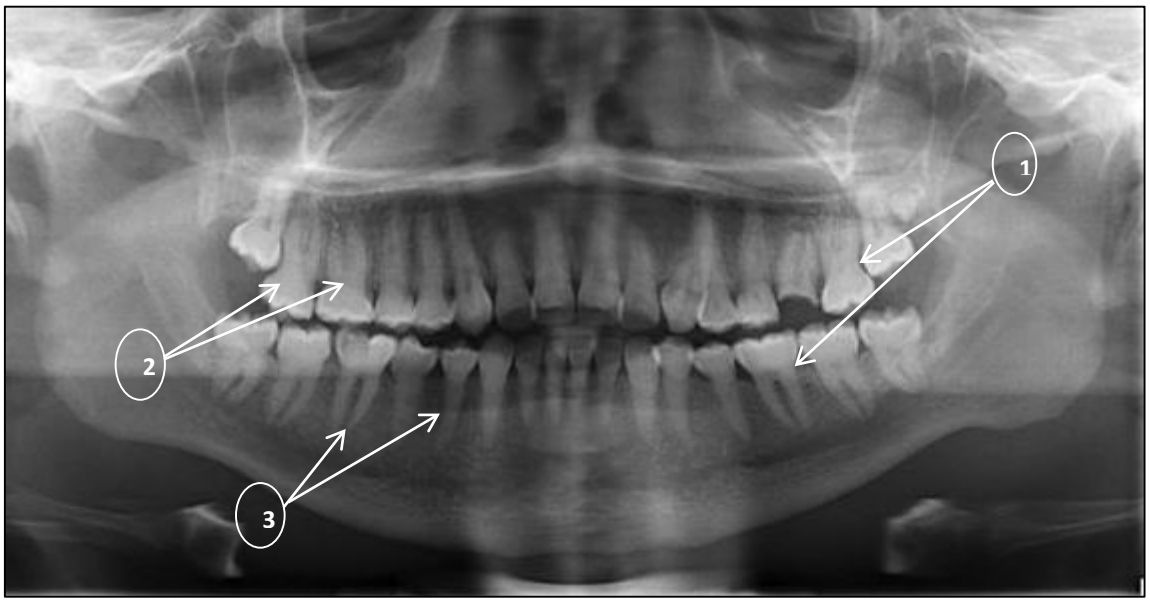

Fig 10.13 Panorex radiograph of DBN 2. Several radiographical features of DI are evident in all his teeth. There is cervical constriction of the molars (1). The pulp chambers are obliterated in almost all of his teeth. There is partial obliteration of the pulp chambers in some other teeth (2). The roots are thin and short (3).

10.4.1 Comment on Findings

Thirty seven affected OI III persons with an unknown genotype were assessed and thirty five (75%) showed clinical and/or radiological features of DI. These findings are consistent with other published findings where DI was present in more than 80% of individuals with the OI III phenotype (Lund et al., 1998, O'Connell and Marini, 1999).

In a minority of individuals with the unknown genotype (WT), their primary dentition was affected with DI and not their permanent dentition but it was impossible to predict in which persons this would occur.

It was assumed that this feature was a manifestation of the unknown genotype.

The clinical presentation of DI associated with OI has been described as being more variable and the diagnosis of DI in the less affected permanent dentition is often difficult to identify (Levin et al., 1981; O'Connell and Marini, 1999). This is a possible reason for the discrepancy in the prevalence; n=29 in the secondary dentition compared with n=34 in the primary teeth (Table X.1). The absence of radiographic confirmation in most cases also contributes to this discrepancy.

OI is a genetically heterogeneous disorder and it is the consequence of mutations at an intracellular level with the abnormality being expressed in the resultant collagen molecules. The resultant phenotypes are a reflection of this intragenic heterogeneity.

During the dental evaluation of an individual with DI it is appropriate for the clinician to initially assess the ability to masticate without discomfort. This factor would be a major consideration in the decision of whether intervention is needed or not. The colour of the teeth would be the next consideration.

Several publications in the dental literature document the management of DI. The challenge highlighted by most authors (Stephen and Beighton, 2002; Teixeira, 2008) is to maintain the primary dentition for as long as possible. Also to subsequently permanently restore the secondary dentition in order to address the functional and aesthetic needs of the individual.

It was the author's experience, that these affected individuals with DI were very concerned about the functional and cosmetic condition of their face and teeth.

Some individuals, especially Black African persons with the homozygous and compound heterozygous mutation in the *FKBP10* gene have clinically unaffected teeth yet exhibited radiographic features of DI to varying degrees, thus, demonstrating a genotypic – phenotypic relationship in terms of the manifestation of DI.

In a minority of individuals with the unknown genotype (WT), their primary dentition was affected with DI and not their permanent dentition but it was impossible to clinically predict in which persons this would occur. Several individuals with DI in their primary teeth reported a more severe presentation in their primary teeth when compared with DI in their secondary teeth.

A description of the radiological features of DI are presented in Chapter 15 (page 174).

10.5 Consolidation of Clinical and Radiological Findings

In an effort to consolidate the information gathered the author tabulated a summary of the clinical and radiological findings (Table X.2). The affected individuals represented in this table are 18 years and older and were only those in whom radiographic investigations were undertaken.

A clinical-radiological score (CRS), created by Scandinavian authors was employed (Malmgren and Lindskog, 2003). Panoramic radiographs of 12 affected persons were obtained; 4 with the homozygous mutation in FKBP10 and 8 affected individuals belonged to the WT molecular category.

Clinical – Radiological Score (CRS):

1: No clinical or radiographic signs of DI

2: Only subtle clinical and/or radiological signs of DI

3: Either obvious clinical or radiological signs of DI

4: Clear clinical and radiographic signs of DI

Table X.2 Clinical radiological scores in affected individuals obtained from their dental radiographs

CRS	*FKBP10* (HOM)	*FKBP10* (C_HET)	WT
1	0	0	0
2	4	0	0
3	0	0	0
4	0	0	8

The 4 *FKBP10* (HOM) individuals displayed clinically normal teeth but after radiographic examination were given a CRS of 2.

The 8 affected persons with no identified mutation (WT) exhibited marked clinical and radiological features of DI and hence were given a CRS of 4.

In the Scandinavian study (2003) fifty two persons with OI were examined and exfoliated or teeth extracted for orthodontic purposes were obtained from all individuals and analysed histologically for signs of dysplastic dentin. Teeth from 20 unaffected control individuals were also examined. There was a statistical difference in the lower dysplastic dentin score in healthy controls individuals and those with OI and no apparent DI. The higher dysplastic dentin score correlated with a higher CRS (Malmgren and Lindskog, 2003).

The author concludes that the 'normal' teeth in affected individuals do have a degree of dysplastic dentin. The findings of this project in terms of DI are consistent with the observations of the Scandinavian study (Malmgren and Lindskog, 2003).

These authors further concluded that the degree of dysplastic dentin correlated with severity of the disorder and indicated that the degree of dentin dysplasia highest in their cohort of OI III affected persons' (Malmgren and Lindskog, 2003).

Conversely, the findings of this project do not show a correlation between the severity of the condition and the degree of dentin dysplasia. The subtle CRS changes evident in the dentin of persons with the *FKBP10* (HOM) positive mutations are most probably an expression of genetic and epigenetic factors which are associated with OI III in South Africa.

10.6 Recommendations for Further Investigation

It is imperative to obtain teeth samples from the *FKBP10* HOM_c.[831dupC][831dupC], the *FKBP10*_C HET_c.[831dupC][831delC] and some individuals in whom the molecular defect has not as yet been identified (WT). These samples would ideally consist of exfoliated and extracted teeth and would be subjected to electron microscopic analysis. Coronal and radicular dentin must be evaluated as well as mantle dentin for dysplastic changes. Reports suggest that the degree of dysplastic change varies between these areas in a tooth with radicular dentin exhibiting the most severe dysplastic change (Malmgren and Lindskog, 2003). This procedure would enable the morphology of dentine to be described at a histological level and these findings would allow a more comprehensive genotype – phenotype correlation in terms of the dysplastic changes in the dentin in persons affected with OI III in SA.

Currently there is optimism that medical therapies such as the administration of bisphosphonates may lead to an improvement in form and function of OI affected persons. Histological examination of a

tooth from a late adolescent affected individual, who has received bisphosphonates since childhood, would help identify any therapeutic effects of bisphosphonates on the dental phenotype.

Longitudinal studies are necessary in order to document the dental changes in individuals with OI III.

To the best of the author's knowledge, there are no reported studies concerning the results of orthodontic care in OI III affected individuals in South Africa. These patients will be followed up and the challenges associated with their care and their orthodontic outcome will be documented in the dental literature.

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CHAPTER 11: Cape Mixed Ancestry Persons: General Data, Dental and Molecular Observations

11.1 General Physical Condition, DI and Molecular Findings

11.2 Case Reports of Affected CMA Persons

11.3 Comment

Preamble

During the course of the clinical investigations the author was introduced to five individuals of Cape Mixed Ancestry heritage who presented with the OI III phenotype and shared similar craniofacial and orodental features. The general investigation findings, with the emphasis on dental features, in particular DI, in these persons are documented and discussed in this chapter. The craniofacial manifestations are reviewed and described in Chapter 12.

The term 'Cape Mixed Ancestry' (CMA) is used in SA to describe a segment of the population that have descended from the intermarriage of white settlers, African indigenous people and Asian slaves brought to SA from Dutch colonies.

They live predominantly in the Western Cape in the urban and rural areas around Cape Town, however, several persons have migrated to Johannesburg, Pretoria, Port Elizabeth, East London, and Durban.

The CMA group of affected individuals were phenotypically defined as having OI III with short stature and multiple fractures. They differed from the majority of the Black African persons with OI III by virtue of their longevity and presence of DI. Their molecular status also differed as they were negative for the determinant mutation in *FKBP10* described in exon 5 *(see Chapter 7).*

11.1 Age, General Physical Condition, DI and Molecular Findings

The affected persons examined at the University of the Western Cape (UWC) dental school were members of the Cape Mixed Ancestry population group and were designated CPT2, CPT3, CPT4, CPT5 and CPT6 (Fig 11.1 – Fig 11.10). They were represented by alphabetical and numerical designations pertaining to the investigation centre and the chronological order in which they were examined. Their clinical data are presented in Table XI.1.

Each person had limited oral opening and all their teeth were discoloured consistent with moderate to severe DI. The sclerae of their eyes were white in every instance and there was no hearing loss. None of the individuals had received bisphosphonate therapy.

The clinical and radiological features of DI have been discussed in detail in Chapter 15 and they are revisited in the context of this chapter.

Neither the homozygous nor the compound heterozygous mutations described in Chapter 7 in the *FKBP10* gene were identified in this group of individuals. They were, therefore, given the molecular designation 'wild type'.

Table XI.1 Clinical Findings of Cape Mixed Ancestry persons

Affected Individual	Date of Birth	Age When Seen (Years)	Affected Relatives	Gender	No. of Fractures	Height (cm)	Mobility
CPT2	20/04/1952	62	5	F	>50	96	Chairbound
CPT3	02/05/1993	21	0	F	>50	93	Chairbound
CPT4	30/05/1986	28	0	F	>50	95	Walks with an aid
CPT5	30/05/1986	28	0	F	>50	95	Walks with an aid
CPT6	20/12/2001	13	0	F	>20	80	Chairbound

Comment:

It is of interest that all 5 affected persons were female. CPT 4 and CPT 5 were twins. The disorder occurred sporadically in the other affected individuals except the family of CPT 2 *(see below).* The phenotypic features and radiographic manifestations of each patient are described in the brief case reports which follow.

11.2 Case Reports of CMA Affected Persons

11.2.1 CPT 2

Forty years ago, affected individuals in two interrelated families were reported (Horan and Beighton., 1975; Sillence et al., 1986). These persons were the prototypic OI III affected persons described in SA. CPT 2, then 22 years of age and now aged 60 years (Fig 11.1 and Fig 11.2), was a member of one of these families. In one family, two of 14 siblings had OI while in the other, four of thirteen individuals were affected with OI. The original pedigree of the kindred is shown in Fig 11.3.

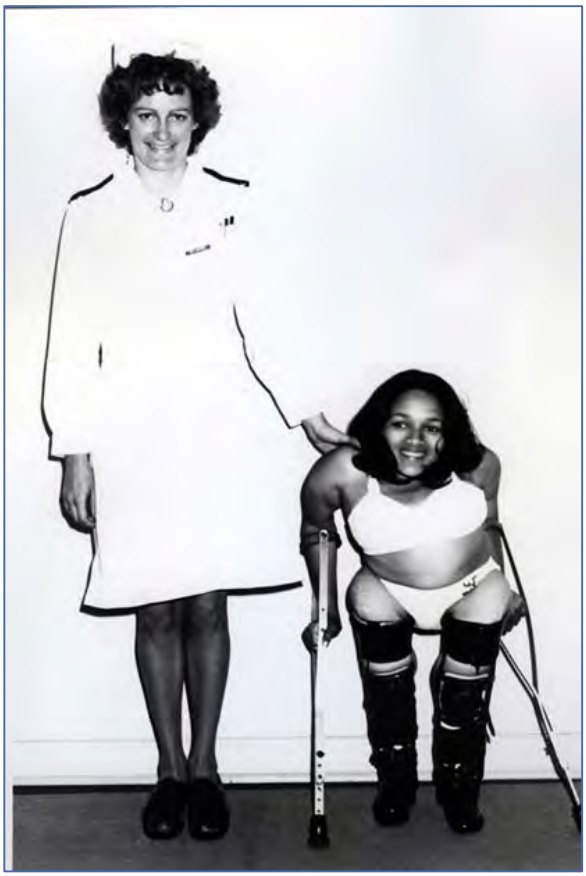

Fig 11.1 CPT 2. Aged 22 years in calipers

Fig 11.2 CPT 2 . Aged 62 years. She is chairbound

These families shared the common CMA genetic heritage but there was specific information that they also had Black African, Scottish and Indian heritage. The fathers of the affected siblings were an uncle (II-1) and nephew (III-3) who married sisters (III-1 and III-4). Despite the lack of consanguinity, from pedigree data, it can be assumed that the parents shared a considerable percentage of their genes. The parents and their progenitors were unaffected.

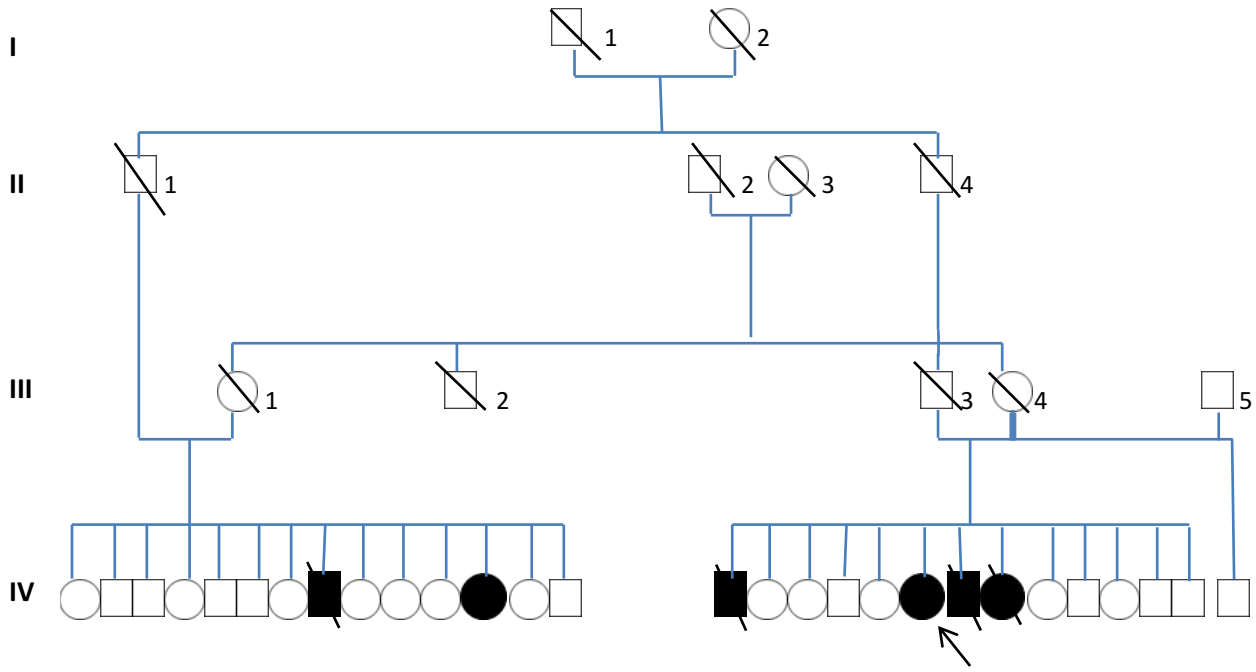

Fig 11.3 The Pedigree of the Kindred (Horan and Beighton, 1975). CPT 2 was the proband

The Proband, CPT 2, had sustained several fractures by the age of 2 years and in early childhood had been institutionalized at a home for disabled children in Cape Town until 14 years of age. In 1975, at the age of 22 years, she was documented as being 105cm in height with severe scoliosis and pronounced bowing of the femora and humeri. At that time she walked with the aid of long leg callipers and crutches (Fig 11.1) and she had minimal bluing of the sclerae.

In 2014, person CPT 2 was re-examined by the author and her clinical manifestations were documented. She was chairbound; 96 cm in height (Fig 11.2), her teeth were discoloured and showed mild features of DI (Fig 11.4). She gave a dental history of severely discoloured primary teeth and considers that her secondary teeth are less severely discoloured.

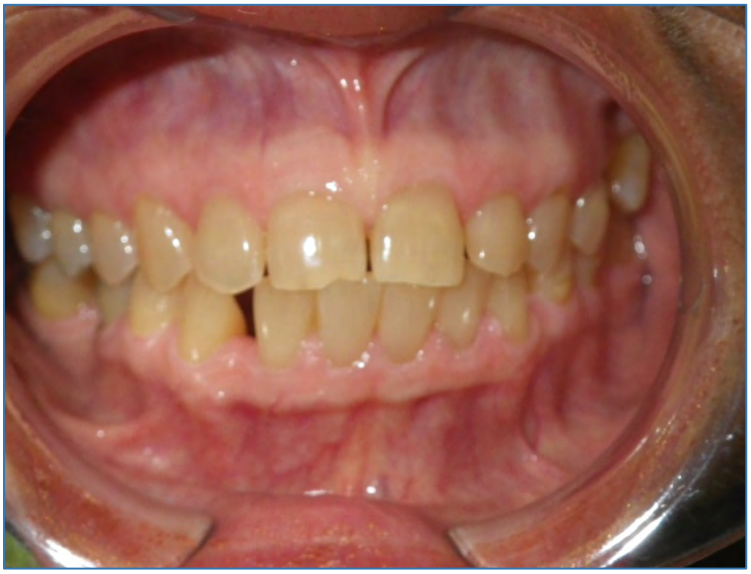

Fig 11.4 CPT 2. An Intraoral picture. Her teeth are yellow and moderately translucent.

A cone beam CT was requested by a maxillofacial surgeon after CPT 2 was referred for an evaluation of pain in the region of her right TMJ which was exacerbated when chewing. She also experienced intermittent tingling and numbness in her right arm. Frequent sinus infections and nasal obstruction were also troublesome. Her hearing and mental faculties were normal.

11.2.2 CPT 3

CPT 3 was the only affected person in her family. Her non-consanguineous parents and a male sibling were normal. In 2014, at 21 years of age, she was 90 cm in height, and was chairbound with severe scoliosis and pronounced bowing of her femora and tibia (Fig 11.5). She had slight difficulty hearing but her sclerae were normal.

She gave a history of severe DI in her primary dentition and severe DI was evident in her secondary dentition (Fig 11.5). Deposits of interdental calculus were present and during oral prophylaxis, moderate gingival bleeding was observed.

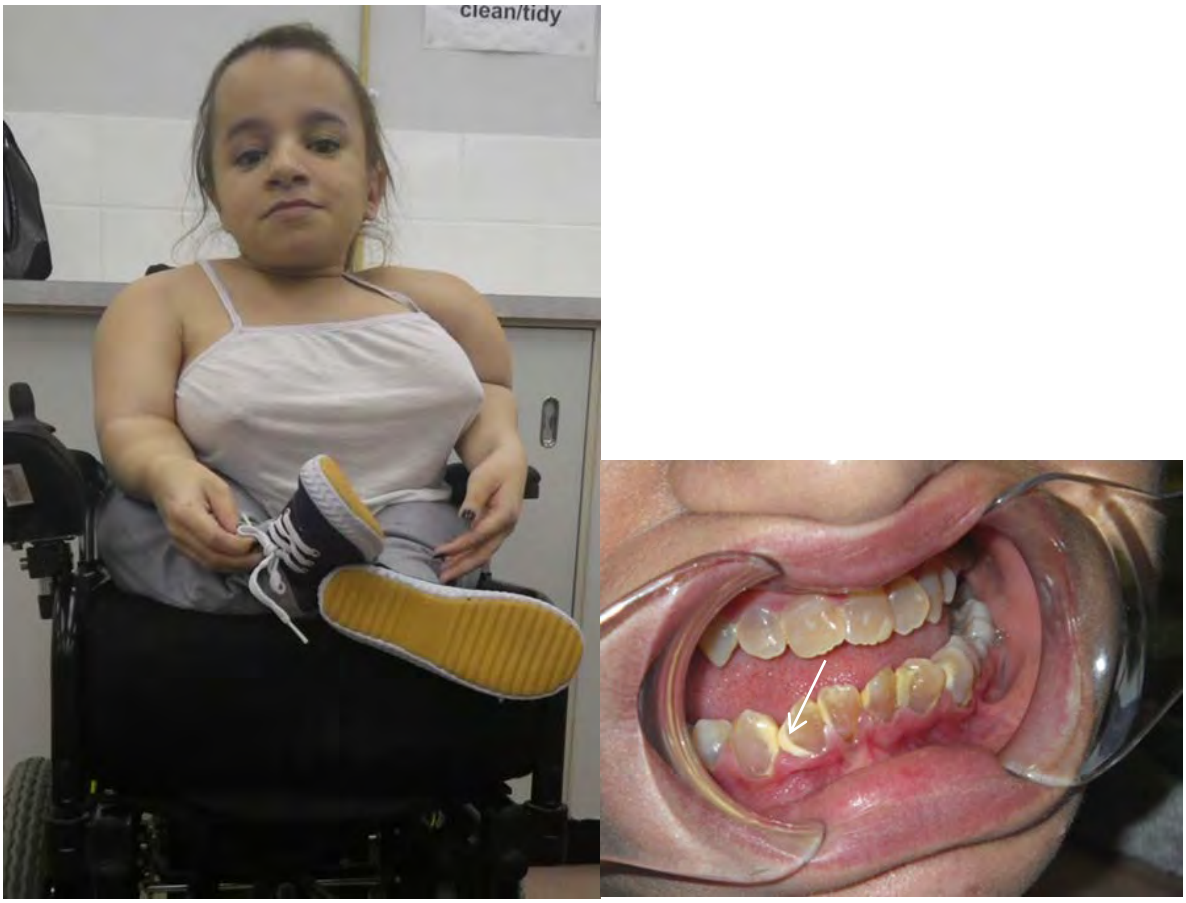

Fig 11.5 CPT 3 is chairbound and 90 cm in height. Mandibular prognathism is apparent and DI is evident in all her secondary teeth. Deposits of interdental calculus are obvious (arrow).

As a young woman, she was understandably concerned about the appearance of her teeth and was referred to the department of restorative dentistry at UWC. A previously obtained panorex radiograph was made available to the author (Fig 11.6) and a CBCT was requested by the attending prosthodontist.

The presence of DI in all of her teeth was confirmed on a panorex radiograph (Fig 11.6). Optimal radigraphic images of any kind were impossible to obtain due to difficulty in positioning due to her short stature and chairbound situation.

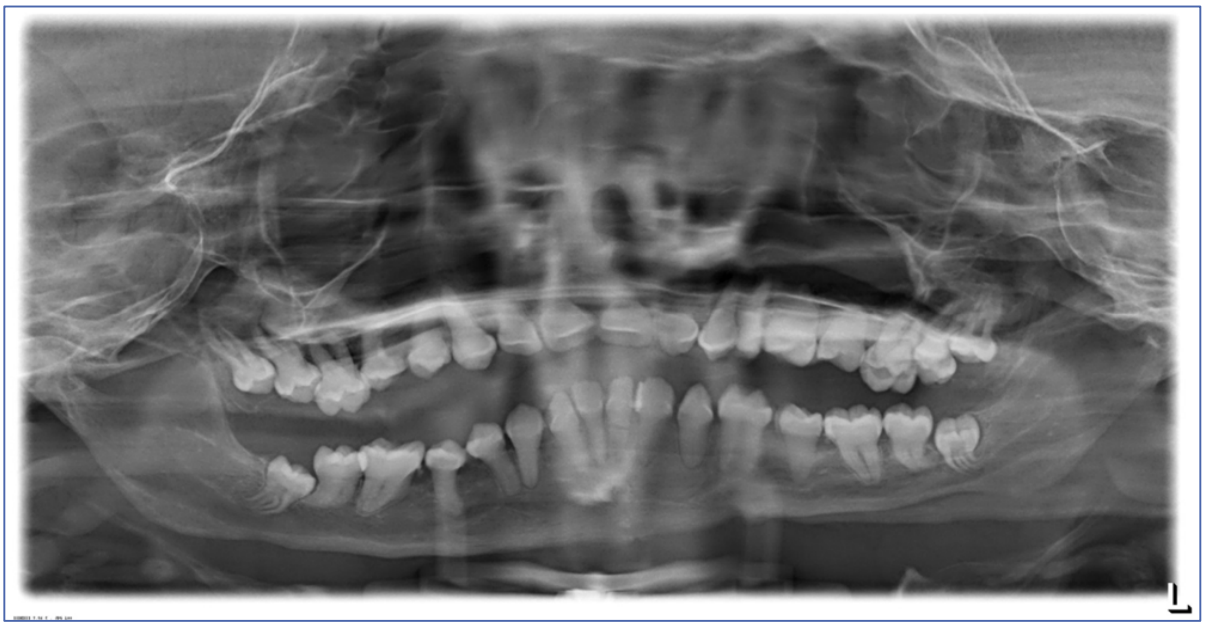

Fig 11.6 Panorex of CPT 3. The image is distorted due to difficulty with patient positioning. All teeth show features of severe DI. The lamina dura is absent and there is severe generalized osteoporosis of her craniofacial bones.

A description of the radiological features of DI are presented in Chapter 15 (page 174).

11.2.3 CPT 4 and CPT 5

CPT 4 and CPT 5 are twin sisters (Fig 11.7) and are the only affected persons in their family. Their parents were unaffected and non-consanguineous. There was no history of the disorder in any of their parents' progenitors. The sisters were 93 cm in height and both had marked kyphoscoliosis.

Fig 11.7 CPT 4 and CPT 5 are twin sisters, aged at 28 years. Marked kyphoscoliosis and prominent mandibular prognathism is evident.

They gave a history of severely discoloured primary teeth which fractured easily. At 28 years of age, they had prominent mandibular prognathism, an anterior open bite, severe DI and interdental calculus (Fig 11.8).

A panorex radiograph obtained in 2011 of CPT 5 showed features of severe DI (Fig 11.9).

A CBCT image of both individuals was requested by a specialist prosthodontist and orthodontist, but as with the previous patients, optimal images were impossible to obtain due to difficulty with positioning.

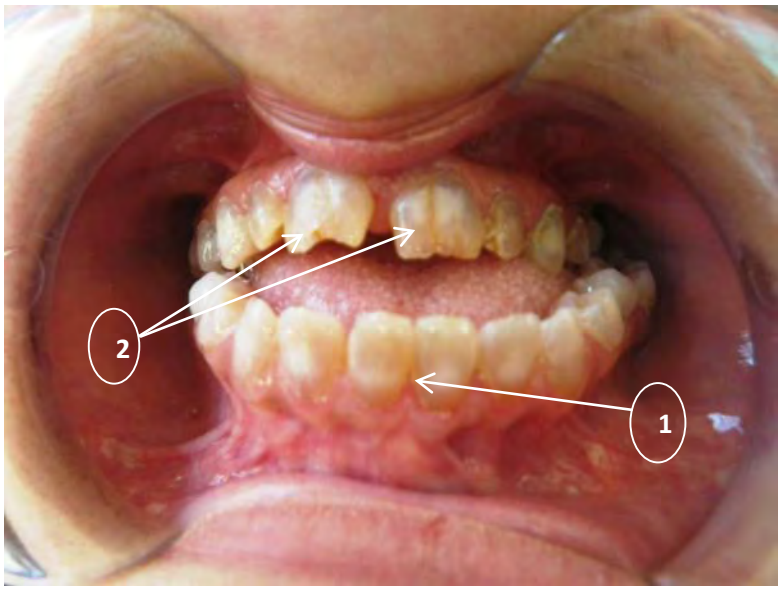

Fig 11.8 CPT 4. An intraoral picture. Clinical features of DI are evident in all her teeth. Minimal deposits of interdental calculus are observed (1) and enamel fractures (2) are present on teeth 11 and 21.

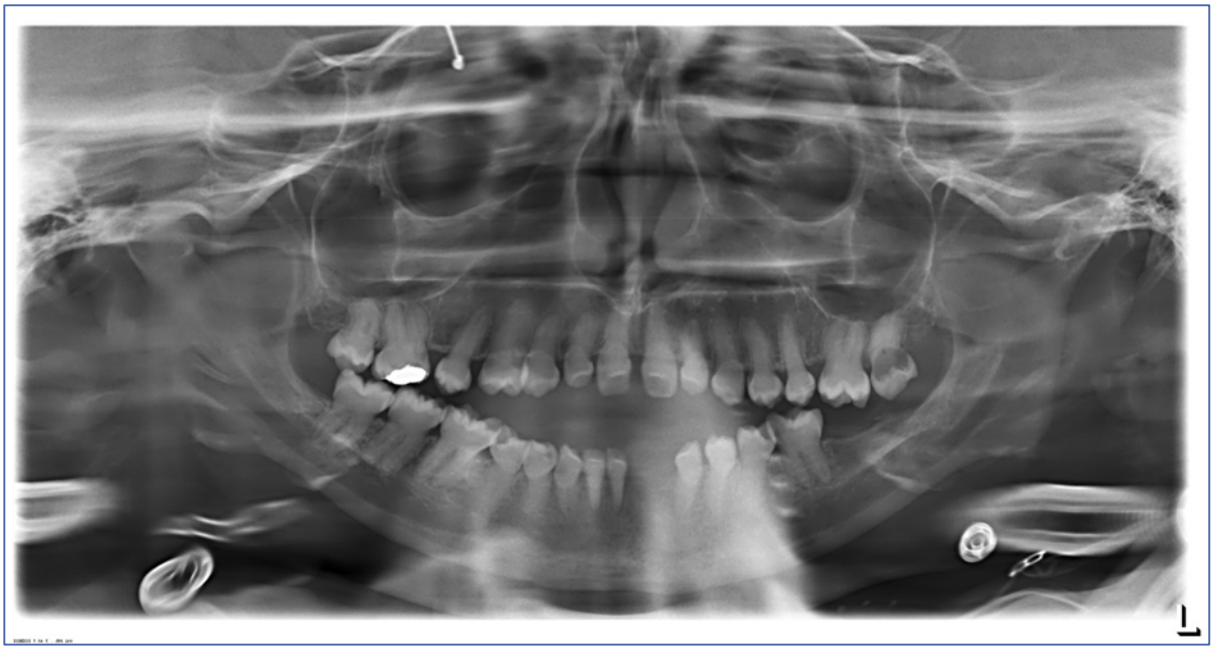

Fig 11.9 Panorex of CPT 5. The image is distorted due to difficulty with patient positioning. All her teeth show radiological features of DI. The lamina dura is absent.

11.2.4 CPT 6

At 13 years of age, CPT 6 chairbound (Fig 11.10). She is the only affected person in her family. Her non-consanguineous parents are normal and there is no history of the OI in any progenitors. She has a younger unaffected female sibling. Her parents stated that she had a dental history of severe discolouration of her primary teeth with marked attrition and early loss. Her secondary teeth were all moderately discoloured, translucent and multiple carious lesions were observed. Mandibular prognathism was also present.

Due to non-cooperation from CPT 6, it was impossible to obtain dental radiographs.

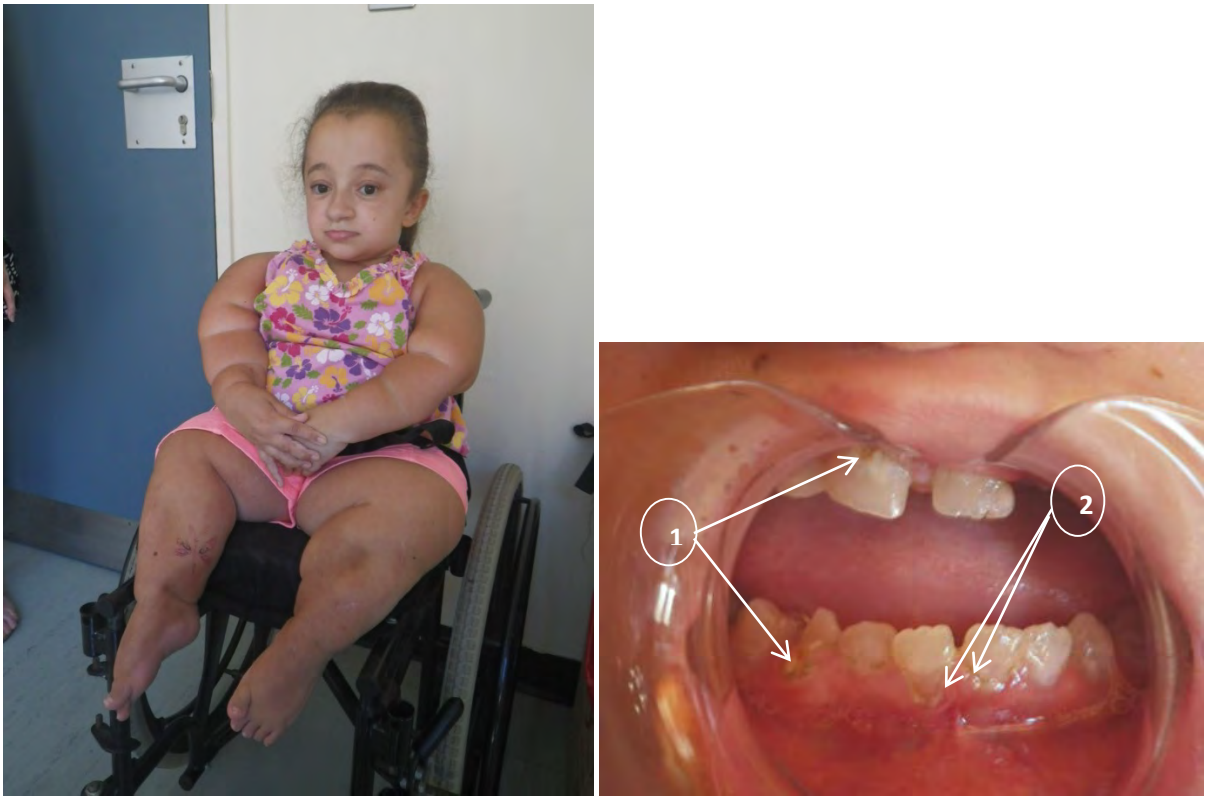

Fig 11.10 CPT 6. Chairbound at the age of 13 years. Mandibular prognathism is evident. All her permanent teeth are affected with DI. Multiple cervical carious lesions (1) and interdental calculus (2) are present.

11.3 Comment

The 4 adult affected individuals of CMA heritage, namely CPT 2, CPT 3, CPT 4 and CPT 5 ranged in age from 21 years to 61 years and had severe physical deformity. They achieved an average height of 95cm and each of them had experienced 50 or more fractures. Although none of these individuals had received bisphosphonate therapy, longevity was a major feature. CPT 6 at age 13 years had already experienced 20 fractures and was chairbound.

A dental history of severely discoloured primary teeth with attrition and early exfoliation was obtained from each of these persons. The colour of the crowns of their secondary teeth varied from yellow to brown and they were opalescent. There was chipping, fracture and focal loss of the enamel. Radiographic images confirmed the presence of bulbous crowns and almost complete obliteration of the pulp chambers. The roots of the teeth were thin and short.

Extensive dental intervention, management and appropriate referral was necessary due to the longevity of the individuals, the severity of the disorder and the extent of their DI.

These observations suggest that the underlying gene defect has the same or a similar effect on bone and dentine. In this cohort of affected persons, a positive correlation between severity of the disorder and the presence and severity of DI was apparent. Several authors have documented the association between OI III and the expression of severe DI (Schwartz and Tsipouras, 1984; Lund et al., 1998; O'Connell and Marini, 1999). These findings are, however, contrary to those observed in the Black African persons with the homozygous and compound heterozygous *FKBP10* molecular genetic status and Indian persons with the unknown molecular status.

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CHAPTER 12: Cape Mixed Ancestry Persons: Craniofacial and Periodontal Observations

Preamble

General phenotypic, dental and molecular findings of the five affected persons of Cape Mixed Ancestry heritage were presented in Chapter 11. Their craniofacial and periodontal manifestations are documented and discussed in this chapter.

The craniofacial and periodontal manifestations of the 5 CMA persons are described and representative images are presented in order to depict these findings. Each craniofacial feature described is followed by a brief comment. For the sake of expediency, please refer to more detailed comments on the craniofacial manifestations in Chapter 9 as well.

12.1 Occlusion and Palatal Anatomy *(The types of occlusion and malocclusion recognized in dentistry are described in Appendix 4)*

In this context, a malocclusion is defined as a morphological feature of the dental, skeletal and soft tissue deviations from the norm.

A clinical orodental evaluation of the 5 CMA persons, whom ranged in age from 13 to 62 years revealed dental and skeletal Class III malocclusions and marked mandibular prognathism. Posterior crossbites and a flattened palate were evident in all of these individuals.

Due to gradual shortening of their cervical spine, the chins of the 5 CMA persons were resting on their chests.

Comment:

(see Chapter 9, page 90).

Class III malocclusions, crossbites and open bites are common dental and craniofacial complications in persons with OI III (O'Connell and Marini, 1999; Waltimo-Siren et al., 2005). The abnormal craniofacial and occlusal development hinder chewing and compromise aesthetics. Orthognathic surgery maybe necessary for the correction of these occlusions (Kindelen et al., 2003).

Occlusal status is determined clinically and radiographically, in particular cepahlometrics. Cephalometric values *(see Appendix 5)* define the type of malocclusion and enable the identification of either a true or relative skeletal or dental Class III malocclusion.

A 'relative class III' malocclusion has been described by Waltimo-Siren et al. (2005) and suggests a concordant relationship in size between the maxilla and mandible. Reductions in the vertical jaw dimensions have been observed in individuals with OI III and it has been suggested that this a cause of the relative mandibular prognathism. These researchers proposed that it may be beneficial to OI III affected individuals to have their dento-alveolar height increased by orthodontic means. This alteration would secondarily rotate the mandible downwards and backwards and thereby reduce functional and aesthetic difficulties (Waltimo-Siren et al., 2005).

The cephalometric values of this group of CMA individuals *(see Appendices 6 and 7)* indicate a definite dental and skeletal Class III malocclusion, contrary to the 'relative Class III' malocclusion described in OI III affected persons by Waltimo-Siren et al. (2005). It can be proposed that differences in the genetic heritage of these patients may be the basis of this discrepancy.

To the best of the author's knowledge, no longitudinal cephalometric surveys in OI III affected persons in SA have been reported in the literature.

Since cephalometric analyses are crucial to indentifying the occusal status of patients, cephalometric radiographs of affected persons with similar forms of OI III within the different population groups in SA, could be obtained. For age and sex correlation, cephalometric radiographs of control unaffected persons would also be necessary. This baseline information would help predict the dental and craniofacial features in OI III which can be altered by orthodontic and orthognathic surgical means.

It is possible that there might be a correlation between a specific mutation and abnormalities in the dental and craniofacial phenotype in CMA OI III affected persons. Equally, epigenetic factors such as muscular forces and head posture may also play a role.

12.2 Periodontal status

Bitewing intraoral radiographs are ideal in the radiological assessment of the periodontium, but, it was imperative to minimize the radiation exposure levels in every instance. For this reason, available panorex and CBCT images were examined and periodontal findings were reported.

The periodontal status was assessed clinically by measuring the plaque and gingival indices, periodontal pocket depths and by radiographical investigations.

The 4 individuals showed a radiographic absence of the lamina dura and had an average pocket depth of 4.5mm. Clinically, interdental and subgingival plaque and calculus was evident in each person except CPT 2, who had recent oral hygiene prophylaxis. The affected individuals also experienced moderate to severe gingival bleeding on probing.

Comment

It was evident that the affected persons had periodontal disease and it is possible that this may be related to their malocclusion and difficulty in accessing all areas of the mouth during oral hygiene practices. In the broader context and in the CMA persons, severe clinical DI often presents with fractured enamel which facilitates the adhesion of plaque and the formation of calculus. Referral to a

periodontist is would be helpful at this stage in order to improve oral hygiene and prevent premature exfoliation of their teeth. The radiographic absence of the lamina dura suggests a compromise of the alveolar cortical bone which may aggravate the progression of periodontal disease once plaque pathogens enter the subgingival locale and if this region is not thoroughly cleansed. These circumstances require frequent intensive oral hygiene prophylaxis.

12.3 Temporo-mandibular joint (TMJ)

The status of the TMJ was assessed from a detailed clinical history and observation of the range of movements of the jaw.

The head of the mandibular condyles showed a mild to moderate deviation in shape (Fig 12.1) and there was an absence of superficial cortical bone in all affected persons except CPT 6.

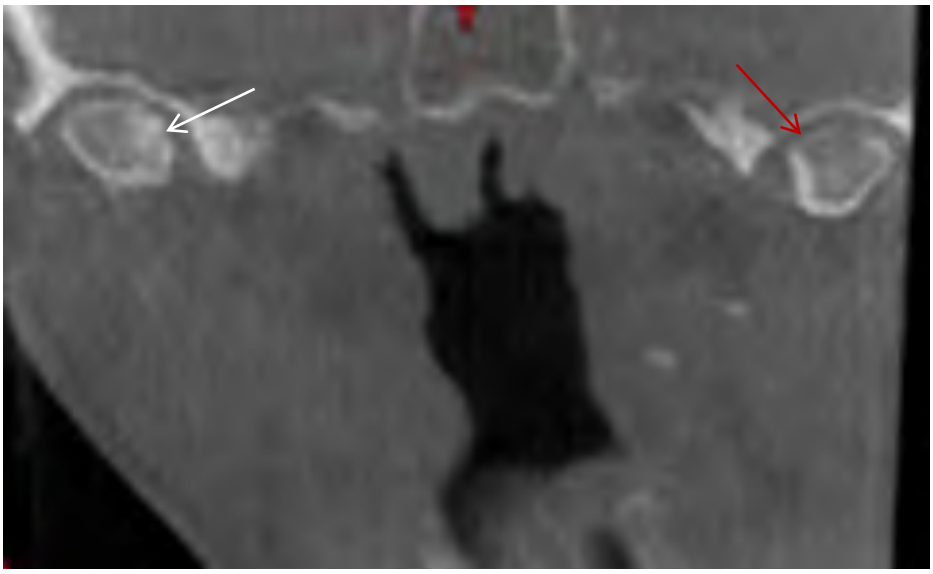

Fig 12.1 Coronal CBCT image of CPT 4. The mandibular condyles are asymmetric (arrows). There is a loss of surface cortical on the head of the left condyle (red arrow)

As with the Black African persons described in Chapter 9, there was an average of 5mm limited lateral movement of the mandible and a marked reduction in the maximum opening of the mouth in all individuals.

CPT 2 gave a history of pain in her left TMJ during mastication and mouth opening. Her jaw deviated to the right during opening and there was left unilateral flattening of the articular eminence which was evident on a CBCT image (Fig 12.2).

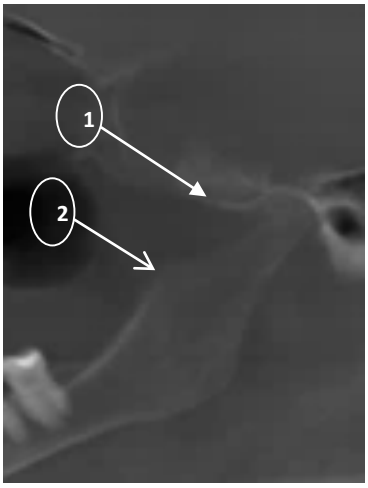

Fig 12.2 Cropped CBCT image of CPT 2. Sagittal section of the left TMJ. The articular eminence is flattened (1). The coronoid process is almost non-existant (2). Severe generalized osteopaenia is evident.

The joint spaces were reduced in size particularly the posterior joint space in CPT 3 (Fig 12.3).

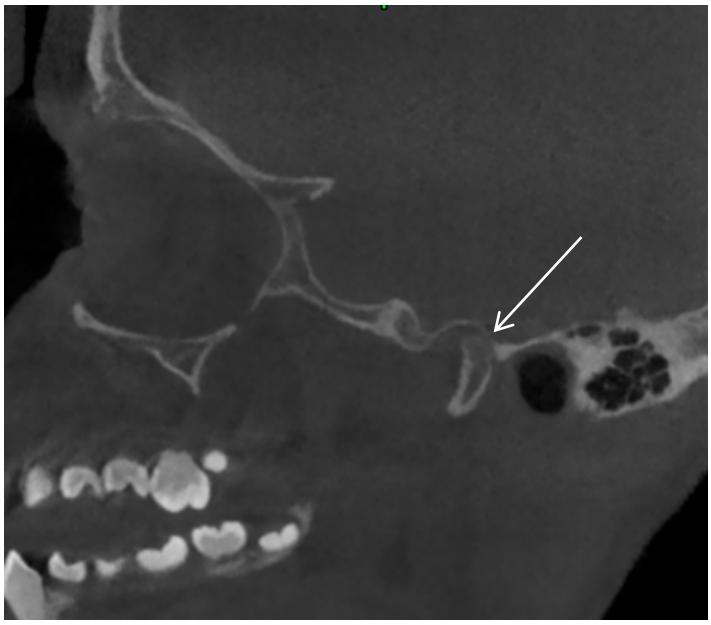

Fig 12.3 Cropped CBCT image of CPT 3. Sagittal view of the TMJ. A reduction in the posterior joint space is evident (arrow).

Comment

Four affected individuals displayed a limited range of movement of the mandible and a deviation in the shape of the head of the condyle except CPT 6 who was uncooperative.

CPT 2 experienced pain in the region of her TMJ and it was suggested that this discomfort was due to irregularities in the anatomy of the articular components of her TMJ. She was referred to a physiotherapist for further management.

The condyle of the mandible and the base of the skull undergo endochondral ossification, similar to long bones, during their growth and maturation process. The condylar cartilage is a secondary cartilage unlike the epiphyseal growth plates in long bones. The condylar and base of skull cartilage continue to be active even after an individual has reached his maximum height. This activity is related to changes in functional demands and defective growth of these structures is related to the defect in the connective tissue matrix.

Longitudinal studies are necessary in these affected individuals to determine the possibility of further progression of TMJ disorders.

12.4 Paranasal Sinuses

Assessments of the sinuses included a clinical history and an evaluation of CBCT images. All the affected persons gave a history of difficulty breathing and recurrent sinus infections.

The radiographic assessment and findings in terms of the paranasal sinuses were confirmed by a consultant radiologist.

All individuals showed abnormalities associated with their sinuses. These observations are tabulated (Table XII.1) and illustrated by representative CBCT images (Fig 12.4 and Fig 12.5).

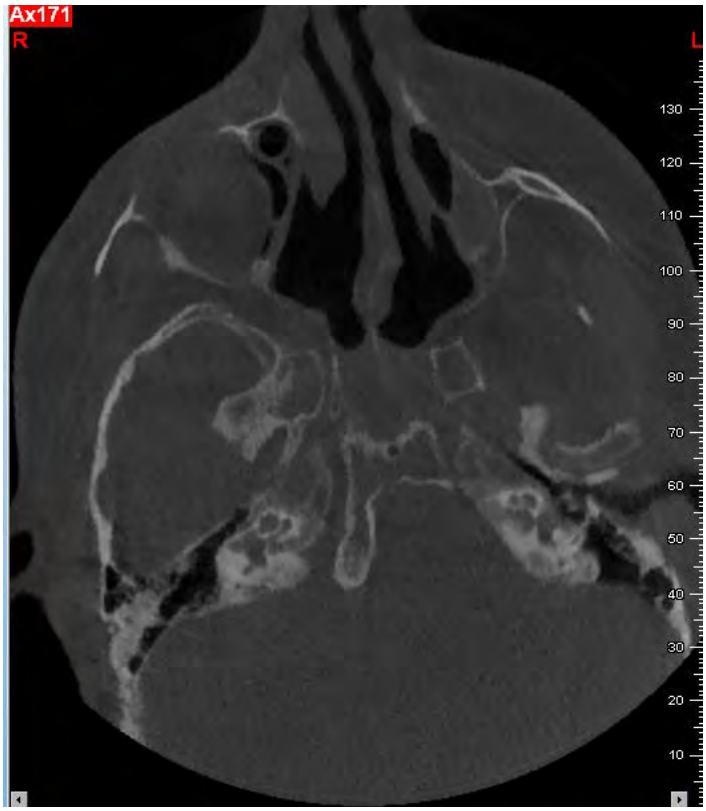

Fig 12.4 An axial image of CPT 3. There is asymmetry of craniofacial structures. The maxillary sinuses are opacified.

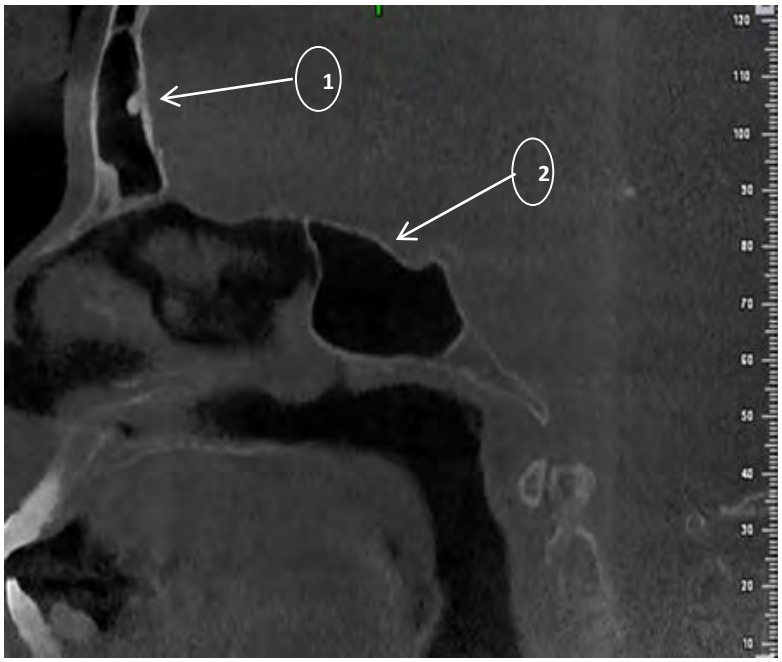

Fig 12.5 Cropped CBCT image of CPT 2. The osteoma in the frontal sinus (1) and the 'J' shaped sella turcica (2) is evident. There is generalized severe osteoporosis of the craniofacial bones.

Table XII.1: Observations of paranasal sinuses from CBCT images

PARANASAL SINUSES	CPT2	CPT3	CPT4	CPT5
Frontal	Osteoma in R side L is hyperplastic and extends behind the orbit	L is hypoplastic	WNL	WNL
Ethmoid and Mastoid air cells	WNL	Diminished number of air cells	Diminished number of air cells	Diminished number of air cells
Sphenoid	L is hyperplastic	WNL	WNL	WNL
Maxillary	WNL	Both are hypoplastic	WNL	WNL

Abbreviations used in Table XII.1

L: left

R: right

WNL: Within normal limits

Comment

The significance of these sinus changes in these individuals is uncertain. To the best of the author's knowledge no published data is available concerning sinus observations in OI III affected individuals.

Longitudinal studies are necessary in these persons in order to determine the development of the changes and the possible clinical consequences of these sinus irregularities.

12.5 Cranial Base Observations

Affected persons CPT 2, CPT 3, CPT 4, and CPT 5 exhibited features of cranial base anomalies; the most consistent feature being a 'J' shaped sella turcica (Fig 12.5, Fig 12.8).

CPT 2 experienced intermittent tingling and numbness in her right arm. The discomfort in her arm was most likely a neurological complication of the basilar invagination (Fig 12.6).

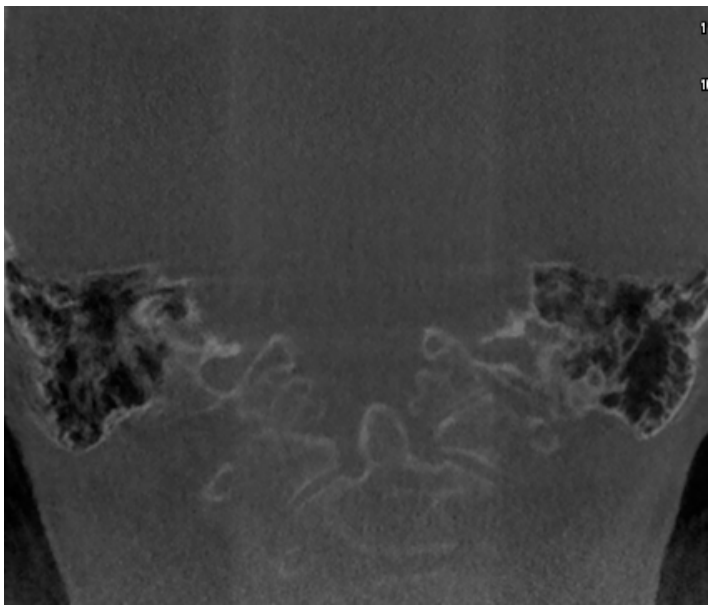

Fig 12.6 Coronal view of the cervical region of CPT 2. Basilar invagination was confirmed by a consultant radiologist.

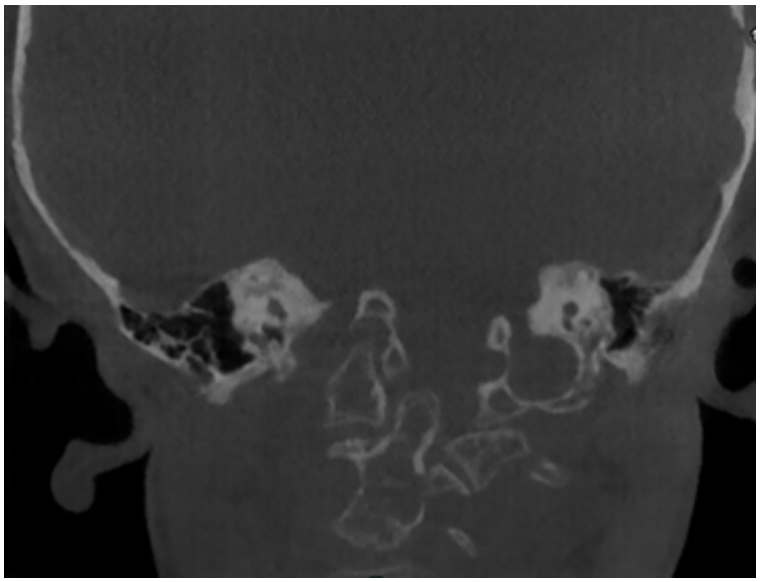

Fig 12.7 CPT 3. Coronal view of her severely malaligned cervical spine and basilar invagination is evident.

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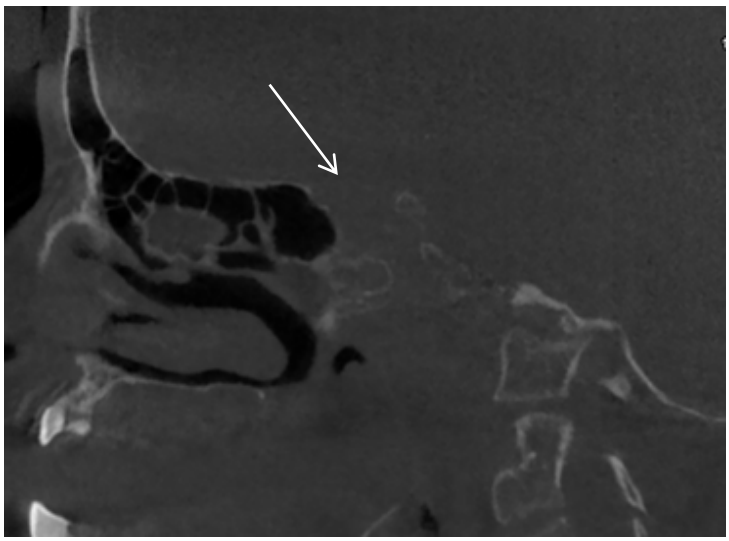

Fig 12.8 Cropped sagittal CBCT image CPT 3. There is marked generalized osteopaenia of the craniofacial bones. A 'J' shaped sella turcica is somewhat evident (arrow).

Please refer to Chapter 9 (page 96) for detailed comments on cranial base anomalies.

Concluding comment

The craniofacial dysmorphology of the CMA persons with OI III, was severe. An awareness of these manifestations by the dental fraternity is warranted since adolescent and adult affected persons may be extremely concerned about the cosmetic condition of their face and dentition and often seek dental and craniofacial management.

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CHAPTER 13: Indian Affected Persons: General Data, Molecular, Dental and Craniofacial Observations

Preamble

Three affected persons of Indian decent, with an unusual OI phenotype, are described and discussed in this chapter.

The majority of South Africa's Asian population is Indian in origin who descended from indentured workers brought by the British Colonial Government to work on the sugar plantations of Natal in the 19th century. These individuals were predominantly Bengalis and Tamils who came via Kolkata and Chennai respectively. Muslims from Gujarat and Punjab arrived in SA from 1870 onwards. Many persons in these 3 founder populations have retained their cultural and genetic identity (Bhana and Brain, 1985, Dhupelia-Mesthrie, 2000).

Several AR genetic disorders have been documented by Winship and Beighton (2011) in the South African Indian population. Some of these conditions include sickle cell anaemia, thalassaemia, OI III and osteoporosis pseudoglioma (Beighton et al., 1987).

During the survey of OI III, 3 persons of Indian heritage with DI, skeletal fragility and ocular involvement were introduced to the author. They are included in this study and their general phenotypic features, molecular findings as well the abnormalities in their dentition are described. Their craniofacial and periodontal manifestations are also included in this chapter.

13.1 General Physical Condition

Table XIII.1 Clinical Findings of Indian affected persons.

Affected Individual	Date of Birth	Age When Seen (Years)	Affected Relatives	Gender	No. of Fractures	Height (cm)	Mobility
DBN6	11/08/1995	19	0	F	>15	112	Walks with an aid
DBN9	22/11/2012	2	0	F	>5	50	Cannot crawl/walk
PMB20	11/03/1999	15	0	F	>10	110	Walks with an aid

Affected persons DBN 6, DBN 9 and PMB 20 (Fig 13.1 and Fig 13.2) were examined at Greys Hospital and Inkosi Albert Luthuli Central Hospital (IALCH) in Kwa-Zulu Natal.

It was of interest that DBN 6 and PMB 20 were similar phenotypically and had a common ancestral background. They both had limited oral opening and their permanent teeth were yellow and translucent consistent with the clinical features of moderate DI. They gave a history of severe DI in their primary teeth.

Their sclerae had a slight blue tinge in keeping with a score 2 on the Sillence 5 point scale. In this population group, this scleral colour may be considered as normal.

Molecular investigations of the *FKPB10* locus in exon 5 identified in the Black African persons were negative for the persons of indian decent.

13.2 Case Reports of Affected Indian Persons

Affected unrelated persons PMB 20 (Fig 13.1) and DBN 6 (Fig 13.3) were of Indian decent with normal unaffected parents and no affected siblings or relatives. Their parents could not rule out the possibility of consanguinity as their ancestral origins were from the same region of India. Both PMB20 and DBN6 were receiving bisphosphonate therapy, but not on a regular basis due difficulty in attending the clinics. DBN 9 was the only child of unaffected non-consanguineous parents. No clear images were obtained of DBN 9 as she was uncooperative (Fig 13.5).

13.2.1 PMB 20

PMB 20 was 15 years of age, 110cm in height and walked with an aid. She had an unaffected male sibling. All her permanent teeth showed clinical and radiological features of moderate DI. She gave a history of severe DI in her primary dentition with enamel fractures, severe attrition and early tooth loss. Marked mandibular prognathism, an anterior open bite and bilateral posterior crossbites were observed (Fig 13.1). No obvious carious lesions were evident. The crowns of teeth 15, 16, 25 and 26 were hypoplastic and the occlusal anatomy of the molars was atypical. She had mild visual impairment of unknown aetiology.

Fig 13.1 PMB 20 aged 15 years. She walks with an aid. Clinical DI is present in all of her permanent teeth. Her teeth range in colour from blue- grey in the molars to amber and opalescent in the anterior teeth. Mandibular prognathism, an anterior open bite (1) and bilateral posterior cross bites (2) are another feature. Mild interdental calculus deposits (3) are present.

The primary concern of PMB 20 was the colour of her teeth for which she was referred to a prosthodontist and an orthodontist. A CBCT was requested by both dental specialists. A previously obtained panorex radiograph was available to the author.

Radiographic features of DI were evident in all of her teeth. There was flexion and dilaceration *(see Appendix 3)* of the roots of her molars (Fig 12.2). These features were most likely due to her impacted 3rd molars.

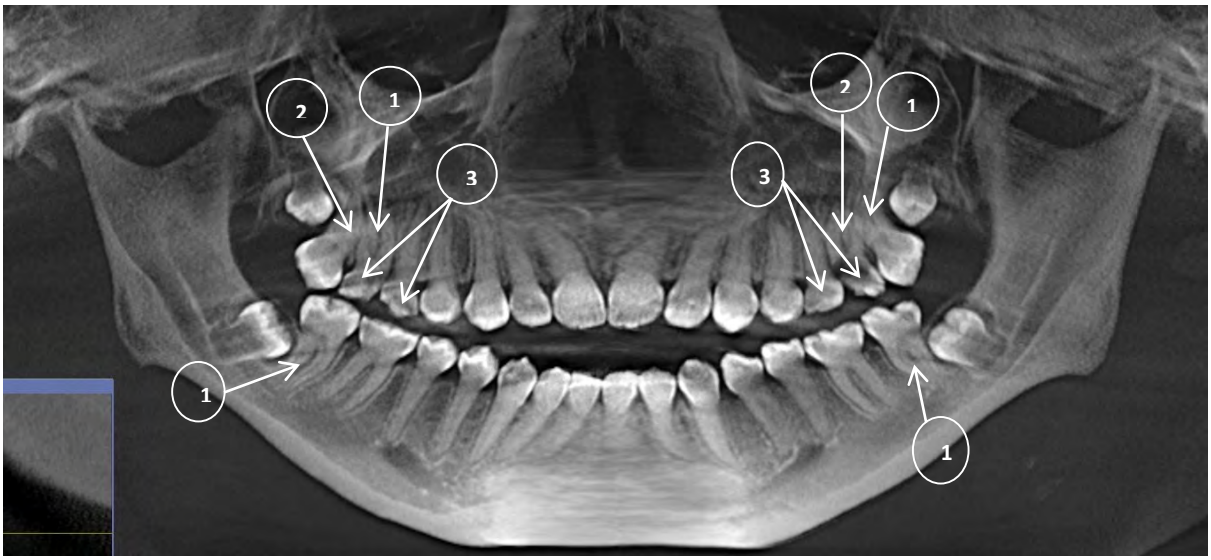

Fig 13.2 Panorex of PMB 20. Radiological features of DI are evident in all her teeth. Flexion of the roots of the 16, 27, 37 and 47 are seen (1). Roots of the 17 and 26 are dilacerated (2). The crowns of the 15, 16, 25 and 26 are hypoplastic (3).

13.2.1 DBN 6

DBN 6 was the only affected person in her family. She had unaffected parents and 3 unaffected male siblings. At 19 years of age, she was 112cm in height, walked with an aid and was mildly visually impaired (Fig 13.3). The nature of her visual disability was unknown and has not yet been investigated.

As with PMB 20, it was not logistically possible to obtain a specialized ophthalmic evaluation during the course of the project.

She had mild mandibular prognathism and she was undergoing orthodontic treatment for the malalignment of her teeth. Her dental history was also suggestive of severe DI in her primary teeth with early exfoliation.

A panorex radiograph and CBCT images were made available to the author by the consultant orthodontist.

Moderate radiographic features of DI were evident in all of her teeth on panorex views (Fig 13.4). Her molars, the 17, 27 and 37 are mesotaurodontic.

Fig 13.3 DBN 6 aged 19 years. She walks with an aid. There has mild clinical discolouration of her permanent teeth. Minimal deposits of calculus are present (arrows)

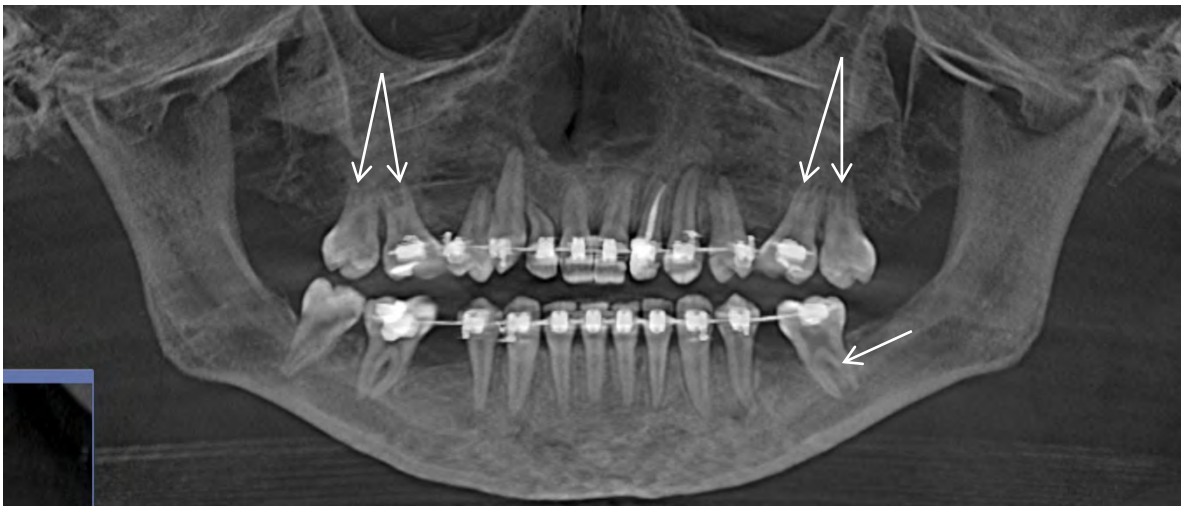

Fig 13.4 Panorex of DBN 6. Moderate radiographic features of DI are evident including cervical constriction of the molars and partial obliteration of the pulp cavities and root canals. Features of mesotaurodontism are present in molars 16, 17, 26, 27 and 37 (arrows). There is dilaceration and flexion of the roots of several teeth (12, 22, 34 and 47). Her 18, 28, 38 and 48 were congenitally absent.

DBN 9 was 2 years of age at clinical examination and the only affected member of her family. She had short malaligned limbs and was unable to crawl. Previous radiographical investigations revealed the

characteristic skeletal features of OI. She had not as yet been investigated for any visual problems. She was uncooperative and clear clinical pictures were difficult to obtain (Fig 13.5). A visual intraoral examination revealed the presence of 2 discoloured anterior primary mandibular incisors, suggestive of DI.

Fig 13.5 DBN 9 at 24 months was unable to crawl or walk.

13.3 Comment:

The persons of Indian ancestry, DBN 6 and PMB 20, were born in South Africa and although a definite history of consanguinity could not be established it maybe relevant that the progenitors of both individuals hailed from Gujerat province of India.

Although rare, Osteoporosis-pseudoglioma Syndrome (OPPG) has been documented in individuals from Gujerat (Beighton et al., 1985, Gong et al., 1996) and in their descendants born in South Africa (*see Chapter 18).* Individuals DBN 6 and PMB 20 were not investigated for OPPG, but the possibility that these individuals actually have OPPG, cannot be discounted. An attempt to contact their ophthalmologists by the author was unsuccessful. An ophthalmic opinion and further molecular investigations are warranted.

The other recognized disorder to be associated with eye abnomalities and vertebral compression fractures is spondylo-ocular syndrome. Currently, there is no review specifically addressing the patterns of visual impairment in OPPG and spondylo-ocular syndrome (Munn et al., 2015). The general

phenotypic manifestations in individuals with spondylo-ocular syndrome is platyspondyly consequent to early onset progressive osteoporosis with eye findings which include cataracts, retinal detachment and nystagmus (Munn et al., 2015).

No association between Dentinogenesis imperfecta and the degree of skeletal severity of the disorder was observed in DNB 6 and PMB 20. This observation is consistent with the findings of Petersen and Wetzel (1998).

13.4 Craniofacial Observations

The craniofacial observations are reported on using the same anatomical approach as the Black African and CMA persons. Comments on these findings were presented in Chapters 9 and 12. For the sake of expediency, please refer to these comments.

13.4.1 Occlusion and Palatal Anatomy

Oral and craniofacial evaluations of PMB 20 and DBN 6, revealed a dental and skeletal Class III malocclusions and varying degrees of mandibular prognathism. A posterior crossbite and an anterior openbite was evident in PMB 20.

13.4.2 Periodontal Status

The periodontal status of these individuals was assessed clinically and radiographically.

Each individual, DBN 6 and PMB 20, showed a loss of the lamina dura and they had an average pocket depth of 5mm. Interdental and subgingival plaque and calculus were evident and they had moderate to severe gingival bleeding on probing.

13.4.3 Temporo-mandibular joint (TMJ)

As in the CMA persons, the TMJ status was assessed clinically and radiographically.
The condylar heads showed a moderate deviation in shape (Fig 13.6) and there was an absence of superficial cortical bone in PMB 20 and DBN 6.
Both individuals had limited lateral movement of the mandible and showed a significant reduction in the maximum opening of the mouth.

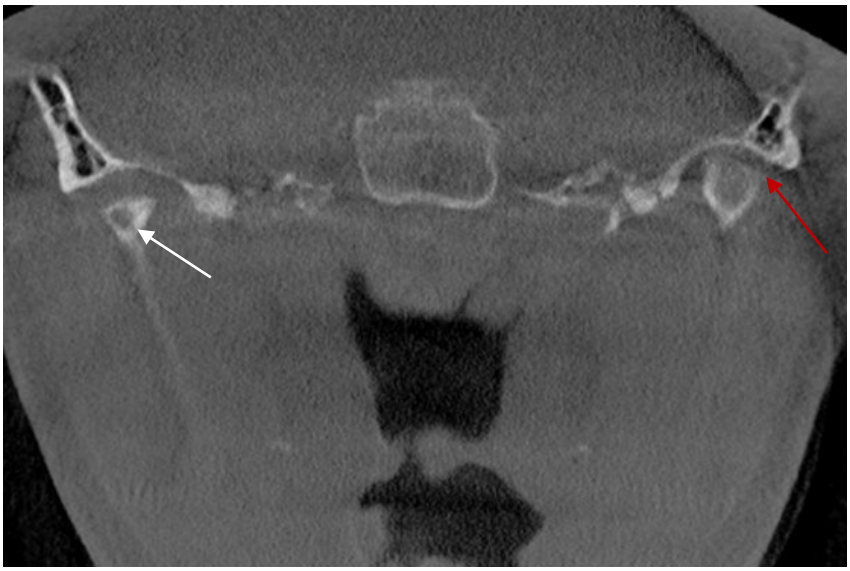

Fig 13.6 Coronal CBCT image of PMB 20. The mandibular condyles are asymmetric (arrows). There is a loss of surface cortical bone on the head of the left condyle (red arrow)

13.4.4 Paranasal Sinuses

PMB 20 and DBN 6 gave a clinical history of difficulty breathing and recurrent sinus infections.

Both individuals had radiographic abnormalities associated with their sinuses. These observations are tabulated (Table XIII.2). The radiographic assessment and findings in terms of the paranasal sinuses were confirmed by a consultant radiologist (Fig 13.7).

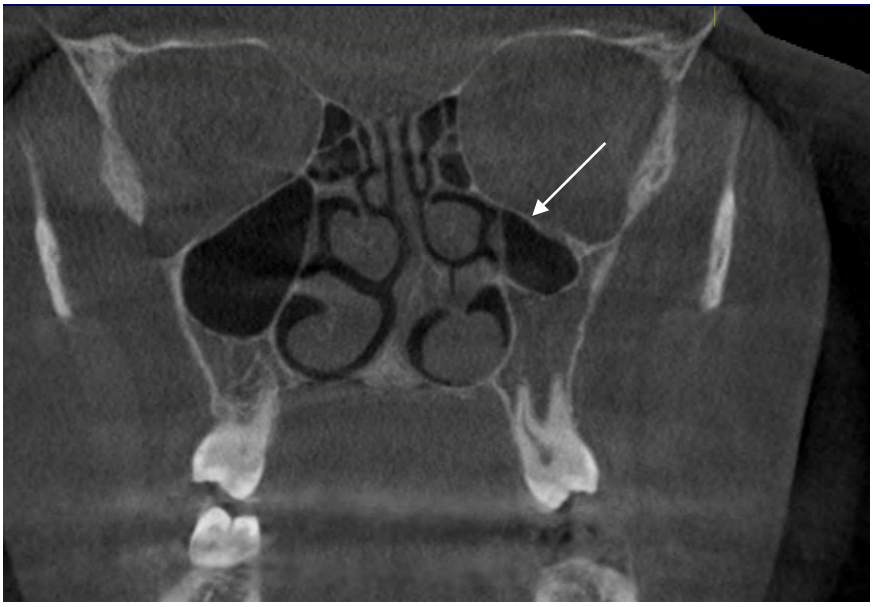

Fig 13.7. DBN 6. Left hypoplastic maxillary sinus (arrow)

Table XIII.2: Observations of paranasal sinuses from CBCT images

PARANASAL SINUSES	DBN 6	PMB 20
Frontal	WNL	L and R are hypoplastic
Ethmoid and Mastoid air cells	Diminished number of air cells	Diminished number of air cells
Sphenoid	WNL	WNL
Maxillary	L is hypoplastic	R is hypoplastic

Abbreviations used in Table XIII.2

L: left

R: right

WNL: Within normal limits

13.4.5 Cranial Base Observations

Affected persons DBN 6 and PMB 20 had cranial base anomalies, the most consistent feature being a 'J' shaped sella turcica (Fig 13.8).

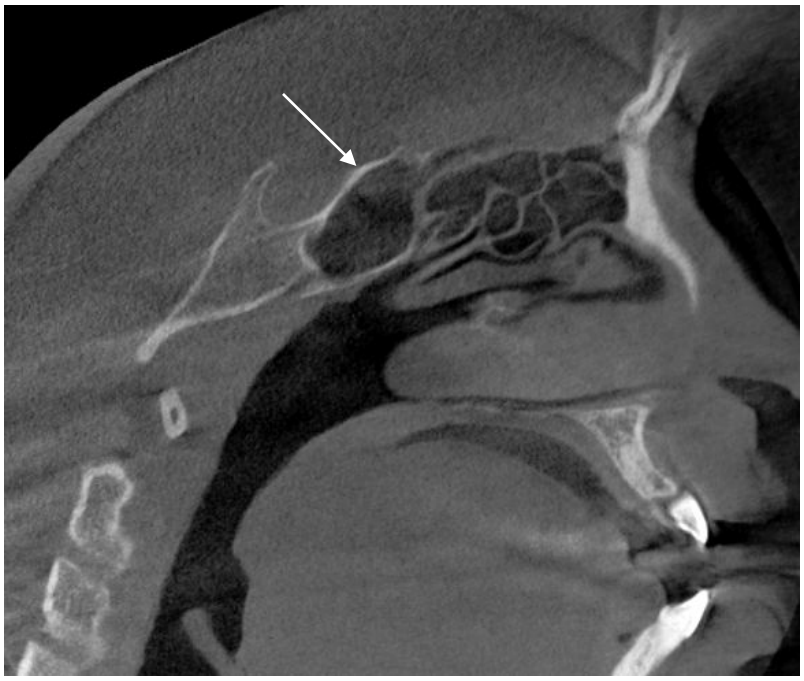

Fig 13.8 PMB 20. A 'J' shaped sella turcica is evident (arrow)

13.5 Concluding Comment

Awareness of the craniofacial and dental manifestations of specific genetic conditions common in the Indian community of SA would facilitate optimal management.

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Section IV: Discussion

This section contains three chapters in which relevant issues which impact on the dental management of affected persons are reviewed and discussed in detail.

CHAPTER 14: Bisphosphonate Therapy

Preamble

The administration of bisphosphonate therapy in OI III affected patients is relevant to the dental and craniofacial management of the affected individuals. In particular, bisphosphonate induced osteonecrosis of the jaws is a rare but potentially devastating problem. The majority of the persons with OI III in this study had received or were currently receiving bisphosphonate therapy. There is concern and uncertainty among members of the dental fraternity regarding management and bisphosphonates. For this reason a review and discussion of bisphosphonate therapy in the dental context was undertaken.

14.1 Introduction

Since the seminal report of Albright (1981), a significant advance in the medical management of OI has been the implementation of bisphosphonate therapy. These are synthetic analogs of pyrophosphate which inhibit bone resorption by being deposited on the bone surface and are ingested by osteoclasts with consequent apoptosis of these cells. Bisphosphonates also demonstrate anti-angiogenic activity by inhibiting vascular endothelial growth factor and the resultant formation of new blood vessels (Varun et al., 2012).

Impressive radiological and clinical improvements have been observed in persons with different forms of OI III and the fracture rate has usually diminished. Nevertheless, bisphosphonate therapy has generally had little effect on the progression of the condition in OI III affected individuals with a mutation in the *FKBP10* gene. These findings, as demonstrated by illustratrations of siblings QQ 2 and QQ 3 (*see Chapter 7)* are consistent with those described by Sillence in which he states that OI III affected persons with a mutation in the *FKBP10* gene do not respond optimally to cyclic intravenous bisphosphonate therapy, particularly Pamidronate. There are no reported instances of Pamidronate being associated with osteonecrosis of the jaws (ONJ) in OI III. In circumstances where affected persons did not respond optimally to Pamidronate, Zoledronic acid has been used.

A significant observation during the course of this project was no clinical evidence nor a history of osteonecrosis of the jaw (ONJ) in any affected person.

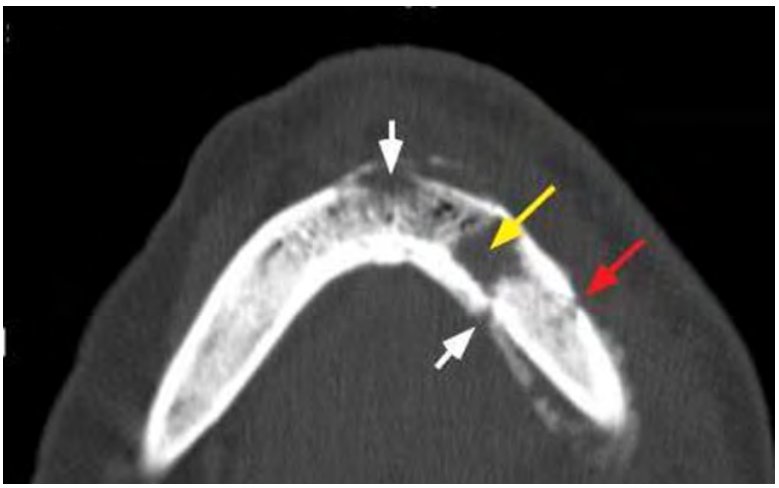

Fig 14.1 CT scan of the mandible of an adult patient. ONJ is evident (arrows) after receiving bisphosphonate therapy.

Google: http://www.aboutcancer.com/osteonecrosis_of_the_jaw.htm (November 2015)

It has been suggested that bisphosphonates, when used in persons with OI III, does not affect the deposition of abnormal collagen matrix. These Individuals will have increased bone volume but the quality of bone remains the same (Marini and Smith, 2015).

14.2 Bisphosphonate Therapy and Dentistry

The jaws are susceptible to osteonecrosis due to several anatomical and physiological factors. Bisphosphonates tend to accumulate in the bones of the jaws due to the high vascularity and turnover rate. The forces of mastication and consequent tension on the periodontal ligament ensures a high turnover rate of alveolar bone and the thin oral mucosa can easily be traumatized during dental procedures which would allow oral microbes to track into the mucoperiosteal region of the jaws (Marx et al., 2005). The pathophysiology of ONJ has been described as multifactorial involving factors such as marked suppression of angiogenesis, altered functioning of oral mucosal cells, the oral microbial flora may be altered, an anti-inflammatory effect and a genetic predisposition (Allen and Burr, 2009). Bisphosphonate uptake results in decreased remodelling of the alveolar bone and a sclerotic lamina dura (Borromeo et al., 2011).

In the dental context, several case reports and cohort studies have linked bisphosphonate therapy and osteonecrosis of the jaw (ONJ) in adults (Marx, 2003; Khan et al., 2008; Barush et al., 2011; Varun et al. ,2012). Despite extensive adult data; to date there has been no published data of ONJ in children. The only dental association in children was a report of a 1.67 year delay in tooth eruption in children that received bisphosphonate therapy (Kamoun-Goldrat et al., 2008).

Members of the dental fraternity such as restorative dentists, periodontists, orthodontists and maxillofacial surgeons often manage children with OI III on bisphosphonate therapy and it is the author's experience that there is uncertainty as to how to manage this patient group. Trepidation was also raised by orthodontists when treatment was planned on children and young adults on bisphosphonate therapy with regard to the feasibility of orthodontic extractions and tooth movement. For these reasons a brief review of the literature on the topic of bisphosphonate therapy and dental complications has been undertaken and a summary is proffered below.

Various clinical settings in dentistry may potentially be affected if an individual has a history of or is currently receiving bisphosphonate therapy.

14.2.1 Dental Implants

Although bone graft surgery and dental implants are considered potential risk factors for the development of ONJ in individuals receiving bisphosphonate therapy, studies in this regard have reported no incidences of ONJ.

14.2.2 Periodontics

The potential beneficial effects of bisphosphonates on periodontal disease have been explored. Bisphosphonates have been noted to have paradoxical effects in the oral cavity with the potential beneficial effects on periodontal disease by increasing the density of alveolar bone and yet increasing the risk of ONJ (Borromeo et al., 2011). In OI III affected individuals, the lamina dura is absent suggesting decreased mineralization of the alveolar bone. This feature places these persons at risk for the development of periodontal disease and consequent alveolar bone loss. The presence of periodontal disease may necessitate invasive periodontal procedures or dental extraction, and hence increase the risk of ONJ.

14.2.3 Orthodontics

In children with OI, bisphosphonates are effective in their management. No cases of ONJ have been reported and the extraction of teeth is not contraindicated in these children (Brown et al., 2008; Schwartz et al., 2008). These authors suggest that age may be a protective factor. Increasingly, adult affected individuals with bisphosphonate exposure are now seeking orthodontic care. A literature search has revealed no case reports of ONJ developing during orthodontic care. Bisphosphonates may compromise orthodontic treatment in that tooth movement involves bone resorption and deposition. It has been shown that bisphosphonates can reduce the rate of orthodontic tooth movement due to their inhibition of bone resorption by osteoclast apotosis and reduced bone vasculature. Inhibition of orthodontic tooth movement has been described in four cases with a history of bisphosphonate exposure (Rinchuse, 2007; Goss, 2008). No studies have specifically implicated orthodontic treatment as a factor in increased ONJ risk, but there is evidence that prolonged orthodontic treatment may intensify the potential for ONJ (Ghoneima et al., 2010).

14.2.4 Endodontics

In affected persons with a history of bisphosphonate therapy, endodontic treatment is preferred over extraction in order to minimize the risk of ONJ.

14.2.5 Oral Surgery

Dental extractions and surgical procedures need to be as atraumatic as possible and good oral hygiene is crucial in order to ensure optimal healing in an environment of reduced blood supply, sclerotic bone and reduced bone turnover (Chahine et al., 2008; Borromeo et al., 2011).

14.3 Antibiotic Prophylaxis

A survey of dental specialists and dentists in the UK revealed that their management of paediatric patients on bisphosphonates ranged from no precautions to antibiotic prophylaxis. It was also highlighted that OI centres in the UK often entertain several calls from dental practitioners requesting management advice of this group of individuals and hence it is evident that guidance in this regard is necessary (Christou et al., 2012).

The question of antibiotic prophylaxis during dental intervention arose when patients with OI III had orthopaedic rods. There is currently conflicting published information in this regard. It has been suggested that antibiotic prophylaxis is not required when dental treatment is undertaken (O'Connell and Marini, 1999). This suggestion has been substantiated by a case report of a boy of 10 years with OI and no family history of the disorder. Dental surgery was performed without the suspension of bisphosphonate therapy and no antibiotics were administered. Eighteen months later at his follow-up appointment, he showed no signs of ONJ (Costa et al., 2014).

14.4 Dental Management Protocol

Currently, no established protocol has been formulated regarding the dental management of persons with OI III on bisphosphonate therapy.

It has been suggested that bisphosphonate therapy should be discontinued 8-15 days prior to simple procedures such as a dental extraction and 4 months prior to invasive surgery such as an osteotomy (Ruggiero et al., 2009; Schwartz et al., 2008). In both circumstances, these authors recommend antibacterial prophylaxis.

It has also been documented that although bisphosphonate therapy withdrawal may not interfere with the bisphosphonate previously assimilated into the bone, withdrawal of therapy may expedite the healing process of the injured tissues by averting the anti-angiogenic effect of bisphosphonates (Lee et al., 2014).

In patients where bisphosphonate therapy has already been instituted, the American Association of Oral and Maxillofacial Surgeons (Ruggiero et al., 2009) and the Japanese 'Allied Task Force Committee of Bisphosphonate-Related Osteonecrosis of the Jaw' recommend that dental procedures be performed prior to the bisphosphonate dose reaching a high level (Yoneda et al., 2010).

14.5 Recommendation

The author recommends that, in order to obtain baseline information and a correlation of the dental craniofacial manifestations and bisphosphonate therapy in OI III in SA, cephalometric radiographs of affected persons, who have not received bisphosphonate infusions be compared with OI III affected persons that have received bisphosphonate therapy. In this way the effect of bisphosphonate therapy on the dental and craniofacial structures can be identified.

14.6 Conclusion

Several reports have suggested that there is little risk of ONJ in paediatric OI III dental patients receiving bisphosphonate therapy (Brown et al., 2008; Chahine et al., 2008; Schwartz et al. 2008).

When dental treatment is vital in this group of children on bisphosphonate therapy, communication with the child's medical team is essential. Patients and their parents or carers must be educated in the importance of maintaining good oral hygiene and having regular dental evaluations in order to prevent dental disease.

The Canadian Association of Oral and Maxillofacial Surgeons established a multidisciplinary task force that reviewed all relevant research and current literature related to ONJ (Khan et al., 2008). These authors concluded that although ONJ was identified as a risk factor in oncology patients receiving high dose intravenous bisphosphonates, low dose bisphosphonate use in patients especially children, with OI and osteoporosis did not pose a risk for the development of ONJ and no causal link was established (Barasch et al., 2010).

It should also be considered that as bisphosphonates are retained in bone for many years, therefore in theory, any dental intervention in this period may result in ONJ.

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CHAPTER 15: Hereditary Dentin Dysplasia (HDD)

Preamble

The features of the hereditary dentin dysplasias (HDD) are relevant to the dental findings in this project. The definition, history of the terminology and the development of the current classification is outlined and discussed in this chapter. The aims are to address confusion that has arisen in the literature on HDD and to provide clarity on the use of appropriate terminology.

15.1 Definition

The hereditary dentin dysplasias (HDD) such as dentinogenesis imperfecta (DI) and dentin dysplasia (DD) are a group of genetic conditions characterized by an abnormal dentin structure due to disturbances in the formation, composition, or organization of the dentin matrix and affects either the primary or both primary and secondary dentition to varying degrees. These disorders result from mutations in the genes encoding the major protein constituents of dentin notably collagens and phosphoproteins.

15.2 Dentine and Dentinogenesis

Dentin is a protective covering of the pulp of the tooth. It is mineralized tissue that constitutes the body of the tooth and serves as a support for the overlying enamel and cementum (Fig 15.1). Dentin is approximately 70% mineral, 20% organic matrix and 10% water. The organic matrix is primarily composed of type I collagen.

Non- collagenous proteins such as dentin sialoprotein (DSP), dentin glycoprotein (DGP) and dentin phosphoprotein (DPP) constitute a further 10% of the organic matrix of dentine. These proteins are encoded by the dentin sialophosphoprotein gene, *DSPP*. The proteins, DSP, DGP and DPP undergo post translational modifications which control mineralization of dentin (de la Molla et al., 2014). Dentin matrix is secreted by end-differentiated cells termed odontoblasts which are mesenchymal in origin.

Non-syndromic genetic abnormalities of dentine are associated with mutations in the *DSPP* gene (Kim and Simmer, 2006).

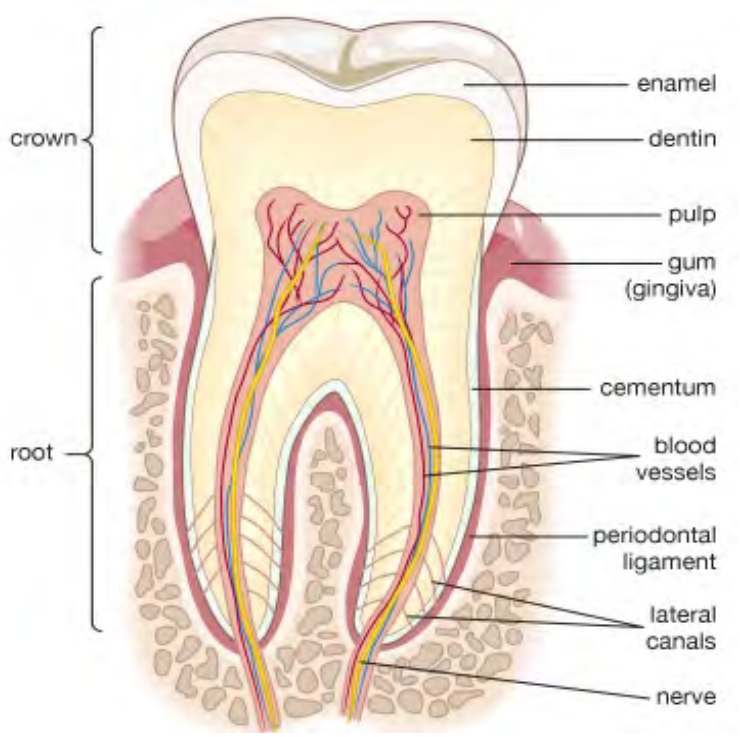

Fig 15.1 Diagrammatic representation of a cross section through a molar tooth www. Britannica.com

(June 2015)

15.3 Clinical Appearance of Hereditary Dentin Dysplasias

The affected teeth are amber, brown or blue in colour (Fig 15.2, Fig 15.3). Marked attrition and abrasion may result from hypomineralization of the dentin and the consequent reduction in microhardness (Hodge et al., 1940; cited by Lygidakis et al., 1996; Teixeira et al., 2008). Periapical abscess formation without pulpal exposure, tooth mobility and early loss of teeth due to periodontal involvement are important complications.

Dentin may be exposed due to shearing of the tooth enamel resulting from an abnormal dentine-enamel junction (DEJ) (Fig 15.4). Electron microscopic studies have shown abnormal scalloping at the DEJ and a consequent weaker bond between dentin and enamel. There are also abnormalities in the structure and mineralization of dentin (Biria et al., 2012).

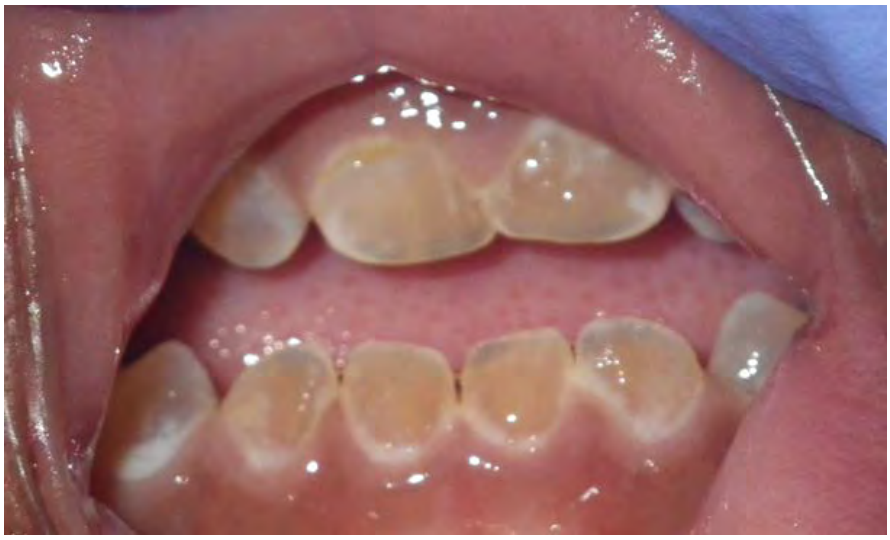

Fig 15.2 Intraoral picture of PMB 17, aged 4 years. His primary teeth show clinical features of DI. His anterior teeth are amber and translucent at the incisal third. His lower canines have a bluish hue.

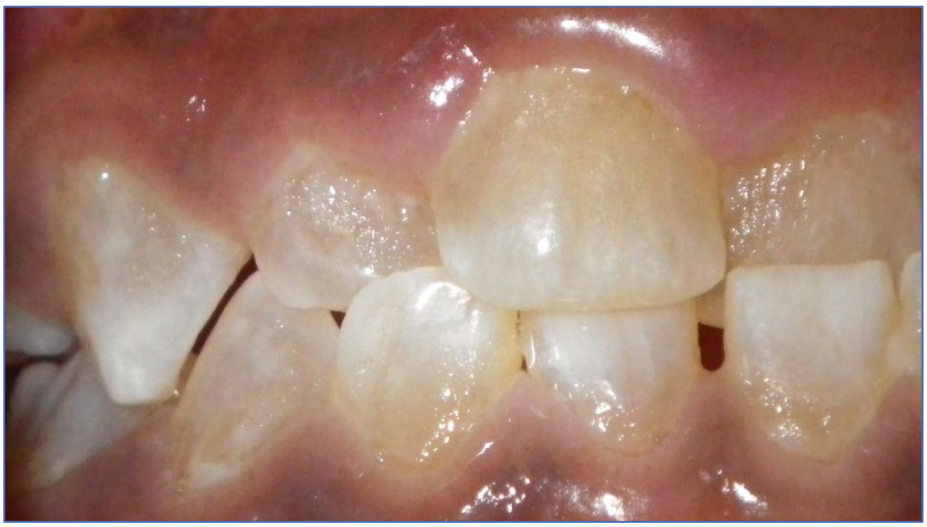

Fig 15.3 Intraoral picture of PMB 5 aged 6 years in the mixed dentition period. His primary and secondary teeth are yellow and moderately translucent.

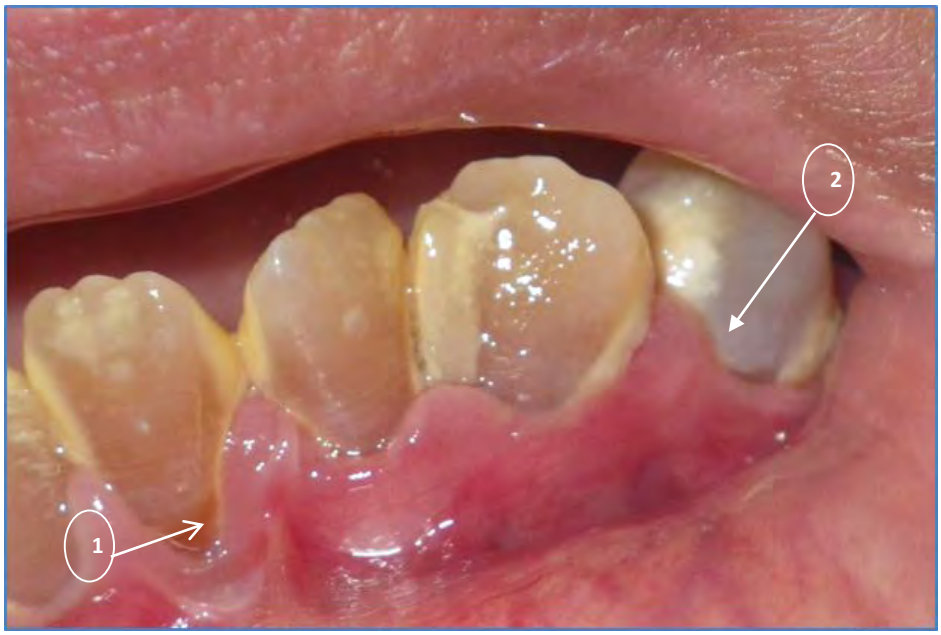

Fig 15.4 Intraoral picture of CPT 3. The lower permanent teeth are amber and there are focal areas with loss of surface enamel (1). The first lower premolar is translucent with a bluish hue (2).

15.4 Diagnosis of Hereditary Dentin Dysplasias

The diagnosis of HDD is based on a family history with a pedigree construction and a comprehensive clinical examination. Molecular diagnosis may be useful in the future as several disease causing mutations have been identified. Genetic conditions which may be associated with HDD are listed in Table XV.1. A knowledge and awareness of these conditions and their possible dental manifestations is necessary by dental clinicians in order to understand the pathogenesis and aid in the dental management of affected persons.

Table XV.1 Syndromic Genetic Conditions which may be associated with HDD

SYNDROMIC CONDITION	SYNDROMIC DESCRIPTION
Chediak-Higashi syndrome [OMIM 241500]	AR disorder that compromises the immune system
Papillon-Lefevre syndrome [OMIM 245000]	AR condition characterized by periodontitis and palmoplantar keratoderma
Goldblatt syndrome [OMIM 184260]	Rare AD condition associated with chondrodysplasia
Kostmann disease [OMIM 202700]	AR condition that causes severe congenital neutropaenia
Schimke immune-osseous dysplasia (SIOD) [OMIM 242900]	AR condition associated with short stature, kidney disease and a compromised immune system
Branchio-skeleto-genital syndrome [OMIM 211380]	AR condition with mental retardation, maxillary hypoplasia, mandibular prognathism, broad nasal bridge, pectus excavatum, fused cervical spine
Hypophosphatasia [OMIM 241510]	AR condition which affects the development of the teeth and bones
Ehlers-Danlos syndrome (Several types)	AR disorder of connective tissue with severe joint laxity and skin extensibility
Osteogenesis imperfecta (heterogeneous condition)	Familial condition characterized by brittle bones
Osteodysplastic and primordial short stature with severe microdontia and opalescent teeth and rootless molars [OMIM 210720]	AR disorder characterized by intrauterine growth retardation, severe short stature and microcephaly

Other disorders that may have clinical features similar to HDD, but differ at a radiological and histological level include congenital erythropoeitic porphyria, cyclic neutropaenia, Histiocytosis X and discolouration due to tetracycline administration.

15.5 Classification of Hereditary Dentine Dysplasia

The Shields classification proposed that HDD be divided into 5 types, specifically, three types of DI and two types of DD (Shields et al., 1973).

The 5 divisions of the Shields classification are summarized below:

DI type I

This dental phenotype is only described in persons affected with OI. Clinically the teeth are amber and translucent with marked attrition in both primary and secondary dentition.
Radiographically, there is pulpal obliteration due to dentine hypertrophy. This process occurs just prior or soon after eruption. A spectrum of change is often seen, even within a single individual, ranging from total pulp obliteration to apparent normal dentine. The teeth often have short constricted roots.

DI Type II

There are many radiographic and clinical similarities to DI type I. There is complete penetrance of this isolated AD trait and OI is not a component. Bulbous crowns with marked cervical constriction are a feature. Sensorineural hearing loss has been reported as an infrequent syndromic manifestation (Barron et al. 2008). All teeth of both the dentitions are involved and mutations in the gene encoding dentin phosphoprotein and dentin sialoprotein are responsible for this condition.

DI Type III

This AD type of isolated DI is known as the 'Brandywine' form and had originally been recognised in a tri-racial isolated population in Maryland and Washington DC. The clinical features are variable and resemble those seen in DI type I and II. Radiographically, the teeth appear hollow due to dentin hypotrophy and the primary teeth often show pulp exposures (Witkop, 1971).

Dentin Dysplasia Type I

This dentinal defect is extremely rare and the teeth are clinically unremarkable. Radiographically the roots are conical with an apical constriction or absent in severe cases. The first sign of this condition is tooth mobility which leads to premature exfoliation of teeth. Periapical lesions are common without any associated pathology. The causative gene anomaly has not as yet been identified and the pathological process is not understood.

Dentin Dysplasia Type II

The primary dentition shows features resembling DI type II yet the permanent dentition is either unaffected or shows mild radiographic anomalies such as 'thistle tube' deformity of the pulp. Pulp stones are often present.

The Shields classification was based on clinical phenotypes and lacked any molecular genetic information concerning the inherited disorders of dentin.

Following the availability of molecular data regarding the cause of each dentin disorder, confusion arose both in the literature and among dental practitioners.

It was suggested at the OI-consensus conference in Norway (1999) that abnormal dentin in association with OI be termed 'DI-like' and should be used instead of DI type I (Shields classification). The term 'DI-like' would refer to affected persons whose teeth were clinically and radiologically aberrant. It would include the presence of other, less apparent, dentinal aberrations as well. This point is further substantiated by the comment that 'the correspondence and linking between OI and DI is still to be worked out' (Bloch-Zupan et al., 2012).

These terminological shortcomings were subsequently addressed and a revision of the classification was suggested (de la Dure-Molla et al., 2014). After molecular genetic evaluation of HDD, these authors indicated that conditions DI type II, DI type III and DD type II are variations in severity of the same pathological process. Shields DI I was not included in the proposed new classification of HDD since these authors also considered the pathogenesis of Shields DI I to be different to that of Shields DI II, DI III and DD II.

This classification, with modifications by the author is presented in Table XV.2.

Table XV.2 Former Shields and proposed revised classification for HDD (de la Dure-Molla et al., 2014) – amended by the author to include DI associated with OI (AR and AD) and the genes involved

OMIM	Shields Classification (Former classification)	Proposed revised classification	Gene involved
125400	DD type I	Radicular dentin dysplasia	Unknown
125420	DD type II	DI: Mild form	*DSPP*
125490	DI type II	DI: Moderate form	*DSPP*
125500	DI type III	DI: Severe form	*DSPP*
*	DI type I associated with AD OI, AR OI	**	AD: *COL1A1, COL1A2* AR: *FKBP10, LEPRE1, CRTAP, PPIB*

* OMIM number is given according to the type of OI

** DI associated with OI is syndromic and not included in the proposed new classification since the authors (de la Dure-Molla et al., 2014) consider that it is a manifestation of an entirely different pathological process.

15.6 Dentinogenesis imperfecta (DI)

Dentinogenesis imperfecta is an inherited disorder affecting dentin. The resulting defective dentin manifests as discoloured teeth that are prone to attrition and fracture.

Witkop (1975) proposed a new classification for DI which suggested that DI associated with OI is a unique entity (Table XV.3). A recent review on the aetiology and nomenclature of DI and a presentation of a case of Shields DI II further highlights the fact that DI associated with OI is a distinct disorder which is clinically, radiologically and histologically similar to DI associated with a mutation in the *DSPP* gene (Devaraju et al., 2014). These authors suggested that the most appropriate classification was that described by Levin in 1978 and is published in Oral Pathology textbooks (Neville, 2005; Schafer, 2006) (Table XV.3).

Table XV.3 Various classifications of DI (Devaraju et al., 2014)

Shields (1973)	Witkop (1975)	Revised according to Levin 1978 (Neville et al., 2005; Schafer et al., 2006)	Clinical Presentation
DI I	DI	No substitute	OI with opalescent teeth
DI II	Hereditary Opalescent Teeth	DI I	Isolated opalescent teeth
DI III	Brandywine isolate found only in a population of southern Maryland (USA)	DI II	Isolated opalescent teeth

In this thesis, the author has used the term 'DI' only in the syndromic context such as when abnormalities in the dentin are recognized clinically and/or radiologically in individuals with OI.
DI associated with AD OI occurs in a significant proportion of individuals in whom mutations in the *COL1A1* (17q21.31 – q22.05) or *COL1A2* (7q22.1) have been identified. These genes encode the pro-alpha-1 or pro-alpha-2 chains of collagen type I respectively.

DI associated with AR OI is a variable feature in individuals with mutations in the following genes, *FKBP10, LEPRE1*, *CRTAP* and *PPIB* (Devaraju et al., 2014, de la Dure-Molla et al., 2014).

15.7 Radiographical Features of Hereditary Dentin Dysplasias

Following the perusal of the literature (Barron et al., 2008; Biria et al., 2012; de la Dure-Molla et al., 2014), the author proposes that a spectrum of changes can be identified depending on the severity of the condition. The following list has been formulated which highlights the radiological features of abnormal dentin:

- Crown dysmorphology (bulbous crowns to mild occlusal abnormalities)
- An accentuated constriction at the cemento-enamel junction
- Variable obliteration of the pulp chambers (narrowed roots to abnormally large root canals)
- Taurodontism
- Periapical radiolucency with or without pulp exposure

15.8 Spectrum of the Clinical and Radiographical Features of Hereditary Dentin Dysplasias

The clinical and radiological characteristics of HDD, in particular DI, vary according to the degree of severity of expression of the disorder. These features are summarized in Table XV.4.

Table XV.4 Clinical and Radiographical signs of HDD, in particular DI, ranging from mild to severe, compiled by the author after perusal of relevant published literature

Dental phenotype (variability of HDD criteria)	Mild severity	Moderate severity	Severe
Crown discolouration	Normal to light grey	Blue, grey, amber or opalescent	Brown opalescent
Crown dysmorphology	Mild to non-existent	Bulbous and short	Bulbous and short
Attrition	Mild to non-existent	Increased – from enamel chipping to disappearance of entire crown	Increased – from enamel chipping to disappearance of entire crown
Pulp Obliteration	No	Narrowed pulp to complete obliteration	Enlarged pulp with 'shell teeth' appearance
Thin and short roots	Mild variation from normal	Increased severity	Large pulp chambers
Periapical pathology	no	Increased number of lesions	Increased number of lesions

Various authors have made suggestions with regard to the terminology of abnormal dentin (Devaraju et al., 2014; de la Dure-Molla et al., 2014). Nevertheless, confusion still exists and the published literature has not yet provided clarity on the accepted use of the appropriate nomenclature.

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CHAPTER 16: Taurodontism

16.1 Definition

16.2 Aetiology

16.3 Diagnosis and Classification

16.4 Radiological Features

16.5 Clinical Challenges

16.6 Conclusion

Preamble

Taurodontism is one of the manifestations of dysplastic dentin. This feature was identified radiographically in 2 individuals with OI III and the boys affected with Pyle disease and Osteolysis. Taurodontism, although not common, is an important occurrence that may influence the dental management of patients, therefore, a brief review and discussion of Taurodontism is provided in this chapter.

16.1 Definition

Taurodontism literally means 'bull-like teeth'. It is the enlargement of the body and pulp chamber of a multirooted tooth. There is consequent apical displacement of the pulpal floor and a lack of constriction at the cemetoenamel junction. Taurodontism is a manifestation of a developmental disturbance of the dentin of a tooth. It appears most frequently as an isolated anomaly, but its association with several syndromes and abnormalities has also been reported (O'Carroll et al., 1991; Jayashankara et al., 2013).

16.2 Aetiology of Taurodontism

Taurodont teeth are usually molars and can be defined as a change in tooth shape caused by the failure of Hertwig's epithelial sheath diaphragm to invaginate at the proper horizontal level (Ashwin and Arthi, 2006). Another suggested cause of taurodontism is that it is an expression of a Mendelian recessive trait that results in a mutation which causes an odontoblast deficiency during dentinogenesis of the root (Ashwin and Arthi, 2006; Jafarzadeh et al., 2008).

16.3 Diagnosis and Classification of Taurodontism

Although permanent molars are most commonly affected, taurodontism has also been observed in the deciduous dentition. Taurodontism can be unilateral or bilateral and any one or more dental quadrants can be affected (Jafarzadeh et al., 2008).

The incidence of taurodontism has been reported to be generally lower than 1% with a peak of 3% in the Inuit and American Indians (Jasper and Witkop, 1980). Taurodontism was relatively common amongst the European Neandertals. It is also found on occasion in people living today.

A taurodont appears as a clinically normal tooth since the roots of the affected tooth lies below the alveolar margin. Its distinguishing features can only be recognised from diagnostic radiographs (Bharti et al., 2009).

Taurodontism has been classified by Shaw in 1928 into 3 types (Fig 16.1) notably hypotaurodontism, mesotaurodontism and hypertaurodontism (Jasper and Witkop, 1980).

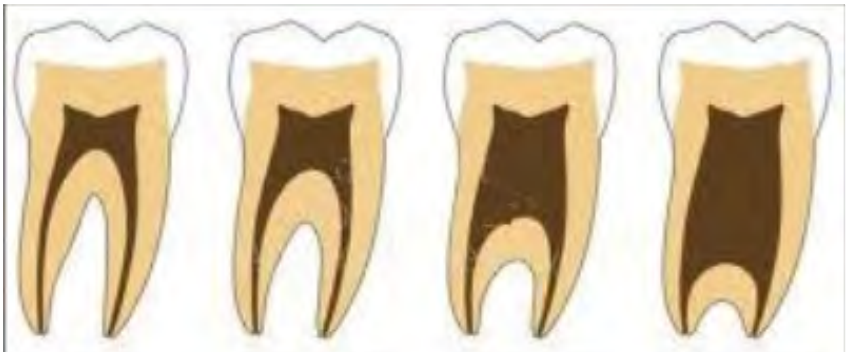

Fig 16.1 Diagrammatic representations of taurodontic teeth

Hypotaurodontism is the moderate enlargement of the pulp chamber at the expense of the roots. In mesotaurodontism, pulp is quite large and the roots are short, but still separate. Hypertaurodontism consists of cylindrical roots where the pulp chamber nearly reaches the apex and then divides into channels.

16.4 Radiographic features of Taurodontism

This anomaly either can appear as an isolated trait or it may be associated with other genetic syndromes such as hypophosphatasia, Klinefelter syndrome, Down syndrome, X-chromosome aneuploid syndrome, Mohr syndrome, tricho-dento-osseous syndrome and Maroteaux-Lamy syndrome (Bhat et al., 2004; Jayashankara et al., 2013).

The radiographic characteristics of taurodont tooth are an extension of the pulp chamber into the elongated body of the tooth, shortened roots and root canals despite a normal crown size (Fig 16.2). In older individuals and those with a course diet, taurodontism may be less obvious due to the deposition of secondary and tertiary dentine. Therefore, clinical caution must be exercised when interpreting an expression of taurodontism in molars with marked occlusal wear (Jafarzadeh et al., 2008).

In individuals with dentine dysplasia a differential diagnosis of taurodontism may be made at the early stage dentinogenesis since the pulp chambers may be large resembling those found in taurodontism. In children and young adults, the developing molars may have radiographic features similar to taurodonts, however, the recognition of open apical foramina and incomplete root formation would aid in the appropriate diagnosis (Mohan et al., 2013).

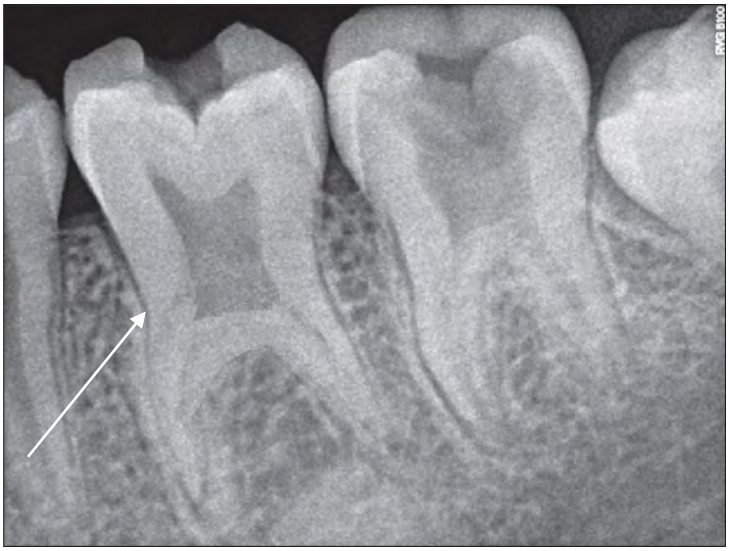

Fig 16.2 Radiographic image of a molar with features of taurodontism(www.contempclindent.org)

16.5 Clinical Challenges associated with Taurodontism

Features of taurodontism were identified in DBN 4, DBN 6 and 2 other individuals with an excessively rare thin bone disorders namely Pyle Disease and Osteolysis (*see Chapters 17 and 18).* Pulp therapy on taurodontic teeth is a dental challenge. There may be increased haemorrhage during access into the pulp chamber and complete removal of the necrotic pulp tissue might be difficult. Since the roots are short and the pulpal floor is placed apically, extreme care is warranted to prevent perforation of the pulp cavity and root canal. Lukinmaa (1987) described features of taurodontism in 3 of 49 persons with OI II and Malmgren and Norgren (2002) identified taurodontism in 20 of 48 persons with OI.

These observations suggest that diagnostic radiographs are important in the identification of taurodontic teeth in persons with OI III in order to deliver preventive dental care.

Further studies should be directed towards attempting to identify the incidence of taurodontism in the OI III affected individuals in SA and to investigate the possibility that general disturbance during development of molar teeth plays a role in the aetiology of taurodontism.

16.6 Conclusion

Although taurodontism is a dental rarity, an awareness of the aetiology, anatomic and radiographic features, possible dental complications and its association with other syndromes is crucial.

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Section V: Rare Genetic Thin Bone Disorders in SA

Preamble

During the course of the investigations, three other rare genetic thin bone disorders, which closely resembled OI III and were initially diagnosed as OI, were investigated and documented. These conditions were Pyle Disease (Chapter 17), Osteolysis (Torg-Winchester Syndrome)(Chapter 18) and Osteoporosis-pseudoglioma Syndrome (Chapter 20).

CHAPTER 17: Pyle Disease

17.1 Introduction

17.2 Literature Review

17.2.1 General

17.2.2 Dental and Craniofacial

17.3 Case Report

17.4 Comment

17.1 Introduction

Pyle disease [OMIM 265900] is a rare AR skeletal dysplasia in which gross radiographic changes contrast with mild variable clinical features including genu valgus, mild limitation of extension of the elbows and palpable widening of the proximal region of the clavicles.

The radiographic manifestations of this condition are significant under-modelling and expansion of the metaphyseal regions of the tubular bones with thin cortices. Mild sclerosis of the cranial bones is a variable feature.

In South Africa, three affected persons have been identified and documented. Two were members of a large consanguineous Afrikaner family and the third individual was also of Afrikaner decent (Raad and Beighton, 1978; Heselson et al., 1979). In addition to these persons, a boy, aged 10 years, of Cape Mixed Ancestry (CMA) heritage attended the RXH Genetics clinic in 2013 with a history of fractures following minor trauma. An initial provisional diagnosis of OI was modified to Pyle disease following radiographic investigations. To the best of the author's knowledge, no reports exist of Pyle disease in a person of CMA heritage. This boy forms the subject of this chapter.

17.2 Literature Review

17.2.1 General Literature

This disorder was initially defined and designated by Edwin Pyle, an orthopaedic surgeon in the USA. He described a 5 year old boy who had knock knees and under-modelling of the metaphyses of his tubular bones (Pyle, 1931; Komins, 1954). The disorder was subsequently named familial metaphyseal dysplasia by Bakwin and Krida (1937). To date there are approximately no more than 20 reported cases in the literature.

In the past, there has been semantic confusion between Pyle disease and Craniometaphysial dysplasia (CMD). CMD is a more common condition and has both an AD and AR mode of inheritance. The term 'Pyle disease' has been used erroneously to describe CMD and this has resulted in several mis-diagnoses. This issue was clarified when Gorlin et al. (1970) emphasized the differences between these conditions and stated that CMD is similar to Pyle Disease. In Pyle Disease there is an absence of cranial nerve compression with milder skull involvement but more obvious long bone abnormalities (Faden et al., 2007). Subsequently, the 2010 revision of the Nosology and classification of genetic skeletal

disorders listed Pyle disease as a separate entity from CMD (Warman et al., 2010). The syndromic identity of Pyle disease has been perpetuated in the 2015 Nosology (Bonafe et al., 2015).

In a review of Pyle Disease it was stated that the manifestations are reasonably consistent (Beighton, 1987). Nevertheless, a report of a 4 year old female in Turkey described a child from consanguineous parents who presented with unusual manifestations of Pyle disease, specifically severe spinal scoliosis, distal humeral and proximal ulnar expansion and femoral shortening (Percin et al., 2003). These authors suggested that Pyle disease is not a benign condition as was previously accepted, but one that can present with severe clinical abnormalities. The molecular basis of Pyle disease has not as yet been elucidated and at this stage it is uncertain whether this case represents the severe end of a phenotypic spectrum or a separate syndromic entity.

17.2.2 Dental and Craniofacial Literature

A search of the medical literature revealed a paucity of information pertaining to the dental and craniofacial features of Pyle disease. To the best of the author's knowledge there is only one report published in an oral health journal (Narayananan et al., 2006). These authors documented an affected girl, aged 17 years who presented to a dental clinic with pain in the lower right quadrant of her mouth in the region of tooth 46. An intraoral examination revealed missing permanent teeth, retained primary teeth, and dental crowding. A panoramic radiographic showed discontinuity of the lamina dura, generalised rarefaction of the jaws and flared necks of the mandibular condyles. A subsequent skeletal survey revealed radiographic changes which were suggestive of Pyle disease.

The dental and craniofacial observations in individuals with Pyle disease have been briefly mentioned in a few articles which primarily focused on other aspects of this disorder. These are listed in Table XVII.1.

Table XVII.1 References to articles in which Dental and Craniofacial Features in Pyle disease are documented

Reference	Dental and Craniofacial Features
Bakwin and Krida, 1937	Carious and misplaced teeth
Gorlin et al., 1970	Dental malocclusion. Rounded mandible with an obtuse angle. Mild mandibular prognathism
Raad and Beighton, 1978	Total dental clearance in childhood due to malpositioned teeth
Heselson et al., 1979	Carious teeth. Dental malocclusion. Mandibular prognathism
Beighton, 1987	Carious teeth and mandibular prognathism
Vohra, 1987	Supernumary teeth
Percin et al., 2003	Dysmorphic face, thin lips, sharp chin, 'bruised' teeth
Narayananan et al., 2006	Missing permanent teeth. Retained primary teeth, and dental crowding. Discontinuity of the lamina dura
Gupta et al., 2008	Mild facial dysmorphism, maligned teeth and a small chin

17.3 Case Report

A boy, of CMA heritage, aged 10 years, presented to the UCT genetics clinic at RXH. He had suffered multiple fractures of his wrist and fingers following minor trauma. Radiographical studies of the patient were diagnostic of Pyle disease. On a recall visit he was referred to the dental clinic for an evaluation of his oral health status.

The affected individual had an unaffected older female sibling aged 16 years. His parents indicated no history of consanguinity, but they stated that their third degree relatives had originated from the same remote geographical region of the Western Cape. There were no links in terms of the family's surnames with the previously described South African patients (Heselson et al., 1979).

The affected boy was of normal intelligence and his developmental milestones showed no deviations from the norm. Clinically, his height, weight and head circumference were within normal limits. He gave a history of frequent joint pain. His sclerae had a blue tinge but it is unclear if this is a clinical feature of Pyle disease or a manifestation of his demographic background.

His facial features were mildly dysmorphic with prominent ears and a flat frontal upper third of the face (Fig 17.1).

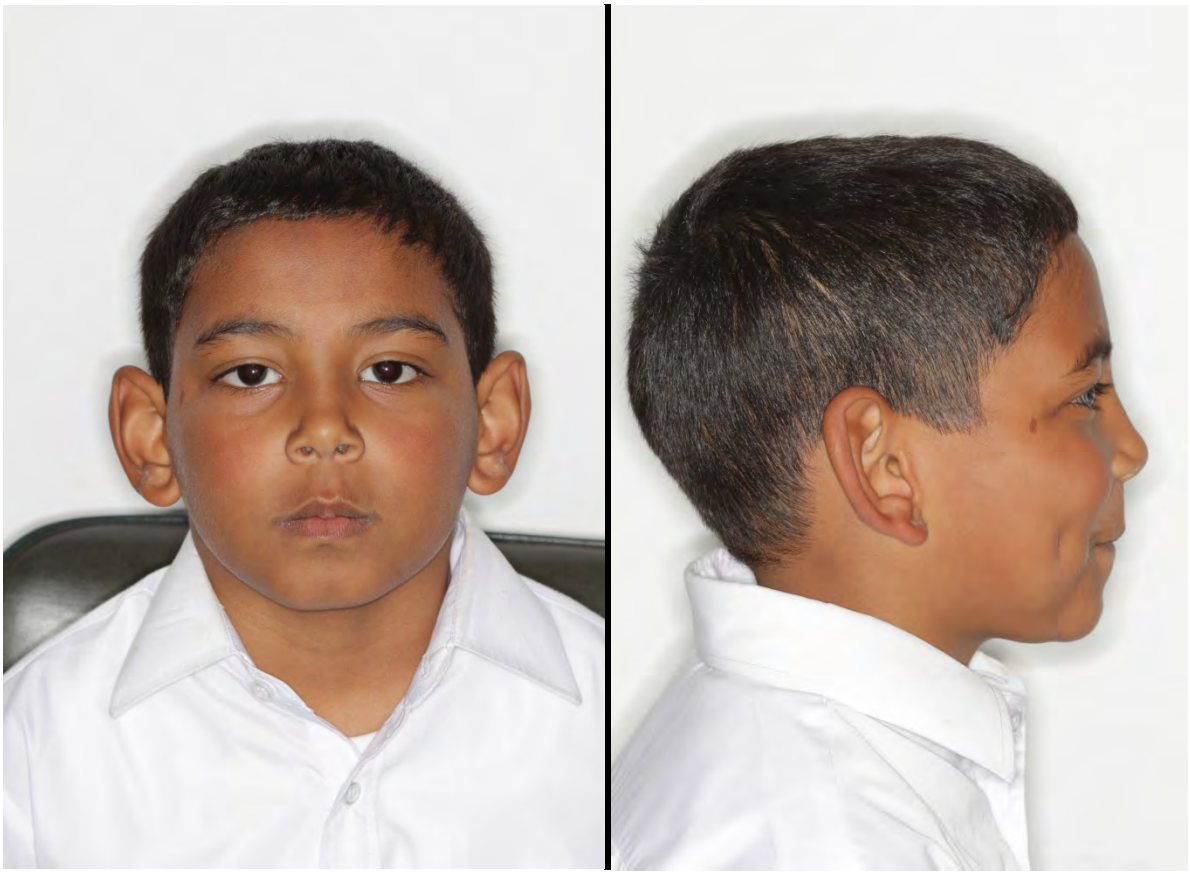


Fig 17.1 A frontal and profile view of the affected boy. Prominent ears and a flat frontal superior third of his face are evident

Routine biochemical and biological investigations yielded normal results.

A skeletal survey revealed the following features:

Skull (Fig 17.2)

- A flat forehead
- A thin calvarium
- Wormian bones

Long Bones (Fig 17.3, Fig 17.4)

- Gross metaphyseal expansion of upper third of both femora and tibiae (Erlenmeyer flask deformity)
- Thin cortices of the long bones

Mild metaphyseal expansion was evident on radiographs of the mother and sister of the affected boy. These changes were consistent with the mother and sister being potential heterozygotes.

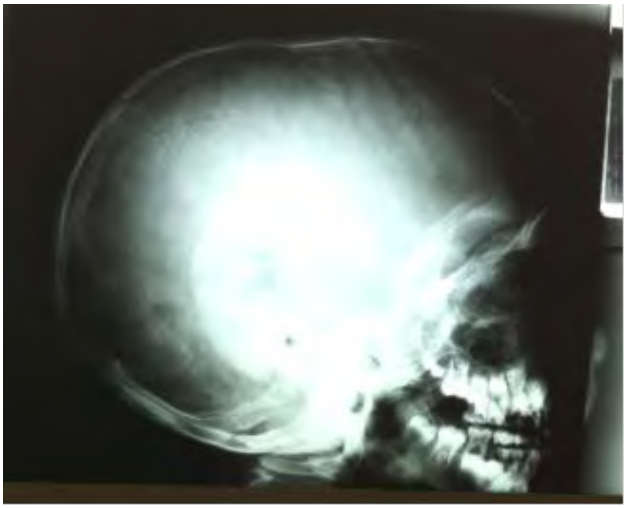


Fig 17.2 A lateral skull radiograph reveals multiple wormian bones

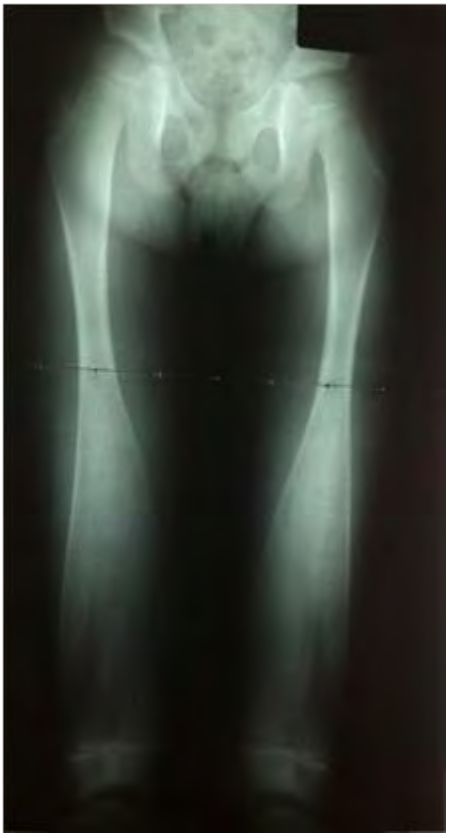


Fig 17.3 Erlenmeyer flask deformity of the femora

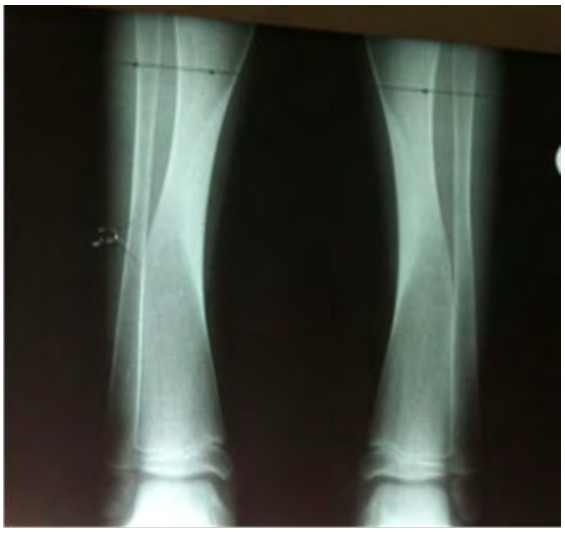


Fig 17.4 Erlenmeyer flask deformity of the tibiae

An intraoral examination revealed the presence of his first permanent molars and his maxillary and mandibular permanent incisors. No other permanent teeth were visible. His oral hygiene was good and carious lesions were evident. There was crowding of his upper anterior dentition and teeth 12 and 22 were palataly displaced (Fig 17.5). He also had a high arched palate (Fig 17.6).

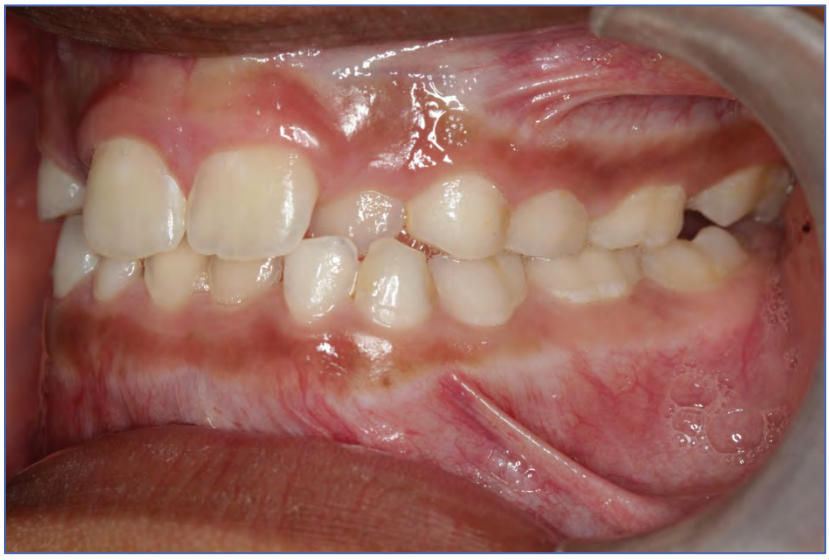


Fig 17.5 An intraoral image of the teeth in occlusion. There is crowding of his upper anterior teeth and there are several retained primary teeth. He has a Class III dental occlusion *(Refer to Appendix 14)*

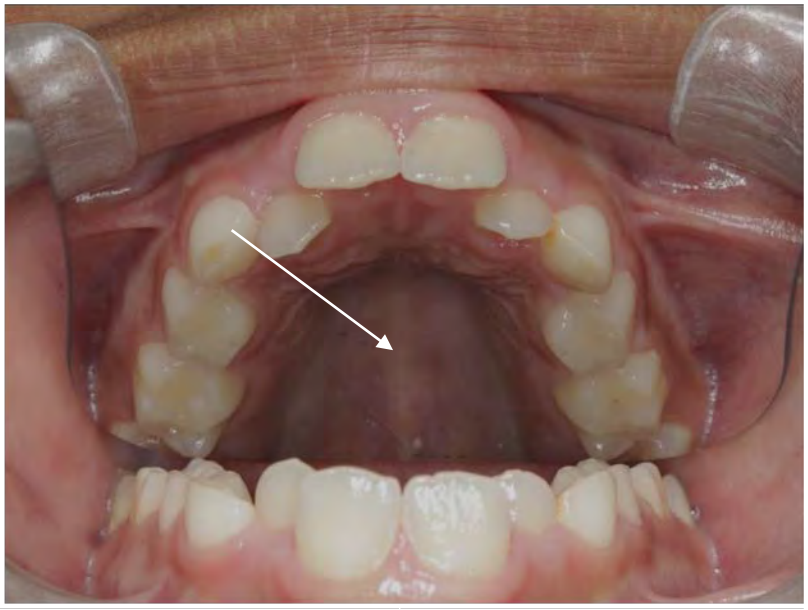


Fig 17.6 An intraoral image with a high arched palate (arrow)

Due to the dental crowding, panoramic (Fig 17.7) and cephalometric radiographs (Fig 17.8) were obtained in order to assess the integrity of the dentition and to facilitate the necessary referral to the department of orthodontics.

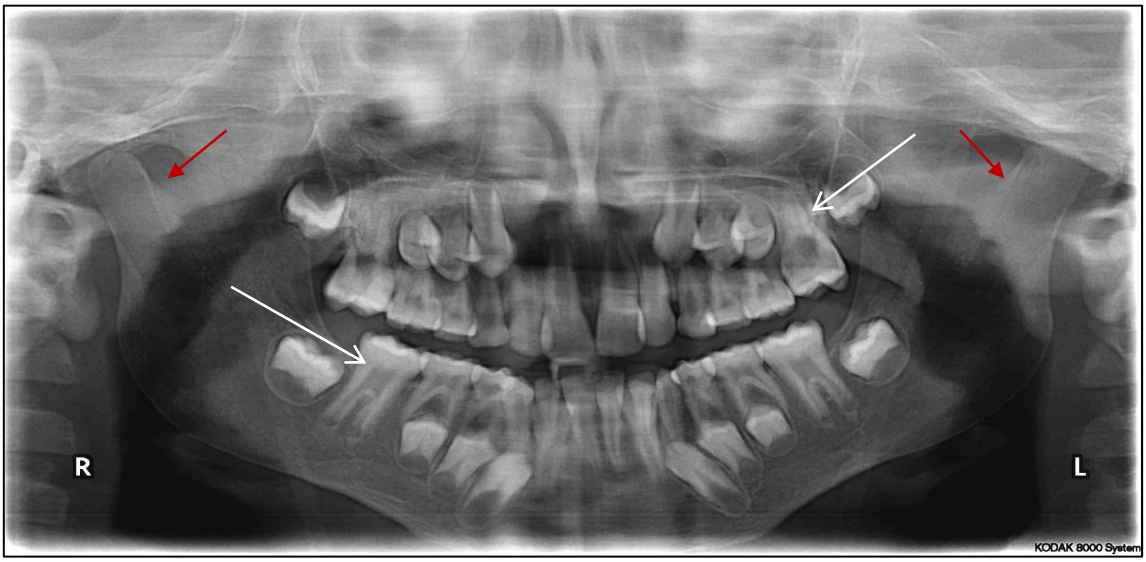


Fig 17.7 Panoramic radiograph of the affected boy. There is dental crowding and delayed exfoliation of several primary teeth. Mesotaurodontism of the upper and lower first permanent molars is evident (arrows). The mandibula condyles lack a constriction at the neck (red arrows).

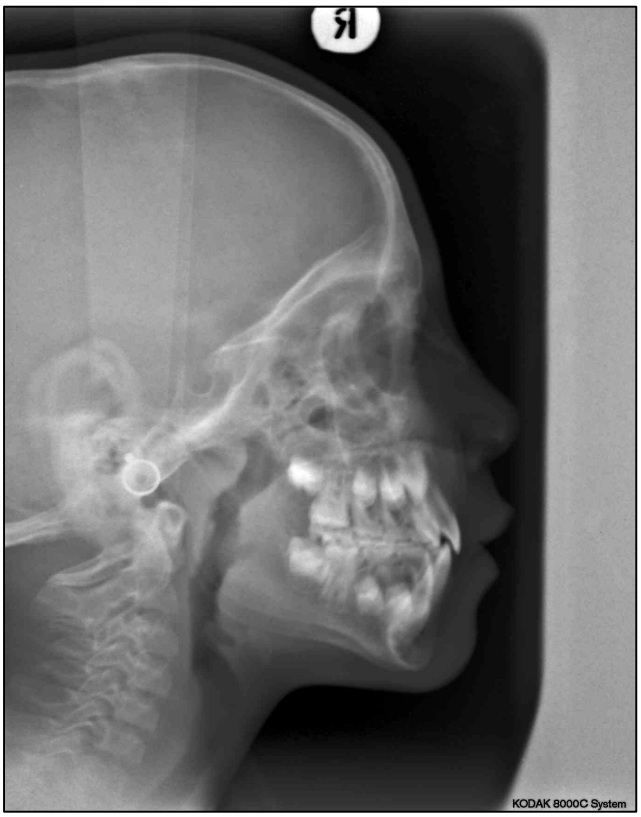
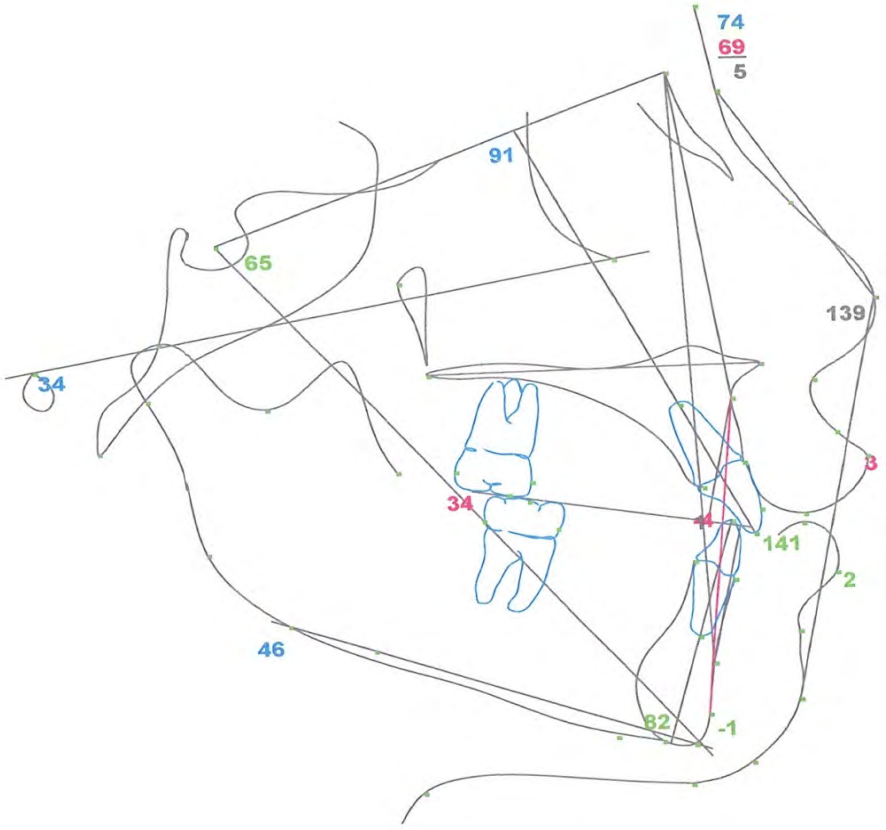


Fig 17.8 Cephalometric radiograph



Cephalometric tracing of the affected boy

	Value	Norm	Std Dev	Dev Nor	
Interincisal Angle (U1-L1) (°)	141.1	130.0	6.0	1.8	*
IMPA (L1-MP) (°)	82.3	95.0	7.0	-1.8	*
ANB (°)	5.6	1.6	1.5	2.6	**
Lower Lip to E-Plane (mm)	1.8	-2.0	2.0	1.9	*
Upper Lip to E-Plane (mm)	2.9	-3.2	2.0	3.0	***
MP - SN (°)	45.9	33.0	6.0	2.1	**
SNA (°)	74.1	82.0	3.5	-2.3	**
SNB (°)	68.6	80.9	3.4	-3.6	***
U1 - SN (°)	90.8	102.4	5.5	-2.1	**
L1 - NB (mm)	4.0	4.0	1.8	0.0	
U1 - NA (mm)	-0.5	4.3	2.7	-1.8	*
U1 (labial surface) to NA (mm)	1.0	4.3	2.7	-1.2	*
Pog - NB (mm)	-1.2	1.5	1.7	-1.6	*
Soft Tissue Convexity (°)	139.2	135.9	4.0	0.8	
SN - GoGn (°)	44.8	32.0	5.0	2.6	**
Facial Angle (FH-NPo) (°)	79.7	87.2	3.0	-2.5	**
Wits Appraisal (mm)	-4.5	-1.0	1.0	-3.5	***
FMA (R4 Version) (°)	34.3	25.3	4.5	2.0	**
L1 Protrusion (L1-APo) (mm)	1.2	2.7	1.7	-0.9	
S - A (mm)	74.9	89.8	-17%		
Mandibular Length (Jarabak G - Me	54.4	76.2	5.0	-4.4	****
Maxillary length (ANS-PNS) (mm)	45.7	51.6	4.3	-1.4	*
Y-Axis -- Downs (SGn-FH) (°)	65.2	60.7	3.4	1.3	*
Nasolabial Angle (Col-Sn-UL) (°)	106.4	102.0	8.0	0.6	
Overjet (mm)	3.5	2.5	2.5	0.4	
Overbite (mm)	1.6	2.5	2.0	-0.5	

SUMMARY ANALYSIS

Fig 17.9 Cephalometric tracing of the affected boy

The panoramic and cephalometric radiographs revealed retained primary mandibular incisors. There was a delay in the eruption and root apexification of the permanent teeth by approximately 3 years. The first permanent molars, especially the 36 and 46, showed features of mesotaurodontism. The lamina dura was absent and there was generalised rarefaction of the jaw with thinning of the cortical bone. The neck of the mandibular condyle lacked its normal constriction (Fig 17.7).

A cephalometric analysis indicated a steep cranial base, a skeletal Class III and a dental Class III molar relationship. The mandible and maxilla were retrognathic hence his flat facial profile. In the orthodontic context, the growth of an individual's craniofacial bones is predicted using images of the cervical vertebrae. This feature could not be utilized due to the abnormal shape and density of his cervical vertebrae.

Following an orthodontic evaluation, it became apparent that extraction of some teeth were necessary. A CBCT was subsequently requested by the orthodontist and the maxillofacial surgeon for a comprehensive evaluation of his cervical spine and the formulation of a treatment plan.

Comparing the CBCT images of the boy to three other children of the same age, it was evident that his craniofacial bones showed osteoporotic changes especially in the jaws and cervical vertebrae (Fig 17.10 and Fig 17.11). There was also a reduction in the number of trabeculae together with a decrease in the density of bone. The thickness of the cortical bone of the zygomatic arch, maxilla, mandible and vertebral bodies of the boy was markedly thinner compared to the three normal children. The palatal vault was higher (Fig 17.10) than in the other normal children.

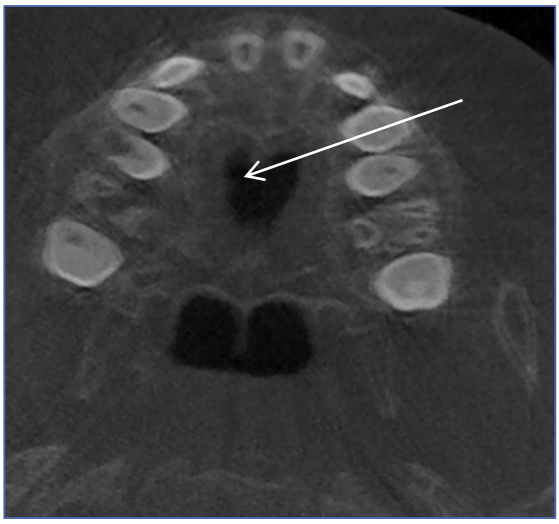


Fig 17.10 High arched palate (arrow)

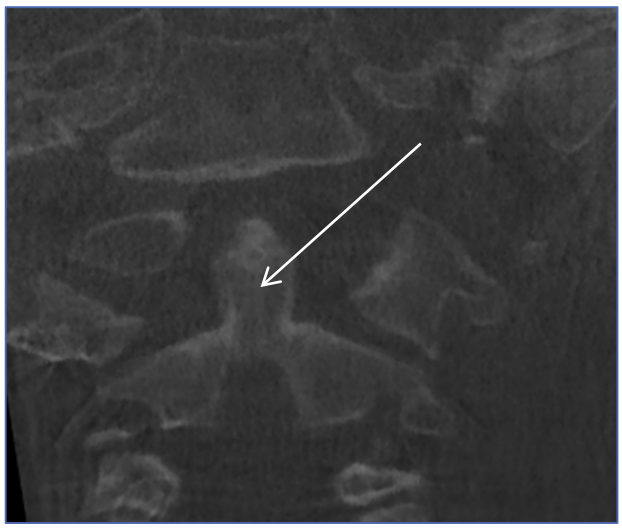


Fig 17.11 Abnormal shape and decreased density of C2 (arrow)

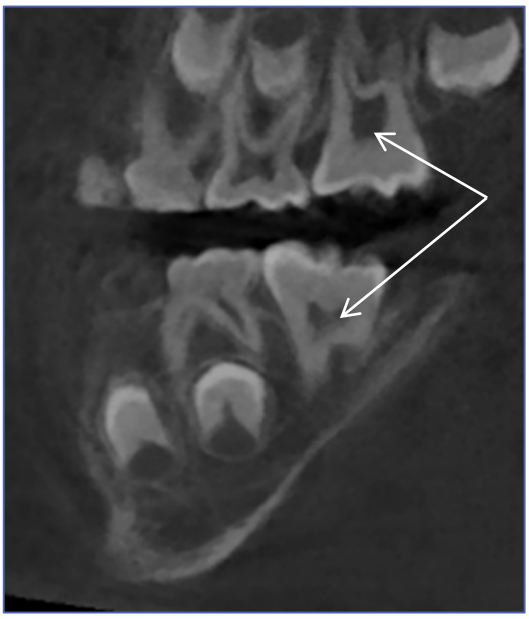


Fig 17.12 Mesotaurodontism of his first permanent molars (arrows)

Since the lower primary incisor, tooth 51, had recently exfoliated, the author compared the ultrastructure of the enamel (Fig 17.13) and dentine to that of a tooth 51 from a normal child using a scanning electron microscope (SEM). The SEM images of the root surface of both children were inconclusive.

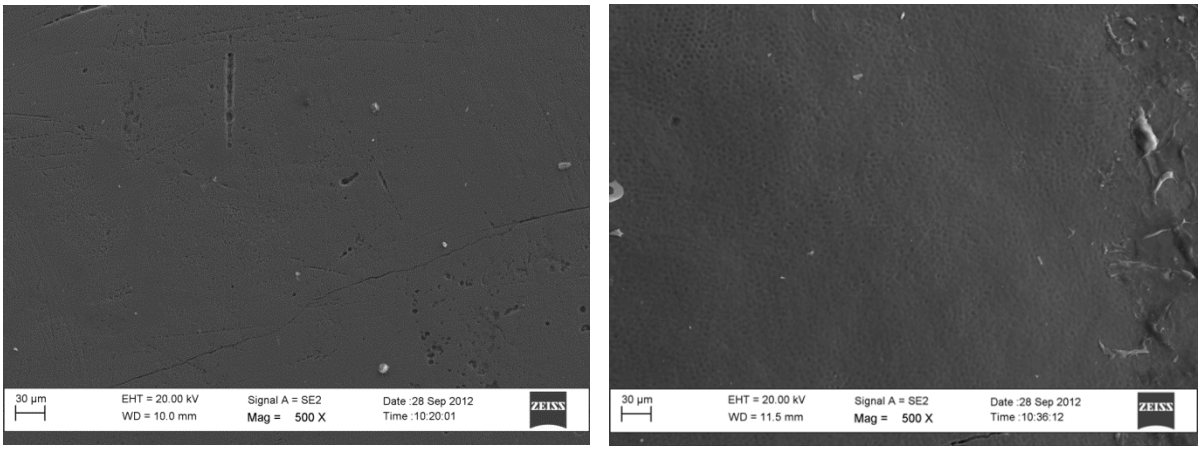


Fig 17.13 SEM digital image of the enamel surface of a tooth from a normal child (left) and evidence of surface enamel porosity (right) in the tooth of the affected boy

The author documented this observation but whether this is a syndromic dental feature, is questionable. The boy did not have any carious lesions, hence, the clinical significance of the porosity of the enamel is unclear.

The percentage of the various ionic components of the surface of the crown and the root were also measured and compared. These values are tabulated in Table XVII.2.

Table XVII.2 Ionic components of the tooth surface of an unaffected child compared with the tooth surface of the affected boy

	Normal Child:	Affected Boy:
Element	**Crown Atomic percentage**	**Crown Atomic percentage**
O	65.95	68.74
Na	0.72	0.78
Mg	0.15	-
P	13	11.95
Cl	0.38	0.32
Ca	19.8	18.21
Total	**100**	**100**
Element	**Root Atomic percentage**	**Root Atomic percentage**
N	21.66	19.49
O	68.89	73.41
Na	0.42	2.64
Al	-	0.16
Si	-	0.76
Mg	0.3	-
P	3.52	1.01
S	0.52	1.16
CL	0.25	0.74
K	0.07	0.09
Ca	4.37	0.52
Total	**100**	**100**

There were minor differences in the atomic percentage of the elements between the enamel of the crown and roots of a normal child and the affected boy. In particular, the element magnesium was absent from the boy. The author considered these discrepancies a noteworthy feature although their significance remains uncertain.

17.4 Comment

There is a paucity of literature regarding the dental and craniofacial manifestations and management of Pyle disease. The affected boy had presented with retained deciduous teeth as well as delayed development and eruption of his permanent teeth. The available literature suggests that these findings are not unique to the boy (Narayananan et al., 2006).

Concerns arise regarding possible bone fragility, in the context of trauma to the jaws during extractions and surgical intervention. Favourable post osteotomy healing has been reported in Pyle disease (Lindberg and Watts, 1997). Nevertheless, it is recommended that minimum force be used during dental procedures.

The lack of cortical bone around the roots of the teeth, suggested by the absence of the lamina dura, requires vigilant oral hygiene practice since the boy may be at risk for the accelerated development of periodontal disease.

It is also necessary for him to avoid a cariogenic diet in order to prevent carious lesions, especially on his molar teeth. Root canal treatments on mesotaurodontic teeth have proved a challenge *(See Chapter 16 for the clinical challenges associated with taurodontism).*

Although the affected boy requires orthodontic treatment for maligned teeth, the progress and outcome are uncertain. The absence of the lamina dura is indicative of compromise in the integrity of the periodontal ligament. A healthy periodontal ligament as well as optimal activity of osteoclasts and osteoblasts is necessary for successful orthodontic therapy. In this context it is relevant that a histological examination of a section of bone from the proximal femoral metaphyseal area revealed paucity in the number of osteoclasts (Percin et al., 2003).

If the need for general anaesthesia arises, it is important for the anaesthetist to be aware of the abnormality in shape and density of the odontoid process and hence ensure gentle manipulation of the patient's airways.

Documentation and further study of a larger number of cases may confirm that Pyle disease causes rarefaction of the jaws and would help establish a more consistent description of the dental and craniofacial manifestations.

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CHAPTER 18: Osteolysis (Torg-Winchester Syndrome)

18.1 Introduction

18.2 Literature Review

18.2.1 General Literature

18.2.2 Dental and Craniofacial Literature

18.3 Case Report

18.4 Comment

18.1 Introduction

The Osteolyses are a group of rare genetic disorders which are characterized by progressive resorption of bone. This process, which is maximal in the articular regions of the limbs, leads to significant physical handicap. Pathological fractures represent an additional complication. The skeleton in the Osteolyses is radiolucent and the manifestations resemble those of Osteogenesis Imperfecta.

In South Africa, over the last 40 years, only 4 affected persons have been reported in the literature, three in the first report (Beighton et al., 2007) and one in the second report (Bertie et al., 2013). The latter person, a boy of Zulu stock with the Torg-Winchester Syndrome, forms the subject of this chapter.

18.2 Literature Review

18.2.1 General Literature

The nomenclature and classification of the Osteolyses was initially based upon the anatomical distribution of the affected regions and terms such as 'carpo-tarsal osteolysis' and 'multicentric osteolysis' came into use. With the delineation of specific osteolysis syndromes, eponyms were also employed. These included 'Winchester' (Winchester et al., 1969) and 'Torg' (Torg et al., 1969).

Winchester et al. (1969) reported two siblings from Puerto Rico who presented with a connective tissue disorder characterized by a short stature, joint contractures, corneal opacities, osteoporosis, carpal-tarsal osteolysis, stiff joints, skin lesions and coarse facies. In the same year, Torg et al. (1969), described 3 siblings mild to moderate osteoporosis, osteolytic changes of the bones of the hands and feet, skin manifestations that resembled Winchester syndrome but with subcutaneous nodules and less severe skeletal involvement.

In the period, 2000 to 2002, an entity termed 'Nodulosis-Arthropathy-Osteolysis' (NAO) resembled the Torg syndrome, but comprised severe osteolysis and osteopenia, painful subcutaneous nodules was documented in the endogenous Arabian population (Al-Aqeel et al., 2000; Al-Mayouf et al., 2000; Al-Otaibi et al., 2002).

Zankl et al. (2005) suggested that Winchester syndrome was caused by a homozygous mutation in the active site of matrix metalloproteinase2 gene (*MMP2*) and Rouzier et al. (2006) recorded a homozygous *MMP2* mutation in a patient diagnosed with Winchester syndrome. Thereafter, Zankl et al. (2007) identified two separate mutations in the *MMP2* gene which resulted in complete loss of

matrix metalloproteinase activity. These mutations were in the *MMP2* gene at chromosome 16q13 in persons with Torg syndrome, Winchester syndrome and NAO syndrome. On this basis, they suggested that these disparate disorders represented a continuous clinical spectrum which resulted from intragenic heterogeneity in the *MMP2* gene.

As cases accumulated, it became evident that there was considerable clinical overlap between the putative entities and the combined eponym 'Torg-Winchester syndrome' [OMIM 259600] came into use with NAO syndrome regarded as an allelic variant. In the Torg-Winchester syndrome the wrists and ankles are often affected and there is eventual dissolution of the carpals and tarsals (Vanatka et al., 2011).

Other Osteolyses which were listed in the 2010 revision of the International Nosology of Genetic Skeletal Disorders (Warman et al., 2011), included Familial expansile osteolysis, Progeria (Hutchinson-Gilford type), Hadju-Cheney syndrome and Multicentric carpal-tarsal osteolysis with and without nephropathy.

The current nosology revision (Bonafe et al., 2015) places the Osteolyses in group 28 and confirms that mutations in *MMP2* primarily contribute to the phenotypic presentation of the Torg-Winchester syndrome.

18.2.2 Dental and Craniofacial Literature

A literature search for 'Torg-Winchester syndrome' and 'heritable osteolyses' revealed a paucity of information pertaining to the orofacial manifestations of these conditions. Course facial features and gum hypertrophy were mentioned by a few authors (Winchester et al., 1969; Zankl et al,. 2007). The only article found in oral and maxillofacial publications detailed the clinical features of the Winchester syndrome (Prapanoch et al., 1992). The authors described a 40 year old woman with course facial features, underdeveloped maxillary sinuses, a prognathic mandible, several impacted teeth, mild gingivitis and a submucous cleft palate. Zankl et al. (2005) described the clinical features of an Italian child whose 'teeth were discoloured and said to chip easily'. Beighton et al. (2007) documented 3 black South African patients, one of whom was described as having 'prognathism'.

18.3 Case Report

During visits to the metabolic bone clinic at Grey's Hospital, the author was introduced to a boy with a confirmed diagnosis of Torg-Winchester syndrome (Bertie et al., 2013). The dental and craniofacial manifestations of this boy form the main subject of this chapter.

A boy, aged 11 years, belonging to the Zulu community of KwaZulu Natal was examined by the author. His parents and siblings were unaffected and no relative had a similar disorder.

He presented to the orthopaedic clinic with pain and deformity of both hands (Fig 18.1) and both legs (Fig 18.2). His intellect and general development were normal. He developed deformities of both his hands and knees at the age of 6 years. He was chair bound and experienced discomfort on physical examination. The results of routine and specific biochemical and haematological investigations were normal.

Fig 18.1 Deformities of both wrists and hands

Fig 18.2 The left knee is swollen and tender

Available radiographs of his hands disclosed an absence of carpal bones of the right wrist joint and osteolysis of the distal region right ulna (Fig 18.3). Images of his feet revealed deformities of the tarsus and widened lucent metatarsals (Fig 18.4).

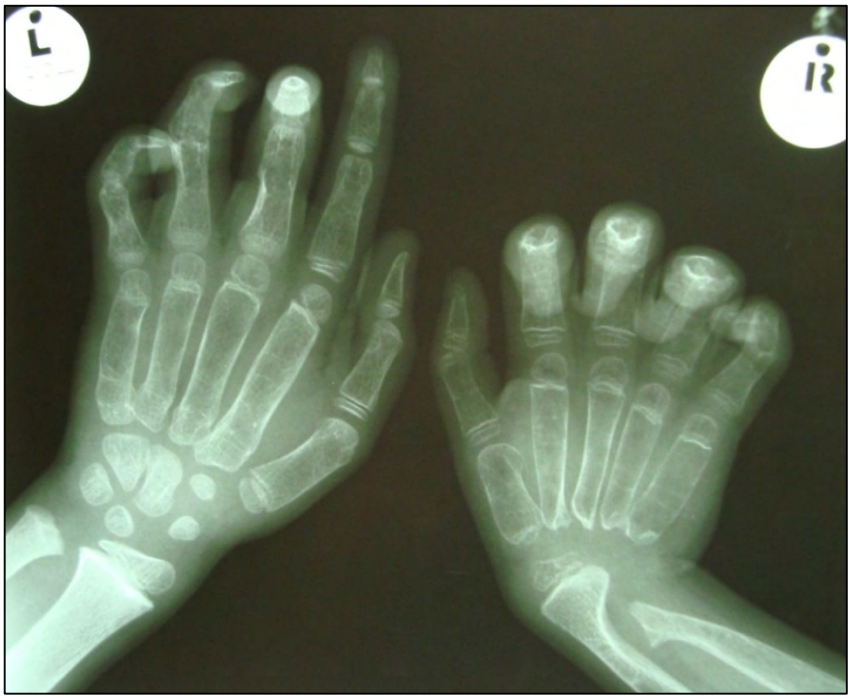

Fig 18.3 Absence of the carpal bones in the right wrist with widened lucent metacarpals and osteolysis of distal ulna (Courtesy of Dr J Bertie)

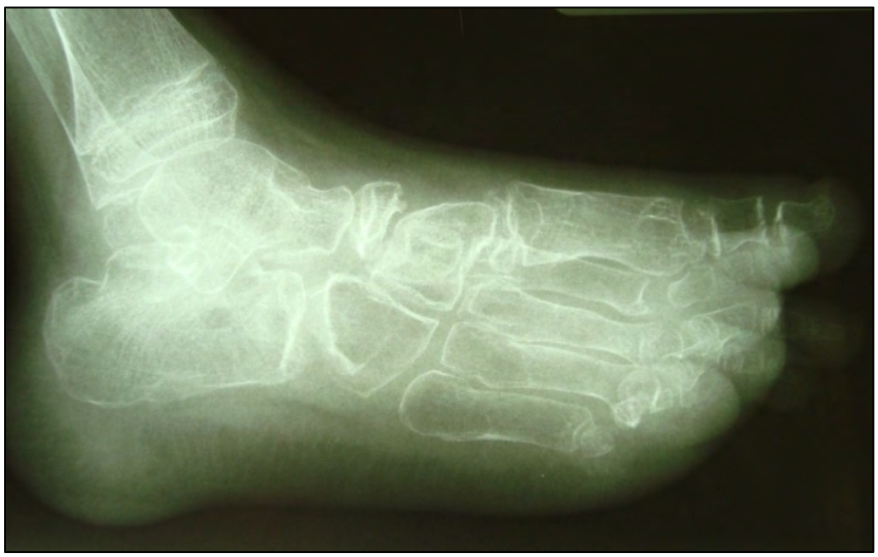

Fig 18.4 Diffuse osteopaenia of the foot with deformity of the tarsus and widened metatarsals

(Courtesy of Dr J Bertie)

A clinical assessment of his craniofacial features revealed frontal bossing, a flattened nasal bridge, ocular hypertelorism and normal sclerae.

An intraoral examination was completed with difficulty due to the tense musculature and pain in the region of the temporomandibular joint (TMJ) during opening of his mouth. His maximum oral opening was 20mm. Moderate gingivitis was evident but there were no obvious carious or periodontal lesions. His plaque index was 3 and localized staining was present on teeth 13, 23, 32 and 42 (Fig 18.5, Fig 18.6). These minor abnormalities could be attributed to the boy's inability to hold a toothbrush due to the resorptive deformities of his hands and wrists. Feeding and occasional tooth brushing were performed by his uncle who was his primary care-giver.

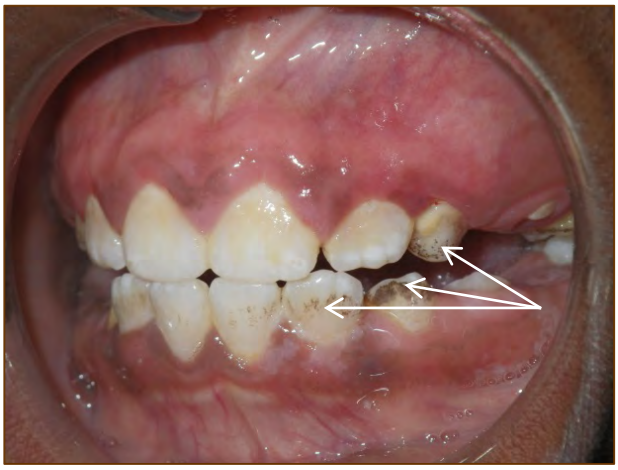

Fig 18.5 Stained teeth (arrows)

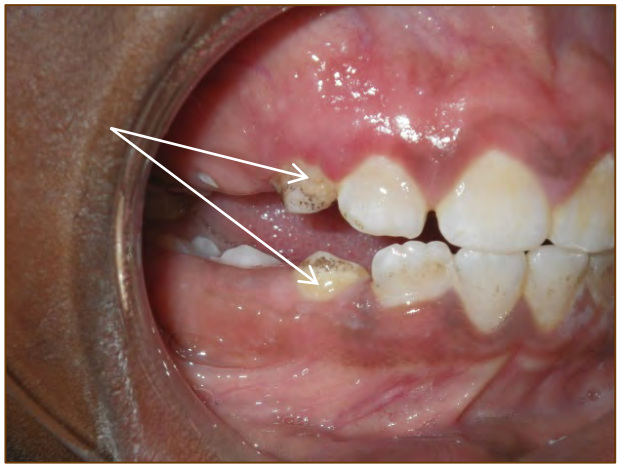

Fig 18.6 Visible plaque on the cervical region of his teeth (arrows)

The affected boy experienced difficulty in chewing due to tenderness in the TMJ area and a soft diet was necessary. This problem was most likely related to his partially erupted permanent molars and premolars. Mild gingival hypertrophy was noted in the posterior regions of both maxillary and mandibular jaws.

A cone beam computed tomographic (CBCT) investigation was requested by a local orthodontist in order to evaluate his oral and dental and status. In particular, the delayed eruption of his permanent teeth and the integrity of his TMJ were matters of concern.

CBCT Report:

The radiographer encountered difficulty in positioning of the patient since movement of his head and jaw resulted in discomfort. Due to an incomplete field of view, vertebral body evaluation was impossible. Mild generalized osteoporosis was evident and asymmetry of the craniofacial structures were apparent (Fig 18.7). The nasopharyngeal airway was patent. Other airway spaces such as ethmoid air cells and nasal cavity appeared patent, but the right maxillary sinus was partially opacified (Fig 18.7).

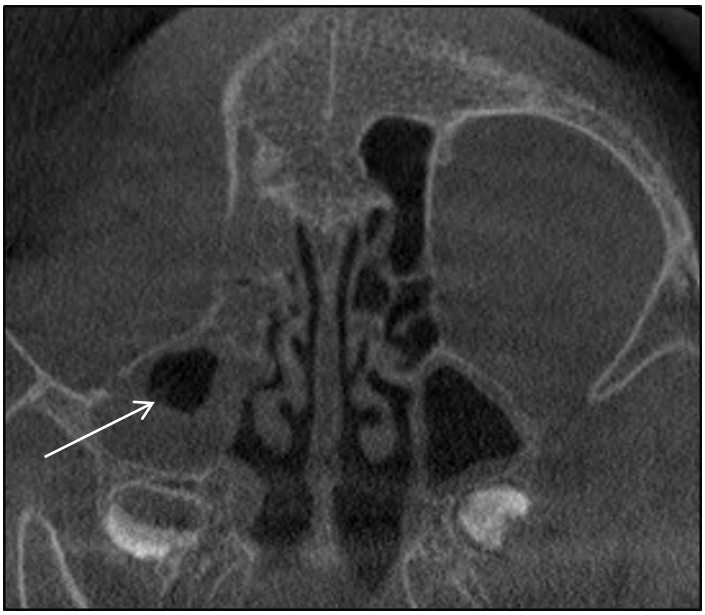

Fig 18.7 Coronal section of the craniofacial tissues. Generalized osteoporosis, asymmetry and partial opacification of the maxillary sinus (arrow) is evident

The right mandibular condyle head was hypoplastic and the surface cortical bone on the left condylar head was thin and uneven (Fig 18.8).

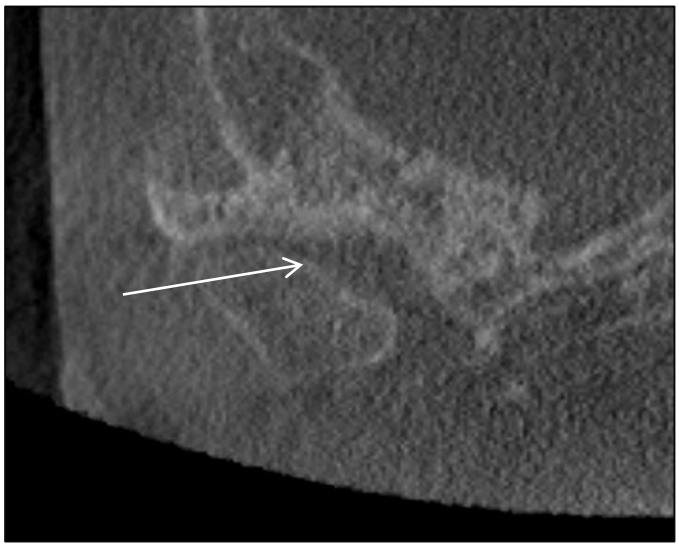

Fig 18.8 Coronal view of left mandibular condyle showing thin cortical bone and an uneven surface morphology (arrow)

Dental findings: (Fig 18.9, Fig 18.10)

Delayed development of the mandibular first molars with only two-thirds of root completion was evident. Normal permanent teeth eruption tables suggest that the first mandibular molars should have completely erupted by age 7 years with root completion by age 9.5 years (Phillips and van Wyk Kotze, 2009; AlQahtani et al., 2010). There was also a delay in the root development of the first and second premolars.

The coronal pulp chambers were large, suggestive of hypotaurodontism, and multiple intrapulpal calcifications were visible.

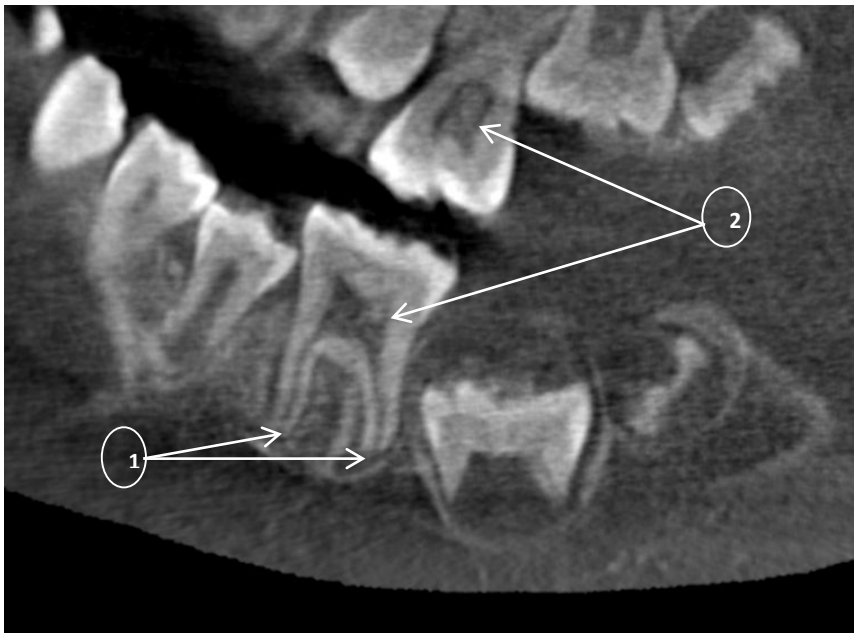

Fig 18.9 First mandibular molar (L) with 2/3rd of root development completed (1). Large coronal pulp chambers are suggestive of hypotaurodontism and contain several intrapulpal calcifications (2).

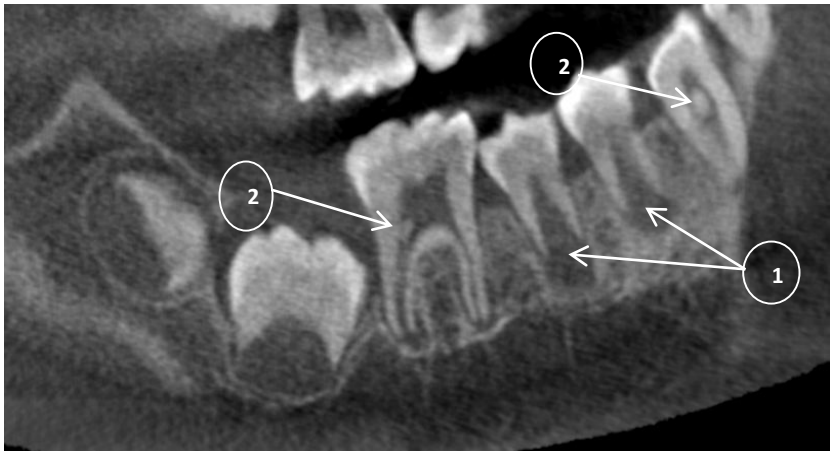

Fig 18.10 First mandibular molar (R) with 2/3rd of root development completed. Delayed development of the roots of the first and second premolars is depicted (1). Multiple intrapulpal calcifications are evident (2).

18.4 Comment

Skeletal lysis and consequent limb deformity is progressive in the osteolyses. Unfortunately, due to the loss of the carpal bones of the affected boy's right hand and osteolysis of the carpal bones of his left hand, any attempt at promoting independence proved to be difficult. The patient is currently totally dependent on personal and social support from his uncle. The importance of dental hygiene was emphasized since routine dental care, such as, a scaling and polishing was very uncomfortable for the boy and challenging for the dental practioner.

Bisphosphonate treatment has been undertaken in view of the bone's propensity to fracture following insignificant trauma. Nevertheless, the efficacy of bisphosphonate therapy in the osteolyses is uncertain as is the effect on the dentition (Bachrach and Ward, 2009).

The dental and craniofacial observations, presented in detail in this chapter, are likely to be syndromic components of the disorder. Whether or not they are features of other forms of the Osteolyses can only be a matter of conjecture due to the rarity of this disorder.

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CHAPTER 19: Osteoporosis-pseudoglioma Syndrome

19.1 Introduction

19.2 Literature Review

19.3 Case Report

19.3.1 Family Background

19.3.2 Affected Person 1

19.3.3 Affected Person 2

19.4 Discussion

19.1 Introduction

The Osteoporosis-pseudoglioma syndrome (OPPG) [OMIM 259770] is a rare autosomal recessive disorder in which bone fragility and frequent fractures are associated with serious ocular changes. The skeletal manifestations closely resemble those of osteogenesis imperfecta while hyperplasia of the vitreous and the eye and corneal opacities can mimic the appearance of intraocular glioma. The manifestations are progressive and affected individuals may have considerable physical handicap and visual disturbance.

To the best of the author's knowledge, there has been no mention in the literature of dental changes or malocclusion consequent to craniofacial malformations in OPPG. In view of the similarity of OPPG to osteogenesis imperfecta, and the occurrence of dental abnormalities in the latter, clinical appraisal, comprehensive dental imaging and subsequent prosthodontic and maxillofacial management have been undertaken in an affected South African male and his uncle of Indian stock. The findings are documented, depicted and discussed in this chapter.

19.2 Literature Review

The association of the clinical features of ocular involvement and bone fragility was initially described by Pellathy (1931). Early reports of OPPG, 1967 to 1986, concentrated predominantly on the clinical presentation of the syndrome (Saraux et al., 1967; Bianchine et al., 1972; Neuhauser et al., 1986; Superti-Furga et al., 1986). Meyer (1955) described an atypical form of Osteogenesis Imperfecta (OI) using the designation 'Lobstein's disease'. It has since been suggested that this condition might have been an instance of OPPG (Arantes et al., 2011).

There have been other instances of reported phenotypic confusion between OI and OPPG (Beighton, 1985; Superti-Furga et al., 1986; Teebi et al., 1988). The disorder has been described with mild mental retardation (Neuhauser et al., 1986) and with congenital heart disease (Teebi et al., 1988). Other documented manifestations included wormian bones, frontal bossing and hyperextensible joints (Heide, 1981). Blue sclera is not a typical feature of OPPG, but it has been reported in two patients (Teebi et al., 1988).

A family of Indian origin, domiciled in Durban, South Africa in which 4 brothers and 2 cousins were reported as having a severe form of Osteogenesis imperfecta together with blindness (Beighton et al., 1985). It was subsequently pointed out that the diagnosis in this kindred was in fact OPPG (Superti-Furga et al., 1986).

The condition has a wide geographical distribution and it is present in several disparate countries. In 1985, 21 patients from 8 families were reviewed and their geographic origins suggested an elevated frequency in Mediterranean countries (Frontali et al., 1985). Later, in 2005, in a study conducted in the USA, the clinical and molecular findings were described in 37 probands and a population incidence of 1 in 2 million was estimated (Ai et al., 2005). In 2008, a further 9 new cases were reported at the Amish Research Clinic in Strasburg (Streeten et al., 2008). To date affected individuals have been reported in France (Saraux, 1967; Frontali, 1985), South Africa (Beighton, 1985), Greece (Frontali et al., 1985; Bartsocas et al., 1982), India (Shaharao et al., 1999), the USA (Ai et al., 2005; Streeten et al., 2008) and Tunisia (Marques-Pinheiro et al., 2010).

Gong et al. (1996) reported that the OPPG gene was located at the chromosome region 11q12-13. The authors used a combination of 'traditional linkage analysis and homozygosity mapping'. They analysed 16 DNA samples including biological specimens from the South African family. Thereafter, Gong et al. (2001) showed that mutations in the low density lipoprotein receptor related protein 5 gene (*LRP5*) caused OPPG. These authors stated that *LRP5* affects bone mass accrual during growth and heterozygous carriers of the mutant *LRP5* gene have reduced bone mass when compared to matched controls. The affected individuals fail to reach an adequate peak bone mass (Streeten et al. ,2008). These findings have been further confirmed by the demonstration that inactivation of *LRP5* in osteocytes resulted in impaired bone size and mass in response to mechanical loading (Zhao et al., 2013). Using biological material from the studies of Gong et al. (2001), the specific mutation in the South African family was identified as 3804delA (Ai et al., 2005).

Another genetic syndrome with a similar phenotype to OPPG is the Spondylo-Ocular syndrome (SOS) which was initially reported by Schmidt et al. (2001). The condition is characterized by osteoporosis, eye involvement with or without intellectual disability and hearing impairment. The molecular defect is a homozygous frameshift mutation in *XYLT2* which results in defective proteoglycan assembly (Munns et al., 2015).

The management of OPPG by administration of bisphosphonates and the success thereof was described by Bayram (2006). It has been recommended that patients with OPPG should begin treatment with bisphosphonates within the initial years of life (Streeten et al., 2008). More recently, Arantes (2011) provided therapeutic insight into the management of OPPG and supported the rationale for using an osteoanabolic agent.

19.3 Case Report

19.3.1 Family Background

The progenitors of the affected persons arrived in South Africa circa 1890 from Gujarat in the North Western region of the Indian sub-continent. The kindred were consanguineous and several relatives in India were said to have had the condition. The pedigree of the kindred is depicted in Fig 19.1.

The family was initially investigated three decades ago and case details were published under the erroneous title 'The Ocular Form of Osteogenesis imperfecta' (Beighton et al., 1985). The accurate diagnosis of OPPS was established thereafter (Superti-Furga et al., 1986).

The condition remains rare in South Africa and no other affected families have been identified in any of the populations of this country or in any other region of Sub-Saharan Africa.

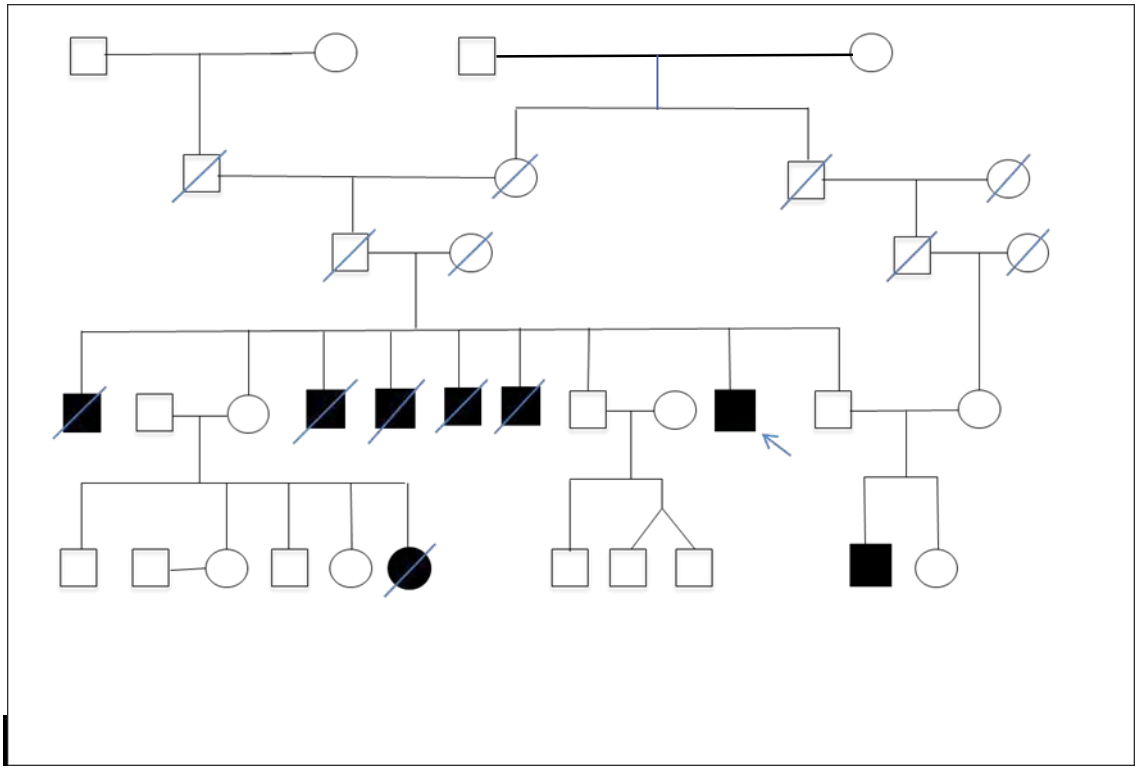

Fig 19.1 The pedigree of the affected family

19.3.2 Affected Person 1 (AP 1)

The affected nephew was born in Durban, South Africa, in 1967. He was blind at birth and in infancy hyperplasia of the vitreous was diagnosed by an ophthalmologist. At age 5 years he was admitted to the New Horizon School for the blind in Pietermaritzburg. His performance at this institution was good and he is currently satisfactorily employed as a radio disc jockey.

He was diagnosed with osteogenesis imperfecta at the age of 10 years on the basis of radiographic investigations. He recollected having sustained approximately 4 fractures of his lower limbs which has resulted in limb deformity (Fig 19.2). At age 16 years his teeth did not show signs of dentinogenesis imperfecta (Beighton et al., 1985).

Fig 19.2 AP 1. Aged 45 years. He is blind and deformities of his legs are apparent

Clinical examination of his oral cavity in 2013 revealed that 6 teeth were missing. These had become loose and were subsequently removed by the patient. Tooth numbers 12 and 22 were congenitally absent. His anterior teeth were splayed and discoloured with a mobility index of II (Miller's index). His plaque and gingival indices were 2 and 3 respectively (Fig 19.3). His average periodontal pocket depths were 5mm, suggestive of periodontal bone loss. No carious lesions were evident. His palate was shallow and wide. These features could be attributed to the combination of the tongue thrust position that he adopted when swallowing, due to an anterior open bite and periodontal bone loss.

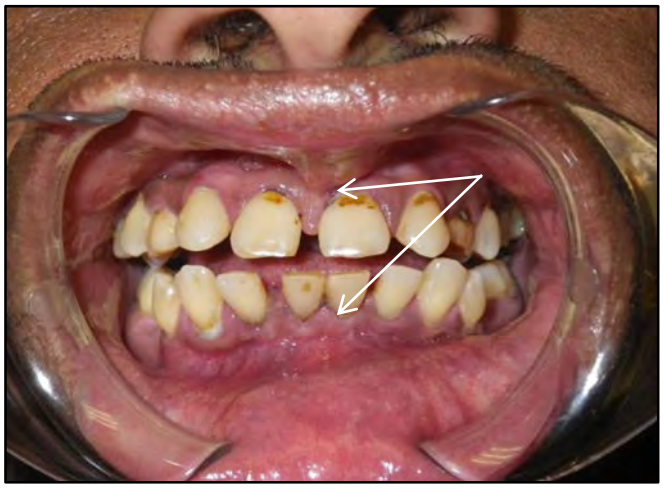

Fig 19.3 AP 1. His anterior teeth are splayed and focally discoloured. There is an accumulation of plaque and subgingival calculus (arrows)

He was advised to improve his oral hygiene and referred to a specialist periodontist in Johannesburg. In view of his diagnosis of OPPG, and before any dental treatment was initiated, a cone beam commuted tomography (CBCT) of AP 1's maxillofacial region was requested by the clinician. He was subsequently referred to a maxillfacial surgeon for management of his impacted molars.

The CBCT reports of AP 1 and AP II were compiled with the assistance of a consultant radiologist.

CBCT Report

Field of view: Medium

Bone (Fig 19.4)

- Mild osteoporosis was evident in the trabecular bone of the mandible. The cortical bone was normal
- Generalized loss of trabeculation of cancellous bone has resulted in enlarged marrow spaces
- The maxilla shows marked osteoporotic changes with the cortical bone outline incomplete in some areas.
- The hard palate was hypoplastic, shallow, and had an irregular cortical outline
- There was generalized loss of the lamina dura

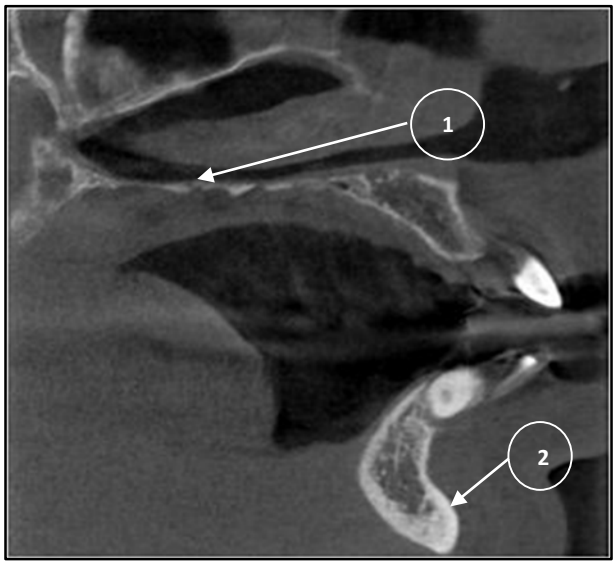

Fig 19.4 Sagittal image of the jaws. The cortical bone of the mandible is prominent and there is mild loss of trabeculation. The maxilla is osteoporotic and the palatal bone is hypoplastic.

Teeth (Fig 19.5)

- The upper and lower anterior teeth were severely splayed
- Retained deciduous canines (53 and 63) were seen
- The 12 and 22 were congenitally missing.
- Teeth 35 and 45 were extracted.
- Rampant decay was observed.
- Several peri-apical radiolucent lesions involving the molar teeth were evident
- The 28 was vertically impacted and the 38 and 48 were horizontally impacted.
- A pericoronal radiolucency was associated with the impacted 48.
- The roots of tooth 28 encroached into the maxillary sinus.
- There was a root remnant of tooth 18.

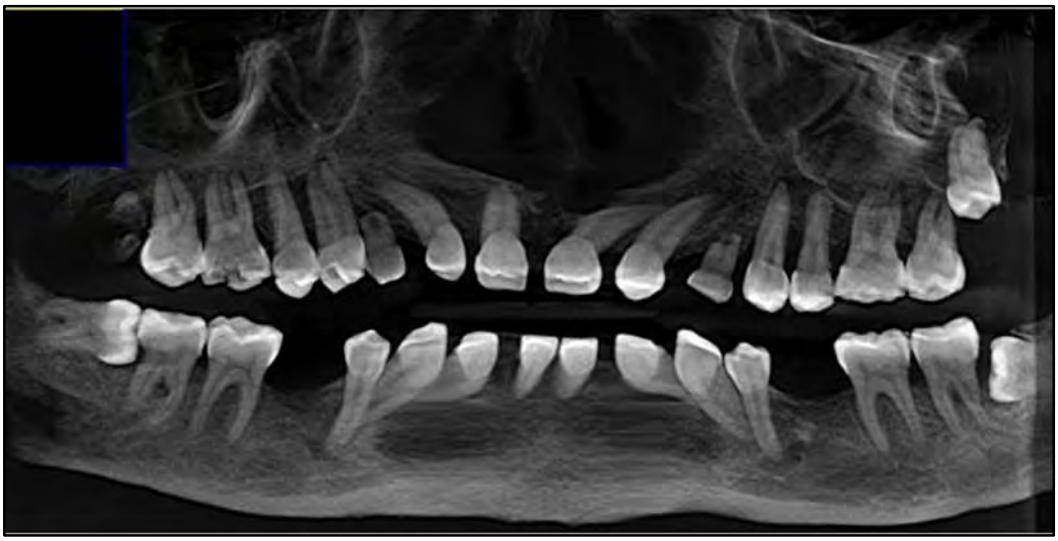

Fig 19.5 Panoramic image of AP 1 showing generalized loss of lamina dura, retained deciduous teeth (53, 63), carious lesions, impacted 3rd molars, root remnants of 18 and periapical radiolucent lesions

Bone densitometry scanning was conducted on the panorex of AP 1. The mean pixel intensity value (PI) and the panoramic mandibular index (PMI) from the digital panoramic radiograph of SB were calculated. These results were compared to that of a healthy South African male of Indian decent aged 45 years. In this way the dental practitioner was able to assess the patient immediately and formulate a treatment plan that would result in minimal morbidity (Devlin, 2012).

A brief description and definition of the indices investigated are provided below.

1. Mean pixel intensity (PI) – The pixel intensity values were obtained using the Kodak Dental Imaging Software which allows for post-processing qualitative and quantitative analysis. Two areas of interest were noted and were designated ROI 1 and ROI 2.

- Region of Interest (ROI) – In order to avoid superimposed anatomic structures or impactions as well as regions of alveolar bone which could be affected by periodontal conditions, a 1×1 cm square area inside of the gonial angle and the body of the mandible in the canine-premolar area on one side of the mandible was selected and these were designated as ROI 1 and ROI 2 respectively.

2. Panoramic mandibular index (PMI) (Benson et al., 1991) – This index is the ratio between the width of the lower mandibular cortex in the mental area and the distance between the lower margin of the mandible and the upper or lower margin of the mental foramen. A ratio below 0.41 is regarded as an indicator of osteopenia.

3. Klemmeti Index (Klemmeti et al., 1993) **-** This index denotes the presence of semi-lunar/ lacunar defects along the endosteal margin or presence of forms of cortical residues.

Table XIX.1 Bone densitometry scanning results of AP 1 compared with that of an unaffected adult male

DENSITOMETRIC ANALYSIS	AP 1	HEALTHY ADULT MALE Age 45 years
PIXEL INTENSITY (PI)		
- ROI 1	93.24	115
- ROI 2	81.80	86
- Mean PI	87.52	100
MORPHOMETRIC ANALYSIS	**AP 1**	**HEALTHY ADULT MALE Age 45 years**
Mandibular cortical width	3.42 mm (mean)	6.44mm (mean)
Klemmeti Index	C 2	C 1
Panoramic mandibular Index	Not possible to obtain due to inability to discern the borders of the mental foramen	0.28

Affected Person II (AP 2)

The affected uncle (AP 2) was born in 1949 in Durban. He recollected that as a young boy, he was blind in his left eye and only had partial sight in his right eye. At 15 years of age, he became completely blind and when examined at the age of 63 years he had opacities of the globes of both eyes (Fig 19.6). Available clinical reports stated that he had 7 fractures of his long bones during childhood that resulted in marked limb deformities (Fig 19.7). He became chair bound at the age of 25 years.

Fig 19.6 AP 2. Completely blind at age 63

Fig 19.7 AP 2. Anterior bowing of his lower legs resulting from fractures sustained in childhood

His teeth, at the age of 35 years had no evidence of dentinogenesis imperfecta (Beighton et al., 1985) but a recent dental history suggests that he had lost some of his teeth by this time. By the age of 45 years AP 2 had himself removed approximately 30 teeth which had become mobile possibly due to severe periodontal compromise. Currently, he was edentulous with marked resorption of both the maxillary and mandibular ridges. His oral mucosa overlying the mandibular and maxillary alveolar ridges was soft, focally erythematous and ulcerated. He had worn the same set of dentures for the last 15 years and his diet was restricted to soft easily chewable food.

Before beginning the process of making a new denture the hard tissue status of his maxilla and mandible was evaluated. The prosthodontist requested a CBCT scan.

CBCT Report (AP 2)

Field of view: Full: This includes the frontal bone, maxilla and the mandible.

The mandible and maxilla were edentulous.

Sinuses (Fig 19.8)

- The frontal sinus was absent
- The first air spaces visible were the ethmoidal air cells
- There was complete opacification of the right maxillary sinus
- The mucosa of the left maxillary sinus was thickened and there was a focal area which had a "soap bubble" appearance
- Bilateral choncha bullosa of the superior turbinates was observed
- An area of complete loss of maxillary sinus peripheral bone was detected in the region of the upper right 1st and 2nd premolars which resulted in only a mucosal separation between the sinus and the oral cavity.

A soft tissue calcification was visible in the left head and neck region suggestive of a carotid artery calcification.

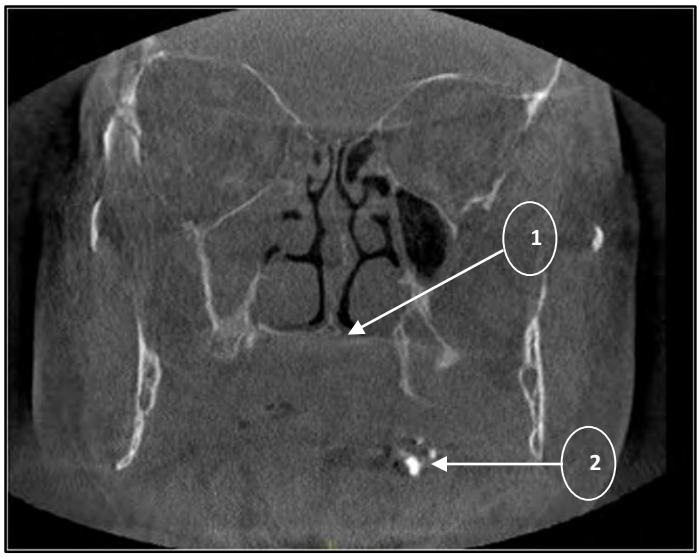

Fig 19.8 CBCT of AP 2: Coronal slice showing generalized osteoporosis of the facial bones especially the palate (1). A soft tissue calcification suggestive of a calcified carotid artery plaque (2).

Bone

- There was marked generalized osteoporosis of the skull and maxilla.
- Severe generalized loss of trabeculation of the jaws was observed.
- There were sparse cortical bone margins throughout the skull and the maxilla.
- The palate was shallow and hypoplastic.
- The head of the mandibular condyle was hypoplastic and abnormally shaped.
- Dysplastic changes of C1 and C2 were evident (Fig 19.9).
- The arch of the atlas appears fused to the base of the skull (Fig 19.9)
- Severe hypoplasia of the odontoid process with features suggestive of a subchondral cyst was noted (Fig 19.9).
- The mandible, although severely resorbed, showed cortical density within normal limits (Fig 19.10)

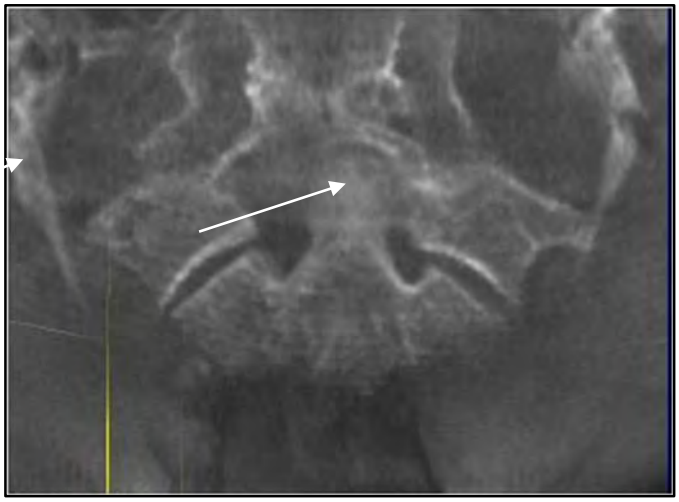

Fig 19.9 C1 and C2 of AP 2. His odontoid process is hypoplastic with evidence of a subchondral cyst (arrow).

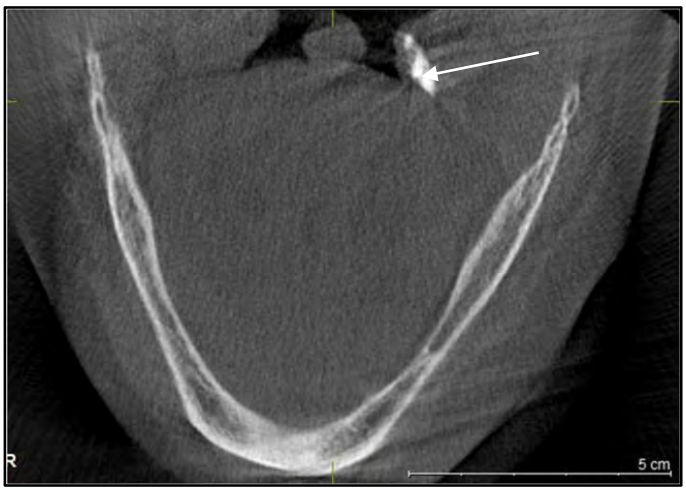

Fig 19.10 Cropped CBCT image of AP 2. The cortical bone of the mandible has minimal osteoporotic changes. Soft tissue calcification (arrow)

An interesting radiological observation was noted in the mandible of AP1 and AP2. The cortical bone of the mandible displayed minimal osteoporotic changes when compared with the rest of the craniofacial skeleton. This surprising finding was the antithesis of what was observed in other thin bone disorders. No obvious increased mechanical loading could be identified and this anomaly remains unexplained.

19.4 Discussion

The 6 affected members of the family had brittle bones with associated blindness and the pedigree data are consistent with autosomal recessive inheritance. At the time of their diagnosis, genetic counselling as well as dedicated medical and social care were the only help that could be offered to these patients and their families. In the South African Indian community marriages are often consanguineous and it can be postulated that there is a risk that further affected persons could be born in the extended family.

The presence of osteoporosis in OPPS has important implications for the dental manifestations and management. In particular, it is likely that the early loss of teeth in the affected uncle and nephew is related to this process. Osteoporosis of the jaws poses a risk of fracture during tooth extraction and due to the marked hard tissue changes evident on the CBCT, further investigation into the bone

mineral density (BMD) of the jaws were requested by the surgeons in order to establish the risk of this complication.

Although the T-score for BMD is presently the most widely accepted criterion to determine fracture risk (WHO, 1998), it also presents with several disadvantages, as these tests are not readily available, are costly and non-portable (WHO, 2004).

Radiographic density from dental radiographs can be assessed employing either linear measurements (morphometric analysis such as cortical thickness or the panoramic mandibular index) or by measuring optical density, followed by comparison with a standard (densitometric analysis). The need for a low-cost, easily available triage screening tool has led researchers to assess mandibular bone density from dental radiographs which are routinely performed for dental diagnosis and procedures. This assessment of the radiographic density enables a linear measurement (morphometric analysis) and an optical density measurement (densitometric analysis). The digitalization of the radiographs provides a further tool for quantitatively and qualitatively assessing BMD and architecture. A digital image is made up of an array of small, square or rectangular areas arranged in rows and columns called 'picture elements' or 'pixels'. Each pixel has a specific numeric value assigned to it known as 'pixel intensity (PI)' which is a measure of the blackness or whiteness of a region on the radiograph on a gray scale from zero (for totally black) to the highest value of 225 (for totally white). Pixel intensity has been recognised as a simple and useful method to estimate BMD (Law et al., 1996).

Digital radiography enables the use of post-processing software to determine PI and panoramic mandibular index (PMI), thereby assessing the BMD. Studies have shown that BMD levels in the mandible are comparable with levels in the lumbar spine, femoral neck and the forearm (Klemetti et al., 1993; Horner and Devlin, 1998; Devlin, 2012).

Although OPPG is well documented in the medical literature, perusal of the literature has revealed no description of OPPG in any dental, maxillofacial or oral health journal. The only reports attained in the general medical literature suggested the occasional occurrence of micrognathia (Neuhauser et al., 1976). The absence of dentinogenesis imperfecta in the South African Indian family was specifically mentioned by Beighton et al. (1985). Swaboda et al. (1988) described carious primary teeth but healthy secondary teeth and Teebi et al. (1988) noted the presence of yellow teeth in an affected person. The craniofacial appearance is usually normal although two siblings were reported in Finland as having a short philtrum with a prominent mouth region (Somer et al., 1988). Two children with wide and prominent mouths were also described by De Paepe et al. (1992).

It has been recommended that patients with OPPG should begin treatment with bisphosphonates in the early years of life (Heide, 1981). The general management of OPPG by administration of bisphosphonates and the success thereof has been documented (Bayram et al., 2006). More recently, Arantes et al. (2011) provided therapeutic insight into the management of OPPG and supported the rationale for using an osteoanabolic agent. Zhao et al. (2013) suggested that increasing *LRP5*-induced signalling in osteoblasts of persons with OPPG may be beneficial in the treatment of osteopaenia and osteoporosis. The effects of bisphosphonate therapy on the teeth and associated structures in OPPG, if any, have not been mentioned in the literature.

Both AP 1 and AP 2 had marked generalised osteoporosis and physical handicap with associated blindness.

AP 1, being blind at birth had developed the skills essential to personal hygiene including tooth brushing. Given the status of his periodontal bone loss and oral hygiene, intense periodontal root planning with plaque and calculus removal was performed. Care was taken not to overextend the neck in order to maintain the alignment of the cervical vertebrae. Further guidance in terms of his tooth brushing technique was provided with the hope of maintaining masticatory function for as long as possible.

AP 1 was informed of the presence of impacted teeth. Due to the osteoporotic nature of his maxilla and mandible as evident by his BMD values, regular observation was advised with treatment to commence only if the teeth or his temporomandibular joint became symptomatic.

AP 2 was chair bound, and difficulties in positioning were encountered in during the CBCT investigation. In particular, it was necessary for him to be raised to a position where the wheelchair did not inhibit the rotating arm of the machine.

Following the clinical and radiological examinations, it was decided that a new denture would be constructed that included a cushioned base to ensure stability and prevent trauma to the oral tissues. He was advised to continue on a soft easily digestible diet.

Dental treatment commenced only on confirmation that his intraoral infections were cleared as a previous swab of the erythematous area stained positive for Candida hyphae.

Impression taking was a challenge as BB had difficulty breathing through his nose. During the procedure, it was necessary to advise him to lean forward in order to facilitate easier breathing and to prevent gagging. Instability of the cervical spine was a potential problem and care was taken not to extend his neck and tilt his head upwards. Although several impressions were attempted, only one

fairly acceptable impression was obtained due to the almost complete loss of his hard tissue support in the region of his palate.

AP 2 was also referred to a physician for further investigations into the origin and location of the soft tissue calcification which eventually was confirmed as a carotid artery calcification. He is currently under the care of a consultant physician.

OPPG is similar to OI in terms of its pathology and the disorder has serious clinical consequences. The improved molecular knowledge of this syndrome over the past decade has facilitated genetic counselling as well as provided successful genetic management options.

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Section VI: Conclusion

CHAPTER 20: Concluding Comments

APPENDIX:

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2. **Tooth Numbering**
3. **Tooth Anomalies**
4. **Occlusion**
5. **Practical Cephalometrics**
6. **Cephalometric tracing of CPT5**
7. **Cephalometric tracing of CPT3**
8. **Affected Persons Clinical Details**
9. **Research Participant Information Sheet**
10. **Ethics Approval: 2013 - 2014**
11. **Ethics Approval: 2014 - 2015**
12. **Ethics Approval: 2015 - 2016**

CHAPTER 20: Concluding Comments

Preamble

This final chapter encompasses the challenges confronted by dental practitioners when managing individuals with inherited thin bone disorders. Particular difficulties, in management which are encountered by the affected persons are also portrayed. Recent advances in therapy are highlighted.

20.1 Introduction

The aim of this study was to document and elucidate the dental manifestations in persons with Inherited Disorders of Connective Tissue in South Africa.

This report presents the clinical and radiographical, dental and craniofacial observations in 72 OI III affected individuals. Sixty-four were of Black African ancestry, 5 were of Cape Mixed Ancestry heritage and 3 were South Africans of Indian decent.

20.2 Challenges

20.2.1 Dental Practitioner: Clinical Evaluation and Management

An early and detailed dental and craniofacial evaluation is important in persons with inherited skeletal dysplasias in order to develop a treatment and maintenance plan and to facilitate timeous intervention. The challenges encountered during this process are discussed below.

Radiographs

Radiographs are an important diagnostic tool in the evaluation of an individual. Optimal panorex, cephalometric and CBCT images were difficult to obtain due to the short stature and physical deformity of many individuals. Persons that were chairbound proved to be especially difficult to position. (*See Chapter 6 and Appendix 5).* Representative clinical and radiological images of PMB 1 (Fig 20.1, Fig 20.2) are depicted below in order to exemplify the dilemma faced by the radiographer.

Fig 20.1 PMB 1. Chairbound with severe physical deformity.

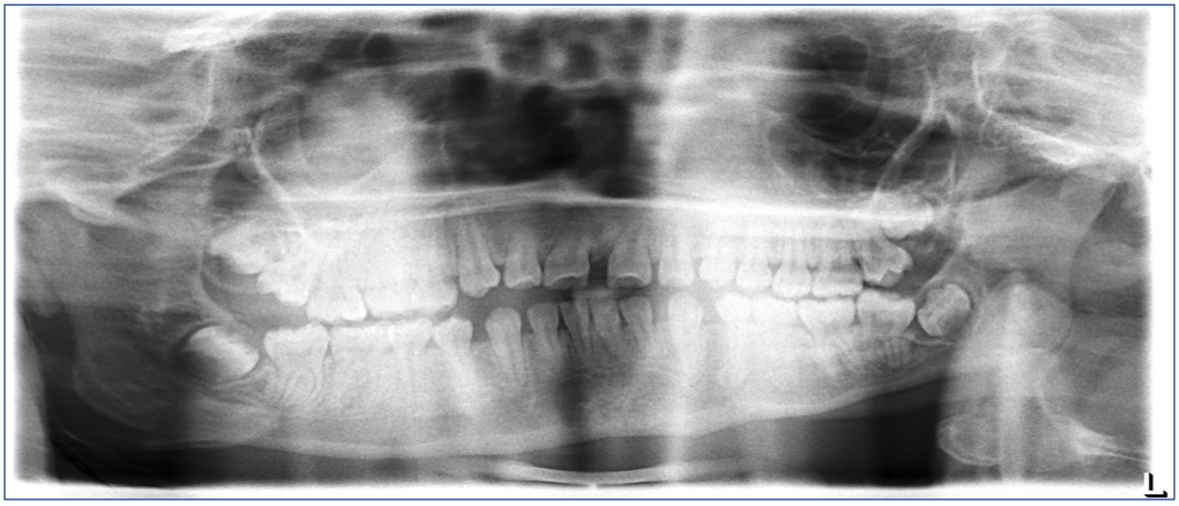

Fig 20.2 Distorted panorex radiograph of PMB 1. Positioning of patient was difficult.

A CBCT image of PMB 1 could not be obtained. The severe deformity of her cervical spine which resulted in a short neck and elevated shoulders prevented the complete rotation of the arm of the CBCT machine around the craniofacial and orodental region.

The Dental Chair

In addition to a short stature, several affected persons had kyphoscoliosis. Many individuals had difficulty climbing onto the dental chair, lying flat on their backs and extending their necks. Some chairbound persons struggled to move onto the dental chair while a few adult chairbound individuals could not be moved and had to be managed while sitting.

Manipulation of the Head and Restricted Jaw Opening

The awareness of the compromised cervical spine of affected persons necessitated special care where the patient was allowed to self-position for comfort and safety.

Secondary skeletal changes such as basilar invagination (BI) were observed in CBCTs of 12 individuals of the 15 CBCTs obtained. For these reasons, positioning of the head during radiographic and dental procedures was strictly monitored. Lateral cephalometric radiographs were also used to assess the relationship between the bodies of the first two cervical vertebrae and foramen magnum. The presence of basilar invagination was confirmed by a consultant radiologist. Awareness of this feature is warranted and due prudence is necessary when managing these individuals. Persons with BI may or may not present with signs of neurological complications. These findings are consistent with results

of a study by Sillence (1994) where the highest frequency of BI was observed in individuals with OI III and OI IV.

Limited access to the oral cavity was influenced by difficulties with extension of the neck and changes in head positioning. Several affected individuals had restricted opening of their mouths which proved to be extremely demanding in terms of dental evaluation and management.

Dentinogenesis imperfecta

When DI was present, the teeth exhibited several anomalies which were clinically challenging. These abnormalities included discoloured teeth, abrasion and fracture and loss of enamel, constriction at the coronal-radicular junction, thin short roots and obliterated pulp chambers.

When present in primary teeth, DI was more severe and it was essential to try and prevent teeth breaking down, repair them as necessary and attempt to maintain the teeth until the secondary teeth emerged. If the secondary teeth are also affected with DI, a dental material that is aesthetically pleasing must be used. The patients should be observed closely and their teeth and restorations repaired when necessary. Permanent restorations such as full coverage crowns are an expensive option.

It is strongly recommended that persons with severe DI be monitored and dentally evaluated every 6 months from the age of 1 year. Unfortunately, in developing countries appropriate facilities are not available.

Craniofacial Defects

Craniofacial defects have a direct impact on masticatory function and the dento-facial appearance. A frequent presentation was a Class III malocclusion and several individuals, during the course of this project, were referred to an orthodontist for correction. Orthodontic treatment is expensive and necessitates several visits. It is relevant that in local circumstances many affected persons do not have the resources to seek orthodontic management.

The conventional method of management is orthognathic surgery which is normally performed when growth has been completed. Although complex, favourable outcomes for these procedures have been reported in the literature (Bell and White, 2000).

An assessment of the level of skeletal and dental maturity is necessary for the formulation of both orthodontic and orthognathic surgery management plans and to decide the onset of treatment. In the orthodontic context, in unaffected individuals a radiograph of the hand and wrist is obtained or the

anatomy of the cervical vertebrae is assessed from a cephalometric image. This is in order to determine future craniofacial growth which is necessary to formulate a comprehensive orthodontic and orthognathic treatment plan. In OI III affected persons, the defective mineralization of the bone and the compression of the cervical vertebrae posed difficulties in this regard.

20.2.2 Affected Persons: Dental Management

Access to Dental Care

Many affected persons lived in areas distant to health care facilities and had to travel long distances. Their short stature and bone fragility resulted in difficulty and discomfort during the use of public transport.

Most parents and carers reported difficulty in obtaining dental services for their children and in accessing a dental office. Four children were denied dental treatment by dentists who admitted that they were not adequately trained and that their clinical environment was not conducive to treating persons with their condition.

Economic constraints were the most often recorded barrier to accessing optimal dental care.

Adolescent and Adult Persons

Some adolescent and young adult persons expressed regret that their disability, at some time or the other, had prevented them receiving appropriate dental care.

Eight affected individuals together with their parents expressed concern when medical records were transferred from the paediatric to the adult care facility. The greatest challenge for these persons was the lack of appropriate dental facilities equipped to treat and manage the dental and craniofacial anomalies inherent in their disorder. Economic constraints continued to be an obstacle to accessing dental care.

Several persons reported that maintaining an appropriate body weight for their height was a constant challenge. Although they were aware of the need for good nutrition, active movement and strengthening exercises, they indicated a scarcity of resources and guidance in this regard. Persons who were unable to control their weight were in most instances chairbound and unable to be helped into the dental chair.

Dentinogenesis imperfecta

It was the author's experience, that DI affected persons were extremely concerned about the functional and cosmetic condition of their face and teeth. There are several articles published in the dental literature that documents the management of DI (Stephen and Beighton, 2002; Teixeira, 2008) which highlights restorative techniques that address the functional and aesthetic needs of the affected individual.

20.2.3 Comment

Short stature, shortness of the neck, limited opening of the mouth and mobility make procedures such as radiographic examination, impression taking, bonding of orthodontic brackets and dental material and oral hygiene, exigent for both the patient and the dental practitioner.

A detailed dental and craniofacial investigation is necessary in persons with an inherited thin bone skeletal disorder in order to identify any primary or secondary abnormalities.

Ideally, early dental intervention in children with DI is important in order to maintain the primary teeth in the mouth for as long as possible. This would ensure the correct vertical dimension of the occlusion as well as the functional needs of the individual, and would create a favourable environment for the eruption of the permanent teeth. A paediatric dentist would primarily be involved at this stage of dental care and successful management would require regular recall visits.

Many affected persons reached adolescence and young adulthood and often had concerns about the functional and cosmetic condition of their face and dentition. Theoretically, at this stage referral to an orthodontist, a maxillofacial surgeon, a prosthodontist and a periodontist, as determined by the patients' needs, would be necessary.

The heterogeneity of the patient population emphasizes the requisite multidisciplinary approach to developing a comprehensive treatment plan and monitoring progress. Unfortunately, economic constraints and the lack of appropriate dental facilities precluded necessary and adequate management.

20.3 Recommendations

Dental examination and appropriate treatment planning for the management of individuals with OI III and other thin bone disorders should ideally involve communication between dental specialists in the fields of paediatric dentistry, periodontics, orthodontics, oral surgery, oral radiology and prosthodontics. Collaboration between specialists in different fields of medicine is of paramount importance in order to deliver high quality comprehensive healthcare.

The development of facilities for the management of affected persons, particularly adolescent and adult individuals, warrants attention.

Given that many affected individuals now live beyond the second decade, loss of teeth becomes a reality; however, little published information exists about edentulousness and denture problems such as muscle activity, salivary secretion and quality of the oral mucosa in individuals with thin bone disorders. To the best of the author's knowledge no published data exists on the insertion of dental implants in persons with these disorders.

Several reports describe the role of connective tissue cells such as osteoblasts, fibroblasts and osteoclasts in the pathogenesis of skeletal disorders. In the dental context, limited information is available about the role of odontoblasts in the laying down of predentine.

The paucity of knowledge in these areas suggests the need for research collaboration on such issues. Multicentre studies of clinical problems may be a way to obtain results and information.

The nomenclature of heritable dentin dysplasia was introduced at the time when the molecular genetic background was unknown. The author proposes that the term 'dentinogenesis imperfecta' be used only in the setting of OI to avoid confusion among dental practioners. In other instances the term 'DI-like' might be appropriate.

20.4 Concerns

The dental and craniofacial manifestations of persons with thin bone disorders, are highlighted in this thesis.

Dental concerns are:

- Dentinogenesis imperfecta
- Taurodontism
- Retention of primary teeth and delayed eruption of secondary teeth

Craniofacial concerns are:

- Platybasia
- Basilar invagination
- A 'J'- shaped sella turcica
- Malocclusion
- TMJ anomalies
- Sinus anomalies
- Limited mouth opening

In south Africa, the awareness of these anomalies in affected persons is important in order to facilitate correct diagnoses and develop appropriate management strategies.

20.5 Update on Therapeutic Measures

In addition to bisphosphonates, growth hormone has been shown to increase the bone mineral density on its own (Marini et al., 2003) or in combination with bisphosphonates (Antoniazzi et al., 2010). In these projects, however, there was no decrease in the rate of fracturing (Bargman et al., 2012). The use of growth hormone to improve the short stature of persons with OI III is currently under active investigation but at this point there is insufficient evidence to support the regular use of growth hormone in children with OI (Bargman et al., 2012).

Researchers are developing approaches that would either suppress (Dawson and Marini., 2000) the expression of mutant collagen genes or replace the mutant cells with progenitor bone cells (Guillot et al., 2008). A small group of children with severe OI showed minimal improvement in their bone phenotype after the administration of mesenchymal stem cells with osteoblastic potential (Horwitz et al., 1999). A decade later an improvement in the histological bone phenotype after the infusion of

mesenchymal stem cells with osteoblastic potential in mice models with OI was reported (Mehrotra et al., 2010).

Denosumab is a receptor activator of nuclear factor-κB ligand inhibitors which inhibits osteoclast formation and bone degradation. A study has shown that denosumab normalized the elevated markers of bone resorption in 4 children with OI IV (Semlar et al., 2012). Data on the effect of denosumab on fracture rate and bone pain in affected children are not available.

Sclerostin antibody treatment in mice models of OI has demonstrated an improvement in the fragility of long bones (Sinder et al., 2013). This approach may be a potential new therapy option for children with OI.

A recent report suggests that distraction osteogenesis may be considered as a reconstructive option for some of the craniofacial deformities of persons with OI III (Black and Denny., 2014). Although these authors discuss a case of mandibular lengthening in an individual with hemifacial microsomia and OI, they suggest that the technique can be successfully used in the setting of OI.

20.6 Conclusion

In Osteogenesis imperfecta and other related thin bone disorders awareness is warranted in terms of the provision of resources at a socio-political level.
In South Africa, a developing country, there are enormous economic constraints and resources at every level are limited to virtually non existant in many areas. In the face of a burgeoning population, it is hoped that this deficiency is recognized and addressed in the context of national health care.

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APPENDIX:

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APPENDIX 1

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APPENDIX 2

TOOTH NAMES AND NUMBERS

The teeth of both jaws are arranged in symmetrical arches and the number of teeth on both sides of the midline is the same.

The midline is represented by an imaginary point between the central incisors of each arch.

The teeth are numbered according to the system proposed by the FDI (Féderation Dentaire Internationale). In each half (quadrant) of each jaw, the following teeth are located from the midline backwards and each tooth is given a number (Fig 1).

Right side of Jaw ***Left side of Jaw***

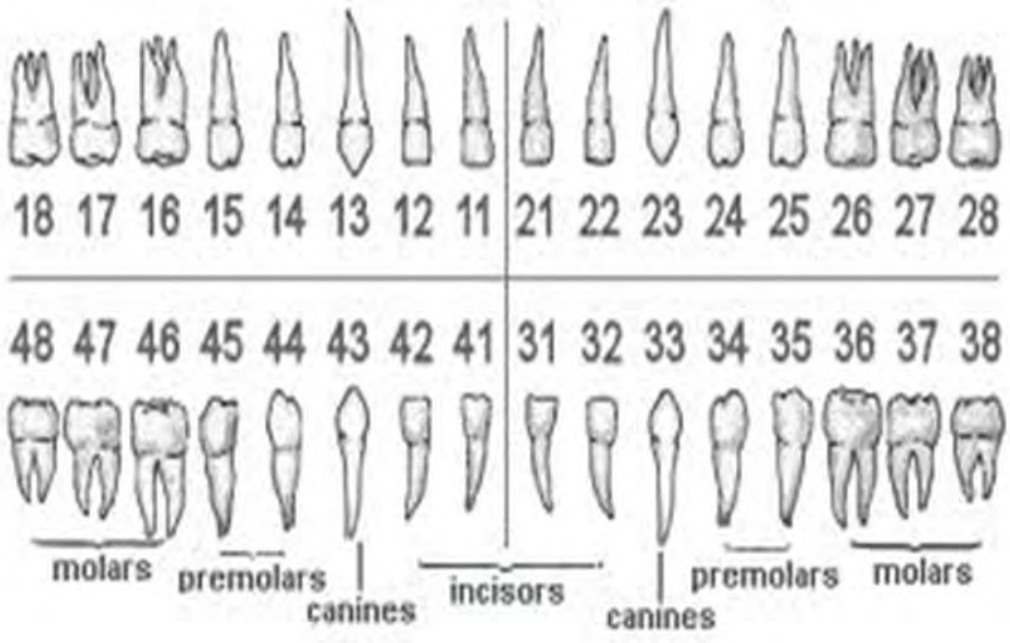


Fig 1: Tooth names and numbers according to the FDI

The author has used the FDI system of tooth numbering described above.

The basic morphology of teeth is described and depicted in order to facilitate the understanding of concepts pertaining to tooth morphology.

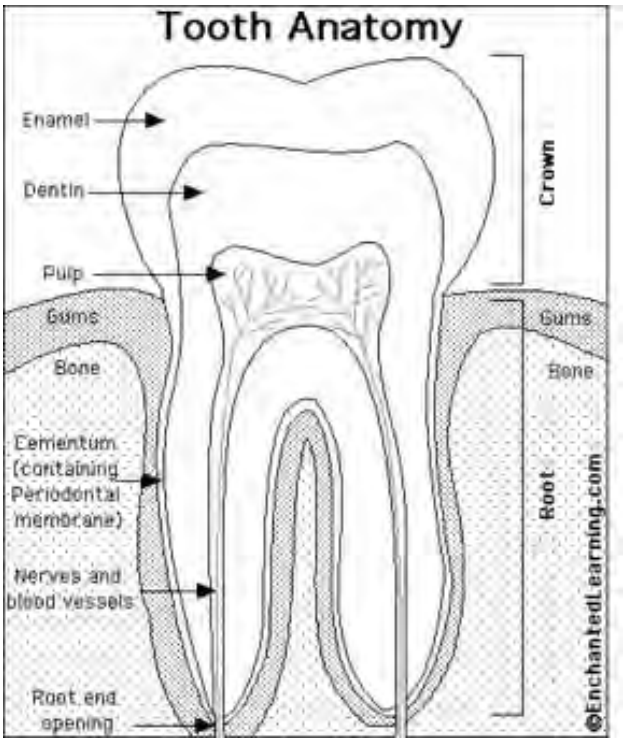


Fig 2. Anatomy of a molar tooth with supporting structures

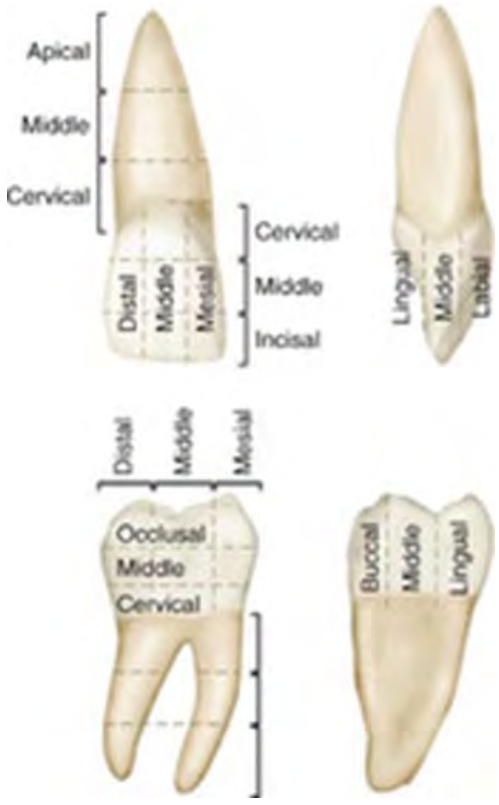


Fig 3. An illustration of the various tooth surfaces and the divisions of the crown and root

APPENDIX 3

TOOTH MORPHOLOGY: DEVIATIONS FROM THE NORM

Only conditions relevant to this project are outlined below.

Teeth form from the interaction of 2 germ layers namely the ectoderm and mesoderm. The mesoderm in the head and neck region is termed ectomesenchyme because of the intermingling of mesenchymal and neural crest cells.

Enamel is formed from ectodermal components and dentin, pulp, cementum and the periodontium are formed from ectomesenchyme.

Any disturbance in the interaction between the 2 germ layers may result in a tooth that deviates from the norm.

Disturbance in size

Microdontia implies teeth that are smaller than normal. Generalized microdontia is uncommon and associated with conditions such as pituitary dwarfism and a few rare genetic syndromes. More often, microdontia is limited to just one or two teeth. "Peg-shaped" upper lateral incisors and small third molars are frequently seen in dental practice. Peg-shaped incisors tend to be familial (Fig 1).

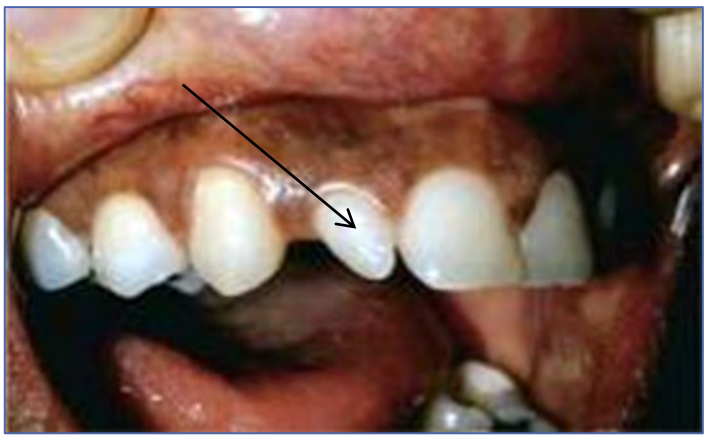


Fig 1. Peg-shaped lateral incisor (arrow)

Disturbances in Number

Anodontia is the congenital absence of all teeth namely when there is complete failure of all teeth to develop. *True anodontia* is an extremely rare.

Partial anodontia is the failure of one or more teeth to develop. It is much more common than complete anodontia. Third molars, lower second premolars, and upper lateral incisors are the most common congenitally absent teeth.

Supernumerary teeth are 'extra' teeth. Most occur in the maxilla. Most supernumerary teeth do not erupt and are often detected on radiographs.

Disturbances in Eruption

Premature eruption of all of the teeth, either deciduous or permanent, may suggest an underlying endocrine dysfunction such as hyperthyroidism.

Delayed eruption can be due to local, systemic or genetic factors. Radiographs are useful in evaluating early or late eruption of teeth. This feature is also detected by comparing intraoral clinical findings to standard tooth eruption tables.

Impacted teeth are those that have failed to erupt and remain buried in the alveolar bone (Fig 2). Usually, some barrier to eruption will be evident on the X-ray film. The third molars and maxillary canines are the most frequently impacted, followed by premolars and supernumerary teeth.

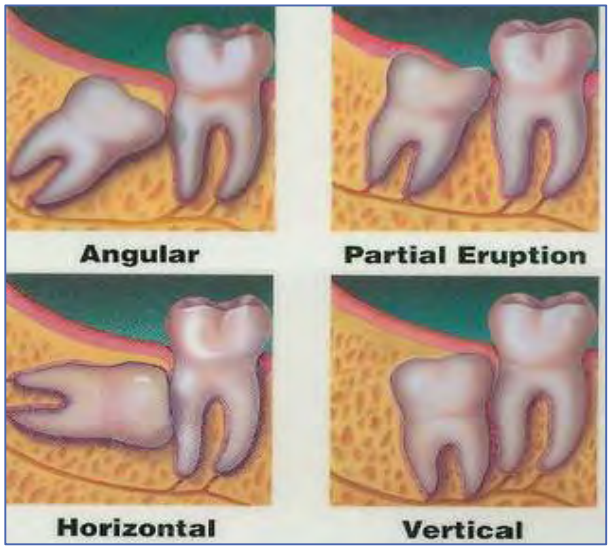


Fig 2. Impacted molar teeth. Google: www.napervilledentist.com (November 2015)

Disturbances in Shape

Dilaceration is a severe bend in the long axis of the tooth. The bend it located at the junction between the crown and the root. The angle can be as great as 90 degrees.

Flexion is a deviation or bend restricted just to the root portion of the tooth. Usually the bend is less than 90 degrees.

APPENDIX 4

OCCLUSION (DENTAL AND SKELETAL)

When teeth in the maxillary arch come into contact with those of the mandibular arch in any functional relation, they are said to be in occlusion.

Dental malocclusion is an incorrect relationship between the teeth of the maxilla and mandible when the jaws close. The shape of the jaws or birth defects may also cause a malocclusion which is often hereditary.

Optimal occlusion and deviations have been described by several authors over the years namely Angle in 1887, Schuyler in 1929 and Lucio in 1963 (Nelson and Ash. 2010). The classification of the occlusion of an individual is important when a diagnosis and treatment plan is structured. The most frequently used classification is that originally described by Angle and is based on the interdigitation of the mesiobuccal cusp of the maxillary first molar and the mesiobuccal groove of the first mandibular molar (Fig 1, Fig 2, Fig 3 and Fig 4).

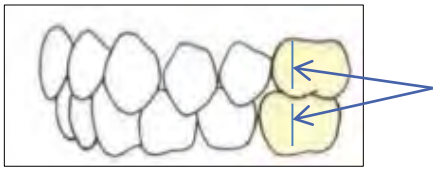


Fig 1. Normal occlusion. The mesiobuccal cusp of the maxillary first molar and the mesiobuccal groove of the first mandibular molar interdigitate (arrows) and the rest of the teeth are well aligned relative to each other.

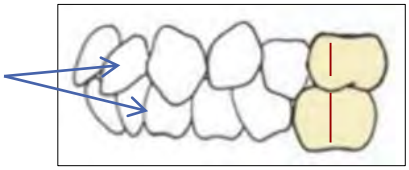


Fig 2. Class I malocclusion. Although there is interdigitation between the mesiobuccal cusp of the maxillary first molar and the mesiobuccal groove of the first mandibular molar, the line of occlusion is incorrect because of several malpositioned teeth (arrows)

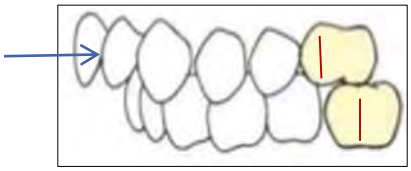


Fig 3 Class II malocclusion

The mesiobuccal cusp of the maxillary first molar is positioned forward. This often results in the maxillary incisors being proclined or an increase in the maxillary overjet (arrow).

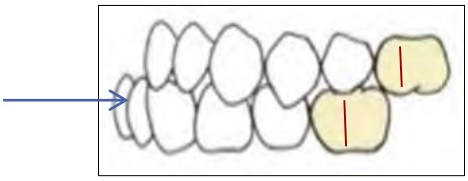


Fig 4 Class III malocclusion

The mesiobuccal cusp of the maxillary first molar is posterior to the mesiobuccal groove of the mandibular first molar. This often results in a mandibular overjet (arrow). The facial profile in these individuals is often a mandible which protrudes forward beyond the normal limits of the face.

Skeletal malocclusions are indicative of an abnormal relationship between the size of the mandible and maxilla and are often associated with a skeletal disharmony of the face. This can severely affect aesthetics and frequently causes mastication and speech problems. A Class I skeletal relationship is considered normal and a Class II skeletal malocclusion is suggestive of a retrognathic mandible. A Class III skeletal malocclusion is suggestive of a prognathic mandible. A skeletal malocclusion can only be established in adolescents and older individuals when growth is complete and can be confirmed using cephalometric values.

An edge to edge bite is the meeting of the incisal edges of the upper and lower anterior teeth during functional occlusion. This bite is often present in persons with a dental and skeletal class III malocclusion. An edge to edge bite is also frequently identified in children with only deciduous teeth and in those that are in the mixed dentition period, from approximately 1.5 years to 12 years. This characteristic in a child may precede the development of an adult Class III dental and/or skeletal malocclusion.

APPENDIX 5

IMAGING TECHNIQUES

The imaging facilities used during this survey were only available at specialized dental centres. The structure of the apparatus used is described and depicted in detail in order to highlight the difficulties encountered when attempting to position an individual with short stature and severe physical deformity.

Panorex

The panorex image is obtained using a digital panorex machine which during exposure moves around the head of the patient enabling a two dimensional view of all craniofacial structures (Fig 1, Fig 2).

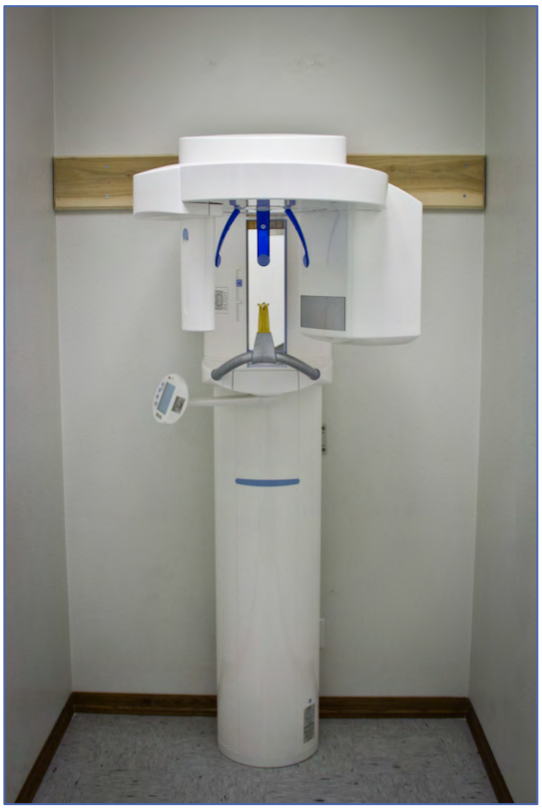


Fig 1. An example of digital panorex machine

Fig 2. Correct patient positioning is imperative

(https://www.schickbysirona.com)

Cephalometric Radiographs *(see Appendix 6)*

Cone-beam computed tomography

Cone-beam computed tomography (CBCT) scans are a variation of traditional computed tomography (CT) scans. Dental CBCTs were developed as a means of producing similar types of images but with a much smaller and less expensive machine that could be placed in a dentist's office (Fig 3). The dental profession uses the CBCT system that rotates around the patient's head and data is captured using a cone-shaped x-ray beam (Fig 4). An optimal image is dependent on correct patient positioning. A three dimensional image of dental structures, soft tissues, nerve pathways and bone in the craniofacial and cervical region is generated in a single scan.

Fig 3. Image of a CBCT machine used by dental specialists

(https://www.schickbysirona.com)

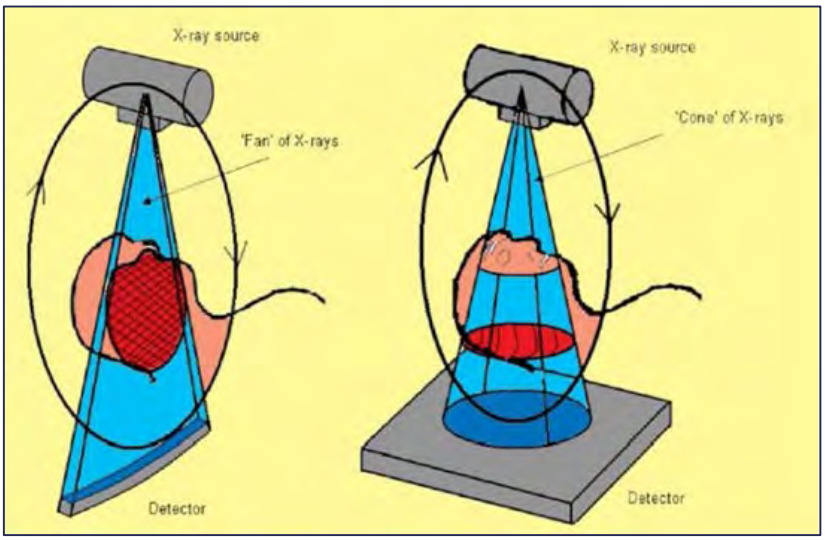


Fig 4. A cone-shaped x-ray beam captures a 3D image of the craniofacial region (https://www.schickbysirona.com)

Radiographic images were obtained only when they were necessary in terms of clinical management and when these resources were available.

APPENDIX 6

PRACTICAL CEPHALOMETRY

(Courtesy of Dr A Hudson, Department of Orthodontics, UWC)

Background

In cephalometrics the skull can be considered to be composed of 5 structures namely the cranium, the cranial base, the maxilla and mandible and maxillary and mandibular dentitions. All cephalometrics analyses describe the interrelationship of these components in a vertical, horizontal and a sagittal plane. It is the interpretation of lateral skull radiographs taken under standardized conditions.

The patient is placed in a Cephalostat (Fig 1). This enables the patient to be positioned with their head oriented at 90^{o} to the X-Ray beam at a distance of 5ft from the tube. The film is placed 15 inches from the head. This is a standard under which all cephalometric radiographs are taken worldwide. It ensures that radiographs taken at different centres are directly comparable.

Fig 1: Correct positioning of the patient

The film is then traced and various standard landmarks, lines and angles are measured and recorded. This allows comparison with normal values for a population and assessment of growth and/or effects of treatment.

The following analysis is a combination of the Steiner, Ricketts, Tweed, McNamara analyses and the 'Wits' appraisal which is the analyses used by the author in the interpretation of the various cephalometric radiographs of the affected persons.

Below is a cephalometric radiograph. The soft tissue outline as well as the tongue and pharynx are evident. All the hard tissue references points should be clearly visible. The image is traced either manually using a lightbox in a dark room or by various computer programmes.

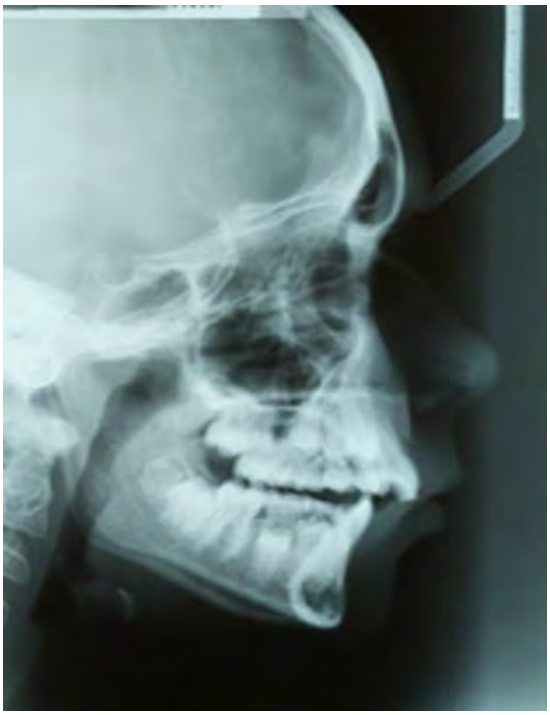


Fig 2: The patient is in the 'Natural Head Position', this is the patient holding their head as if they looking off into the distance. There is a scale to allow calculation of the radiographs magnification. Collimation has been used so the soft tissues are clearly seen

Tracing technique

The following structures must be outlined (Fig 3):

1. Soft tissue profile of face (forehead to chin)
2. Sella turcica
3. Frontal bone and nasal bone
4. Orbital floor
5. External auditory meatus
6. Maxilla, upper 1st molar and upper central incisor
7. Mandible, mandibular symphysis, lower 1st molar and lower central incisor

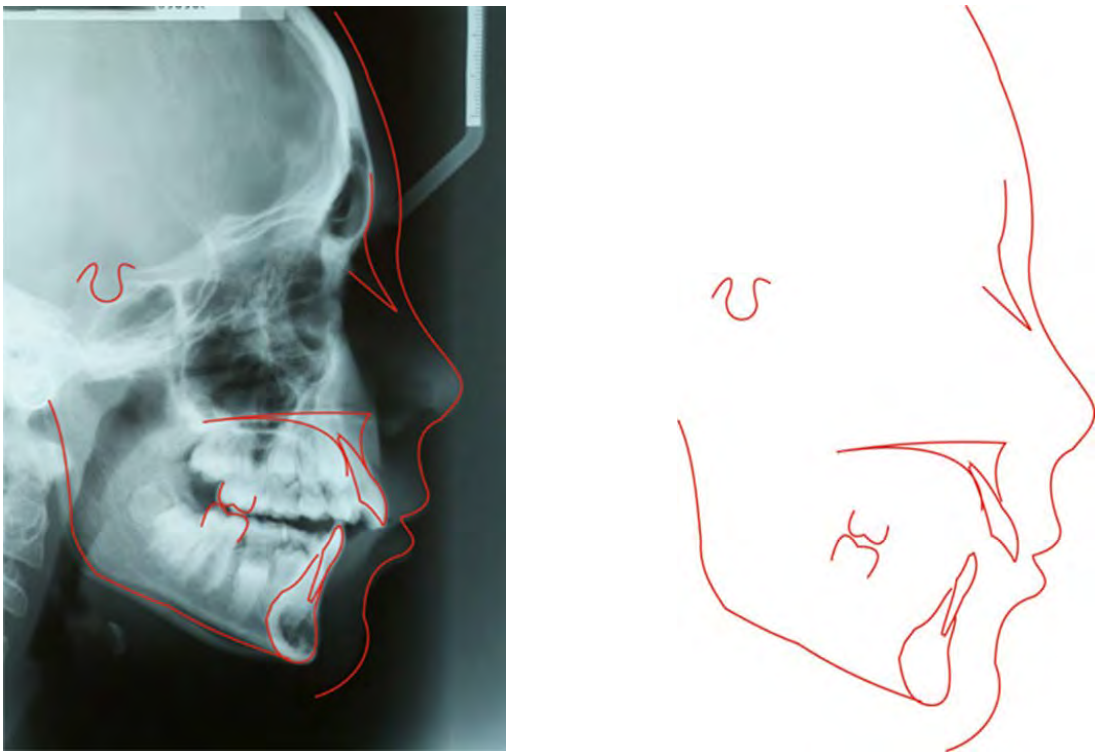


Fig 3: Tracing of the important maxillofacial structures

Cephalometric points:

Identify and mark the following landmarks (Fig 4)

S Sella: *Mid point of sella turcica*

Ba Basion is the lowest point on the anterior rim of the foramen magnum (Fig 5)

N Nasion: *Most anterior point on fronto-nasal suture*

Or Orbitale: *Most inferior anterior point on margin of orbit*

Po Porion: *Upper most point on bony external auditory meatus*

ANS *Anterior Nasal Spine*

PNS *Posterior Nasal Spine*

Go Gonion: *Most posterior inferior point on angle of mandible*

Me Menton: *Lower most point on the mandibular symphysis*

A point: *Position of deepest concavity on anterior profile of maxilla*

B point: *Position of deepest concavity on anterior profile of mandibular symphysis*

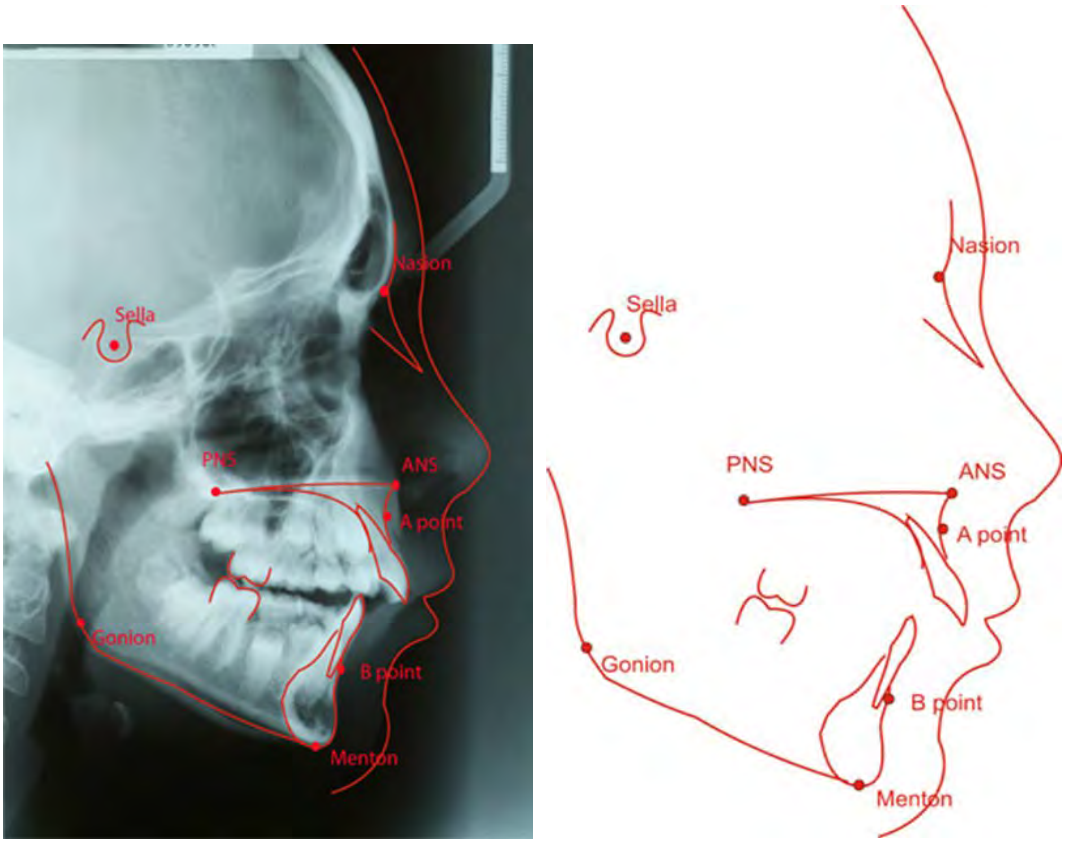


Fig 4: A ceph tracing showing important maxillofacial landmarks

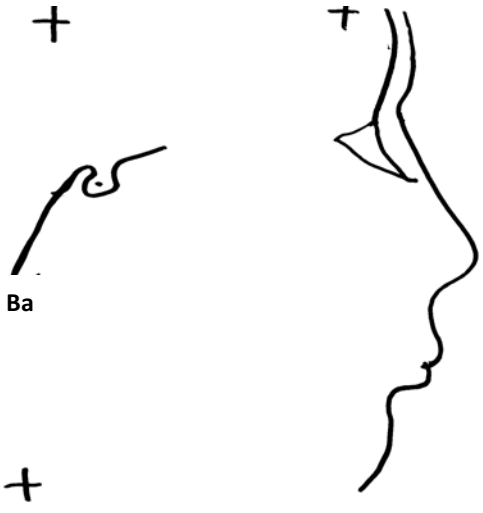


Fig 5: Extend the outline of sella turcica posteriorly to the anterior inferior margin of the foramen magnum – this landmark is called Basion (Ba) - the lowest point on the anterior margin of foramen magnum, at the base of the clivus.

Lines/planes (Fig 6)

The reference planes are:

Frankfort Plane - Equivalent to the true horizontal when patient is standing upright

Sella Nasion plane (SN) – representing the anterior cranial base

Basion –nasion plane (Ba-N) – dividing the skull from the face.

Maxillary Plane (PNS-ANS) - Gives inclination of maxilla relative to other lines/planes.

Mandibular Plan (**Go–Me)** - Gives inclination of mandible relative to other lines/planes.

The angle MMPA - Maxilla to Mandibular Planes Angle (Maxillary plane to Mandibular plane) This is the inclination of the maxilla relative to the mandible, this in turn indicates the relative proportions of face height and acts as an indicator for future growth direction.

S - N Line: *Indicates orientation of anterior cranial base.*
N – A: *indicates relative position of maxilla the cranial base*
N – B: *indicates relative position of maxilla the cranial base*

The angles SNA; SNB; ANB indicates relative position of maxilla/mandible to each other and to the cranial base

Long axis of upper central incisor/lower central incisor (root apex to incisal edge) - *allows measurement of the angulation of incisors to maxilla/mandibular planes.*

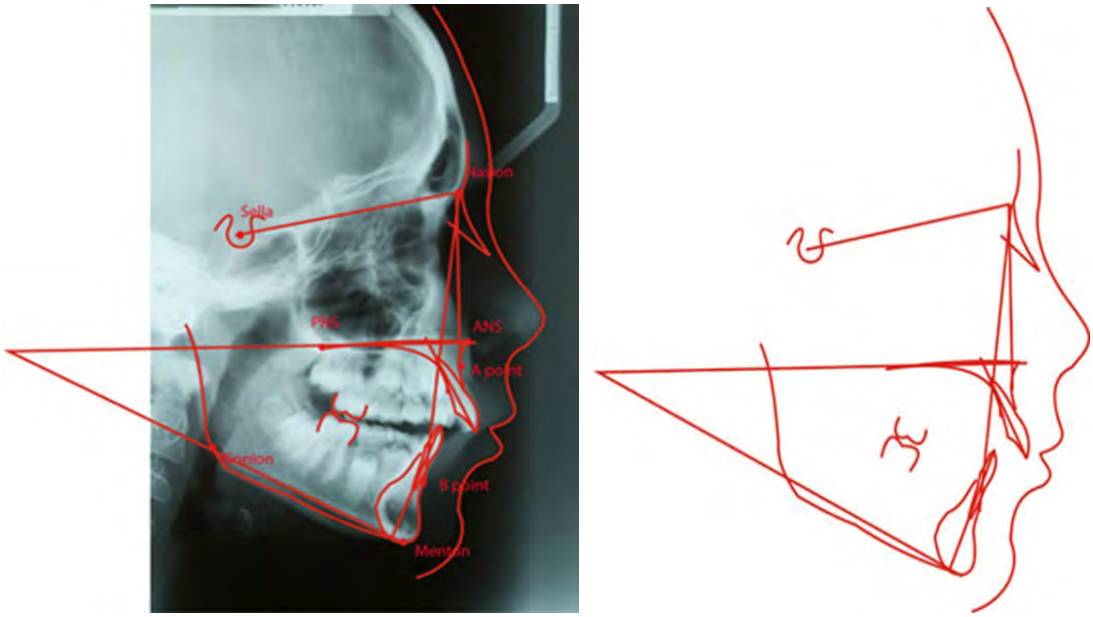


Fig 6: Important lines and planes drawn in

Finally measure the various angles

Analysis/Interpretation of tracing

By comparison of angular measurements with normal values one can interpret the results of ones analysis to give a diagnosis of the patient's presenting skeletal pattern. Comparison of the findings from the original and final cephalometric radiographs will allow you to assess the outcome of treatment.
(Standard deviation in brackets):

SNA = 81^{o} (±3)
SNB = 79^{o} (±3)
ANB = 3^{o}(±2)

Interpretation of SNA/SNB/ANB angles:

If SNA or SNB greater or less than the normal - this indicates that the mandible or maxilla is either positioned anterior or posterior. This may be due to a difference in jaw growth and size.

ANB indicates the relative position of maxilla to mandible, and allows the measurement of the extent of the jaw size/position discrepancy.

ANB 2-4^{o}= Class I skeletal pattern

ANB > 4^{o}= Class II skeletal pattern

ANB < 2^{o}= Class Ill skeletal pattern

Interpretation of MMPA:

MMPA (max/mand planes angle) 27^{o}(±4)

Gives an inclination of the maxilla relative to the mandible, this in turn indicates the relative proportions of face height and acts as an indicator for future growth direction (Forward or Backward rotation).

Interpretation of Incisor to maxilla/mandible angles:

Gives a measurement of the extent of the proclination or retroclination of the incisors

1 - Mx - Upper incisor to Maxilla angle - 109^{o} (±6)
1 - Mn - Lower incisor to Mandible angle - 93^{o} (±6)
OR
if MMPA is not normal (ie greater or less than 27^{o}) the 'normal' lower incisor - Mn angle is calculated as 120^{o} minus MMPA

Cephalometric analysis: Values used in SA

		Caucasian Norms 9years	Negroid Norms 9years	Patient values	Interpretation
SOFT TISSUES	**S-Line**	0-1mm			
	Naso labial angle	90-110mm			
	Lip thickness	14-16mm			
	Lip tension	1mm			

SKELETAL	**Ba-N-A**	61^0 +/- 3			M	P	R
	SNA	81^0 +/- 3	85^0 +/- 2		M	P	R
	SNB	80^0 +/- 2	81^0 +/- 2		M	P	R
	ANB	2^0 +/- 2	5^0 +/- 2		I	II	III
	WITS	- 4^0 to 4			I	II	III

Abbreviations: M: mesiognathic (normal) **P:** prognathic **R:** retrognathic

I: Skeletal Class I (normal) **II:** Skeletal Class II **III:** Skeletal Class III

GROWTH	**Facial axis**	90^0			N	V	H
	Mand plane angle	32^0 +/- 2	34^0 +/- 2		N	V	H
	UFH : LFH	45 : 55			N	V	H

Abbreviations: UFH:LFH : Upperfacial height : Lowerfacial height

N: Normal **V:** Vertical **H:** Horizontal

DENTO-ALVEOLAR	**Interincisal angle**	131mm	114mm		N	P	R
	Mx incisor : NA	22^0			N	P	R
	Mx incisor : NA	4mm			N	P	R
	Md incisor : NB	25^0			N	P	R
	Md incisor : NB	4mm			N	P	R
	Occlusal plane	14^0					

Abbreviations: Mx: Maxillary **Md:** Mandibular **N:** Normal **P:** Protrusive **R:** Retroclined

<u>Interpretation of Skeletal values</u>

Ba-N-A:

The normal value is 61^0 (+/- 30)

If the value is higher than the normal range of values then the maxilla is prognathic. The normal range could be interpreted as mesiognathic while less than normal would be interpreted as retrognathic

SNA: The normal Caucasian value is 81^0 (+/- 3), while the Negroid norm is 85^0 (+/- 2).

SNB: The normal Caucasian value is 80^0 (+/- 2) while the Negroid norm is 81^0 (+/- 2)

ANB: This angle reflects the relationship between the maxilla and the mandible. The ANB allows us to classify a patient skeletally as Class I, II or III (Steiner classification). Class I has an ANB value of 2^0 (+/- 2^0) in Caucasians whilst in the Negroid population a ANB of 5^0 (+/- 2) constitutes a skeletal Class I. A diagnosis of Class II can be made if ANB has a greater value than the above range, and Class III if ANB is smaller.

The **'Wits'** appraisal (Fig 7) relates the upper jaw to the lower jaw. It represents a skeletal relationship. A perpendicular line is drawn from Point A to the occlusal plane (AO) and then the same from Point B to the occlusal plane (BO). The distance between AO and BO is the Wits value.

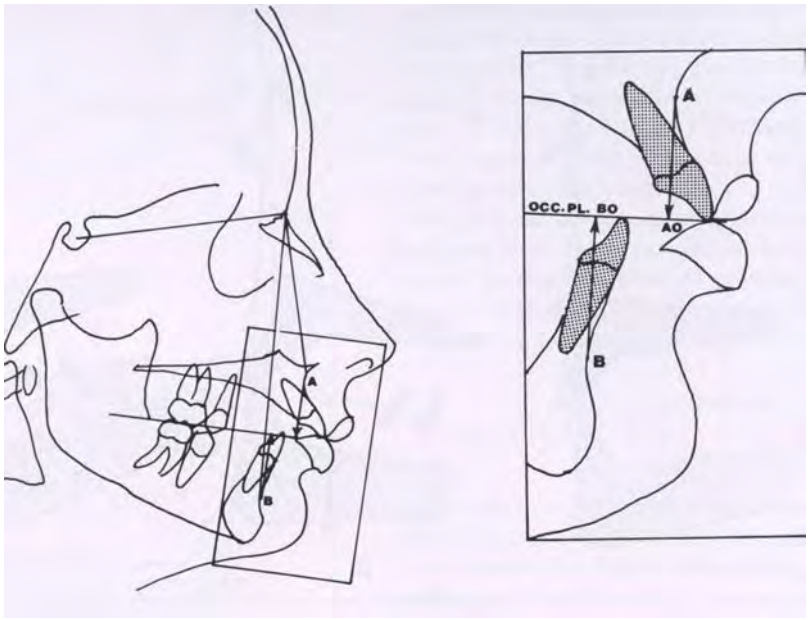


Fig 7: Wits appraisal ceph tracing

Interpretation of 'Wits' appraisal

AO is usually in front of BO and is given a positive value (Class I or a Class II skeletal relationship). When BO appears in front of AO it is given a negative value (Class III skeletal relationship).

The normal Caucasian values are:

Normal = 0,

Class II = 4mm or greater

Class III = -4mm or less

Interpretation of Growth direction

The Mandibular plane (Go- Gn) is measured in relation to the S–N plane.

Normal Caucasian value is 32^0 (+/- 2)

Normal Negroid value is 35^0 (+/- 2)

Values greater than these indicate a vertical growth pattern (hyperdivergent)

Values less than these indicate a horizontal growth pattern (hypodivergent)

The relationship between upper (UFH) and lower facial height (LFH) as a percentage (Fig 8).

UFH is measured from N-ANS,

LFH is measured from ANS to menton

Interpretation

In a well balanced face the percentage is in a ratio of 45/55.

An increase in the LFH component of the ratio indicates a vertical growth pattern. A LFH of less than 55% indicates a horizontal growth pattern

In this example the UFH is 43% and the LFH is 57% and therefore showing a vertical growth tendency

Convert measurements to a percentage: 47mm and 61mm

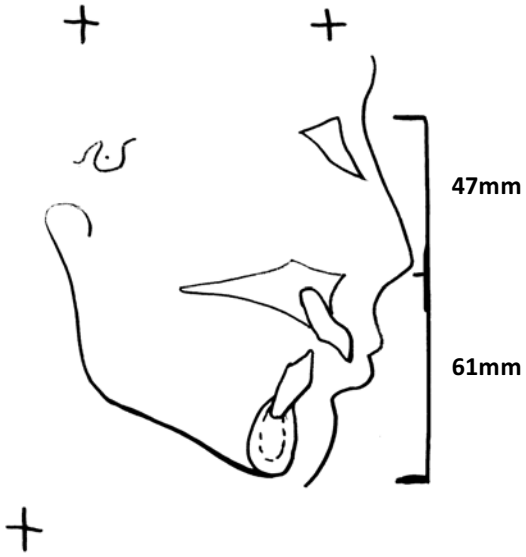


Fig 8: Measurements used to determine growth tendency

<u>Interpretation of Dento-Alveolar findings</u>

The inter-incisal angle indicates the relationship between the upper and lower incisors (Fig 9).

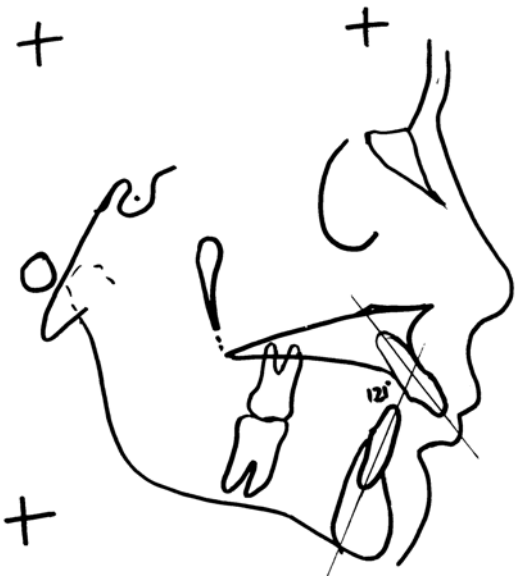


Fig 9: Diagram highlighting the inter-incisal angle

The normal value is 131º. An increased angle indicates one or both incisors, (upper and lower), are retroclined, while a decrease in this angle indicates that one or both of the incisors are proclined.

In our example the value is 121º - indicating incisor proclination without indicating if it is upper, lower or both that are proclined.

Determine the relations of the upper incisors to the maxilla (Fig 10). According to Steiner this is an angular as well as a linear value. The upper incisor is measured to the NA line. The linear value is measured from the incisal tip to the NA line. The angular measurement is the angle between the long axis of the upper incisor and the NA line.

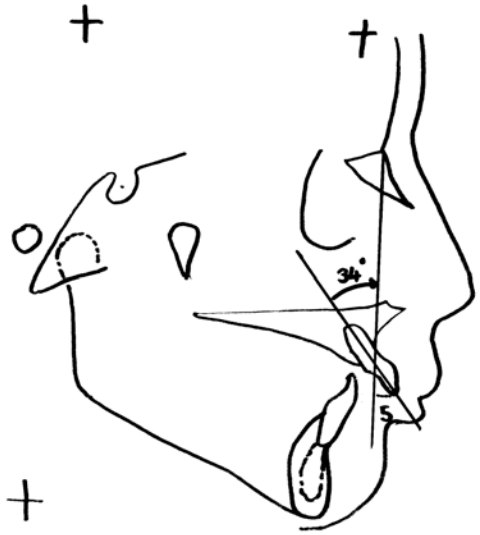


Fig 10: Illustration of the upper incisors to the maxilla

The linear value indicates whether the Mx incisors are protruded, retruded or normally positioned. The normal value is 4mm.

The angular measurement indicates whether the maxillary incisors are proclined retroclined or a normal inclination. The normal value is 22º and 4mm.
Measure the lower incisor in relation to the NB line.

The occlusal plane which was drawn previously can now be measured using the S-N plane as reference (Fig 11). This value illustrates the cant of the cranial base relative to the occlusal plane.

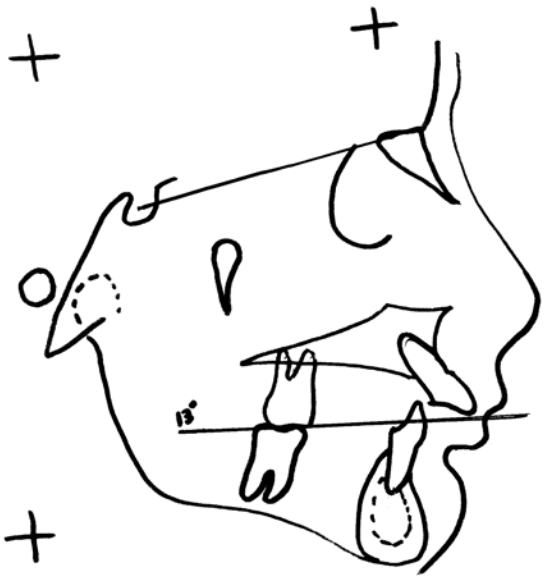
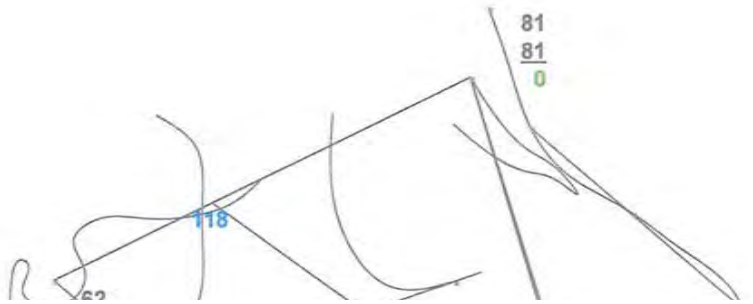


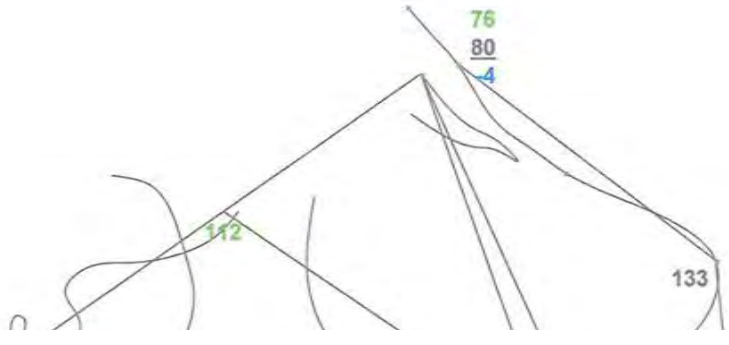
Fig 11: Occlusal plane measured using S-N

The normal value is 14º according to Steiner. There are 2 variables that may affect the size of this angle – the cant of SN and the cant of the occlusal plane.

APPENDIX 7



APPENDIX 8



APPENDIX 9

AFFECTED PERSONS DETAILS:

Name: _____

DOB: _____ Sex: _____

Linguistic group: _____ Linguistic subgroup: _____

Date: _____

Where seen: _____ File No: _____

Patient address: _____

_____

_____

Contact details: _____

Referred by: _____ Tel. No. _____

Specific diagnosis:

_____

_____

_____

Brief clinical history:

- Pregnancy: _____
- Birth: _____
- Fractures: _____
- Operations: _____

Brief family history:

- Affected relatives: _____
- Parent cosanguinity: _____

X Rays: _____

Report of findings:

_____

_____

_____

_____

CLINICAL FEATURES:

General condition: _____

Height: _____ Weight: _____ Head circumference: _____

Limb deformity:

_____

Spinal malalignment: _____

Webbing: _____

Colour of sclera: 1_____ 2_____ 3_____ 4_____ 5_____

Other manifestations:

_____

_____

_____

_____

DENTO/ORO/CRANIOFACIAL FEATURES:

Extra-oral /Facial features:

External Abnormalities: _____

_____

Facial Symmetry: _____

Facial profile:

Covex: _____

Flat: _____

Concave: _____

Maxillary/Mandibular/Protrusive: _____

Maxillary/Mandibular/Retrusive: _____

Lip Posture:

Together relaxed: _____

Together strained: _____

Habits:

Tongue thrust:

_____

Lip wedge: _____

Digit sucking: _____

Bruxing: _____

Other: _____

Comments: _____

Intra-oral hard tissue /dental findings:

Dentition:

Teeth Present/Absent:

Primary				55	54	53	52	51	61	62	63	64	65			
Secondary	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Secondary	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
Primary				85	84	83	82	81	71	72	73	74	75			

Caries:

Primary				55	54	53	52	51	61	62	63	64	65			
Secondary	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Secondary	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
Primary				85	84	83	82	81	71	72	73	74	75			

Decalicified/stained teeth: _____

Midlines: Relative to mid-sagittal plane: _____

Maxillary: mm (R or L) _____

Mandibular: mm (R or L) _____

Overbite: mm _____

Overjet: mm _____

Frena:

Upper: _____

Lower: _____

Oral Hygiene: _____

Radiographical Findings: _____

_____

_____

Pathology: _____

_____

_____

_____

Comments: _____

Treatment plan: _____

_____

_____

Intra-oral soft tissue findings:

_____

_____

_____

_____

_____

TO DO(CHECK LIST):

Document clinical findings: _____

Consent forms: _____

Extraoral and Intraoral photographs: _____

Tooth for histology: _____

Imaging: Panorex: _____ Ceph: _____

Cone Beam: _____ EM: _____

Dental report to referring clinician: _____

APPENDIX 10

RESEARCH PARTICIPANT INFORMATION SHEET: Adult

Study Title: Dental Implications of Inherited Connective Tissue Disorders (ICTD's) in South Africa.

Principal investigator's name: Dr Manogari Chetty

Contact details of principal investigator: email: drmchetty@mweb.co.za

Cell No. 0814472284

Supervisor's name: Professor P Beighton

You are invited to take part in a clinical research study.

Before you decide whether or not you wish to take part, you should read the information provided below. Take time to ask questions and don't feel under pressure to make a quick decision.

You should clearly understand the risks and benefits of taking part in this study. This process is known as 'informed consent'.

You don't have to take part in this study. If you decide not to take part it won't affect your future medical or dental care.

You can change your mind about taking part in the study at any time. Even if the study has begun, you can still opt out. You don't have to give a reason. If you do opt out, rest assured it won't affect the quality of treatment you get in the future.

Why is the study being done?

This research study is being undertaken to document the dental manifestations in persons with ICTDs in South Africa. These observations and findings will identify the dental needs of affected persons. They will also contribute to the understanding of the pathogenesis of the dental features of these disorders and facilitate the formulation of appropriate protocols for dental management.

Who is organizing and funding this study?

This research project is being conducted by Dr Manogari Chetty and Prof Beighton as supervisor for the purpose of obtaining a PhD project in Human Genetics from the University of Cape Town. Where necessary, this project is funded by monies present in Prof Beighton's research fund.

Why am I being asked to take part?

You are being asked to take part because you have a confirmed diagnosis of an inherited connective tissue disorder.

How will the study be carried out?

This study has a predominant clinical component in which dental and craniofacial abnormalities in affected persons will be documented. The dental status of persons with IDCTs attending the UWC-UCT Special Dental Clinic, Red Cross Children's Hospital will be assessed and documented. Investigation of persons with IDCTs at special institutions for the physically handicapped and at collaborating academic centres will be undertaken in Cape Town, Bloemfontein, Kimberly, Durban and Pietermaritzburg.

What will happen to me if I agree to take part?

This is an ongoing study which was registered in April 2012. If you have an ICTD your details will be recorded on a data capture form. You will then be clinically examined (intra and extra oral examination). Intra oral and extra oral pictures will be taken only with your consent. If you refuse to have your pictures taken, you may still participate in this study. Radiographs

of your oro-facial region will be taken. This is dependent on the necessity of these investigations and the availability of these facilities.

What are the benefits?

The findings of this study will contribute to the understanding of the dental features of these disorders and help formulate appropriate protocols for the dental management of affected individuals.

Any dental treatment that you may require will be provided at no cost to you.

What are the risks?

There are no, if any risk at all to you as a research participant. This study necessitates no invasive procedures. There is no risk of physical, psychological, social or economic harm to the participant or his/her family during this study.

Will it cost me anything to take part?

There are no costs at all to you as a research participant. All expenses eg, travel will be taken care of from research funds.

Is the study confidential?

- Written informed consent will be obtained from all participants on standardized forms which will be available in English, Afrikaans, Xhosa and if necessary any other indigenous language.
- All information will be stored in password protected computers. Written information will be stored in a locked office.
- All personal identifiers will be changed when the data are published.
- Photographs will only be used with the eyes hidden and with informed consent.

If you have any further questions or need any further information now or at any time, please contact:Name: Dr Manogari Chetty

RESEARCH PARTICIPANT INFORMATION SHEET:

Parent/Guardian

Study Title: Dental Implications of Inherited Connective Tissue Disorders (ICTD's) in South Africa.

Principal investigator's name: Dr Manogari Chetty

Contact details of principal investigator: email: drmchetty@mweb.co.za

Cell No. 0814472284

Supervisor's name: Professor P Beighton

Your child is invited to take part in a clinical research study.

Before you decide whether or not you wish for your child to take part, you should read the information provided below. Take time to ask questions and don't feel under pressure to make a quick decision.

You should clearly understand the risks and benefits of your child participating in this study. This process is known as 'informed consent'.

Your child does not have to take part in this study. If you decide that you do not wish for hi/her to take part it won't affect your child's medical or dental care.

You can change your mind about your child participating in the study at any time. Even if the study has begun, you can still decide to withdraw your child from the study. You don't have to give a reason. If you do withdraw your child from the study, rest assured it won't affect the quality of treatment your child will receive in the future.

Why is the study being done?

This research study is being undertaken to document the dental manifestations in persons with ICTDs in South Africa. These observations and findings will identify the dental needs of affected persons. They will also contribute to the understanding of the pathogenesis of the dental features of these disorders and facilitate the formulation of appropriate protocols for dental management.

Who is organizing and funding this study?

This research project is being conducted by Dr Manogari Chetty and Prof Beighton as supervisor for the purpose of obtaining a PhD project in Human Genetics from the University of Cape Town. Where necessary, this project is funded by monies present in Prof Beighton's research fund.

Why am I being asked to take part?

Your child is being asked to take part because he/she has a confirmed diagnosis of an inherited connective tissue disorder.

How will the study be carried out?

This study has a predominant clinical component in which dental and craniofacial abnormalities in affected persons will be documented. The dental status of persons with IDCTs attending the UWC-UCT Special Dental Clinic, Red Cross Children's Hospital will be assessed and documented. Investigation of persons with IDCTs at special institutions for the physically handicapped and at collaborating academic centres will be undertaken in Cape Town, Bloemfontein, Kimberly, Durban and Pietermaritzburg.

What will happen to me if I agree to take part?

This is an ongoing study which was registered in April 2012. If your child has an ICTD his/her details will be recorded on a data capture form. He/She will then be clinically examined (intra and extra oral examination). Intra oral and extra oral pictures will be taken only with your consent. If you refuse to have your child's pictures taken, he/she may still participate in this

study. Radiographs of your child's oro-facial region will be taken. This is dependent on the necessity of these investigations and the availability of these facilities.

What are the benefits?

The findings of this study will contribute to the understanding of the dental features of these disorders and help formulate appropriate protocols for the dental management of affected individuals.

Any dental treatment that your child may require will be provided at no cost to you.

What are the risks?

There are no, if any risk at all to your child. This study necessitates no invasive procedures.

Will it cost me anything to take part?

There are no costs at all to the research participant. All expenses eg, travel will be taken care of from research funds.

Is the study confidential?

- Written informed consent will be obtained from all participants on standardized forms which will be available in English, Afrikaans, Xhosa and if necessary any other indigenous language. In the case of minors, consent will be obtained from their parents and where possible, assent will be obtained from children.
- All information will be stored in password protected computers. Written information will be stored in a locked office.
- All personal identifiers will be changed when the data are published.
- Photographs will only be used with the eyes hidden and with informed consent.

If you have any further questions or need any further information now or at any time, please contact:

Name: Dr Manogari Chetty

RESEARCH PARTICIPANT INFORMATION SHEET: Child

Study Title: Dental Implications of Inherited Connective Tissue Disorders (ICTD's) in South Africa.

Principal investigator's name: Dr Manogari Chetty

Contact details of principal investigator: email: drmchetty@mweb.co.za

Cell No. 0814472284

You are invited to take part in a research study.

The results of this study will help identify the dental needs and treat other affected children just like you.

If you agree I will look in your mouth with a mirror and take pictures of your teeth. You might need to have an x ray of your mouth taken. This will help me treat you.

You will experience no pain or discomfort.

You are welcome to ask questions before you decide if you would like me to examine you.

You are welcome to chat with your parents as well before you agree.

If you decide that you would not like to take part in this study, you just have to let me know. I will not ask you any questions and you will receive your medical and dental care as always.

If you agree for me to examine you, and you then change your mind, you just have to let me know and I will immediately stop.

I will keep all your information private

CONSENT FOR PARTICIPATION IN STUDY: (Adult)

STUDY TITLE: Dental Implications of Inherited Connective Tissue Disorders (ICTD's) in South Africa.

1. I have read and understood the information sheet about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction. Yes……. No…….

2. I understand that I do not have to take part in this study and that I can opt out at any time. I understand that I don't have to give a reason for opting out and I understand that opting out won't affect my future medical and dental care. Yes……. No…….

3. I am aware of the potential risks of this research study to me. Yes……. No…….

4. I give permission for researchers to look at my medical records to get information. I have been assured that information about me will be kept confidential. Yes……. No…….

5. I have been given a copy of the information sheet and this completed consent form.

Yes……. No…….

Patient Name: ……

Patient signature (adult): ……

Child assent (7-17 years): ……..

To be completed by the principal Investigator

I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a way that they could understand. I have explained the risks involved as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them.

Principal Investigator Name: ……

Qualifications: ……

Signature: ……

Date: ……

NB: three copies to be made:

- Research participant
- Principal Investigator
- Institution records

CONSENT FOR PARTICIPATION IN STUDY:

(Parent/Guardian-Child)

STUDY TITLE: Dental Implications of Inherited Connective Tissue Disorders (ICTD's) in South Africa.

1. I (parent/guardian) have read and understood the information sheet about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction. Yes……. No…….

2. I understand that my child does not have to take part in this study and that I can have him/her withdrawn from the study at any time. I understand that I don't have to give a reason for withdrawing my child from the study and I understand that withdrawing my child won't affect his/her future medical and dental care. Yes……. No…….

3. I am aware of the potential risks of this research study to my child. Yes……. No…….

4. I give permission for researchers to look at my child's medical records to get information. I have been assured that the information about my child will be kept confidential.

Yes……. No…….

5. I (parent/guardian) have been given a copy of the information sheet and this completed consent form. Yes……. No…….

Patient Name (minor): ……

Parent Name: …….

Parent signature: …….

Child assent (7-17 years): ……..

Guardian name: …….

Guardian signature: ……

To be completed by the principal Investigator

I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a way that they could understand. I have explained the risks involved as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them.

Principal Investigator Name: ……

Qualifications: ……

Signature: ……

Date: ……

NB: three copies to be made:

- Research participant
- Principal Investigator
- Institution records

PATIENT CONSENT TO CLINICAL PHOTOGRAPHS AND PUBLICATION: (Parent/Guardian – Child)

TO WHOM IT MAY CONCERN

I, the undersigned

……in my capacity as parent/guardian consent to photographs being taken of ……..as requested. I understand that these photographs will be stored appropriately, treated with the utmost confidentiality and be part of my child's dental records.

I hereby give consent for the images of my child to be used ONLY for that I have indicated with a tick:

____ Record purposes and for my child's future management

The photographic images will form part of the information collected for your child's care and treatment and will be kept confidential at all times.

____ Education and Training purposes

The photographic images maybe used for teaching purposes and viewed by health professionals outside of the UWC Faculty of Dentistry. The images may be used in talks, conference presentations, posters or on the Internet to help train other health professionals in the management of dental and oral diseases

___ Approved research purposes and publications

This may involve the photographic images being used in medical or dental publications, journals, textbooks, conference material, e-publications and on the Internet. Images will be

seen by health professionals and researchers who use the publications in their professional education. The images may be seen by the general public. Images will not be used with identifying information such as name, however, full confidentiality is not guaranteed.

___ Other Purposes (please specify): ……..

- I understand that all efforts will be made to conceal my child's identity but that full confidentiality cannot be guaranteed
- I understand that my consent or refusal will in no way affect my child's dental care

Patient Name (print)……

Parent/Guardian if patient is under 18 years of age (print name): ……

Parent/Guardian Signature: ……

Date: ……

Child assent (7-17 years): ……..

Principal Investigator print name: ……..

Principal Investigator signature: ……..

Date: ……..……

Requesting Clinician name (print)…….……

Date: …….. Department: …….. Phone: ……

Patient Name (print): ……

Views Required: ……

Required for (tick): Records ____ Teaching/ Lectures____ Research____ Publication ____

Images taken by: …… Date: ……..

Location where copies are stored: ……..

PATIENT CONSENT TO CLINICAL PHOTOGRAPHS AND PUBLICATION: (Adult)

TO WHOM IT MAY CONCERN

I, the undersigned

……consent to photographs being taken of myself as requested. I understand that these photographs will be stored appropriately, treated with the utmost confidentiality and be part of my dental records.

I hereby give consent for these images to be used ONLY for that I have indicated with a tick:

____ Record purposes and for my future management

The photographic images will form part of the information collected for your care and treatment and will be kept confidential at all times.

____ Education and Training purposes

The photographic images maybe used for teaching purposes and viewed by health professionals outside of the UWC Faculty of Dentistry. The images may be used in talks, conference presentations, posters or on the Internet to help train other health professionals in the management of dental and oral diseases

___ Approved research purposes and publications

This may involve the photographic images being used in medical or dental publications, journals, textbooks, conference material, e-publications and on the Internet. Images will be seen by health professionals and researchers who use the publications in their professional

education. The images may be seen by the general public. Images will not be used with identifying information such as name, however, full confidentiality is not guaranteed.

___ Other Purposes (please specify): ……..

- I understand that all efforts will be made to conceal my identity but that full confidentiality cannot be guaranteed
- I understand that my consent or refusal will in no way affect my dental care

Patient Name (print)……

Patient signature: ……

Principal Investigator print name: ……..

Principal Investigator signature: ……..

Date: ……..……

Requesting Clinician name (print)……

Date: …….. Department: …….. Phone: ……

Patient Name (print): ……

Views Required: ……

Required for (tick): Records ____ Teaching/ Lectures____ Research____ Publication ____

Images taken by: …… Date: ……..

Location where copies are stored: ……..

CONSENT FOR DNA ANALYSIS AND STORAGE

1. I, ……., request that an attempt be made using genetic material to assess that I / my child / my unborn child (delete where not applicable) might have inherited a disease causing mutation in the gene for ……..

2. I understand that the genetic material for analysis is to be obtained from blood / saliva (delete where not applicable).

3. I request that no portion of the sample be stored for later use…….. (tick if applicable)

OR

I request that a portion of the sample be stored indefinitely, for 5 years, for 1 year, until the study is completed (delete where not applicable) for

- Possible re-analysis
- Analysis for the benefit of members of my immediate family
- Research purposes, subject to the approval of the Research Ethics Committee, provided that all information will remain confidential

4. The result of the analysis will be made known to me, via my doctor(s), in accordance with the relevant protocol, if and when available.

5. If clinically relevant, I authorise that the results may be made known to family members.

6. I have been informed that:

- the analysis procedure is specific to the genetic condition and cannot determine the complete genetic make-up of an individual.

- the genetics laboratory is under an obligation to respect medical confidentiality

- genetic analysis may not be informative for some families or family members

- even under the best conditions, current technology of this type is not perfect and could lead to incorrect results

- where biological material is used for research purposes, there may be no direct benefit to me

7. I understand that I may withdraw my consent for any aspect of the above at any time without this affecting my future medical care.

8. All of the above has been explained to me in a language that I understand and my questions answered by:

Doctor/Consultant: …… Date: ……

Patient/Parent: …….. Date: ……

Laboratory Findings: _____

_____

_____

_____

_____

_____

APPENDIX 11

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za
www.health.uct.ac.za/research/humanethics/forms

02 May 2013

HREC REF: 203/2013

Dr M Chetty
c/o Prof P Beighton
Human Genetics
Level 3 WBN
FHS

Dear Dr Chetty

PROJECT TITLE: DENTAL IMPLICATIONS OF INHERITED CONNECTIVE TISSUE DISORDERS IN SOUTH AFRICA

Thank you for addressing the issues raised by the Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year till the 28 May 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

sAriefdien

APPENDIX 12

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA			
This serves as notification		**:umentation described below.**	
☐ Approved	Annual progress report	Approved until/next renewal date	30/5/2015
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	21/5/2014

Comments to PI from the HREC

1. Protocol information

Date form submitted	21/05/2014		
HREC REF Number	203/2013	Current Ethics Approval was granted until	28/05/2014
	Dental Implications of Inherited Connective Tissue Disorders in South Africa		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☐x No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Manogari Chetty		
Department / Office Internal Mail Address	Human Genetics		

RESEARCH ETHICS COMMITTEE
2014 -05- 21
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

1.1 Does this protocol receive US Federal funding?	☐ Yes	☐x No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

APPENDIX 13

UNIVERSITY OF CAPE TOWN

HREC office use only (FWA00001637: IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	3/5/2016
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	16/03/2015

Comments to PI from the HREC

HUMAN RESEARCH ETHICS COMMITTEE
16 MAR 2015
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

1. Protocol information

Date (when submitting this form)	13/03/2015		
HREC REF Number	203/2013	Current Ethics Approval was granted until	May 2016
Protocol title	Dental Implications of Inherited Connective Tissue Disorders in South Africa		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☐x No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study			
Principal Investigator	Dr Manogari Chetty		
Department / Office Internal Mail Address	Human Genetics drmchetty@mweb.co.za; peter.beighton@uct.ac.za		

1 1 Does this protocol receive US Federal funding?	☐ Yes	☐x No
1 2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No
1 3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget	☐ Yes	☐x No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)