Return of a Fragile X Syndrome Genetic Result:

Exploring the feedback of Individual genetic findings and their relation to traditional knowledge in a village in Cameroon.

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Thesis submitted to the University of Cape Town
In fulfilment of the requirements of PhD degree in Genetic Counselling

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Declaration

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

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1. **Kamga, K. K.,** de Vries, J., Nguefack, S., Munung, N., & Wonkam, A. (2020). Lived experiences of Fragile X Syndrome caregivers: A scoping review of qualitative studies. *Frontiers in Neurology, 11*, 128. DOI:10.3389/fneur.2020.00128
2. **Kamga, K. K.,** Nguefack, S., Minka, K., Wonkam Tingang, E., Esterhuizen, A., Nchangwi Munung, S., de Vries, J., & Wonkam, A. (2020). Cascade Testing for Fragile X Syndrome in a Rural Setting in Cameroon (Sub-Saharan Africa). *Genes, 11*(2), 136. DOI:10.3390/genes11020136
3. **Kengne Kamga K**, De Vries J, Nguefack S, Munung NS, Wonkam A. Explanatory models for the cause of Fragile X Syndrome in rural Cameroon. J Genet Couns. 2021;00:1-10. DOI:10.1002/jgc4.1440
4. **Kamga K. K.,** Nchangwi Munung, S., Nguefack, S., Wonkam, A., & de Vries, J. (2020). A poisoned gift: genetic guilt, diagnostic closure, and communicating about genetic risk for Fragile X Syndrome in a Cameroonian family. *journal of genetic counselling.* (Under review).
5. **Kengne Kamga K**, Munung NS, Nguefack S, Wonkam A, De Vries J. Negotiating political power and stigma around fragile X Syndrome in a rural village in Cameroon: A tale of a royal family and a community. Mol Genet Genomic Med. 2021;9(3):e1615. DOI:10.1002/mgg3.1615

Signature: Signed by candidate **Date:** 2nd February 2020

Student Name: Kengne Kamga Karen **Student Number:** KRNKEN003

Preface

Fragile X Syndrome (FXS) is the most common genetic cause of intellectual disability and Autism Spectrum Disorder. It is caused by the expansion of Cytosine, Guanine, Guanine (CGG) repeats at the 5' untranslated region of the Fragile X Mental Retardation gene 1 (*FMR1*). This gene codes for the Fragile X Mental retardation protein, and the absence of this protein leads to FXS. This condition is transmitted through an X-linked dominant pattern and is known to affect approximately 1 in 3600 males and 1 in 8000 females in some countries. However, the global prevalence of FXS is not known because the data reported is based on research from the western world. There is no evidence of the prevalence, burden or outlook of Fragile X in African countries, translating into an urgent need to investigate rare genetic conditions like FXS in Africa. The related publications throughout the registration period of this PhD project aimed to explore the impact of returning positive FXS results to an affected family in Cameroon and to explore the community's traditional knowledge of inherited forms of intellectual disability.

Research concept and Funding

The candidate conceptualised the research proposal under the supervision of Professor Ambroise Wonkam and Professor Jantina de Vries. The project formed part of the Human Heredity and Health in Africa (H3Africa), Individual Findings in Genetic Research in Africa (IFGeneRA), Ethical, Legal and Social Implications (ELSI) Collaborative Centre that is co-directed by Professors Wonkam and de Vries funded by the National Institute of Health (NIH).

Candidate contribution

Guided by the supervisors, the candidate's contribution to the publications included in this thesis was conceptualising and designing the research project, sampling and recruiting participants, analysing experimental results, drafting the full manuscripts, and incorporating revisions from co-authors and journal reviewers.

Publications

Synthesis and drafting of all texts included in this thesis were executed in full by the candidate, after which revisions from all co-authors were similarly incorporated before submission to the journal by the primary supervisor. After review, the candidate, with the primary supervisor addressed all the reviewer's comments. The specific role of the candidate in the included publications is clearly defined in each chapter.

The format of this thesis by publication aimed to contribute significantly to scholarship on the ethics and other aspects regarding the genetics of Fragile X Syndrome. In addition, the inclusion of these published works also aimed to i) set a path that would strengthen the academic career of the candidate; ii) increase his candidacy for continued financial support from bodies that support this work, namely the IFGeneRA, Genetic Medicine of African populations (GeneMAP) and the University of Cape Town; iii) qualify his participation and attendance to academic conferences and training workshops. The candidate successfully attended several specialised national and international conferences in Cape Town, Tunisia, Mali, and the United States of America, and lastly; iv) the published work forms essential parts of a consistent body of research that aligns with the Faculty of Health Sciences policies. These policies promote the publication of thesis research work to disseminate knowledge generated and further improve the profile of the institution and the candidate.

Published articles included:

1. **Kamga, K. K,** de Vries, J, Nguefack, S, Munung, N, & Wonkam, A. (2020). Lived experiences of Fragile X Syndrome caregivers: A scoping review of qualitative studies. *Frontiers in Neurology, 11*, 128. DOI:10.3389/fneur.2020.00128
2. **Kamga, K. K,** Nguefack, S, Minka, K, Wonkam Tingang, E, Esterhuizen, A, Nchangwi Munung, S, de Vries, J, & Wonkam, A. (2020). Cascade Testing for Fragile X Syndrome in a Rural Setting in Cameroon (Sub-Saharan Africa). *Genes, 11*(2), 136. DOI:10.3390/genes11020136
3. **Kengne Kamga K**, De Vries J, Nguefack S, Munung NS, Wonkam A. Explanatory models for the cause of Fragile X Syndrome in rural Cameroon. J Genet Couns. 2021;00:1-10. DOI:10.1002/jgc4.1440
4. **Kamga K. K,** Nchangwi Munung, S, Nguefack, S, Wonkam, A, & de Vries, J. (2020). A poisoned gift: genetic guilt, diagnostic closure, and communicating about genetic risk for Fragile X Syndrome in a Cameroonian family. *journal of genetic counselling.* (Under review).
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This project and thesis are presented in three components: 1) scoping review of qualitative literature of the lived experiences of FXS caregivers; 2) cascade counselling and testing for FXS in a rural setting of Cameroon; and 3) a qualitative component which describes the explanatory model for FXS, the effects of receiving a FXS genetic diagnosis and the stigma which is associated with FXS in this rural Cameroon community. Under Rules GP6.7 of University of Cape Town's (UCT) Doctoral Degree Board, the candidate has met all requirements and approval as follows:

1. The candidate's proposal to include publications in the current thesis was approved by the UCT Faculty of Health Sciences' Doctoral Degrees Board.
2. The thesis contains an adequate summary, introduction, a chapter on the aims and objectives, a comprehensive academic discussion of the results that forms the basis for the conclusions and perspectives drawn from this research.
3. Each results chapter with publications included is preceded by a synopsis of how the publications directly link to the aims and objectives of the project and the thesis.
4. All included publications were written and published during the candidate's tenure (from 2018) as a PhD student.

The candidate,

Signed by candidate

Dr Kengne Kamga Karen, MD

Abstract

Introduction: Fragile X Syndrome (FXS) is the most common genetic cause of intellectual disability (ID) and Autism Spectrum Disorder (ASD). It is caused by the expansion of CGG (Cytosine, Guanine, Guanine) repeats at the 5' untranslated region (UTR) of the Fragile X Mental Retardation gene 1 (*FMR1*). This gene codes for the Fragile X Mental retardation protein, which is responsible for healthy brain development. This condition is transmitted through an X-linked dominant pattern and is known to affect approximately 1 in 2500–4000 males and 1 in 7000–8000 females.

In 2011, two siblings received a positive diagnosis of FXS at the Child Neurology Unit of the Yaoundé Gynaeco-Obstetric and Paediatric hospital in Cameroon. Informal data from the first consultation with their mother (P0), showed that she related her children's condition to a curse from her maternal grandfather, the village's chief. This prompted us to ask four research questions for this project: What is the transmission pattern for FXS in this family? How do families and communities explain the pattern of FXS and other inherited forms of ID in the village? What is the impact of receiving a genetic diagnosis on individuals, families, and communities? And what are the stigma experiences around FXS in this community? As a first step to gather empirical work, a scoping review of the lived experiences of FXS caretakers was conducted. It was revealed that these experiences could broadly be summarised into four main themes, namely: grief experiences, challenges of living with FXS, coping mechanisms, and the need to plan for the future of children with FXS. From this review, it was noted that healthcare workers had limited knowledge and a lack of expertise regarding FXS, whilst there was an overall lack of African qualitative literature on FXS. This set the precedent for the second and third components of the project.

Methodology: An ethnographic approach was used in this study. Snowball sampling was used to recruit 92 participants who were 18 years old and above. A topic guide was used to gather data through 10 focus group discussions and 23 in-depth interviews with NVivo 12 used for data analysis. The questionnaire explored participants' understanding of FXS, their lived experiences, the stigma association with FXS, and the effects of receiving a positive or negative genetic diagnosis. Moreover, cascade counselling and testing for FXS was offered to 46 participants. Data gathered from this component was analysed using Epi-info 7.2. and pedigrees were drawn using Cyrillic 3.0.400.

Results & Discussion: Cascade testing included 58% of participants (n = 27/46) that were females. The FXS laboratory diagnosis of females showed 14.81% (n = 4/27) with a full mutation, 37.04% (n = 10) had a premutation and 48.15% (n = 13/27) were normal. On the other hand, 21.05% (n=4/19) males had a full mutation. The analysis of this family's pedigree further revealed that the founder of this family was probably a normal transmitting male carrier.

Moreover, people in the community and this family described the causes of FXS or inherited forms of ID in four different explanatory models. The curse model was the primary explanatory model and is based on a curse from the chief who bewitched his daughters and wives because they did not mourn his ID servant. Other explanations were the spiritual model that relates FXS to a punishment from God and the psychosocial model, which attributes FXS to events in the prenatal and perinatal periods. Finally, the genetic model is an emerging explanation resulting from the return of the FXS genetic result.

Furthermore, receiving a genetic diagnosis resulted in two main themes which were psychological adaptation and communication of the genetic risk of FXS. Receiving a diagnosis was associated with happiness and relief, while the latter described genetic guilts, survivor guilt, and frustrations associated with a family history of FXS and taking care of developmentally delayed children.

Lastly, in this community, we identified public stigma directed towards the royal family and courtesy stigma experienced by the royal family members. Most interviewees believed that people from the royal family should have a unique way of addressing FXS children from the chieftaincy because of their position in society. Due to their social position, the royal family uses their status to negotiate marriages with community members.

Conclusion: Early detection of carrier status will increase family planning options through genetic counselling, premarital screening, and prenatal diagnosis. My findings identified specific sociocultural challenges that should be addressed during the development and implementation of genetic counselling services. Returning the result of a genetic test can create feelings of guilt in the patient and their relatives. Over time, these families can develop coping mechanisms that revolve around preparing future generations about the risk of having FXS. Hence, health care workers or people who are comfortable talking about FXS should serve as intermediaries for affected families.

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Abbreviations

ASD – Autism Spectrum Disorder

CGG – Cytosine, Guanine, Guanine

ELSI – Ethical, Legal and Social Implications

FMR1 – Fragile Mental Retardation Gene 1

FMRP – Fragile Mental Retardation Protein

FXPOI – Fragile X Associated Premature Ovarian Insufficiency

FXS – Fragile X syndrome

FXTAS – Fragile X Associated Tremor/Ataxia Syndrome

GeneMAP – Genetic Medicine of African populations

H3Africa – Human Heredity and Health in Africa

ID – intellectual disability

IFGENERA – Individual Findings in Genetic Research in Africa

mRNA – messenger RNA

NIH – National Institute of Health

PCR – Polymerase chain reaction

UTR – untranslated region

Chapter 1: Introduction

Fragile X syndrome (FXS) is the main genetic cause of intellectual disability (ID) and Autism spectrum disorder (ASD). It occurs due to a mutation on the Fragile X Mental Retardation gene 1 (*FMR1*) found on the X chromosome (Coffee et al, 2009; Peprah, 2012; Santoro et al, 2012). This mutation is related to a CGG (Cytosine, Guanine, Guanine) repeat expansion at the 5' untranslated region of the *FMR1* gene. According to the World Health Organisation (2020), the mutation at this site can be found in 1 out of 2000 males and 1 out of 259 females, and the incidence of FXS is about 1 out of 3600 males and 1 out of 4000–6000 females. Although the CGG expansion is responsible for over 98% of cases, FXS can also occur because of point mutations affecting the FMR1 (Peprah, 2012; Santoro et al, 2012).

The translational product of FMR1, Fragile X Mental Retardation Protein (FMRP), is found in high concentrations in the testes and the brain (McLennan et al, 2011; Santoro et al, 2012). It is thought that FMRP is responsible for transporting about 4% of messenger RNA (mRNA) from the nucleus to the synapse of neurons. A close analysis of brain tissue from humans and mice with FXS reveals an abnormal dendritic spine, which in normal circumstances helps to increase contact with other neurons through synapses. This dysfunction in the formation of synapses and neuronal circuits results in impaired neuroplasticity that can reflect the individual's memory and learning capacities (Bassell & Warren, 2008; McLennan et al, 2011; Santoro et al, 2012). It has long been suspected that this is involved in the sensory pathophysiology of FXS (Bureau et al, 2008). Besides this, FMRP has been implicated in several signalling pathways targeted by several drugs currently undergoing clinical trials (McLennan et al, 2011; Santoro et al, 2012).

The diagnosis of FXS and carrier status was first achieved in the 1970s through cytogenetic analysis. Cells were cultured in a folate-deficient medium and then assessed for the fragile site on the X chromosome. Hogan et al, (2012) reported that this technique was not reliable because of its low specificity and sensitivity. However, since the advent of new technologies from the 1990s, we now have molecular techniques with higher sensitivities and specificities that can be used to diagnose FXS and determine carrier status (Hogan, 2012). The most readily available technology is the Polymerase Chain Reaction (PCR) coupled with southern blotting. PCR is used to determine the length of the CGG triplet repeats, particularly for the normal/premutation allele, while southern blotting can assess the methylation status of the expansion alleles (Chen et al, 2011; Filipovic-Sadic et al, 2010; Garber et al, 2008; Kanwal et al, 2015). This method is only used to count the number of CGG repeats in the *FMR1* gene and

not access deletions and missense mutations that may be involved with this gene. In this light, the *FMR1* gene's sequencing is necessary if there is a clinical suspicion of FXS (Garber et al, 2008).

When counting the number of CGG repeats, diagnosis normally points to one of three main categories, namely, normal, FXS premutation, and full FXS mutations for the *FMR1* gene. In healthy individuals, the number of CGG repeats on the *FMR1* gene varies between 5 and 44, with a mean of 30 repeats (Maddalena et al, 2001; Peprah, 2012; Santoro et al, 2012). However, a grey zone exists between 45-54 repeats, and these alleles are also known as intermediate suspension alleles. On the other hand, when the number of CGG repeats range between 55-200 repeats, it is considered as a premutation and above 200 repeats, the allele is considered a full FXS mutation (Crawford et al, 2001; Lozano et al, 2016; Maddalena et al, 2001; McLennan et al, 2011; Nolin et al, 2003). As alleles get longer and longer, and DNA polymerase becomes unstable, intermediate alleles can expand to become a premutation allele. Hence, a premutation allele can become a full FXS mutation allele. With the full FXS mutation, the Cytosines in the CGG are methylated by a DNA methylase. This methyl group causes the chromatin to condense and shut-off *FMR1*. This is what gives the characteristic appearance to the X chromosome when viewed under a microscope (Colak et al, 2014).

Fragile X syndrome follows an X-linked dominant pattern of inheritance with reduced penetrance and variable expressivity (Dobyns et al, 2004; Garber et al, 2008). Females with full FXS mutation alleles sometimes present with milder symptoms than males because of the variability that occurs due to X-inactivation (Santoro et al, 2012). Before associating the *FMR1* to FXS, the family pedigree analysis suggested that healthy male carriers could have affected grandchildren with more severe symptoms than their siblings. In this circumstance, genetic anticipation was known to have occurred. This phenomenon is also described as the Sherman paradox (Santoro et al, 2012; Sherman et al, 1985). Males pass on their mutated allele unchanged to all their daughters, while females can increase the length of the CGG repeats in their premutated alleles, resulting in a full FXS mutation in the next generation (Nolin S. L. et al., 2019; Nolin Sarah L et al., 1996). Hence, females with an *FMR1* mutation can pass on a full FXS mutation allele to their children, and theoretically, there is a 50% chance of having an affected child at every pregnancy (Marco & Skuse, 2006).

FXS manifests with subtle signs in the early stages of development. As individuals evolve in life, they might be asymptomatic or present changes in their physical appearance, developmental milestones or social behaviours. They may also develop psychiatric disorders

and present with some abnormalities in their neurological state. The main features seen in this syndrome are large ears, protruding ears, or both; long face characterised by an excess vertical maxillary that could result in the high-arched palate; large testicles in men which is mainly discovered after puberty; and more discrete signs like hyperextensible joints of the thumb (Crawford et al, 2001; Hansen & Hagerman, 2005; Lubala et al, 2018). Males with a full FXS mutation display virtually complete penetrance and will almost always show symptoms of FXS. Females with a full mutation generally display a 50% penetrance due to having a second, normal X chromosome (Santoro et al, 2012).

One area of concern for caregivers and people with FXS is their short-term and working memory. Hall et al, (2008) reported in a longitudinal study that affected children were 55% slower than non-affected children in executing daily tasks and simple commands. In addition, they described the challenges children with FXS had recognising people that they have seen before (Holsen et al, 2008). Other scholars report that whilst individuals with FXS display empathy to those they are familiar with, when in unfamiliar environments, they become depressed (Budimirovic & Kaufmann, 2011; Tranfaglia, 2011). Hyperactivity and attention deficit disorders are also reported to affect mostly males, which is the most common psychiatric disorder in FXS (Goldstein & Reynolds, 2010; McLennan et al, 2011; Tranfaglia, 2011). Seizures are also reported as a common sign in people with FXS. In 2010, Berry-Kravis et al, in their survey of caregivers, found that seizures were a common presenting sign in 14% of males and 6% of females. The seizures were characterised as partial, non-frequent, and amendable with medication (Berry-Kravis et al, 2010).

There are well-known associated syndromes of FXS known to occur in individuals who are carriers of premutation alleles for FXS. These syndromes are Fragile X Associated Tremor/Ataxia Syndrome (FXTAS) and Fragile X Associated Premature Ovarian Insufficiency (FXPOI). Fragile X syndrome associated Tremor/Ataxia syndrome is a progressive neurodegenerative disease seen in approximately half of the male carriers over the age of 70 years old with reduced penetrance in females. Typically, the onset of tremor occurs in the sixth decade of life, with subsequent progression to ataxia and gradual cognitive decline (Peprah, 2012; Santoro et al, 2012). Bili et al, (2010) argued that FXPOI is mostly seen with FXS premutation alleles than with full FXS mutation alleles and concluded that from 100 CGG repeats, the risk of FXPOI is reduced. On the other hand, close to 20% of women with FXPOI will experience their menopause before the age of 40 years (Peprah, 2012; Santoro et al, 2012). Despite this, in 2014, Sherman et al, suggested that women with FXPOI could still get pregnant because their ovaries could occasionally release viable eggs.

As far as life expectancy is concerned, Coppus (2013) in their review suggested that the life expectancy of individuals with FXS was lower than that of the general population. However, death causes were similar to the causes of death in the general population (Coppus, 2013). Living with Fragile X syndrome impacts the lives of the child, the parents, and the caregivers. FXS affects the patient and their family through the psychosocial and financial challenges that come with this neurodevelopmental condition. This impact may assume that certain factors may influence the economic cost of health care, morbidity, and mortality. In low-income countries, no study has been done to date to evaluate this impact. Nonetheless, a few studies in the United States of America (Angelis et al, 2015; Bailey Jr et al, 2012; Iosif et al, 2013; Nazareth et al, 2016; Sacco et al, 2013; Vekeman et al, 2015) and France (Chevreul et al, 2015) have revealed that the burden of FXS could be associated to the high health care cost which may be attributed to medical procedures, hospitalisation, and medications to a lesser extent. Furthermore, the family members may be affected by absenteeism at work, and financial losses related to disability leave that they take. Moreover, there may be a sense of discrimination and stigmatisation in the general population as soon as the diagnosis is made.

Cameroon is an African country found in the northern hemisphere at latitude 7.369722 and longitude 12.354722 (Geodatos, 2020). Also known as “Africa in miniature”, Cameroon has a diverse cultural and linguistic heritage, which mimics Africa’s heterogeneity. Her population was estimated to be 25,876,380 in 2019 (World Bank, 2020). The health care system is organised into private, public, and traditional sectors without universal health coverage. More than 50% of the rural population live in poverty and in these areas, FXS patients frequently depend on financial support and caregiving from family members and regularly consult traditional healers. This implies that people who need a particular type of care may not have access to it because they may not be able to afford the cost of the services (Wonkam et al, 2014; World Bank, 2012). Apart from endemic diseases like malaria, Cameroon, like many other low-and-middle-income countries, is experiencing a surge in the burden of non-communicable diseases, amongst which some have genetic origins (Wonkam et al, 2011a).

The Paediatric Neurology Unit of the Yaoundé Gynaeco-Obstetric hospital is one of Cameroon’s leading hospitals that deal with children with developmental delays. In 2011, two siblings received a positive diagnosis of FXS at this hospital (Nguefack et al, 2013). While investigating these children’s condition, their mother revealed that they come from a royal family from Western Cameroon, where several individuals have symptoms similar to the clinical presentations of FXS. She described the high incidence of mental retardation in the

family and community that was attributed to a “generational royal curse”. Unsatisfied with this explanation, the mother had sought a diagnosis from Western medicine.

Receiving a diagnosis of FXS has proven to be helpful to families. Roy et al, (1995) suggested that genetic counselling services provided to families after diagnosis helped parents to have a better appraisal of what is wrong with their child, thereby, serving as psychotherapy for parents to relieve the psychosocial burden associated with bearing affected children. To date, no empirical study has been conducted on how FXS is understood by African communities and on the effect that receiving a genetic diagnosis has on the lives of those living with or affected by this condition. In this project, the effect of receiving a genetic diagnosis on a family and community affected by Fragile X syndrome living in rural Cameroon was explored. We used this project to explore the relationship between modern genetic knowledge and traditional beliefs about inherited conditions such as FXS.

Chapter 2: Research Methodology

2.1 Introduction

In this chapter, I will present an overview of the study methods and approach, starting with a description of the research site, followed by the aims and the objectives of my study. I will then outline my research design and the sampling strategy before describing the different phases of my research under the procedure section. After this, I will describe the data collection and analysis process. The chapter will conclude with a reflection on my position as a researcher and discuss pertinent ethical considerations. By necessity, the content of this chapter overlaps with the brief methods sections of the published manuscripts that make up the remainder of the thesis, but it transcends the descriptions in those manuscripts by providing a more comprehensive account of the study, complemented by elements that are not generally presented in manuscripts, such as a description of researcher positionality.

2.2 Study site

The district in the Western region of Cameroon where I conducted my study, is characterised by scattered settlements, with approximately 5243 people living in the town and 31686 people living in the rural area (BUCREP, 2010). The village in which I conducted my study is a small locality found in a rural area with a population of approximately 2000 inhabitants. The languages spoken are French, English, Pidgin, and Ngombale, which is the local ethnic language. This community houses the mother (P0) whose children received a positive FXS diagnosis in 2011 from a specialised hospital in Cameroon. Unofficial information from her first consultation revealed that this community had a high prevalence of people with ID, and this was attributed to a curse by the founder of the village. Years later, and still fascinated by this story, the original medical geneticist and consulting paediatrician secured funding and involved me in a more extensive study that aimed to investigate the patterns of inheritance for FXS in the family, and how the family and their community understand FXS.

2.3 Aim

This study aimed to explore the impact of returning a positive FXS result to an affected family in Cameroon and to explore the traditional knowledge of the community towards inherited forms of ID.

2.4 Research questions

We asked the following research questions:

a) Which other members of the patient P0's family are affected by FXS, and what is the pattern of FXS transmission in this family?
b) What are the effects of receiving a genetic diagnosis of FXS on the lives of the indicator family, and how does the genetic diagnosis affect (relations with) other family members and the community?
c) What are the different explanatory models used by the family and the community to explain the high prevalence of ID in their village?
d) What are the traditional perceptions of genetics and the role of stigma in the context of FXS in this village?

2.5 Research design

The research design is one of the most important aspects of a research study as it provides guidance for the research process and the interpretation of the results (Gobo, 2008). In the present study, I used an ethnographic approach (Reeves et al, 2008) to gather data to describe the cultural influences, attitudes, and perception of inheritable ID in this rural community after returning positive FXS genetic results. Data were gathered through focus group discussions (FGDs), in-depth interviews (IDIs), and field observations. This method was used by Gagnon et al, (2019) to propose a more comprehensive assessment of the quality of engagement across professional cultures in implementation studies.

2.6 Sampling strategy and gaining access to the study sample

Sampling is an essential part of research because it helps select a portion of the population, which is representative of the whole. Onwuegbuzie & Collins (2007) explain that this is because careful sampling informs the quality of the conclusions made by the researcher based on the research findings. Therefore, for this research, snowball sampling was used (Handcock & Gile, 2011; Noy, 2008) where the research sample was based on the extended family members of P0 and her community members who agreed to be part of the study through an interview. Participants were recruited voluntarily through snowball sampling, starting with P0 and extrapolating to her extended family with whom she shared her diagnosis and members of her community of origin.

Several selection criteria were employed. The main selection criterion was to target participants who were 18 years and older and were knowledgeable about the high prevalence of ID in the

community of origin of P0. Other selection criteria addressed gender representation and diversity in age. In total, 92 participants were recruited to participate in IDIs and FGDs. To create an atmosphere that fostered confidence and motivated the informants, I conducted my interviews in a manner that resembled a conversation rather than a structured interview. Schober & Conrad (1997) and West et al, (2018) demonstrated that conversational interviews are essential in addressing issues and are missing from more structured interviews. They extrapolated by saying that conversational interviews allow the participants to feel more relaxed and potentially provide more honest answers during the interview (Schober & Conrad, 1997; West et al, 2018).

2.7 Role of the researcher

2.7.1 Researcher professional development

The ethnographic approach requires considerable qualitative research skills from the researcher, and I had to equip myself with the skills necessary to facilitate data collection, analysis, and reporting. This was achieved by familiarising myself with the literature on ethnographic research (Reeves et al, 2008) and having frequent discussions with my supervisors, one of whom (Prof. Jantina de Vries) is a qualitative researcher. I also previously participated in a multisite sickle cell disease ELSI project (Ghana, Tanzania, and Cameroon), where I interacted with participants in Cameroon and conducted all the interviews (Bukini et al, 2019). Furthermore, to enhance my research capacity during the degree, I took a project management course. I also attended two online leadership and project management classes organised by the University of Washington during my PhD. In addition, I attended a writing workshop organised by the Department of Health Sciences Education at the University of Cape Town. This course helped me to improve my reporting skills and find my voice in the academic arena. Lastly, I looked for opportunities that helped me present my work at conferences organised in South Africa, Africa, and the United States of America where I received critical feedback on my study results, which I incorporated into the study. These opportunities allowed me to build the skills and conceptual thinking that ultimately made the data collection, data analysis, as well as drafting this thesis a practical and meaningful experience.

2.7.2 Researcher's background

As a researcher, I believe that sharing information on my experience will shed light on the reasons for my observations and interpretation. Bryman (2016), in his book "Social Research Methods", suggests that qualitative research is often related to the context in which the study

was carried out. In this light, my relationship with the research context can provide much information on how I see the world. I am a 31-year-old Cameroonian physician born in a small city in Western Cameroon called Mbouda. This city can be found about 20 km from the village where I conducted my research. I spent most of my childhood and young adulthood in the Western region of Cameroon. Living in this region during my early developmental stages made me learn about the socio-cultural perceptions of people in the Western region. My parents and I usually spent several weeks in the village to interact with village elders. Following my father's death, I was adopted by the chief of my community, where I observed all the social privileges given to a royal family. The cultural ceremonies that I attended formed a significant part of my cultural values.

As for my academic background, my primary and secondary education took place in the Western region of Cameroon. After completing my secondary education, I moved to Yaoundé, Cameroon's capital, where I completed a Medical Doctor's degree at the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé 1, Cameroon. My passion for mental health lead me to explore the different aetiologies of developmental delay in children less than five years old (Kamga, 2013; Nguefack et al, 2013). After graduating, I was posted as a physician in a rural area of the Southwest region of Cameroon where I worked for five years. In 2018, my supervisor suggested that I pursue a PhD degree at the University of Cape Town (UCT) in the Department of Pathology. My background has, therefore, allowed me to make sense of the realities of the participants in my study.

2.8 Procedure

This study was conducted in three phases:

- Phase 1: Obtain permission and ethical clearance
- Phase 2: Build a trust relationship with the family and the community
- Phase 3: Data collection and analysis

2.8.1 Phase 1: Obtain permission and ethical clearance

This study was approved by the UCT Faculty of Health Sciences Human Research Ethics Committee (HREC) (HREC 003/2019). It was a sibling project under the IFGENERA project, which also received approval from UCT (HREC 782/2017). Furthermore, ethics approval was obtained from the Institutional Committee for Health Research (no. 698/CIERSH/DM/2018) in Yaoundé, Cameroon (Appendix A). Moreover, written informed consent was obtained from

all research participants, including permission to publish images. Administrative authorisations were obtained from the District Medical Officer and the village chief.

2.8.2 Phase 2: Build a trust relationship with the family and the community

A challenge with conducting empirical qualitative research in a rural community revolves around issues of trust, especially if the research team is considered as 'outsiders'. This problem could be an obstacle in establishing rapport and impede access to participants (Camic et al, 2003). Several authors report that if this dilemma is not handled correctly, it may harm the study's validity and render it irrelevant (Anderson & Strupp, 1996; Lambert, 2013). Lambert (2013) showed that using a tape recorder during a session of psychotherapy may influence the answers of patients. In addition, Rogers et al, (1991) demonstrated that an informant's honesty is built from previous interactions with the interviewer and is also a function of the confidence gained through the interaction between the participants and the interviewer. To involve members of this community and to build trust for my project, I organised a series of seven community engagement activities with family and community members between 2018 and 2020. During these activities, I discussed the project with the different participants and probed who would be willing to give their time to my research.

In the course of establishing rapport with the family of P0 and her community, and perhaps partly due to my position as a medical doctor, it gradually became evident through my initial interactions with members of P0's extended family that they expected the project to offer genetic testing for FXS carrier status. Considering that this would be a logical and ethical way of honouring what could manifest as an ancillary care obligation, and after securing ethics approval for this addition to my research proposal, I decided to complement my qualitative research study with a genetic component in which I offered (and reported on) genetic diagnostic tests for FXS to members of P0's extended family. A detailed description of this process is reported in Chapter 4.1 of my thesis. When the results were available, I scheduled meetings with the participants either at the Medical Genetic Unit in Yaoundé or at their nearest health clinic. On the appointment date, post-test genetic counselling was provided to the participants following the existing medical genetics protocol for FXS, and each participant was given their result (Finucane et al, 2012; McConkie-Rosell et al, 2005).

A large part of my activities in 2018 was devoted to careful engagement with the community and the indicator family. Between February and November 2018, I had informal meetings with P0, her extended family members, and community members. My first informal meeting with

the family was during the initial contact with the chief in February 2018. This was the start of rapport building and trust between the family and the research team. I engaged with the expanded family in August 2018 at the chief's palace, where I had an opportunity to present my study to the royal family during their family reunion. I was also frequently in contact with the chief of the village to keep him informed about the project.

While the family had been quite receptive to my research, the community I did my work in was more reserved. The village could be described as a conservative community that does not easily open to foreigners. My first contact with the community was a tough one, whereby people could not freely talk with me. Following a church service in August 2018, I approached the community. My objective was to analyse how receptive the people could be and then try to introduce myself to the community. My meeting with a church elder was the cornerstone of my introduction to the community. She advised that the village pastor could provide introductions to the community. The village pastor then became a pivot to my insertion in the village since he is a child of the village and is broadly trusted. I had several informal discussions with traders during market days. However, most of them were sceptical about talking to us, but communication became much more fluent when the pastor accompanied us.

Moreover, I sought assistance from the village health centre director to help access the community through community relays, who usually assist the health centre in distributing vaccines. This was not a fruitful approach since the centre's director needed an official letter from the district medical officer to accept the research team in the community. This letter was finally signed in October 2018 and when I presented it to the head of the health centre, he was welcoming from that moment onwards.

Following a critical analysis of my work in 2018, I planned my activities for 2019. Early on, I recruited two research assistants who helped me organise my first community engagement activity with family members and health care workers in the village. The first research assistant was the village pastor, who is initially the child of the village. The second research assistant was a university graduate who is an expert in translation who had some knowledge of conducting qualitative research. These community engagement activities were intended to connect and create a conducive environment between the health workers in the village, the family, and the research team (Figure 2.1 and 2.2). The second research assistant also had the responsibility to capture images and assist in transcribing the interviews.

Figure 2.1: Group picture after a community engagement activity (Image supplied by candidate) (participants on this picture give consent for their image to be used)

Figure 2.2: Community talk with quarter heads, health personnel, and some family members (Image supplied by candidate) (participants on this picture give consent for their image to be used)

In July 2019, after a productive face to face meeting with my supervisors, I reconnected with my participants in the village through sensitisation meetings. This sensitisation helped me to approach the chief to add me to the programme of their traditional annual family reunion, which is held annually in August. In August 2019, I participated in a health campaign organised by medical students and physicians originating from the region. My role in this activity was to be one of the consulting physicians. This was also an opportunity to engage with the community and other health personnel in the village that I did not have the chance to meet during my community engagement activity in February that year. Moreover, I engaged with the family by participating in their family reunion on 18/08/2019 (Figure 2.3). The chief and the other relatives who were present were happy about how the project was progressing. They asked many interesting questions such as:

- What is the difference between FXS and autism?
- What is the mode of inheritance of FXS?

- Following the genetic testing, was it possible to say that the curse they have been suffering from is a genetic condition?
- Is there any cure for FXS?

Figure 2.3: Family reunion at the royal palace in rural Cameroon (Image supplied by candidate) (participants on this picture give consent for their image to be used)

After the family reunion, at the local government hospital, I returned the genetic results to participants who had a negative diagnosis. Overall, both the affected family members and the community were welcoming to my study. I have learned that I needed to be patient and act respectfully.

2.8.3 Phase 3: Data collection and analysis

2.8.3.1 Data collection

Data collection took place between February 2018 and February 2020. During this time, 46 people from the family of P0 requested cascade screening and testing, and 92 participants were recruited to participate in the qualitative part of the study through IDIs and FGDs (Figure 2.4). Of these 92 informants, 29 were extended family members of P0, while the rest (n = 63) were community members. Recruitment of family members followed the family reunion I described above. During the family meeting, I presented the study and asked people if they were willing to speak with me about ID in their family. I participated in two of these family reunions, one in 2018 and the other in 2019. I also assisted in a thanksgiving ceremony organised by the family in the village's church. Here, I had the opportunity to talk to some community members who were keen to participate in the study during this event.

As far as the IDIs, I had a telephonic conversation with all the participants to schedule a face-to-face meeting with them. During our face-to-face meeting, we discussed themes around FXS

and ID in the village. I had an in-depth discussion with 17 family members and six community members. Additionally, I conducted 10 FGDs, seven of which involved community members and three of which involved family members. The FGDs took place at the village's church premises or in the city where they lived and where I could secure a space for a group discussion. All the scheduled FGDs involved between 5 and 12 participants. Scholars such as Liamputtong (2011) and Morgan (2002) showed that in FGDs, the number of participants could be as low as five participants per group discussion. Our first FGD had the highest participation rate which could be attributed to our sampling strategy and the community engagement activities that we had organised to raise awareness and mark our village presence.

(a) **(b)**

Figure 2.4: (a) Participants of a focus group discussion. (b) An informal conversation with the initial paediatrician and the current chief of the village (Images supplied by candidate) (participants on this picture give consent for their image to be used)

The interview guide was prepared by listing themes and probes concerning the participant's life and relation to friends, family, neighbours, health, and social situations. I conducted all the interviews, which were audio-recorded and lasted between 27 and 90 minutes. The interviews were conducted either in French, English, or pidgin, depending on the informant's first language. In instances where the informant could not express himself in these languages, the local research assistant helped facilitate the conversation by acting as a translator. Most FGDs IDI's organized with community members were held the church premises where we could secure a room for the purpose. On the other hand, FGDs and IDIs with family members were conducted either in their residences or a conference room in the city they resided. By visiting the participants in their residences, I understood my participants because the place where someone lives can give valuable information about people and the way they are living. Financial constraints of participants were also considered, hence, the decision was taken to

provide reimbursements for travelling to data collection sites, as well as refreshment and snacks during the interviews.

2.8.3.2 Data analysis

Data were analysed in multiple rounds of coding, which led to the identification of general themes from the data. The process began with an open coding scheme developed by myself in consultation with my supervisors when approximately two-thirds of the data was collected. First, I open-coded four transcripts from three IDIs and one FGD. I then discussed emerging themes with my supervisors and used the initial codes to develop a hierarchical coding scheme. Several supervisory discussions were held between myself and my supervisors to resolve discrepancies. These continuous interactions with my supervisors helped refine subsequent data collection stages and helped me to ensure that saturation had been reached (Fusch & Ness, 2015). After obtaining a complete dataset, I applied the hierarchical coding scheme to the full dataset.

Data analysis started while the collection of the data was still in progress, in accordance with recommendations for the analysis of qualitative data (Kvale, 1994). Digital recordings from individual interviews and focus group discussions were stripped of identifying information, and transcriptions were translated from French into English as needed. Transcriptions were reviewed for accuracy then imported, together with the researcher's field observations, into NVivo 12 Qualitative Data Management programme (QSR International, 2020). Inductive coding was used to identify themes emerging from the data (Thomas, 2006). I used thematic analysis (Braun & Clarke, 2012) to identify meaningful patterns across the dataset, both within and between cases, as I read through the transcripts.

2.9 Ethical considerations

Ethics approval for the study was obtained from the UCT and the Institutional Committee for Health Research Yaoundé, Cameroon, before data collection. This study followed the Good Clinical Practice (GCP) guidelines for which I attended a course during the research period. All participants who took part in either IDIs or FGDs were provided with an information sheet. The information sheet and the consent form were presented in French and English to ensure that all individuals understood the material and what they were consenting to. After reading this, they were asked to voluntarily sign a consent form before proceeding with the session (Figure 2.5).

Figure 2.5: IDI participant completing the informed consent form (Image supplied by candidate) (participants on this picture give consent for their image to be used)

For participants who could not understand the information sheet due to low literacy levels, one-on-one support was provided to explain aspects of the study that were not clear, answer questions, and assist during the signing of consent forms. All participants were assured that their information would be confidential, and in case they were uncomfortable sharing information, they were free not to disclose that information. Moreover, participants were free to leave or stop the session at any time, although, none did. All interview transcripts were anonymised, and all possible identifiers were substituted with generic language. All transcripts were kept on a password-protected computer and were only shared on a need-to-see basis between myself and my supervisors. Each participant received compensation for their transportation and time, a snack, and a refreshment.

2.10 Chapter summary

This chapter provided an outline of the study site, aims and objectives, and research questions. It also described the research process by elaborating on the research design, sampling, and the study's different phases. By reflecting on my subjective position as a researcher, I discussed my role as a researcher vis-a-vis data collection. The chapter concluded with an overview of the ethical considerations employed in this study. The next chapter is the results chapter, which will provide some answers to our research questions. I start by elaborating on the cascade testing, then the explanatory models for FXS in the village, followed by the effect of receiving a genetic diagnosis before ending with the FXS concerns of the stigma power relationship in this setting.

Chapter 3: Literature review

Lived Experiences of Fragile X Syndrome Caregivers: A Scoping Review of Qualitative Studies

Kamga, K. K., de Vries, J., Nguefack, S., Munung, N., & Wonkam, A. (2020). Lived experiences of Fragile X Syndrome caregivers: A scoping review of qualitative studies. *Frontiers in Neurology, 11*, 128. DOI:10.3389/fneur.2020.00128

Synopsis

This paper reports on a scoping review of qualitative studies on the lived experiences of Fragile X syndrome caregivers, most of which originated from the United States of America. The aim was to establish common challenges reported for living with FXS, which informed the design of my consequent empirical work. I summarised the findings according to four major themes: grief experiences, challenges of living with FXS, coping mechanisms, and the need to plan future outcomes for children with FXS. The review also reveals a dearth of qualitative studies on FXS in African populations.

Author contributions:

Kengne Kamga Karen (KKK): Conceptualised and designed the scoping review; performed the literature search, interpreted findings; wrote the first draft of the article, and incorporated comments from co-authors; responded to all reviewer comments.

Nchangwi Syntia Munung (NSW): Assisted in applying the eligibility criteria to the manuscripts found in the literature search; assisted in interpretation and writing.

Seraphin Nguefack (SN), Jantina de Vries (JdV), Ambroise Wonkam (AW): Assisted in the design, interpretation, and writing.

Lived Experiences of Fragile X Syndrome Caregivers: A Scoping Review of Qualitative Studies

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Abstract

Fragile X syndrome (FXS) is the most common X-linked monogenic cause of intellectual disability (ID) and Autism Spectrum Disorder (ASD). Taking care of children with ID is challenging and overwhelming due to the multiple facets of caregiving. This scoping review aimed at summarising the qualitative literature on the experiences of families living with FXS, identify key themes and determine the gaps in the extant literature. We conducted a literature search in May 2019 using four databases: PubMed, Web of Science, African-Wide-Information, and Scopus. The keywords used in our search strategy were associated with caregivers, lived experiences, FXS, and qualitative research. All English language articles with full-text reporting were included. Studies associated with other neurodevelopmental conditions and quantitative studies were excluded. We identified 12 out of 203 articles that described the lived experiences of families with FXS. Most articles originated from the United States of America and mothers were the main caregivers. We summarised our findings into four major themes which are: grief experiences, challenges of living with FXS, coping mechanisms and the need to plan for future outcomes. This scoping review highlighted the scarcity of qualitative FXS literature in the African population and frustrations endured by families with FXS due to the low knowledge of FXS by healthcare workers. More research is needed to evaluate the impact of living with FXS in males and fathers.

Keywords: Fragile X syndrome, lived experience, caregivers, scoping review, qualitative research

3.1 Introduction

Fragile X syndrome (FXS) is the most common inherited single-gene condition that causes a range of developmental problems, including learning disabilities and cognitive impairment, and affects about twice as many males as females (Hunter et al, 2014). FXS is caused by a mutation of the Fragile X mental retardation 1 (*FMR1*) gene, which results from an expansion of the CGG (Cytosine-Guanine-Guanine) repeats at the 5' Untranslated region (UTR) of this gene. Fragile X Mental Retardation Protein (FMRP), the translation product of the *FMR1* gene, is a regulation factor that controls most of the proteins important for synaptic maturation and plasticity (Weiler & Greenough, 1999). A mutation in the *FMR1* gene switches off the production of the FMRP, leading to the weakening of synapses in the brain. This eventually leads to impaired brain development and the physical impairments associated with FXS (Hagerman & Hendren, 2014).

In Europe, America, Asia and Australia where molecular diagnostic procedures are well-developed, neonatal units for early screening for genetic diseases like FXS are fully functional and FXS is usually diagnosed early. This could account for the perceived high prevalence in these regions (Peprah, 2012; Yim et al, 2008). However, not many hospitals and institutions in Africa can perform genetic testing for *FMR1* mutations. Therefore, many African FXS patients may have gone undiagnosed due to the reliance on clinical signs and symptoms (Essop & Krause, 2013; Niu et al, 2017) and no referral of patients to specialised centres (Essop & Krause, 2013). The low uptake of genetic testing in African settings could also be due to scarce medical genetics specialists in many African countries. For example, in South Africa in 2013, there were reported to be 11 registered medical geneticists, 42 medical genetic scientists and technologists, and 10 genetic counsellors servicing a population of 51 million (Kromberg et al, 2013). In other African countries, "medical genetics" services are far fewer and are still developing (Wonkam et al, 2011a). Consequently, there have been fewer African FXS-related studies published, that can also contribute to the lack of awareness of FXS, insufficient diagnostic tools and possibly cultural beliefs surrounding mental disorders (Meilleur et al, 2011).

Once diagnosed, the medical management of FXS requires family support which is demanding, overwhelming and can lead to some mental health problems to the caregiver (Pinquart & Sorensen, 2003). Some scholars examined factors which account for parental adaptation to a child's disability. They highlighted that coping with a disability is a multifaceted event which can be experienced in different ways. An alteration in the behaviour and sleep patterns of FXS

children may account for the maladaptation of parents (Bailey Jr et al, 2008; Carotenuto et al, 2019). Hence, this scoping review will map the available evidence of the experiences of families, caregivers and patients living with FXS. We aim at summarising current lived experiences of FXS caregivers, synthesise key findings, and highlight gaps and limitations in the extant literature.

3.2 Methodology

A scoping review method is a rigorous approach to literature reviews, systematically identifying key concepts, theories, evidence, and research gaps (Arksey & O' Malley, 2005; Levac et al, 2010). This scoping review covers global empirical qualitative studies reporting on the lived experiences of people living with FXS from 1980 to 2019. Hammarberg et al. (2016) reported that qualitative methods should be used to answer questions regarding experiences, meaning, and perspective from the participant's angle. Additionally, Seers (2012) noted that findings from primary qualitative research could contribute, through a qualitative synthesis, to a greater understanding of a research area. Hence, only qualitative articles were included in our study.

3.2.1 Identification of Research Question

To guide the search strategy and ensure that a broad range of literature was captured, we asked the questions: "What are the lived experiences of people living with FXS?" This helped us to capture the challenges, frustrations, and coping mechanisms that entail living with FXS.

3.2.2 Searching for Relevant Studies

We identified articles by searching through four electronic databases: PubMed, Scopus, African Wide information and Web of science. The electronic search strategy was developed by the first author (KK) and an experienced librarian at UCT. An example of the search query used is seen below (Table 3.1), where the original search was done in May 2019.

Table 3.1: Search strategy used in the four databases (PubMed, Scopus, Web of science and African Wide Information)

Search component	***Search terms***
Caregivers	Caregiver OR brother OR sister OR mother OR father OR sibling OR parent OR spouse OR spouses OR carrier OR patient
Experiences	Concern OR stigma OR custom OR belief OR stressor OR culture OR challenge OR stress OR resilience OR psychology OR socioeconomic OR Religion OR coping OR behaviour OR (mental suffering) OR Adapt OR emotional OR (Quality of life)
Fragile X syndrome	(Fragile X Syndrome) OR (Fragile X associated Tremor Ataxia Syndrome) OR (Fragile X associated Primary Ovarian Insufficiency) OR (Fragile X Mental Retardation Syndrome)
Qualitative research	(Qualitative study) OR (qualitative research) OR (empirical research)

3.2.3 Selecting Studies and Charting the Data

The electronic search results were downloaded onto EndNote X9.2 which is a bibliographic software. The first (KK) and fourth (SN) authors collaborated to remove duplicates and screened articles to determine whether they should be included in this review. Identified articles were then broadly coded by these two authors using NVivo 12 software. The data obtained were then grouped to form themes. We identified four overarching themes in the articles included in the analysis which are reported in a narrative format for this paper.

3.3 Results

3.3.1 Description of Identified Studies

Overall, the search strategy identified 203 records, 186 from the electronic search results and 17 records from a second search and reading references of retrieved articles. After duplicates were removed, 51 records were screened. A total of 28 full-text articles of potential relevance were retrieved and screened and 16 articles were subsequently excluded. Twelve articles were retained for the final synthesis (Figure 3.1).

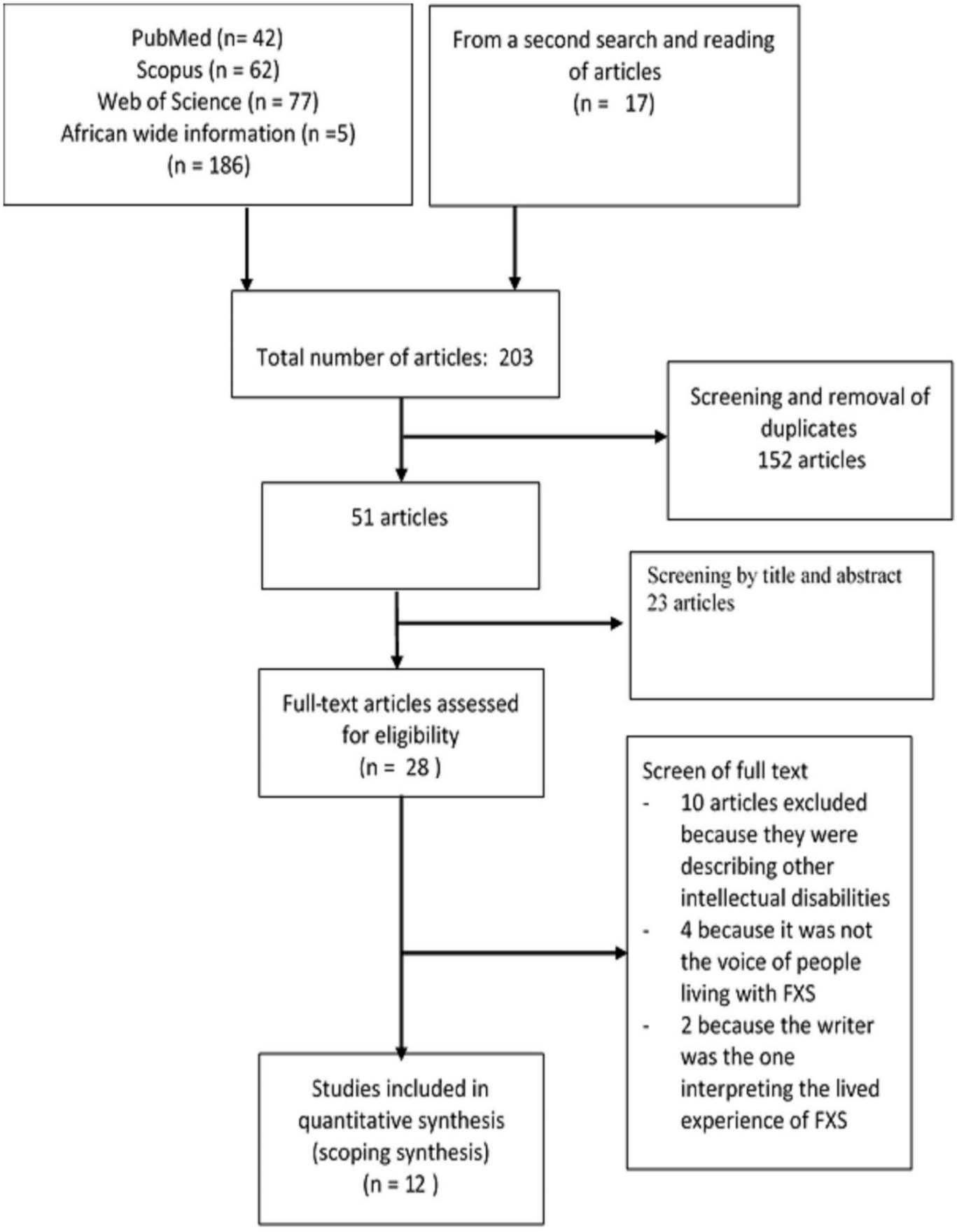

Figure 3.1: Chart describing the article selection process.

3.3.2 Overview of Study Characteristics

The included studies were in English and captured the lived experiences of people directly involved in or affected by FXS. Most studies originated from North America (n = 9 for the United States of America; n = 1 for Canada), one from the Netherlands and one from South Africa. All the studies involved standard qualitative methods (interviews and focus group discussions) with the parents of children with FXS, and the majority (n = 7) involving only mothers (Table 3.2).

Table 3.2: Demographic information of the identified studies

References	Title	Country	Participants	Method(s) used	Site	Themes
Brady et al, (2006)	Communication in Young Children with Fragile X Syndrome: A Qualitative Study of Mothers' Perspectives	USA	Mothers (n = 55)	Interviews	Home and university	Grief, challenges, and coping strategies
Feinstein & Pollack (2016)	"We Don't Have a Plan. We Should Be Working on a Plan.": Obstacles to Caregiver Transition Planning for Individuals with Fragile X Syndrome	USA	Caregiver (n = 37)	FGD and interviews	Phone calls	Grief, challenges, coping strategies, worries about the future
Michie & Skinner (2010)	Narrating Disability, Narrating Religious Practice: Reconciliation and Fragile X Syndrome	USA	Mothers (n = 60)	Interviews	Home	Grief, coping strategies
Minnes & Steiner (2009)	Parent views on enhancing the quality of health care for their children with Fragile X Syndrome, autism or Down syndrome	Canada	Parents (n = 71)	FGD	Conference room	Challenges
Muller et al, (2018)	Mothers' perspectives on challenging behaviors in their children with Fragile X Syndrome	USA	Mothers (n = 53)	Interviews	Home and university	Challenges

Poehlmann et al, (2005)	Family Experiences Associated with a Child's Diagnosis of Fragile X or Down Syndrome: Evidence for Disruption and Resilience	USA	Mothers (n = 11)	Interviews	Home	Grief, challenges
Reines et al, (2017)	Parental Perspectives on Pharmacological Clinical Trials: a Qualitative Study in Down Syndrome and Fragile X Syndrome	USA	Parents (n = 9)	Interviews	Phone calls	Worries about the future
Van Remmerden et al, (2019)	Growing up with Fragile X Syndrome: Concerns and Care Needs of Young Adult Patients and Their Parents	Netherlands	Parents and patients (n = 38)	FGD and interviews	Home and phone	Challenges
Visootsak et al, (2012)	Diagnosis of Fragile X Syndrome: A Qualitative Study of African American Families	USA	Mothers (n = 10)	Interviews	Phone calls	Grief, coping strategies
Weber (2016)	Understanding Fragile X Syndrome from a mother's perspective: Challenges and resilience	South Africa	Mothers (n = 1)	Interviews, journal, field notes	Home	Grief, challenges, coping strategies

Weber et al, (2019)	Voice of People with Fragile X Syndrome and their Families: Reports from a Survey on Treatment Priorities	USA	Patents (n = 8)	Interviews	Online	Challenges
Wheeler et al, (2008)	Perceived Quality of Life in Mothers of Children with Fragile X Syndrome	USA	Mothers (n = 10)	Interviews	Home	Challenges, coping strategies

FGD – Focus Group Discussion; USA – United States of America

Grief and Response to Diagnosis

Grief is a response to the loss of someone or something cherished. When people grieve, they go through five stages which are denial, anger, blame, depression, and acceptance (Kübler-Ross & Kessler, 2005). Six of the studies included in this analysis described grief as an important aspect of the lived experience of caring for a child with a FXS diagnosis (Brady et al, 2006; Feinstein & Pollack, 2016; Michie & Skinner, 2010; Poehlmann et al, 2005; Visootsak et al, 2012; Weber, 2016). A quote from a participant in Visootsak et al,'s study describes this well: "I was devastated. I felt like I was grieving for a child that was still living". Michie & Skimmer (2010) further describe parents losing their sense of direction following the diagnosis.

Denial, the first stage of grief, was described by three authors (Feinstein & Pollack, 2016; Michie & Skinner, 2010; Poehlmann et al, 2005). After receiving the diagnosis, parents go through a series of negative emotions dominated by denial: "Why would something be wrong with one of my kids?" (Michie & Skinner, 2010). Feinstein & Pollack (2016) described that denial does not only happen after receiving a diagnosis; it may also play a factor in delaying the search for a diagnosis: "I didn't think about these things before we found ourselves in this situation." Similarly, Poehlmann et al, (2005) quoted that some parents resolved to dismiss concerns about their children: "In his first year, I remember my father-in-law asking if there was something on his eyes. I said, no. It's normal for kids to look kind of cross-eyed in their first years."

Other stages of grief described by the articles included in this analysis are anger and self-blame. In one of the papers, it was reported that parents were angry with God and considered their child's illness a punishment. Some parents attributed their child's illness to "bad karma" (Michie & Skinner, 2010). Being angry with other people in the community was mainly a result of micro-aggression relating to FXS: "When somebody says, 'Joey's blessed to have you,' I'm like... 'So, what in my life have I done that I deserve this much work?' (Michie & Skinner, 2010). Self-blame was another common emotion described by three authors (Michie & Skinner, 2010; Poehlmann et al, 2005; Weber, 2016). These authors narrated how receiving a FXS diagnosis generated panic attacks in mothers, relating to feelings that they had caused their child's condition.

Most parents were frustrated with the long odyssey of obtaining the diagnosis of their child. The lack of knowledge of physicians and paediatricians with regards to FXS was a concern for parents in this period. The atypical presentation of children may make FXS hard to diagnose, and the parents reported that their children received treatment for the child's symptoms before

finally requesting chromosomal or FXS testing (Minnes & Steiner, 2009; Poehlmann et al, 2005; Van Remmerden et al, 2019; Visootsak et al, 2012; Weber, 2016). Poehlmann et al, (2005) narrated situations of distress arising from the difficulties of the child to attain developmental milestones or the long and difficult process of getting to a diagnosis. After obtaining the diagnosis, mothers were left with limited options and did not know what to do next.

> "*We were just blown out of the water with no clue... it changed our entire life about everything, even who we are... I have in my mind a picture of just walking into doors. Total confusion... it was almost like it had a feeling of throwing you out in the sea and saying I hope you can swim.".*

However, parents who manage to accept this condition keep in mind that they will play the role of primary care provider for the rest of their lives (Brady et al, 2006). Although mothers report receiving some support from their physicians (Weber, 2016), they disclosed that these practitioners lack empathy in giving them the result of their children. Poehlmann et al, (2005) recounted a scenario where a physician was not sensitive in giving back a FXS result to a parent.

> *"We hadn't heard for over a month, the diagnosis... I called him and the doctor came to the phone and said, "Was I supposed to give you the diagnosis?" And I said, "Yes"... and he said "Well then... your child tested positive for Fragile X." He didn't ask if anybody was there with me or if there was a time when my husband and I could come in... that is definitely a poor way to tell you that."*

Upon receiving the diagnosis, parents described receiving support from their spouse and extended family members who could listen and empathise with them (Michie & Skinner, 2010; Visootsak et al, 2012; Weber, 2016; Wheeler et al, 2008). Wheeler et al, (2008) recounted the life of a mother who described how having a supportive husband and/or extended family helped to improve her quality of life.

> *"They (husband's family) have accepted the boys and include the boys and me... And I feel like I can go to them. If we're at a family function and the boys are acting wild, they're like "Oh, so what? They do what they do." Everyone's supportive and understanding and helpful."*

Also having a role model was a great support. Weber (2016) stated the role a psychologist with special needs played in the life of a caregiver in an African setting.

"I know the lady I told you that passed away, remember, she was very good, she was very good... because she also had a disability. And looking at her made me appreciate life and made me realize that if she can carry on each day, so can I."

Challenges of Caring for a Child With FXS

Ten authors described the challenges of caring for a child with FXS (Brady et al, 2006; Feinstein & Pollack, 2016; Minnes & Steiner, 2009; Muller et al, 2018; Poehlmann et al, 2005; Van Remmerden et al, 2019; Visootsak et al, 2012; Weber, 2016; Weber et al, 2019; Wheeler et al, 2008). Throughout childhood and adolescence, parents described challenges in dealing with behavioural difficulties, especially when skills like speaking and communication are compromised. Parents also described concerns about their children's ability to live independently. More so, academic performance, self-care and behaviour were the main concerns for parents taking care of male FXS patients, while social issues were the main concern for parents of female FXS patients (Weber et al, 2019). Worries about the future and dealing with behavioural challenges ultimately reduced the quality of life for families.

Concerning behavioural challenges stubbornness, stereotypic behaviours, aggression, self-injury, impulsivity and social deviance were some behaviours recounted by parents (Feinstein & Pollack, 2016; Muller et al, 2018; Van Remmerden et al, 2019; Weber, 2016). These behaviours were thought to be a result of the non-verbal expression of the children or a way to escape demands, seek attention or obtain tangibles (Muller et al, 2018; Van Remmerden et al, 2019; Weber, 2016). Socially, children were reported to behave inappropriately because they are unable to respect the private space of others and are also unable to change conversation tone or topics. This keeps mothers frustrated and embarrassed (Muller et al, 2018). Moreover, food control, keeping a good personal hygiene and sleep disorders were worries for parents and caregivers (Feinstein & Pollack, 2016; Muller et al, 2018; Van Remmerden et al, 2019).

In addition to social and behavioural challenges, communication patterns of children living with FXS was a worry for caregivers (Brady et al, 2006; Feinstein & Pollack, 2016). Parents believe that their children are not always understood because they communicate non-verbally. Mothers reported frustration with their inability to understand what their child wanted to say. Brady et al, (2006) elaborated on different communication challenges and strategies adopted by mothers. Most mothers tried to guess what their child was trying to say, and they resolved to adopt a trial-and-error strategy which was frustrating for the mother and child.

"I just try a couple of different things and I either hit the right one or I distract him or he gets interested in something else and he kinds of forgets, which is kind of sad, you know, if the little guy isn't getting what he wants."

Supervisory experiences were also addressed by caregivers as challenging. Most children with FXS cannot be on their own without supervision and even adult persons with mild forms of ID still need some coaching and monitoring (Feinstein & Pollack, 2016; Van Remmerden et al, 2019). Van Remmerden et al, (2019) illustrated this dependency by recounting the life of a mother who had a daughter with FXS.

"My daughter lives on her own but she is not independent. My husband and I do everything for her: the finances, cooking and cleaning. Sometimes I feel like I let a 14-year-old move out of the house."

Parents described situations of having difficulties obtaining specialised services or support from the community. In the Dutch (Van Remmerden et al, 2019) and African (Weber, 2016) studies, parents described limited knowledge of health care workers for FXS and limited specialist care and support facilities available. Van Remmerden et al, (2019) elaborated this thought from a mother: "As a parent, you always need to explain what FXS is, even to some physicians. It's so typical for FXS. When you say my daughter has Down syndrome, everybody knows what you're talking about." Parents in a study from the USA reported that even though there is some form of specialised support for FXS in their country, the waiting lists are long, and parents receive little information about how to care for their child following diagnosis (Minnes & Steiner, 2009). A lack of support from family members especially the spouse can constitute a source of distress (Poehlmann et al, 2005; Visootsak et al, 2012; Weber, 2016). Poehlmann et al, (2005) quoted a family who did not have enough support from their relatives and the caring duty was relegated to the mother.

"He was fussy, and I had three kids and was working full-time, and my husband was working and gone most of the time. So, I had to take care of them all at night, and it was a very difficult time. My parents were in a town 40 miles away and they were older, so they really couldn't help much. And my husband's folks were in town, but they weren't much of a support. They had a hard time handling our son's behaviours and outbursts and so they weren't around a lot because they couldn't understand him. So, we really didn't have a lot of support."

Weber (2016) reported that the rarity of FXS in that country also impacts on one patient's ability to find support through more formal means.

> *"It is not easy for someone to go through that. You need support... even with the group we had, there was no kids there that had fragile X. It was just my kids.... The other support groups they were of different disabilities."*

Furthermore, two authors described challenges with the transition from childhood to adulthood (Feinstein & Pollack, 2016; Van Remmerden et al, 2019). Difficulties obtaining services in adulthood was another concern because the available services are limited. In addition, caregivers worry about the complex bureaucratic work which they must go through in order to meet the vocational, residential and caregiving needs of their children. This complex process motivated mothers to give up their personal ambitions and become the primary caregiver for their children.

Moreover, challenges with family planning, romantic life and sexual deviance were addressed by one author. Female FXS patients were concerned about having children; they were discouraged when they found out the stress associated with taking care of a FXS child through their parents. Hence, parents doubted their ability to raise a child and much preferred their FXS children not to attempt to have their own (Van Remmerden et al, 2019).

Finally, starting and maintaining a romantic relationship for an individual affected with FXS is very difficult (Van Remmerden et al, 2019). Sexual deviance was reported by some parents and it was characterised by exhibiting their private parts or masturbating in public places. This behaviour left parents worried since their children could be abused or assaulted by others who do not know their FXS status.

Coping Strategies

Fragile X Syndrome is a disabling condition both for individuals and families and from this review, it appears as if there are two dominant coping strategies employed by the families affected by FXS. Some become advocates for FXS, whilst others give up their dreams and concentrate on the care of their children. To become an advocate for FXS, caregivers described taking courses that empowered them to speak about the illness and to obtain support for their care (Brady et al, 2006; Feinstein & Pollack, 2016; Visootsak et al, 2012).

Obtaining support was another way to cope when parents had children with FXS. Previously, we described that some of the FXS parents end up feeling isolated and depressed—but a subset

of parents seems to have found more positive ways of dealing with FXS. What seems to make the difference is those parents' ability to seek support, either from external support services or from faith. Wheeler et al, (2008) described the persevering and positive attitude of a mother in seeing the progress made by her kids.

> *"I know all those services out there. I'm very positive. I know I'm not missing out on anything. I know I'm on top of the game with my kids. I keep busy. I have a social life. I have friends."*

Besides, some caregivers rely on their faith in God. Reconciliation is the term used by Michie & Skinner (2010) to represent the transition from viewing FXS as a burden or challenge to being more a blessing or God's will. What seems to be different here is that these parents seem to have developed a high level of self-esteem and positive outlook (Brady et al, 2006; Feinstein & Pollack, 2016; Michie & Skinner, 2010; Visootsak et al, 2012; Weber, 2016; Wheeler et al, 2008).

Worries About the Future

Out of the 12 articles retrieved, three describe worries about the future which included the need to plan for housing, financial security and caregiving (Feinstein & Pollack, 2016; Reines et al, 2017; Weber, 2016). Feinstein & Pollack (2016) described instances with parents not having a well-structured plan. In this case, parents were so busy with their daily activities that they did not feel the need to plan for the future of their children.

> *"When [my son] was younger, I thought, yeah, I was 30, 35— that's a good age if they must start living on their own and moving in there. Well, golly geez, that's 4–9 years away. It's time to get moving."*

On the other hand, those with a partial/concrete plan based their plans on their families or organisation they created. They hoped that these entities will provide housing or financial aids to their offspring when they will not be around.

> *"Right now, I think that if something happened tomorrow, my parents are still alive. I've got sisters and a brother. My husband has a sister, and we have close friends. They all understand [daughter living with FXS]'s situation. I think someone would step up. I would hope that my son as he got older would take on the responsibility himself" (Feinstein & Pollack, 2016).*

Moreover, participation in clinical trials for targeted therapies in the future was a concern for caregivers. Reines et al, (2017) described the willingness of parents to participate in experiments that targeted the disease, and not the symptoms. They think participating in the research will either improve their child's condition or give hope for the discovery of a treatment in the future, which will help other families suffering from the same condition. However, these parents were worried about long term and transient side effects of the medication and the logistics that comes with the clinical trial. Also, taking the decision to participate in a trial is a big responsibility which parents are ready to share with family members (spouse, grandparents, the child), health care workers, and other parents in the FXS community.

3.4 Discussion

This scoping review is the first to summarise the qualitative literature on lived experiences of FXS families. Our results provide a comprehensive overview of the challenges, grief experiences and coping strategies developed. The lived experiences with FXS could be grouped into the pre-diagnostic and the post-diagnostic period. Before the diagnosis, several parents of FXS children struggled to receive a diagnosis for their children. This is a time-consuming process and parents can find themselves spending money which could lead to impoverishment (Bailey Jr et al, 2012; Hung et al, 2019). Grief reactions can extend from the pre-diagnostic period to the post-diagnostic period. Parents who accept the condition understand that they will be the primary caregivers of their children and could then integrate that in their living style. They then start to plan for the future of their children (Bailey Jr et al, 2012). However, in some instances, parents are unable to accept their child's condition. They are those who finally have a poor quality of life (Wheeler et al, 2008). Moreover, challenges encountered when living with FXS can either be before or after the diagnosis. These challenges are related to the basic skills of their children and their ability to integrate in society due to communication and behavioural difficulties. Coping strategies that were implemented were related to family and community support (Figure 3.2).

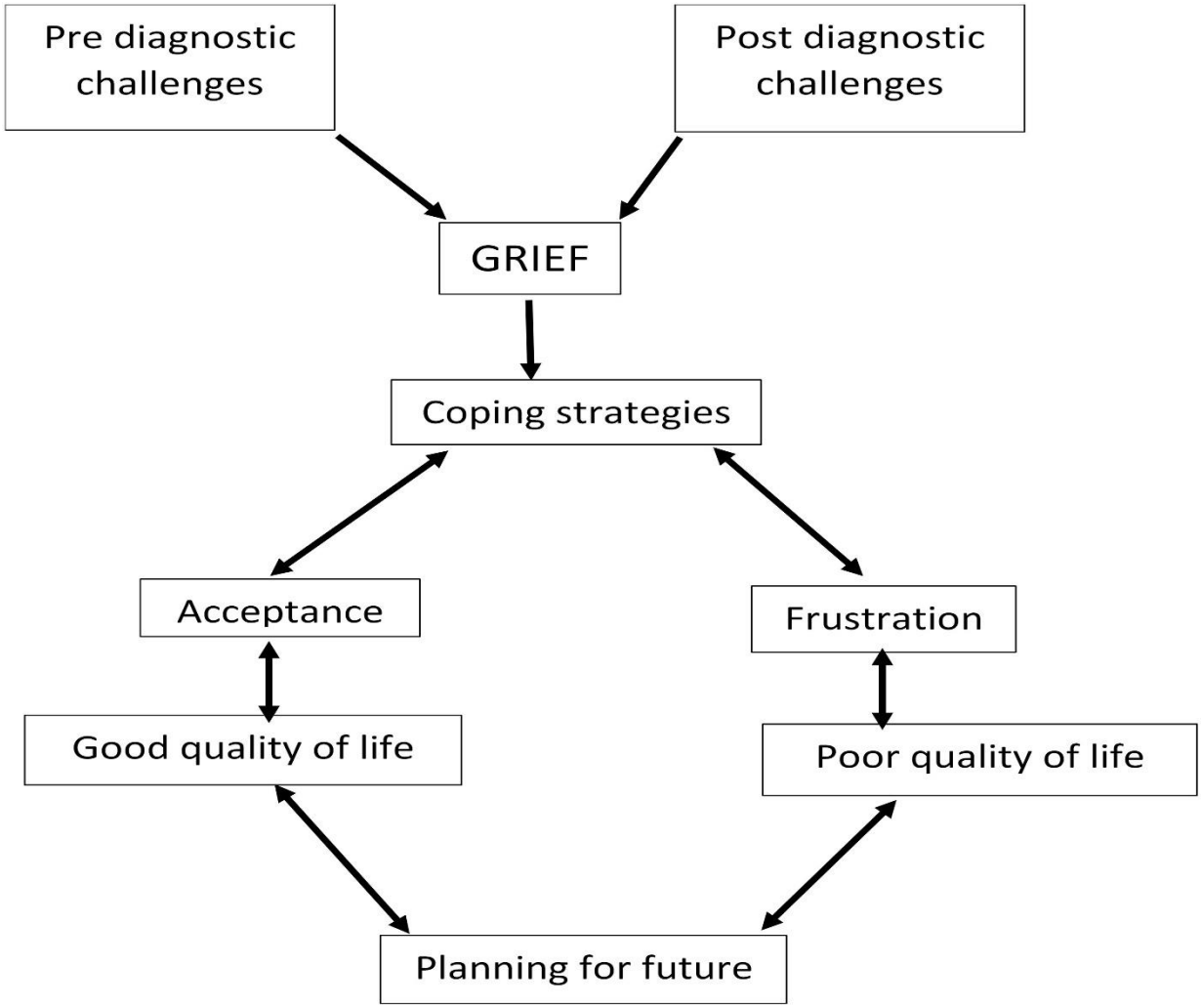

Figure 3.2: Flow chart describing the lived experiences of families with FXS.

3.5 Practical Implications

Most studies illustrated the importance of patients' experiences with the health care system. Adults described the need for a good relationship with their health care providers, to be treated with respect and as a whole person, a need for understandable information about the diagnosis, and valued health professionals who could assist whenever needed. York et al, (1999) reported that educators and health caregivers taking care of Down Syndrome patients, autistic children and FXS children demonstrated to have limited knowledge of FXS. Results from the present review of the literature, in general, show that lack of expertise among health care providers is a major barrier for people with FXS (Minnes & Steiner, 2009; Visootsak et al, 2012). This lack of knowledge about FXS can result in important medical consequences. This may include delays in obtaining an accurate diagnosis, psychological stress due to inappropriate responses to delivering the diagnosis and providing support to affected individuals. In contrast, a lack of trust was created from the apparent unwillingness from health care providers to get involved or to seek information about FXS.

3.6 Research Recommendations

The experiences of living with FXS has never been reviewed before. The present scoping review examined qualitative literature which described the lived experiences of FXS through the narratives of caregivers. From our findings, we could identify gaps in two areas which are: a lack of FXS qualitative studies in Africa, and the limited knowledge of FXS by health care workers. In Africa, very limited literature is found concerning rare monogenic diseases like FXS with only one study found (Weber, 2016). Lim et al, (2012) reported that the burden and caring responsibilities of children suffering from rare neurological disorders in China typically falls on the parents, and this is the case with FXS. Furthermore, Von de Lip et al, (2017) conducted a qualitative systematic review on rare diseases and found that most studies were from Europe and America. Therefore, there is an urgent need to research on such knowledge for FXS in most parts of the world, and particularly in Africa.

3.7 Study Limitations

There are some limitations associated with the conduct of this scoping review that need to be acknowledged. The first was the search strategy which focused on English language studies. However, there could be other relevant literature which was published in other languages. Most of the studies reviewed had mother's voices more prominent—despite the title of the papers invariably using the word "parent or caregivers." Less is known about what fathers are saying, and we cannot assume that the lived experiences are homogenous. Other limitations are related to the heterogeneity and variable scientific quality of the 12 papers included in the review, as well as the focus on qualitative approaches in our design. Indeed, quantitative data obtained from standardised scales measuring quality of life and living experiences in parents with FXS could have provided additional angle and insights.

3.8 Conclusions

Individuals caring for children suffering from FXS face challenges beyond medical issues. Many of the challenges could be diminished by more education and creating awareness about FXS and other inheritable diseases in families and communities. The findings highlight the need for more research on the lived experiences of families with FXS on the African continent while exploring the experiences of fathers and younger individuals to complete the picture provided by this review on caregivers.

Author Contributions

KK and SM: literature search, interpretation, and writing. SN, JD, and AW: design, interpretation, and writing.

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Chapter 4: Results

4.1 Cascade Testing for Fragile X Syndrome in a Rural Setting in Cameroon (Sub-Saharan Africa)

Kamga, K. K., Nguefack, S., Minka, K., Wonkam Tingang, E., Esterhuizen, A., Nchangwi Munung, S., de Vries, J., & Wonkam, A. (2020). Cascade Testing for Fragile X Syndrome in a Rural Setting in Cameroon (Sub-Saharan Africa). *Genes, 11*(2), 136. DOI:10.3390/genes11020136

Synopsis

This paper presents the results of cascade counselling and testing for Fragile X Syndrome in a Cameroonian family. I present the family pedigree in this manuscript which revealed that this family's traditional head was probably a normal transmitting male carrier. I argue that detecting a carrier status early will increase family planning options through genetic counselling, premarital screening, and prenatal diagnosis. Through the analysis of the pedigree, this paper helps us to determine the pattern of FXS transmission in this family.

Author contributions:

Kengne Kamga Karen (KKK): Collected blood samples from study participants; organised the shipping of these samples; managed diagnostic testing at the National Health Laboratory Sciences (NHLS) in South Africa where Fragile X Syndrome analysis was done; developed the family pedigree based on results; returned results to study participants; wrote the first draft of the article, and incorporated comments from co-authors and responded to all reviewer comments.

Khuthala Minka (KM), Alina Esterhuizen (AE), Edmond Wonkam Tingang (EWT): Assisted with DNA extraction and commented on paper drafts.

Syntia Nchangwi Munung (SNM): Assisted with the manuscript writing process.

Séraphin Nguefack (SN): Assisted with study design; data collection; the return of results and commented on paper drafts.

Jantina de Vries (JdV): Assisted with study design and commented on paper drafts.

Ambroise Wonkam (AW): Assisted with study design; analysis and writing.

Cascade Testing for Fragile X Syndrome in a Rural Setting in Cameroon (Sub-Saharan Africa)

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Abstract

Fragile X Syndrome (FXS), an X-linked dominant monogenic condition, is the main genetic cause of intellectual disability (ID) and Autism Spectrum Disorder (ASD). FXS is associated with an expansion of CGG repeat sequence in the Fragile X Mental Retardation gene 1 (*FMR1*) on chromosome X. Following a neuropediatric assessment of two male siblings who presented with signs of FXS that was confirmed with molecular testing, we provided cascade counselling and testing to the extended family. A total of 46 individuals were tested for FXS; among them, 58.70% (n = 27) were females. The mean age was 9.4 (±5) years for children and 45.9 (±15.9) years for adults. Pedigree analysis suggested that the founder of these families was likely a normal transmitting male. Four out of 19 males with clinical ID were confirmed to have a full mutation for FXS, while 14/27 females had a pathologic CGG expansion (>56 CGG repeats) on one of their X chromosomes. Two women with premature menopause were confirmed of being carriers of premutation (91 and 101 CGG repeats). We also identified maternal alleles (91 and 126 CGG repeats) which expanded to a full mutation in their offspring (>200 CGG repeats). This study is a rare report on FXS from Africa and illustrates the case scenario of implementing genetic medicine for a neurogenetic condition in a rural setting.

Keywords: Fragile X syndrome, genetic counselling, full mutation, premutation, Cameroon, Africa

4.1.1 Introduction

Fragile X Syndrome (FXS) is the most common monogenic X-linked condition which causes variable degrees of intellectual disability (ID), Autism Spectrum Disorder (ASD), delay in acquisition of speech and other cognitive skills; affecting one in 7143 males and one in 11,111 females (Clifford et al, 2007; Hoffmann et al, 2019; Hunter et al, 2014; Reiss & Freund, 1992; Thurman et al, 2017). Some individuals with FXS may present characteristics of facial appearance such as a large forehead and prominent ears. Moreover, some of these signs may only occur after puberty which is the case of adolescent males who may develop macro-orchidism. Hence, the diagnosis of FXS cannot rely exclusively on clinical features, but depends on molecular investigations for confirmation (Gabis et al, 2018; Lachiewicz et al, 2000).

FXS is associated with Cytosine Guanine Guanine (CGG) repeat sequence expansion located in the 5' untranslated region (UTR) in the Fragile X Mental Retardation gene 1 (*FMR1*), at the Xq27 position (Jin & Warren, 2000; Santoro et al, 2012). This expansion, which accounts for over 98% of all FXS cases, exists in four allelic forms based on the length of the CGG repeats: normal (5–44), intermediate (45–55), premutation (56–200), and full mutation (>200) (Crawford et al, 2001; Lozano et al, 2014; Niu et al, 2017). Individuals with a full mutation may have methylated *FMR1* genes which turn off the production of mRNA that will translate to protein. The lack of the gene product, Fragile X Mental Retardation Protein (FMRP), is responsible for the clinical features (Maurin et al, 2014; Qurashi et al, 2007).

Fragile X Syndrome follows the traditional pattern of X-linked inheritance. Males who inherit the mutation will be affected, and they will transmit the mutation to all their daughters. Also, females who carry the mutation may present with some degree of ID or behavioural problems and will transmit this mutation to half of their children (Peprah, 2012; Santoro et al, 2012). However, the risk of expansion of the CGG repeats in a premutation allele to a full mutation overlays the transmission pattern of this syndrome (Jin & Warren, 2000; Peprah, 2012). Research on FXS in African population is limited probably due to scarce genomic and genetic services on the continent (Essop & Krause, 2013; Meguid et al, 2014; Wonkam et al, 2011a), and few qualified personnel (Kromberg et al, 2013). Only a few scholars have identified families living with FXS through clinical research (Lubala et al, 2018; Lumaka et al, 2019; Nguefack et al, 2013). It is likely that with the developing medical genetic services in countries such as Cameroon (Wonkam et al, 2011a), this situation will gradually improve.

Cameroon is a central African country which spans almost equally in two main geographical zones: the equatorial rainforest in the south and the tropical savanna and the Sahel region in the north. Its population was estimated to be 25,216,237 in 2018 (World Bank, 2020). Also known as "Africa in miniature", Cameroon has a diverse cultural and linguistic heritage which mimics the heterogeneity found in Africa (Tishkoff et al, 2009). The health care system in Cameroon is organised into the public, private and traditional sectors without universal health insurance coverage. Hence, patients depend on financial support and caregiving from family members and regularly consult traditional healers (World Bank, 2012). Poverty in Cameroon affects more than 50% of the rural population and up to 30% of the urban population, which implies that the necessary medical care for patients may not be satisfied due to the endured financial burden (Wonkam et al, 2006; World Bank, 2012). Besides communicable diseases like malaria, HIV/AIDS and tuberculosis, Cameroon, like many other developing countries are facing a transition with a growing burden of chronic non-communicable diseases, some of which are of genetic origin (Wonkam et al, 2014). Yet, studies show a poor knowledge of genetic diseases and genetic tests among medical students and physicians in Cameroon (Wonkam et al, 2006).

In Cameroon, the Paediatric Neurology Unit at the Yaoundé Gynaeco-Obstetric and Paediatric hospital has a longstanding interest in children with developmental delay (Nguefack et al, 2013). Since 2011, this service has been following up two male siblings, who subsequently had a positive molecular diagnosis for FXS. While investigating these children's condition, we realised that in their extended family, a "Royal family" from Western Cameroon, there were several individuals with similar FXS clinical presentation. Interestingly, the founder of the family happened to be the Chief of the village who had 25 wives and was the maternal great grandfather of the two affected boys. It is a believed in the village that the high number of FXS is a curse that was placed on the princesses by the Chief because they refused to mourn one of his servants who was intellectually disabled.

As part of ancillary care of a social science research project initially designed to understand the community's knowledge of FXS in that particular setting, and as a result of a pressing demand from the family members, we provided genetic counselling and testing for extended relatives in this large family (Wonkam & de Vries, 2020). Cascade testing, which is a systematic process of identifying individuals at risk of contracting a hereditable condition (NIH, 2019), has successfully been practiced in programmes aimed at identifying individuals susceptible of having a genetic condition (Hampel, 2016; McClaren et al, 2013; Newson & Humphries, 2005). In this paper, we aimed to describe the results of this cascade testing for

FXS in a rural setting in Cameroon and to discuss implications of genetic research for rare conditions in Africa.

4.1.2 Materials & Methods

4.1.2.1 Ethical Approvals

The study was performed in accordance with the Declaration of Helsinki. Ethical approval for the study was obtained from the Institutional Committee for Health Research (no. 698/CIERSH/DM/2018) in Yaoundé, Cameroon and the University of Cape Town's Faculty of Health Sciences' Human Research Ethics Committee (HREC: 782/2017). Written informed consent was obtained from all participants who were 21 years of age or older, and from parents or guardians in cases of minors, with verbal assent from participants, including permission to publish photographs.

4.1.2.2 Participants

Scoping meetings aiming at exploring approaches to involve the extended family members in the cascade counselling and testing for FXS was held in 2018 in Yaoundé, between the mother of the boys initially identified to have FXS, and the first, second and last authors, who are respectively general practitioner, neuro-paediatrician, and medical geneticist. At her discretion, she decided to inform family members of the diagnosis. Some family members expressed the interest to be tested, and the above medical professionals were invited to one of their family reunions for formal introduction. A pamphlet explaining the process was provided to family members, that explains FXS and the genetic testing procedure. Family members who expressed interest to be tested had a clinical consultation at the local government hospital. Each participant had a pre-counselling with the objective to provide information about FXS and to identify possible family and community support.

Demographic information was collected via the use of a structured questionnaire, that included sociodemographic variables (age, sex, religion, profession, highest level of education), anthropometric variables (weight, height), and relevant clinical variables. In particular, the participant's neurological status was evaluated by determining the levels of support they needed to attain an optimal personal functioning (Boat & Wu, 2015; Dilip et al, 2013). We classified ID as normal, mild, moderate, severe or profound (Table 4.3 later). Figure 4.1 illustrates the flow diagram for the recruitment of participants. A family pedigree was drawn using the software Cyrillic 3.0.400 (Ken Lange, Los Angeles, CA, USA) (Figure 4.2).

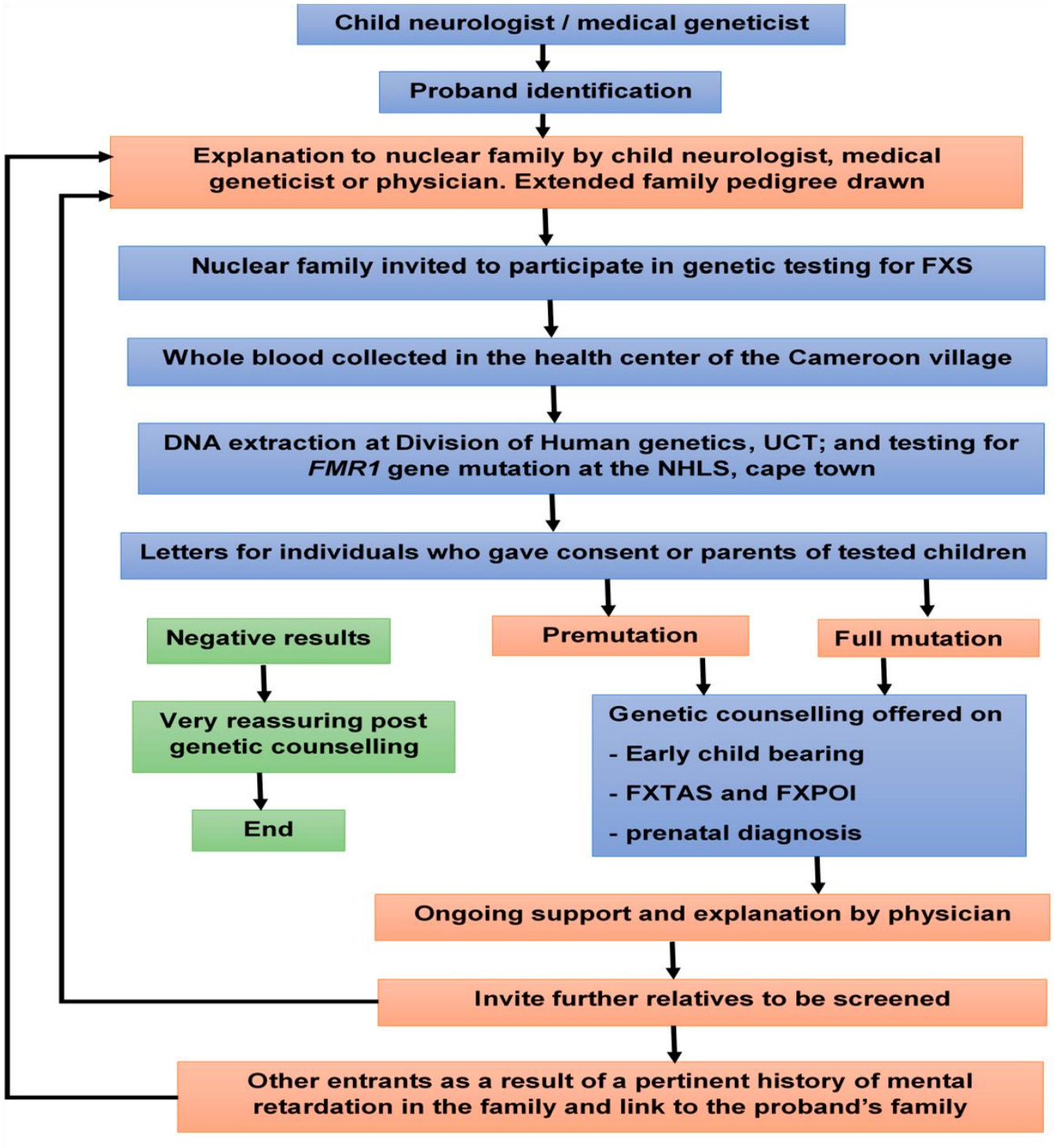

Figure 4.1: Flow chart of cascade testing for Fragile X Syndrome in Cameroon.

FMR1 – Fragile Mental Retardation gene 1; FXS – Fragile X syndrome; FXTAS – Fragile X Associated Tremor/Ataxia syndrome; FXPOI – Fragile X Associated Premature Ovarian Insufficiency; NHLS – National Health Laboratory Service; UCT – University of Cape Town

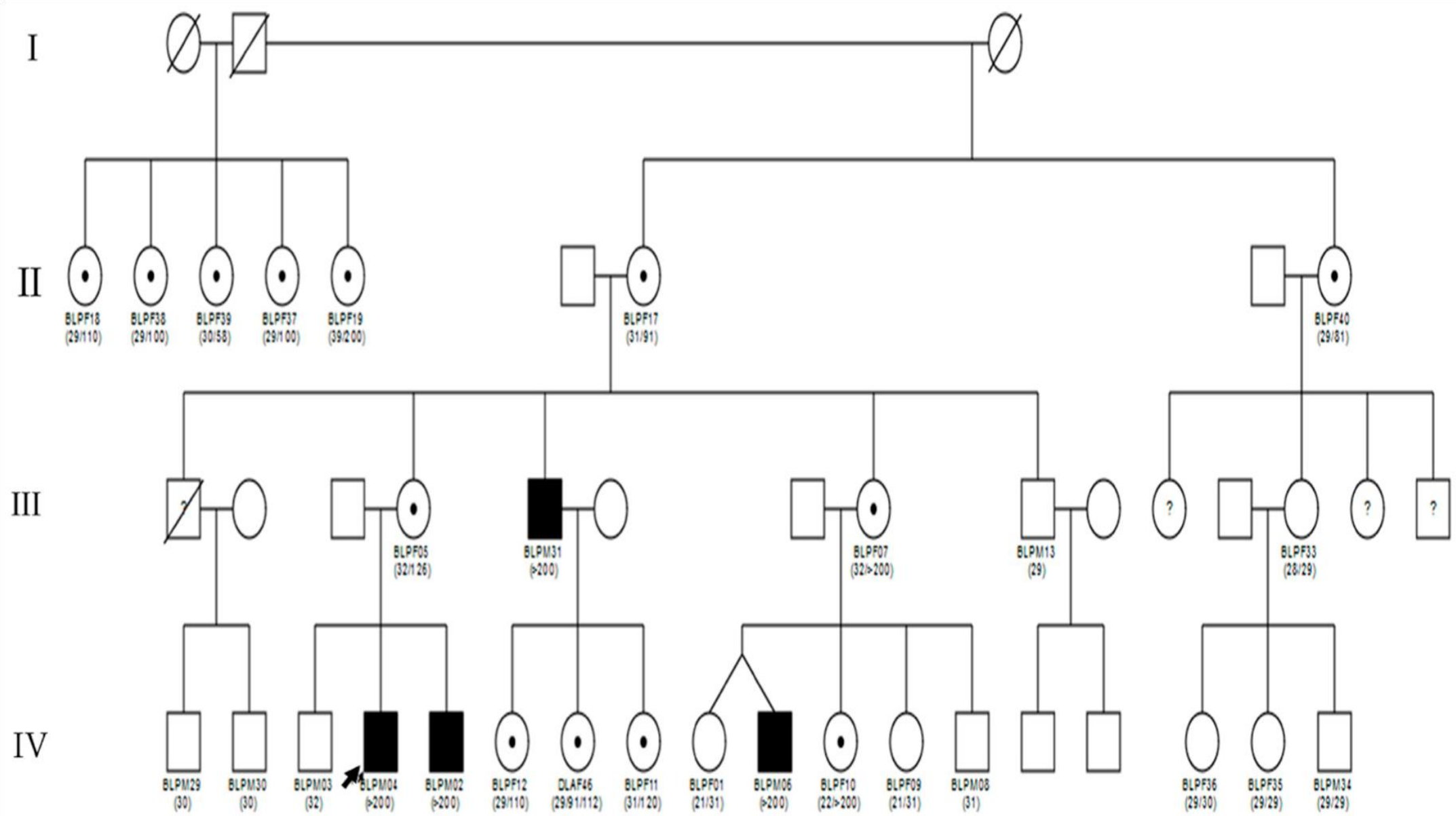

Figure 4.2: Description of our proband's family. The number in brackets below the symbols as the number of CGG repeats in the *FMR1* gene.

All tested participants later received a written report stating whether they were normal, had a premutation or a full mutation for FXS, during a post-genetic counselling session. The counselling and feedback of results were performed by the general practitioner, and as appropriate, further care was done by the neuro-paediatrician.

4.1.2.3 Molecular Analysis

Peripheral blood samples were collected from consenting participants between August 2018 and August 2019. Samples were sent to the Division of Human Genetics, University of Cape Town, Cape Town, South Africa, where DNA was extracted from leucocytes following standardised protocols (according to chemagic™ 360 Nucleic Acid Extractor, Waltham, MA, USA). Sequencing and determination of CGG repeats were performed in an accredited molecular diagnosis laboratory, the National Health Laboratory Service (NHLS), at the Groote Schuur Hospital, in Cape Town, South Africa. Analysis of the disease associated CGG *FMR1* repeat region was performed using the AmplideX *FMR1* PCR kit (Asuragen, Inc, Austin, TX, USA) and capillary electrophoresis (ABI3500 Genetic Analyser, ThermoFisher Scientific, Maltham, USA). Fragment analysis and sizing were performed using GeneMapper® Software 5 (ThermoFisher Scientific, Maltham, NY, USA). Alleles were categorised as normal, intermediate, premutation or fully expanded according to published repeat size ranges (Biancalana et al, 2015; Nolin et al, 2003).

4.1.2.4 Statistical Analysis

Descriptive statistics was used, with Epi-info 7.2 (CDC, USA).

4.1.3 Results

4.1.3.1 Participants Socio-demographic characteristics

Table 4.1 describes the participants. A total of 46 participants were included in the study, 23 children (<18 years old) and 23 adults. Of these, 19 were male and 27 were females (sex ratio of 0.7). The mean age was 9.4 (±5) years old for children and 45.9 (±15.9) years for adults.

Table 4.1: Description of the study participants: FXS mutation, and intellectual disability status.

Variable		N	Mutation Pattern		Total
			PM	FM	
Subject	Male Female	15 13	0 10	4 4	19 27
ID Status of Males	Absent Mild ID Severe ID	14 1 0	0 0 0	0 0 4 0	14 1 4
ID Status of Females	Absent Mild ID Severe ID	13 0 0	8 2 0	1 3 0	22 5 0

ID – Intellectual disability; FM – Full mutation; N – Normal; PM – Premutation

4.1.3.2 Molecular and Pedigree Analysis

Of the 46 participants who underwent Fragile X carrier testing, 28 (60.87%) were normal (CGG repeats < 55); among them, the CGG repeat ranged from 5 to 55 in normal *FMR1* alleles, with the most prevalent alleles being 29 repeats (19.6%), followed by 30 repeats (13.04%) and 31 repeats (13.04%) (Figure 4.3).

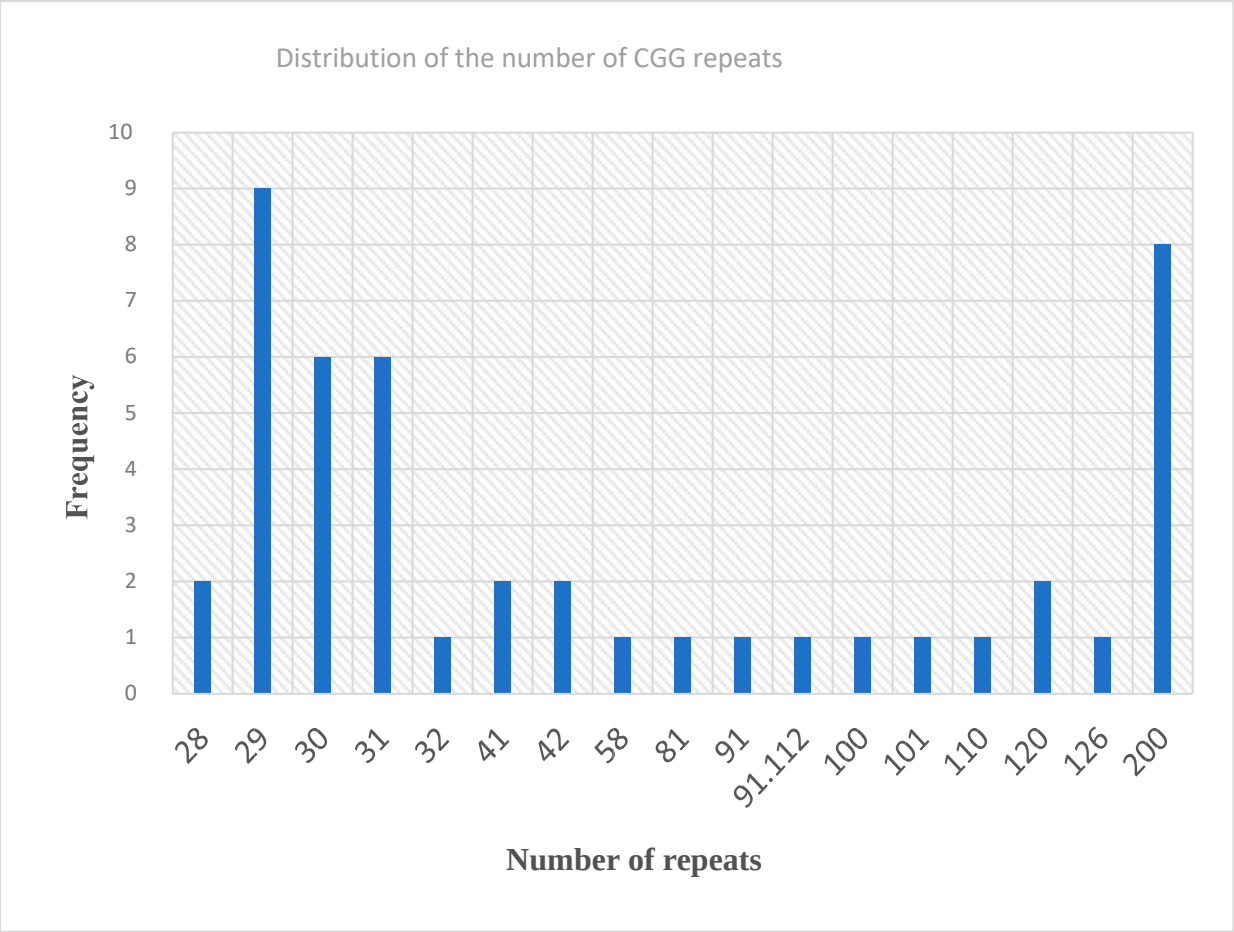

Figure 4.3: Distribution of Cytocine Guanine Guanine (CGG) repeat in the extended family.

Four of the 19 males (21.1%) presented with a full mutation (CGG repeats >200) and were all classified as having a severe ID; one of them had a family with three female children, suggesting a certain social acceptance and tolerance of disability in this specific setting. Among the female participants, 10/27 and 4/27 females had a premutation and a full mutation respectively, giving a carrier frequency for FXS of 51.8% among females. Nine of the 14 females who either had a premutation or a full mutation were normal (64.3%), while the rest (n = 5/14) had a mild ID. Of the five females with mild ID, three had a full mutation for FXS (>200 CGG repeat), and the other two had a premutation (91, 101 CGG repeats) and presented with premature menopause. No cases of Fragile X-associated Tremor/Ataxia syndrome (FXTAS) was reported in the families.

With these results, we were able to describe the pattern of maternal allele transmission. There was an increase in the length of the mutated maternal allele from one generation to the other (Table 4.2). The pedigree in conjunction with the molecular analysis also supported the fact that the great grandfather of our proband, who was the leader of a traditional community in Cameroon, with 25 wives, must have been a normal transmitting male (Figure 4.2). Indeed,

seven of his daughters were screened for the *FMR1* gene mutation in the present study. Six out of 7 were carriers of a premutation (58, 81, 91, 100, 101, 110, CGG repeats), while one had a 200 CGG repeats.

Table 4.2: Consequences of transmitting a maternal PM allele.

Maternal Allele (CGG Repeat) Transmitted	**Child Allele (CGG repeat)**		**CGG Repeat Increase**	**Maternal Allele (CGG Repeats) Not Transmitted**
	Male	Female		
91 (I)	>200	126	+35	31
			+>109	31
		>200	+>109	31
126 (II)	>200		+>74	32
	>200		+>74	32
>200 (III)	>200	>200	0	32
			0	32

CGG – Cytocine Guanine Guanine; PM – Premutation

4.1.4 Discussion

This study is a rare attempt to delineate FXS in an extended family in Africa, and particularly illustrates a case of implementation of genetic counselling and genetic medicine in a rural setting where molecular diagnosis for a genetic disease is inaccessible. This was possible via an intra-African collaboration between paediatricians and a medical genetics team from Cameroon and South Africa, respectively. The identification of a proband with a careful analysis of the pedigree led to the diagnosis of premutation carriers in 10 females. These individuals were previously not aware of their FXS status. By knowing their diagnosis, female carriers were able to understand some relevant clinical presentations such as the risk for premature ovarian failure, and a possible risk of ID in their offspring. Although most children with the premutation do not have neurodevelopmental deficits, recent studies have suggested that some children will manifest learning problems, shyness or anxiety (Renda et al, 2014). This information is important to guide reproductive options such as seeking children earlier in

life and to seek a genetic diagnosis before birth, which is possible in Cameroon (Wonkam et al, 2011b).

The CGG repeat distribution varies among different populations. In this Cameroonian family, the most prevalent allele in normal members of this family was 29 repeats. Hung et al., (2019) also reported a high prevalence of 29 CGG repeat in a population of Chinese women. Moreover, we could identify two families with a premutation that was above 70 repeats and expanded to a full mutation in one generation. Our finding is concurrent with previous reports that an increased number of CGG repeats provides an increased instability of alleles from one generation to the next, resulting in alleles with an increased number of repeats in the progenies (Hung et al, 2019; Nolin et al, 2003). This information is important in counselling carriers since they will need this information to guestimate their chances of having a child with a full mutation.

However, pre-testing and post-testing genetic counselling of FXS can be challenging; specifically, in counselling of the variable phenotypes associated with FXS, especially in female patients with a premutation or full mutation (Mak & Leung, 2017). In our sample size, 14 females had pathologic CGG expansions on their X chromosomes. Five out of 14 had a mild form of ID. The clinically normal female who had a full mutation could be attributed to an unbiased X chromosome inactivation (Ciaccio et al, 2017; Heine-Suñer et al, 2003). A concern with counselling of premutation carriers is explaining the symptoms of FXPOI and FXTAS. FXTAS mostly affects males in their fifties while women still present with premature ovarian insufficiency (POI) by the age of 40 (Jacquemont et al, 2004; Sherman et al, 2005).

4.1.5 Practical Implications

The identification of a positive case of FXS has initiated cascade testing in a rural population where a molecular diagnosis is inaccessible to the population. Information provided in the present study is important for reproductive decisions in individuals tested for FXS. The ability to detect a young female at risk of developing POI before the age of childbearing increases their options of planning to have a family through premarital screening and prenatal diagnosis. Furthermore, through counselling, several relatives were happy to take the *FMR1* mutation test and inform other family members who were sceptical about the screening. Therefore, this study urges the need for screening programmes for targeted FXS which can be extended to other inheritable conditions. This can also lead to the development and strengthening of other genetic services like genetic counselling, prenatal diagnosis and neonatal screening in Africa.

4.1.6 Research Recommendations

Further studies detailing the traditional versus modern molecular knowledge of FXS specifically with respect to the "curse" story needs to be properly explored in this setting using qualitative research and ethnological research approach. In addition, psychosocial burden and possible stigma associated with FXS in this family will also require a specific investigation. Moreover, lived experiences after the return of FXS results to participants in the present study will need to be formally evaluated. Additionally, given that FXS is a rare disease and we expect to have few patients, we advocate for regional collaborations in order to form a pool of patients with FXS and other rare genetic conditions, for future studies. This large family could help in exploring potential genetic modifiers of FXS, including differential methylation status, X inactivation and Adenine Guanine Guanine (AGG) interruptions in female carriers.

4.1.7 Study Limitations

One of the study limitations was the refusal of some affected family members to be tested. So, the population presented in this paper represent only a small fraction of the affected individuals in this family. Besides, we did not probe for Adenine-Guanine-Guanine (AGG) interruptions and the methylation status in our samples which could have aided in predicting the risk of full mutation expansion from premutation and the phenotypic presentation of the different individuals, and possibly explain the relatively high proportion of females with mild to moderate mental retardation.

4.1.8 Conclusions

This study describes the pattern of genetic transmission of FXS in an exceptionally large Cameroon family and the proof of concept of a successful cascade genetic counselling, and molecular testing in a rural setting in Africa. The study is a case scenario of implementing genetic medicine for a neurogenic condition in a rural setting in Africa. Moreover, findings from this research will help increase our understanding of challenges associated with genetic counselling, public knowledge of genetics, and return of genetic results, as well as the psychosocial burden of rare genetic disease in an African setting.

Supplementary Materials: The following Table is available online at http://www.mdpi.com/2073-4425/11/2/136/s1

Table 4.3: Summary classification of Intellectual Disability using four different scales.

Severity Category	Approximate Percent Distribution of Cases by Severity	DSM-IV Criteria (severity levels based only on IQ categories)	DSM-5 Criteria (severity classified based on daily skills)	AAIDD Criteria (severity classified based on intensity of support needed)	SSI Listings Criteria (The SSI listings do not specify severity levels but indicate different standards for meeting or equaling listing level severity.)
Mild	85%	Approximate IQ range 50–69	Can live independently with minimum levels of support.	Intermittent support needed during transitions or periods of uncertainty.	IQ of 60 through 70 *and* a physical or other mental impairment imposing an additional and significant limitation of function
Moderate	10%	Approximate IQ range 36–49	Independent living may be achieved with moderate levels of support, such as those available in group homes.	Limited support needed in daily situations.	A valid verbal, performance, or full-scale IQ of 59 or less
Severe	3.5%	Approximate IQ range 20–35	Requires daily assistance with self-care activities and safety supervision.	Extensive support needed for daily activities.	A valid verbal, performance, or full-scale IQ of 59 or less
Profound	1.5%	IQ <20	Requires 24-hour care.	Pervasive support needed for every aspect of daily routines.	A valid verbal, performance, or full-scale IQ of 59 or less

Author Contributions

Conceptualisation: SN, JdV and AW; methodology: AE and AW; formal analysis: KKK; investigation: KKK, SN and KM; data curation: KKK, KM, EWT, AE; writing—original draft preparation: KKK; writing—review and editing: KKK, SN, KM, EWT, AE, SNM, JdV, AW; supervision: SN, JdV, AW; project administration: SN, JdV, AW; funding acquisition: SN, JdV and AW. All authors read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no competing interests.

4.2 Explanatory models for the cause of Fragile X syndrome in rural Cameroon

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Synopsis

This paper reports on the perceived causes of Fragile X syndrome (FSX) and inherited forms of intellectual disability in a community and members of an affected family in Cameroon. We aimed to understand how people explain the causes of FXS and other inherited forms of intellectual disability in this village. The study results indicated that there were four different explanatory models for FXS used by community members. The curse model was the primary explanatory model described by both community and family members. It is based on a curse from the Chief who bewitched his daughters and wives because they did not mourn his servant that had an intellectual disability. Other explanations were a spiritual model that relates FSX to some punishment from God, and a psychosocial model that attributes the syndrome to events in the prenatal and perinatal periods. Finally, a genetic model emerged following the return of FSX genetic results to affected family members.

Author contributions:

Kengne Kamga Karen (KKK): Design, data collection, coding, and analysis; wrote the first draft of the article, and incorporated comments from co-authors; responded to all reviewer comments.

Nchangwi Syntia Munung (NSM): Assisted in the interpretation of study findings and in the writing process.

Séraphin Nguefack (SN), Jantina de Vries (JdV), Ambroise Wonkam (AW): Assisted in the design and interpretation and commented on various drafts of the manuscript.

Explanatory models for the cause of Fragile X Syndrome in rural Cameroon

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Abstract

Amongst the myriad causes of intellectual disability (ID), Fragile X Syndrome (FXS) is the leading genetic cause. Yet, little is known of how people affected by this condition make sense of it. The present study aimed to investigate the explanatory models for the causes of FXS in an extended family mainly affected by this condition and members of the village from which they originated in Cameroon. Using an ethnographic approach, 92 participants were interviewed (59 females and 33 males) through 10 focus-group discussions and 23 in-depth interviews between April 2018 and February 2020. Data analysis revealed four explanatory models regarding the aetiologies of FXS in the community. Firstly, the curse model described a curse from the chief because of the belief that his wives did not mourn his intellectually disabled servant. Secondly, the spiritual model relates FXS to a punishment from God. Thirdly, the socioeconomic model attributes FXS to events in the prenatal and perinatal periods. Finally, the genetic model describes the pattern of inheritance of the disease in the family. This paper helps to understand the explanatory disease models that exist for FXS in rural Cameroon and could inform genetic counselling practices, community genetic education, and policymakers when drafting protocols for public engagement activities.

Keywords: Fragile X Syndrome, Causal beliefs, Explanatory model, Genetic counseling, Cameroon, Community

What is known on this topic?

In the quest for a diagnosis for Fragile X Syndrome (FXS), it is not unusual for parents and caregivers to develop non-biomedical explanations for the disability of their children. Yet, little is known about what type of explanatory models African populations have with regards to FXS.

What this paper adds to the topic?

This paper clearly establishes how an African community discusses the causal beliefs for Fragile X Syndrome (FXS) in an affected family from a rural community in Cameroon. Through ethnographic methods, it describes the various explanatory models of FXS that are held by family and community members.

4.2.1 Introduction

Fragile X Syndrome (FXS), also known as the most common inherited cause of intellectual disability (ID), is a neurogenic condition that affects twice as many males as females. It is characterized by mild to moderate ID, autistic features, and dysmorphic signs such as large ears and testis (Coffee et al., 2009; Hunter et al., 2014; Parker et al., 2010). Its pathophysiology is related to an expansion of the Cytosine-Guanine-Guanine (CGG) repeat at the 5' non translated region of the Fragile X Mental Retardation gene 1 *(FMR1*) found on the X

chromosome (Jin & Warren, 2000; Santoro et al., 2012). This CGG repeat expansion is transmitted through a dominant X-linked mode of inheritance. Hence, affected males will transmit the gene to all their daughters, while females have a fifty percent chance to pass the trait on to their offspring (Peprah, 2012; Santoro et al., 2012). In Cameroon, in the paediatric neurology unit at the Yaoundé gynaeco-obstetric and paediatric hospital, Nguefack et al. (2013) showed that amongst the children who presented with developmental delays, 1.3% were due to a genetic cause. Amongst these genetic causes, FXS was the leading single-gene cause of developmental delay identified (Nguefack et al., 2013).

Cameroon is a lower-middle-income country with an estimated population of over 25 million as of 2018. Poverty in Cameroon has increased by 12% between 2007 and 2014, and close to 60% of the people living in poverty concentrate in rural areas. Without universal health coverage, patients depend on their family members for financial support, and they also visit traditional healers in ill health (The World Bank, 2019; Wonkam et al., 2014). Like many other developing countries, Cameroon is experiencing the challenges of managing patients with chronic non-communicable diseases, some of which have a genetic origin. Wonkam et al. argue that despite this shift toward managing patients with genetic diseases, physicians and medical students have little knowledge of genetic diseases and genetic testing and suggested that their knowledge could increase with the presence of a genetic service in Cameroon (Wonkam et al., 2006; Wonkam et al., 2011b). In this light, in 2011, two male siblings received a positive molecular diagnosis of FXS at the Yaoundé gynaeco-obstetric and paediatric hospital, Cameroon. Informal data collected at the first consultation from the mother of the two boys indicated that several members of her family related FXS to a curse from the founder of their family. This resulted in a cascade testing that confirmed the pattern of X-linked dominant transmission in the family (Kengne et al., 2020b).

The causal beliefs of intellectual disability by affected individuals and their families could be ways communities interpret and organize illness in their society (Helman, 2007; Sobo & Loustaunau, 2010). The so-called explanatory models (EM) are derived from the Common Sense Model (CSM) described by Diefenbach & Leventhal (1996). The CSM model describes how patients experience chronic, stressful events in five ways, which are: having a name for the condition; knowing how long it will last; identifying the physical, psychological, and social consequences of having the condition as well as developing a curative model for the infirmity (Diefenbach & Leventhal, 1996). Individuals facing a chronic medically unexplained symptom tend to rely on non-biomedical explanations to provide meaning to their condition (Frostholm et al., 2007; Sumathipala et al., 2008). In the quest for a diagnosis for FXS, it is not unusual for parents and caregivers to develop non-biomedical explanations for the disability of their

children due to the long lag time between the identification of the disability and the final diagnosis. In a summary of the available evidence, Kengne et al. (2020) describe that these non-biomedical explanations usually appear to be developed when caregivers are grieving and describe situations where parents link FXS to divine causes (Kengne et al., 2020a; Michie & Skinner, 2010). In their review, Bhikha et al. (2012) found that there is limited research in developing countries, most notably in Africa, concerning explanatory models of illnesses (Bhikha et al., 2012), and to the best of our knowledge, no African study exploring the explanatory model for FXS has been conducted before. In an attempt to fill this gap, we use qualitative research methods to explore the perception of the causes of FXS in a rural community of Cameroon, previously described (Kengne et al., 2020b). The village where this work was conducted has an unusually high incidence of FXS because of a founder effect. Our work aimed to investigate the range of explanatory disease models about FXS specifically, and ID, more broadly.

4.2.2 Methodology

4.2.2.1 Setting

This study was conducted in the community of the patient (P0) who received a genetic diagnosis of FXS for her sons. P0 is a 48-year-old mother of three children, two of whom were diagnosed with FXS, the first two boys described in the introduction, and as previously reported (Kengne et al., 2020b). She originated from a small rural village in the Western region of rural Cameroon, from a family that has an unusually high incidence of FXS. This high incidence is due to a so-called founder effect (Kengne et al., 2020b). People in this village practice agriculture for a living, and more than 50% of the villagers live in poverty. The village is situated about 10km from the main hospital in the region. However, it has a community health clinic that provides primary healthcare. Support services for children with developmental disabilities are rare in the country. The few services that are present are in the two capital cities: Douala and Yaoundé, which are situated more than 400km from the village. Hence, adequate care is not available to most villagers affected by FXS. In this setting, the spoken languages are French, English, Pidgin, and Ngombalé.

4.2.2.2 Study design

In 2011, P0 sought a clinical diagnosis for the condition of two of her children from two of the authors of this manuscript (SN and AW). After receiving the diagnosis of FXS, she shared with her healthcare providers what people in the village, where she originates, believe about FXS. Many years later, and following discussions with P0, we conceived this research project to better understand explanatory disease models used for FXS in the community and the family. It so happens that P0's family is the founding family of the village that still holds the

Chieftaincy. As such, they are a politically powerful and well-known family in the village. This project was part of a larger project which seeks to investigate and understand the effect of receiving individual genetic results in Africa, named IFGENERA, standing for Individual findings in Genetics Research in Africa (Wonkam & de Vries, 2020). Given the enthusiastic, collaborative will of P0 and her family, we decided to use an ethnographic approach (Reeves et al., 2008) to carefully build relationships and understand the dynamics around FXS in the village. P0 introduced us to her extended family and to key opinion makers in the community from which she originates. We interacted with this community for two years. During that time, we sought permission to conduct research in the extended family as well as the village, engaged with stakeholders over multiple events and meetings, developed and piloted our research instruments, and conducted our research.

4.2.2.3 Study participants and sample selection

Snowball sampling was used to recruit family and community members (Noy, 2008). This sampling strategy was to ensure that participants were knowledgeable informants and reflected a range of characteristics of individuals potentially impacted by FXS in the family and community of P0. Following our introduction into the family, the family leader – who is the current Chief of the village –, as well as other senior members of the family were contacted. When the agreement was obtained from the family to participate in the research, they invited us to present the research project at their annual family reunion in 2018 and 2019. During these meetings, family members were invited to participate in the study voluntarily. The details of interested individuals were collected and were later telephonically called to schedule the interviews at a date and place of their preference.

Once the participation of the extended family was secured, we proceeded by seeking community permission for participation. The Chief and elders had already consented, but we also required permission from district authorities as well as key opinion leaders in the village. Following a series of community engagement events to secure permission to recruit in the village, community members were invited to participate in focus group discussions through public announcements and personal invitations.

Participants were men and women, 18 years of age, and older. Participants with FXS were not recruited. Empirical data were collected until saturation, where further interviews did not yield new insights (Fusch & Ness, 2015). A total of 23 in-depth interviews (IDIs) and 10 focus group discussions (FGDs) were conducted. The number of participants in FGD varied between 5 and 12 and were classified either as community members or relatives of P0.

4.2.2.4 Procedure for Data collection

All interviews were conducted between August 2018 and February 2020. The IDIs and FGDs were conducted either in French or English, depending on the first language of the participant. However, during FGDs, some participants expressed themselves in the local language (Ngombalé), which was translated during transcription but recorded in the vernacular in our field notes as a "memo." All the IDIs lasted between 27 and 60 minutes whilst the FGDs lasted between 45 and 90 minutes. All sessions were audio-recorded, and topic guides were used to guide the discussions with participants to understand their perceptions of, amongst others, lived experiences with, the stigma associated with, and the effects of receiving a genetic diagnosis of FXS. At the end of every interview, a genetic information session was offed to participants where all their questions concerning FXS and its mode of inheritance were answered. Participants were given financial compensation for their time and transport. Participants were assured confidentiality, as much as possible, by referring to individuals interviewed in groups with identification numbers rather than their names. In cases where participants knew each other, they were asked if they are willing to share their information with members of the FGD; otherwise, they could participate in the in-depth interview. All interviews were digitally recorded and transcribed verbatim. The topic guide is provided as supplementary material.

4.2.2.5 Analysis

Digital recordings from individual and group interviews were cleaned of identifying information, and transcriptions were translated from French into English as needed. Transcriptions were reviewed for accuracy then imported, with the researcher's memos and field notes, into NVivo 12 qualitative data management program (www.qsrinternational.com). Inductive coding was used to identify themes emerging from the data (Thomas, 2006). Thematic analysis was used (Braun & Clarke, 2012) to identify patterns of meaning across the dataset, both within-case and between-cases, as we read through the transcripts. The analysis involved the search for understanding of similarities and differences among participants concerning knowledge and views related to FXS. The first round of coding was done by KKK when approximately two-thirds of the data was collected. The codes developed, and the memos were discussed with JDV and NSM to ensure that they accurately captured critical details from the transcripts. Insights from this early phase of data analysis guided the final stage of data collection and helped us ensure saturation was reached. After obtaining a complete data set, KKK and JDV collectively developed the hierarchical coding scheme that was applied to the full dataset. KKK coded the full dataset, and through consensus, the study team identified the primary themes that were related to the explanatory models for the causes of FXS, as perceived by participants.

4.2.3 Results

4.2.3.1 Description of the sample

A total of 92 participants agreed to be part of our study, of which 64% were females, and 36% were males. The median age of participants was 42 years old (range: 18-81 years old). Sixty-three out of the 92 participants were community members, while 29 were family members. The majority of the participants had a secondary level of education, and more than 75% were unemployed (Table 4.4). Participants who said they were unemployed lived on agriculture or trading, while employed participants were either teachers, religious leaders, or traditional leaders.

Table 4.4: Demographic characteristics of our population

Variable		**Percentage (%)**
Gender	Male	36
	Female	64
Level of education	Primary	28
	Secondary	59
	University	13
Employment status	Employed	24
	Unemployed	76

4.2.3.2 Name of FXS in the community

Overall, community members appeared to have come to the view that the family of patient P0 – the royal family in the village - was susceptible to having children with FXS (Fig 1). They distinguished between FXS and ID. For instance, when speaking of FXS, participants either used “alienate” or “rheurheu” to describe people with inheritable forms of ID like FXS. In contrast, other forms of ID were referred to as madness, follies, or “Peuh.” An alienate or a “rheurheu” is described as behaving strangely, with fluctuating moods, but is able to live just like any other person. A female participant explained this in a FGD:

> *There is pure madness that we already know. However, when it is an alienate who was born like that, they still think a little. There are times when they go off their senses before*

regaining it again. I can say that this is the type who wants to isolate themselves. The family does not isolate him because they are alienates; they [alienates] do so on their own. **(FGD, Community 1, Female)**

This discussion was followed up with other community members who gave us the meaning of these different names. These explanations were recorded as memos.

In the local language, "rheurheu" means a child who is an Alienate, while "Peuh" means madness. Participants reported that their children are not mad but somewhat alienated. They preferred that we used "rheurheu" in subsequent interviews. This is because "rheurheu" is "better" than "peuh" because you can take care and support a "rheurheu" until he/she even gets married while you cannot do anything for a mad man. **(Field notes 15 October 2018)**

4.2.3.3 Perception of the causes of FXS in the community

In an attempt to understand why there is a high incidence of FXS in P0's family, community members proffered four possible explanatory models: the curse model, the spiritual model, the socioeconomic model, and the genetic model (Figure 4.4).

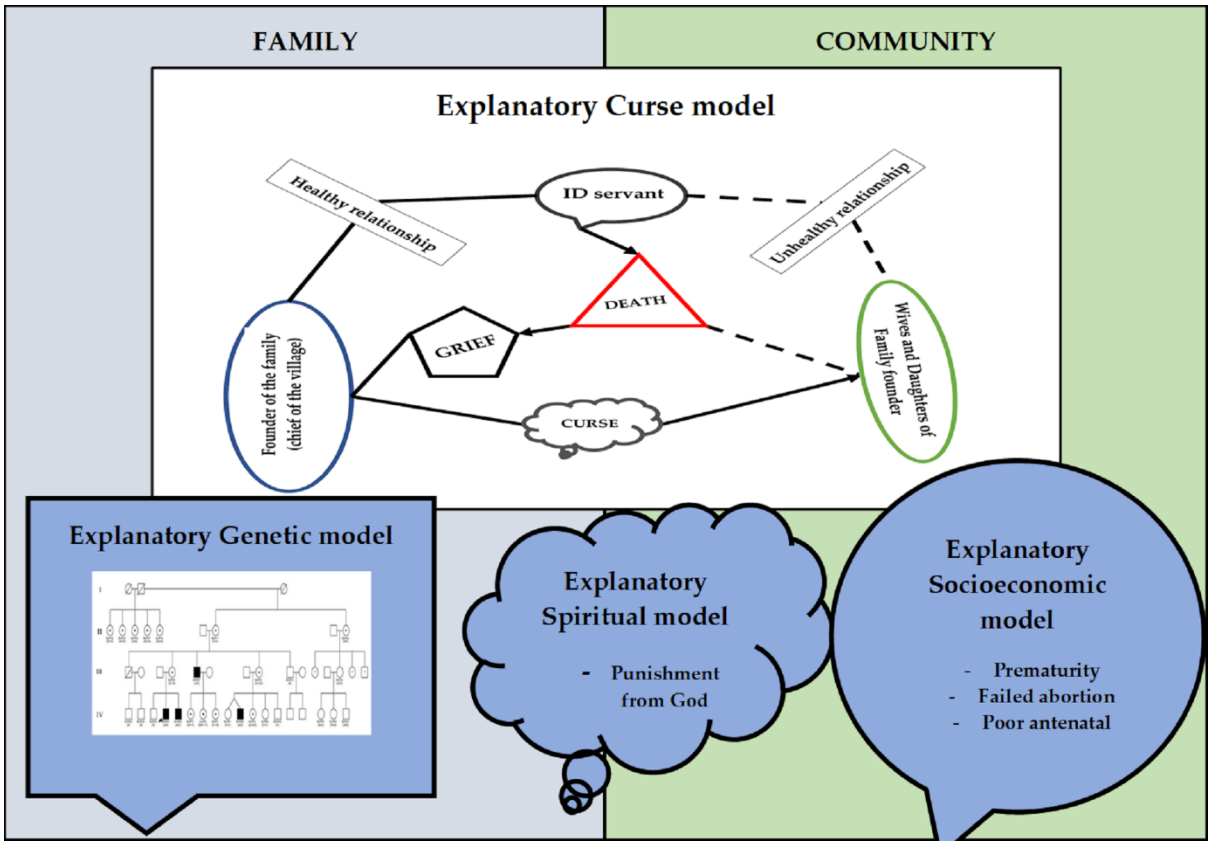

Figure 4.4: Map describing the different explanatory models used in P0's family and community for the cause of FXS.

The curse model

More than 75% of the interviewees spoke about the curse as an explanatory model of FXS in P0's extended family. This social explanation is based on the hypothesis that the founder of family F0 (chief of village) had cursed his daughters for not assisting him in the preparation of the funeral ceremony of one of his servants. An elder of the village suggested that the relationship between the chief and this servant was a positive one, where the servant assisted the chief in all his activities like trading, splitting firewood for the wives, and fetching water.

> *So, the chief bought a slave who was alienated but was physically strong. He wanted his alienate servant to help his wives by splitting the wood and help him with his shopping. He lived for a long time with this alienate servant* **(IDI, community, An elder of the village)**

On the other hand, the physical appearance of the servant did not impose the respect of the women in the palace. Rather, they usually mocked him and did not want to see him.

> *"look how you are, look how dirty you are. Can't you have a bath? It is stuff like that. That is to say, when someone comes to my house, for example, and sees an alienated child; they start to say things that go in the direction of mocking the child.* **(FGD, community 4, Female)**

Considering the caring relationship that existed between the chief and his servant, the chief was furious when his wives and daughters did not assist in the funeral of the disabled servant as he had expected them to be. Instead, they went to the farms with their mothers. The village narrative related to us is that the chief then said that his daughters were going to have alienated children, just like his servant. A female in family F0 recounted this story that is widely accepted by the community and the family members:

> *It is said that when the "rheurheu" died, the chief's wives went to their farms even after knowing that the "rheurheu" was dead they did not tell my father. While the women were on their farms, my father found out that the alienate had died. When the women returned, he asked them why they had not informed him of the death of his servant and why they went to their farms, leaving the servant's corpse unattended. After that, he said: "One day, you too will give birth to a "rheurheu." It is from this moment that we, the children of [the chief], started giving birth to "rheurheu." This latest version seems real because my father cursed his wives and daughters.* **(FGD, Family 4, female)**

This story has gone through several modifications over the years, and this final construct seems more acceptable to the community. However, other interviewees think that the curse is related to the reincarnation of the alienated servant in family F0. A male interviewee reported:

When he died [the alienated servant], the family did not take care of him, and over time we said to ourselves that this is a phenomenon of reincarnation and that it may be the reason why we have mentally deformed children. **(IDI, Family, male 4)**

It is worth noting that traditional customs support this argument since males who die without having children are thought to reincarnate within the family. Hence, it is thought that the curse in the community is the reincarnation of the alienated servant of the chief. "*It is often said that the curse of people who have lived without having a wife or children is very dangerous."* **(IDI, Family, male 5)**

There were also some community members who were not aware of this royal curse, but who also described a belief that people with FXS had a curse placed on them to block their chances of evolving in society.

I think we are in Africa and we are Bantu. Very often, in some families, there is what is called the "curse." We often throw this to some children to block their intelligence and their charisma. So, we would not like them to succeed, so, in my opinion, this can be the cause of inherited ID in some families. **(FGD, community 5, Male)**

Spiritual model

Close to 20% of interviewees mentioned the explanatory spiritual model for the cause of FXS in the family. This model was recounted by religious leaders, some community members, and a small fraction of the relatives of patient P0. The spiritual model described FXS in terms of punishment of God. Using quotations from the bible, participants believed that the origin of people with FXS was a declaration from the founder of the family. Two male participants, one in the FGD and the other through IDI, argued:

When I read the Old Testament, I see that God had punishment in the form of diseases, terrors etc., for all sins. So, I accept that. I believe in my faith. I believe that if someone does something that is wrong, the consequences can fall on him or his descendants. **(IDI, community, male 2)**

Whether it is a curse from the parents or from God, the Bible says He punishes the iniquities of the parents up to the fourth generation. Also, we can be part of this generation that God cursed. So, if we are part of a generation that God has cursed, then what God said about our parents will affect us from generation to generation. If God pronounced the mental retardation curse, well, there are many things, be it poverty, illnesses, and so on, God can do that, and it affects us. **(FGD, community 1, Male)**

Some members of family F0 also shared this view and argued that this punishment is a consequence of the unfair treatment bestowed on the disabled servant. Hence, in order to

prepare future generations of this situation, they were told not to mock intellectually disabled children. If they did, they would receive this punishment from God. Two members of the family elaborated:

> *It may be the work of God; it is bad luck on that side. However, as expressed in the bible, the gospel says, God punishes from the first or the second generation. We think it can be our punishment.* **(IDI, Family male 2)**
>
> *However, we were already prepared for this because we knew that my father's sisters gave birth to alienate children. As their mother already knew what had happened, she always told me that I should never make fun of such a child because we do not know what God has in store for us.* **(IDI, Family, female 9)**

So whilst the spiritual model significantly overlaps with the curse model, what is different is that in the spiritual model, participants see the curse as emanating from God.

Socioeconomic model

The explanatory socioeconomic model for the causes of FXS was supported by about 20% of the interviewees as a possible cause for FXS, and all of them were community members. Members of family F0 did not attribute FXS to socioeconomic factors. The main socioeconomic models described were prematurity, inadequate healthcare, and the use of drugs during pregnancy. A mother in the community reported how the developmental delay of her child is associated with prematurity.

> *He was premature. He was born at six months, and he was 900 g in weight. So, he did not reach 1 kg. The child is now more than two years old; he does not sit down; he does not take anything by hand to eat. He has enough teeth, but he does not work well, he does not do the scrambling well like all children. So, he does not sit.* **(FGD, community 1, female)**

Moreover, other community members reported inadequate care during the prenatal period as being the cause of FXS in the community. A male participant in the community elaborated on this and concluded that it was the lack of some injections that are given during the prenatal period and the poor follow-up during the pregnancy that led to the occurrence of FXS:

> *We think that the cause must be the lack of certain injections during the Antenatal clinic and poor follow up. So, we can say at this point that one of the causes of these alienations may be the fact that the pregnant woman was not administered the required injections, which could positively influence the growth of the child's brain.* **(IDI, community, male 5)**

Most interestingly, participants reported that FXS could be due to unlawful termination of pregnancy, notably if the woman used abortion-inducing medication that failed to terminate the pregnancy.

> *It is said that there are some girls when they are pregnant, they take medication to abort. I do not know if these are traditional medicines or modern medicine. However, if the child does not go out and resists in the belly only coming out at nine months, the child grows until it starts to walk, then it loses the head.* **(FGD, community 4, Male)**

Genetic model

The explanatory genetic model is an emerging model that has not yet been integrated by family and community members. Only patient P0 and one of her cousins discussed this model. After the diagnosis of FXS in the patient P0's family, she was given genetic information related to FXS and the disability of her children.

> *Then he said it is a genetic problem because he asked for the family tree, and he now drew it and explained to me that my grandfather was this person that had many wives; the mother was this person. So, when I was explaining, he was drawing the family tree until he came out with the conclusion. He told me what was wrong with these children would be this thing (FXS), and that it comes from my mother's side, from my mother's paternal grandmother.* **(IDI, family, P0)**

Following this diagnosis, patient P0 could talk to other family members who traced the origin of the condition to her great maternal grandmother, who was having some developmental problems just like her children. She then started doubting the curse model and developed a genetic model based on the information she received during the post counselling information session and her investigations. Her cousin recounts:

> *Recently, they got to know that it had nothing to do with their father killing a fool, that their father never killed a fool. That their grandmother, that is my mother's grandmother, looked somehow like an imbecile. That is where this trait is originating.* **(IDI, Family, P0's cousin)**

4.2.4 Discussion

Our data suggest that in this Cameroonian rural community, people can identify genetic diseases and provide perceptions about the different causes that associate with FXS. Our findings are unique because this was the first study in Cameroon that explores the way cultures address children with inherited forms of ID, such as FXS. The names used to refer to children with ID have been reported in other African countries, like Ghana (Avoke, 2002; Opare-Henaku & Utsey, 2017), but these studies refer to common names which translated to 'being

stupid or a fool' for describing these children. However, Opare-Henaku and Utsey (2017), in their analysis of the concepts used in the "Akan" culture, found that there are different ways of addressing people with intellectual disability based on the severity and/or cause. Similarly, our study shows two names, "Rheurheu" and "Peuh," where "rheurheu" is an inherited and milder form of ID which is more accepted by the community, while "peuh" could be associated to severe forms of ID.

The community in describing FXS also described four explanatory models. We suggest that these models should not be regarded as a final explanatory model but rather as a map (Figure 4.4) of possible explanatory models for FXS in African communities, which represent the framework of an ongoing process in which the community uses to provide meaning for the causes of FXS. Some African scholars from Kenya and Nigeria indicate that ID can have a supernatural aetiology (Bunning et al., 2017; Etieyibo & Omiegbe, 2016). These studies elaborate on jealousy and envy, as well as ancestral displeasure or curses, which were supernatural factors that led to IDs. It is also possible, with the increase of formal education in the community, that the genetic model could become dominant. Such trends were observed in Sickle cell disease (SCD), a genetic condition that is prevalent in Africa. Indeed, SCD cause was initially associated with a reincarnation model called "ogbanje" in communities Nigeria, with malevolent "ogbanje" that differs from others in being revenge-driven, chronically ill and engaging in repeated cycles of birth, death, and reincarnation (Nzewi, 2001; Onwubalili, 1983). Poor knowledge of the disease has a potential impact on family dynamics. Indeed, in Nigeria, family ascribed the disharmony in their marriage to SCD in their children (Bamisaiye et al., 1974).

Furthermore, in rural Kenya, misperceptions regarding inheritance reinforced blaming patterns within families, and low initial recognition of SCD and its cause were associated with poor surveillance practices (Marsh et al., 2011). In contrast, more recent data from Nigeria, from which more than half of the parents had tertiary education, illustrates an improved knowledge of the heritable nature of SCD, and this had a beneficial effect on family dynamics (Brown et al., 2010). Similarly, in Cameroon higher education, occupational status and resources were associated with better knowledge of the heritable nature of SCD and this knowledge was a significant contributor to marriage stability and commitment to SCD-affected children care (Wonkam et al., 2011a)

Other models described in the community are the socioeconomic and genetic explanatory models. The socioeconomic models are related to events in the prenatal period. Nguefack et al. (2013) showed that there are several causes of developmental delay, with the main etiologies being related to perinatal and antenatal causes. The manifestations of FXS could mimic those

of other perinatal causes of developmental delay, which results in the delay of its diagnosis (Christianson et al., 2002; Nguefack et al., 2013).

Whilst the diagnosis of FXS for the heritable form of ID in the rural community of Cameroon has not yet changed the perception of people concerning ID in the village, it has given rise to a new explanatory model, the explanatory genetic model, that is starting to shed some doubts on the narrative of a curse in family F0. The reasons for the non-generalization of the explanatory genetic model is yet to be explored in this family. Diefenbach & Leventhal (1996) argued that patients in the process of seeking the cause of intellectual disability could come across causes that are socially unacceptable and will prefer not to know (Diefenbach & Leventhal, 1996). This study supports the notion that people actively seek meaning for the experiences they face by holding onto a variety of explanations simultaneously. Due to the perceived uncertain cause of intellectual disability in the family, the community and family members utilized several non-biomedical explanations. We can, therefore, suggest that these explanatory models for the cause of FXS are possibly a community construct used to cope with the high frequency of people with FXS in the rural community since they have high respect for traditional customs.

4.2.5 Practice Implications

Our findings suggest that public health programs in Cameroon should not only aim at increasing knowledge and awareness about rare genetic conditions and its management. These programs should also elaborate on the relevance of genetic counselling, testing, and reproductive choice, specifically in the context of a heritable condition such as FXS. Strategies may include concerted efforts to educate families and community members about the genetic cause of Fragile X Syndrome, particularly in the present study setting. This could be achieved by involving and training local health care personnel on communicating genetic information through face-to-face explanation of Fragile X Syndrome, pedigrees analysis, and using information aides consisting of letters, brochures, and resource guides. These tools need to be prepared by the local physicians, and nurses, who are more familiar with the different explanatory models within the community. With a broader knowledge base, community members and leaders might be persuaded to make use of available medical services for genetic counselling. Our findings also provide an insight into the challenges that could be addressed during the development and implementation of genetic counselling services; this may include the traditional knowledge of genetic diseases like FXS. Moreover, this study can also strengthen the current H3Africa ethics and community engagement guidelines and refine qualitative research strategies for our African context. We also show active engagement with a particularly sensitive community, suggest possible stigma due to a devastating and

unknittable condition associated with intellectual disability, and fill a void in our understanding of African perspectives about ID and genetics.

4.2.6 Study Limitations

Our study had a few limitations. The first limitation is related to recall bias because the explanatory model for FXS is mainly based on the participants' ability to recall the different events that had happened. Secondly, our sample was mainly family relatives and literate community members. It could have been more comprehensive with the inclusion of the views of traditional healers of the village because they are the first people that community members will go to in the quest for a solution to their health problems. Thirdly, this study's ethnographic approach may constitute a limitation because participants could have presented exemplary behaviour or told the researcher what they wanted to hear. The study results are only applicable in this setting since ethnographic research findings are particular to the research context in which a study was conducted and cannot be generalized.

4.2.7 Research Recommendations

Future research should engage on how communities address the ethical and social implications of FXS and its associated health condition such as premature ovarian failure in carrier female, and Fragile X associated tremor ataxia syndrome (FXTAS) and reproductive health decisions, including the option of prenatal diagnosis which is now possible in Cameroon (Wonkam et al., 2011). Moreover, whether the perception of explanatory models influence the commitment to the care of FXS-affected individuals, as well as the coping mechanisms to its associated burden in families, will also need to be investigated. Besides, the association of the explanatory models and possible gender stigma associated with families whose female members are a potential carrier of FXS will need to be investigated.

4.2.8 Conclusions

This rural Cameroonian community has multiple ways of explaining the causes of FXS. The different explanatory models for the causes of FXS is a framework that will help the scientific community to understand the socio-political and cultural context of people living in the rural community. This knowledge is also an essential starting point for establishing a collaborative platform between health professionals, educators, and policymakers, who will significantly contribute to the development and evaluation of culturally and sensitive patient-friendly interventions. Furthermore, cited perinatal events in this study draw our attention to the importance of developing programs for early detection of FXS through prenatal diagnosis, neonatal screening, and premarital diagnosis. As the field of genetic counselling focuses on diversity initiatives, including access to genetic testing and counselling services of underrepresented populations, studies such as the one explored in this paper will become

increasingly crucial to informing these initiatives and improving genetic testing and counselling services to all.

Author Contributions

KKK: Design, data collection, interpretation, and writing

NSM: Interpretation, writing.

SN, JDV, AW: design, interpretation, writing.

KKK, JDV and AW confirm that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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We are confirming that this work was conducted to fulfil a Ph.D. degree requirement of KKK. This study was conducted as part of the IFGENERA study, which is funded by the NIH Common Fund H3Africa Initiative (NIH U54HG009790) to AW and JDV.

Compliance with ethical standards

Conflict of Interest

The authors declare that they have no competing interests.

The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Human studies and informed consent

The study was performed following the Declaration of Helsinki. Ethical approval for the study was obtained from the Institutional Committee for Health Research (no. 698/CIERSH/DM/2018) in Yaoundé, Cameroon, and the University of Cape Town's Faculty of Health Sciences' Human Research Ethics Committee (HREC: 782/2017). Written informed consent was obtained from all participants who were all legal adults, including permission to publish photographs. Administrative authorizations were obtained from the local authorities (District Medical Officer and the village chief).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

4.3 A poisoned gift: genetic guilt, diagnostic closure and communicating about genetic risk for Fragile X Syndrome in a Cameroonian family

Kamga K. K., Nchangwi Munung, S., Nguefack, S., Wonkam, A., & de Vries, J. (2020). A poisoned gift: genetic guilt, diagnostic closure, and communicating about genetic risk for Fragile X Syndrome in a Cameroonian family. *Journal of Genetic counselling.* (Under review).

Synopsis

This paper interrogates the experiences of receiving a genetic diagnosis from family members who participated in the cascade testing. It helped us to understand the impact of giving back a Fragile X Syndrome (FXS) results to a family in rural Cameroon. Two main themes emerged from the interviews relating to psychological adaptation and FXS genetic risk communication. Firstly, I describe the happiness and relief that is associated with diagnostic closure. Next, I describe genetic guilt, survivor guilt, and frustration associated with a family history of FSX and taking care of developmentally delayed children. Finally, I highlight the communication styles needed to convey genetic risk to extended relatives and promote resilience.

Author contributions:

Kengne Kamga Karen (KKK): Study design, data collection, interpretation; wrote the first draft of the article, and incorporated comments from co-authors; responded to all reviewer comments.

Nchangwi Syntia Munung (NSW): Assisted in the interpretation of study findings and in the writing process.

Seraphin Nguefack (SN), Jantina de Vries (JdV), Ambroise Wonkam (AW): Assisted in the design and interpretation and commented on various drafts of the manuscript.

A poisoned gift: genetic guilt, diagnostic closure and communicating genetic risk for Fragile X Syndrome in a Cameroonian family

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Abstract

Fragile X Syndrome (FXS) is a genetic disorder that leads to intellectual disability and delays in speech development in males. Receiving a genetic diagnosis of FXS can have an emotional impact on the patient, parents, and the rest of the family. This paper reports on the experiences of receiving a genetic diagnosis of FXS in an extended Cameroonian family. Using an ethnographic approach, we conducted 13 in-depth interviews and one focus group discussion with members of an extended family segregating for FXS. We interrogated their experiences of receiving a genetic diagnosis. Two main themes emerged from the interviews relating to psychological adaptation and communication of FXS genetic risk. First, we describe the happiness and relief that is associated with diagnostic closure. Next, we describe genetic guilt, survivor guilt, and frustrations associated with a family history of FXS and taking care of developmentally delayed children. Finally, we highlight the communication styles used by this family to convey genetic risk to extended relatives and promote resilience. Understanding the complex interaction which occurs during the return of genetic findings will help improve the quality of pre-and post-genetic counselling practices and hence minimize the risk of conflicts. Future studies should focus on designing innovative tools to enhance the process of connecting family members together once they receive a FXS diagnosis or other genetic findings.

Keywords: Fragile X Syndrome, genetic risk, genetic guilt, psychological adaptation, genetic counselling, Africa

What is known on this topic?

Genetic testing raises several ethical issues related to the return of genetic test results. When returning a Fragile x syndrome genetic result, it is essential that this is done to improve the psychological well-being and adjustment mechanisms that are put in place by families.

What this paper adds to the topic?

This paper explores the effect of diagnostic closure, feelings of genetic and survivor guilt, frustrations with a family history of FXS, and the communication styles used by a Cameroonian family diagnosed with having FXS to convey genetic risk information to extended relatives. This study is also essential in enhancing knowledge of the potential benefits and barriers associated with obtaining a genetic diagnosis.

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Abstract

Fragile X Syndrome (FXS) is a genetic disorder that leads to intellectual disability and delays in speech development in males. Receiving a genetic diagnosis of FXS can have an emotional impact on the patient, parents, and the rest of the family. This paper reports on the experiences of receiving a genetic diagnosis of FXS in an extended Cameroonian family. Using an ethnographic approach, we conducted 13 in-depth interviews and one focus group discussion with members of an extended family segregating for FXS. We interrogated their experiences of receiving a genetic diagnosis. Two main themes emerged from the interviews relating to psychological adaptation and communication of FXS genetic risk. First, we describe the happiness and relief that is associated with diagnostic closure. Next, we describe genetic guilt, survivor guilt, and frustrations associated with a family history of FXS and taking care of developmentally delayed children. Finally, we highlight the communication styles used by this family to convey genetic risk to extended relatives and promote resilience. Understanding the complex interaction which occurs during the return of genetic findings will help improve the quality of pre-and post-genetic counselling practices and hence minimize the risk of conflicts. Future studies should focus on designing innovative tools to enhance the process of connecting family members together once they receive a FXS diagnosis or other genetic findings.

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4.3.1 Introduction

Fragile X Syndrome (FXS) is the most common genetic cause of intellectual disability. Persons with FXS often present with significant intellectual impairment, language disorders, autistic features, and socio-behavioural challenges such as anxiety and attention deficit (Crawford et al., 2001; Hunter et al., 2014). FXS is caused by an expansion of the 3 nucleotides, Cytosine-Guanine-Guanine (CGG), on the 5 untranslated region of the fragile x mental retardation 1 gene (FMR1) found on the X chromosome. Most males who inherit the mutation are affected, and they can transmit the mutation to all their daughters. On the other hand, females with the mutation are obligate carriers and transfer the mutation to half of their offspring (Peprah, 2012). Given that the distinctive features of FXS are not easily identifiable at birth, the diagnosis of FXS typically occurs when developmental delays are becoming a concern for parents or caregivers, usually around 2 years of age (Bailey D. B., Jr. et al., 2015; Bailey D. B. et al., 2003; Raspa et al., 2016). Whilst therapy can be used to improve learning disabilities, and anxiety and mood disorders could be clinically managed with existing medications, there is currently no real cure or treatment for FXS (Hagerman & Hagerman, 2002; Niu et al., 2017). Therapeutic approaches are likely to have a significant impact if they are introduced at an early stage, preferably after birth. Equally, early diagnosis prevents a diagnostic odyssey in parents (Bailey D. B. et al., 2003; Bundy et al., 2017).

Advances in genomics have made it possible to diagnose FXS in new-borns and prenatally, although such services remain unavailable in most African healthcare settings (Kromberg et al., 2013; Wonkam et al., 2011). Where testing is available, this is usually through a research project (Kengne et al., 2020; Raspa et al., 2016; Schwartz et al., 2018). Genetic testing raises several ethical issues related to the return of genetic test results, especially when performed as part of research (Bookman Ebony B et al., 2006; Shalowitz & Miller, 2005).

Opinions on whether to feedback research-related genetic test results could be broadly categorized into three views. The first is that individual genetic research results should never be returned to research participants because genetic results generated in the course of research are usually inconclusive and may cause anxiety (Lawrenz & Sobotka, 2008). The second school of thought has it that returning results could blur the line between research and clinical care and therefore should not be fed back, (Forsberg et al., 2009) while the third group argues that researchers have an obligation to return individual research results if they are of clinical significance, scientifically valid and if they provide a potential benefit to participants (Bookman E. B. et al., 2013; Laurie, 2004; Murphy et al., 2008).

In some cases, when researchers opt to return individual genetic research results, there may also be questions of whether they have an obligation to communicate genetic risk to family members. Although it is generally seen as the responsibility of individual families to communicate risk information to relatives, many factors can influence when and how this is done (Bailey D. B. et al., 2014; Gaff et al., 2007). Some people may decide to withhold the information from their relatives either because of the desire to protect them, the difficulties that can occur in overcoming pre-existing familial conflicts, or because they feel it is not worth disclosing those findings. However, others may decide to share genetic information with relatives in a segmental way according to age group or carrier status (Forrest et al., 2003; Gaff et al., 2007; McConkie-Rosell et al., 2011). When returning a genetic result, it is essential that this is done in a way that improves the psychological wellbeing and the coping and adjustment mechanisms that are put in place by families (Forrest et al., 2003; McConkie-Rosell et al., 2009).

There are currently no studies aimed at documenting the experiences of African families who have undergone genetic testing for FXS. Such studies are essential in enhancing knowledge of the potential benefits and barriers associated with obtaining a genetic diagnosis. In this paper, we examine the experiences of a Cameroonian family, several members of which received a genetic diagnosis of FXS. Specifically, we explore the effect of diagnostic closure, feelings of genetic and survivor guilt, frustrations with a family history of FXS, and the communication styles used by this family to convey genetic risk to extended relatives.

4.3.2 Methodology

We conducted this qualitative study with the extended family of a patient (P0) who received a genetic diagnosis for FXS. P0 derives from a large extended family with a high incidence of FXS due to a founder effect. One of the family's ancestors – a founding Chief of a small village in the Western Region of Cameroon - is suspected of having been an asymptomatic FXS transmitting male (Kengne et al., 2020). The family has come to terms with the high number of children with developmental delays through the narrative of a curse thrown on them by the founder of the family (Kengne et al., 2021). Unsatisfied with this explanation, P0 sought a genetic diagnosis for her two sons several years ago, at which point we got to know her. In this manuscript, we report on one component of our larger study, in which we were particularly interested in understanding how receiving a genetic result has impacted on P0 and her nuclear and extended family. Approximately 50% of the population in this village live in abject poverty and are unable to access adequate and specialized medical care, like most populations in similar settings in Cameroon (World Bank, 2012). However, P0's family is slightly better off, with

several members of the extended family have received a university education. In this setting, the spoken languages are French, English, Pidgin, and Ngombale, the local African language.

4.3.2.1 Sample selection

We recruited community members and extended family members of the initial patient (P0) between April 2018 and February 2020. Relying on our relationship with P0 and her nuclear family (F0), we used an ethnographic approach, (Reeves et al., 2008) to 1) engage with her village community and extended family members, and 2) identify potential individuals who could be interviewed. We interacted with this community for two years, allowing us to develop and pilot our topic guide for interview and focus group discussions (FGD) guides. For the larger study, eligible participants were community members of family F0 (chief of the village, elders, traditional healers, and teachers) as well as patient P0 and her extended family, who were 18 years or above. Using snowball sampling, we recruited participants until we arrived at a point of saturation where any further interviews would not add new insights, (Fusch & Ness, 2015) This paper reports on a portion of a more extensive study that aimed to explore individual genetic findings' feedback and their relation to traditional knowledge in a village in Cameroon. In this manuscript, we shall be exploring the impact of returning fragile x syndrome result to an affected family in Cameroon and investigate the effect of this diagnosis on other family members. In the broader dataset, we conducted a total of 23 in-depth interviews (IDI) and ten focus group discussions (FGD). Our analysis will only focus on 13 in-depth interviews and one focus group discussion with extended family members of P0 who received either a negative diagnosis for FXS or where carriers of the mutation. The reason for including carriers was because they were evaluated by a neurologist who concluded that they did not present signs of ID.

Whilst we had planned an interview study with family members, we were initially aiming to explore whether the P0's genetic diagnosis had challenged family beliefs about the high prevalence of this condition. This was partly due to the absence of genetic testing in Cameroon at the time. Yet as we were conducting our research, it became increasingly obvious that our ancillary care obligations in this qualitative study meant that we had to offer genetic testing for FXS to members of P0's extended family (Kengne et al., 2020). By doing so, we then increased the number of family members who had received a genetic diagnostic for FXS and therefore had experiential knowledge of receiving a genetic result (Figure 1). More so, all the participants who took part in the cascade counselling and testing were offered post-genetic counselling and follow-up to help them cope and integrate the new concepts introduced to them.

Table 1 maps the participants whose data we drew on for the current paper, whether they had the first-hand experience of genetic testing and when the interviews were conducted.

4.3.2.2 Data collection

Research ethics approval was obtained from the institutional committee for health research, Yaoundé (No.698/CIERSH/DM/2018), and from the health research ethics committee of the University of Cape Town (HREC:782/2017). Administrative authorizations were obtained from the local authorities (District Medical Officer and the village chief). Written informed consent was obtained from all participants.

The first author and a research assistant conducted in-depth interviews and FGDs. The first author is a Cameroonian physician with experience in conducting qualitative interviews. The research assistant is a university graduate with expertise in translation, and she was briefed on qualitative methods. Some data was also gathered through observations during the ethnographic part of the study in the form of field notes and memos (Birks et al., 2008).

The IDIs and FGD were conducted either in French or English, depending on the language preference of the participants. However, during the FGDs, some participants also expressed themselves in the local language. Where this occurred, the research assistant translated the vernacular on the spot. We also recorded the meaning and use of the vernacular in fieldnotes to assist with data interpretation. Interviews lasted between 27 and 60 minutes and were audio-recorded. A topic guide was used, which covered participants' understanding of FXS, lived experiences with FXS, stigma associated with FXS, and the effects of receiving a (positive or negative) genetic result. At the end of every interview, we had an information session where we answered questions from participants about FXS.

4.3.2.3 Analysis

The interview and FGD recordings were transcribed verbatim and translated from French to English. These transcripts and the researcher's field notes were then uploaded into the qualitative research software NVIVO 12 for data analysis (QSR International, 2020). Inductive coding was used to identify themes emerging from the data (Thomas, 2006). The first round of coding was done by KKK when approximately two-thirds of the data was collected. The emerging codes and the memos were discussed with JDV and NSM to discuss early insights and gaps in the data. Insights from this early phase of data analysis guided the final stage of data collection. After obtaining a complete data set, KKK and JDV together developed the hierarchical coding scheme that was applied to the full dataset. KKK coded the full dataset,

and through consensus, the study team identified the primary themes that were related to the effects of receiving a genetic diagnosis for FXS as perceived by participants.

4.3.3 Results

We collected data at 14 events, which correspond to 13 IDIs and 1 FGD. More than half of the participants were females. The majority of participants had completed at least a secondary level of education (Table 1). Following the analysis of the transcripts, two main themes emerged. These themes were the psychological effects of receiving a FXS genetic diagnosis and the communication of genetic risk with family members and relatives (Table 2).

4.3.3.1 Psychological effects of receiving a diagnosis for FXS

All the interviewees were related to P0 and had received a genetic diagnosis for FXS through cascade testing (Kengne et al., 2020). They spoke about the psychological effects of receiving a genetic diagnosis for FXS. We identified two sub-themes that were associated with changes in the mood as well as social acceptance of children with Fragile X Syndrome in the family. The different themes identified here were happiness and relief, guilt and frustration (Table 2).

Happiness and relief

Overall, participants described being in a state of joy after receiving either a positive or negative result. For instance, patient P0 reported being happy after receiving the results of the FXS genetic test, mostly because she finally had a name for the condition of her children.

> *When they told me the results, I was super happy, so that I asked myself, "there is a result; there is going to be a name to what I have been looking for." So, when they gave me I was happy, I was super happy, and I asked the doctor then, "so, there is a name that could be attributed to what is going on with these children?" and he said "yes" and that is the name of what is happening to these children is the Fragile X syndrome….. When I came out that day, my husband thought that it was a war that they had told me, but I was singing and dancing all over this hospital. And even on the road, I was singing songs of praise; I was just singing and dancing.* **(IDI, Family, patient P0)**

The joy expressed by P0 is related to the long-standing presence of mental disorder in her family, and finally, having a diagnostic closure is a relief for her nuclear family as well as her extended family. She describes this in a quote:

> *Then, I would say the positive aspect that it has brought to my family, my immediate family and my extended family is that I have been able to trace this thing out. I am sure*

that the positive aspect is the fact that I got to know what was wrong with these children, even though it is not curable, it gave me some peace. That is why I am always happy. **(IDI, Family, patient P0)**

For participants who received negative FXS results, their joy was related to the knowledge that their offspring would be free from FXS. This is mainly due to the long-standing history of ID in their family and the stigma associated with having a disabled child in society. A male relative of P0 who received a negative FXS result quoted: "*It makes me happy; it gives me the joy of knowing that I cannot have insane children*." **(IDI, Family, male 8).** In the village, the term 'insane' is used to describe children with FXS.

A cousin of P0 also described how the diagnosis of FXS has moulded the psyche of P0 and shifted the blame that was put on a curse originating from the founder of her family to the acceptance of FXS as a medical condition that should be handled. She said:

It allowed her to have a peaceful mind regarding the situation of her children because now she knows that her children are just sick, that it is not a matter of witchcraft or a curse. **(IDI, family, female 4)**

Guilt and frustration

Raising a child who is suffering from an inheritable condition can be associated with genetic guilt (Clarke, 2016). Genetic guilt is related to the passing of genetic conditions to offsprings. The aunt of P0, describes "genetic guilt" as being that emotional feeling of transmitting the mutation unknowingly to the future generation. She recounts:

We can carry the gene and not develop the disease, but our children can develop it. So, if we have not made insane children, we will be afraid that our children will have them in the future, and if they do not, we will always be afraid that their children too will. What is certain now is that the gene is already there. **(IDI, Family, Female 6)**

More so, survivor guilt is usually felt by relatives who have a family history of a genetic condition. They are worried that their offspring or other family members, though unaffected, can still transmit the mutation to future generations. The current chief of the village expressed survivor guilt. Having received a negative result, he expressed his fears relating to marrying one of his daughters if he had had a positive result.

I told myself that with all the children I make there, maybe my daughter will get married somewhere, and in the meantime, they will say that "oh! you had given us a poisoned gift." **(IDI, Family, male 4)**

Despite diagnostic closure and the happiness that is associated with receiving a genetic diagnosis, P0 describes instances where she felt depressed and frustrated due to the psychological and physical burden associated with taking care of her developmentally delayed children. She recounts:

Sometimes I get frustrated and say, "Papa God! why did you have to give me up to two; why could you not even give me one?" You know that kind of reaction. I would cry, it stresses me, but I can always handle it. I always smile. But, like a human being, you give up, you cry, you feel bad, and you worry. As I was explaining, my children are at home; they talk like madmen. They are talking in a way that you do not understand. **(IDI, Family, patient P0)**

4.3.2.2 Communicating genetic risk with other family members

Most of P0's first and second-degree relatives suggested that communication of the risk of having children with mental disabilities has been going on in the family. However, the transmission of information was limited by factors such as illiteracy or being secretive. P0 and her mother describe that elders usually hide information from younger people. They also discuss the impact of education on the communication of the risk of having mentally disabled children in the family. Hence, the occurrence of mentally disabled children in the family was attributed to a curse.

*We are the last children of [the chief of the village]; there are many others before us. We had an elder sister who died already. We asked them more details; since they were so big, they lived with our father, we asked what they saw or heard, but they said nothing (***IDI, Family, Female 2)**

"Because all of these things have gone to this level just because of our fathers' ignorance. They were not educated so they could not understand that what is happening to the children is just a genetic disease and that they could take the children to the hospital just like I did. Concerning my case, everything was attributed to a curse. As I explained, there are many stories that they could not put their hand on which one was true; you know parents used to hide things to their children with a lot of stories. **(IDI, Family, P0)**

Despite these challenges in the communication of genetic risks, we could identify two types of communication styles in P0's family. (Table 2)

Direct or explicit communication

Being explicit in communicating genetic risk is an approach used by the majority of interviewees. P0 recounts her post counselling experience and the steps she took to communicate with other members of her family. Also, her cousin shed light on the efforts she deployed to communicate these genetic risks with the larger family.

> *I am a very open person, so I do not know how to hide things. I would say the positive aspect that it has brought to my family, my immediate family and my extended family is that I have been able to trace this thing out. I am sure to speak to one or two or three of my cousins after I was advised to inform my cousins, my relatives, about the result that came out and that it is not a curse. It is a genetic problem, and that is the only way we must stop this issue that is happening in our family* **(IDI, Family, P0)**

> *I think she[P0] was able to reach this challenge because now she knows what her children are suffering from, and from that moment on, she can prevent this kind of situation. This is why she decided to inform all her family members about her action since she would not like this disease to continue to develop in the family. She wanted to share her experience with all the children, all her sisters, and cousins who may or may not know her story. From the moment you are a member of the family, it won't surprise you. So that if it happens to you, it won't surprise you.* **(IDI, Family, Female 4)**

Despite this effective style of communication, conflict may arise due to misinformation, stereotypes, or the desire to screen all relatives. This is illustrated in the FGD with family members where a cousin of P0 who had a negative FXS genetic result could not believe that her sister was not willing to do the FXS screening test.

> *What makes you pessimistic in life like that. You must be optimistic. We ask you to do it because by doing it, there is a method, a way to limit that. You cannot do for yourself and leave for your offspring. You cannot be sure if you gave this to the child or not. If tomorrow your child makes you an insane grandchild, what will you say? Now you can avoid that right now.* **(FGD, Family 4, female 38 years)**

Indirect or implicit communication

Another way of communicating genetic risk in this family was through a gentler or indirect process. Most of the carriers and elders in the extended family of P0 adopted this style of communication. Firstly, relatives of P0 used this style of communication to communicate the risk of having premature menopause in the family; even though they did not relate it to the curse as mentioned earlier, it was a significant worry for several family members. P0's relatives accepted that it is a serious concern, especially as some family members reach menopause before their thirtieth birthday. However, because they gave birth early, they were able to have as many as six children. Hence, they tend to advise the younger generation to give birth at a younger age.

> *There are even some who have reached menopause at 28 years, for example; Mama X and Mama Y. They gave birth very early. I, too, gave birth early. If I did not give birth early, I do not think I would have had my 6 children. Yes, we all have early menopause. By the age of 40, at the latest, we are all menopausal. I always tell children to give birth quickly because if they look like the women in my family, at 30, she will no longer be able to give birth.* **(FGD, Family 4, Female, 86 years)**

More so, most family members during the genetic information sessions reported that it would not be surprising if mental disorders and premature menopause that is in their family were attributed to a genetic problem. A male and a female family participant recounted:

> *Already, I was born in a family where there are these kinds of children, which means that, as a family member, it is very likely that genetic mutations will occur in my family, which makes that I am morally prepared to receive the results. Furthermore, my wish would be that we do not stop just at the level of the results but that the current team carries out investigations that can lead them to find a solution to this evil, which is ruining my family.* **(IDI, Family, Male 4)**

> *We got used to this from an early age, but for me, it does not bother and my children too because I explained to them as they grow, I inform them, I advise them until today they are already used to it. I make them live that too because they went to spend the holidays at P0 two or three times, they are already used to it, and they manage this situation very well.* **(IDI, Family, Female 4)**

The reason for accepting a genetic explanation for ID and premature menopause was related to the fact that the respondents were living with this condition in their family for multiple

generations, and both ID and premature menopause have become a new normal for them. This also suggests that they had developed mechanisms that permit them to cope with the situation in such a way that a positive result will not affect them. Instead, these family members advocated for health promotion activities aimed at sensitizing family and community members about the different preventive measures that can be taken to eradicate this disease. Several relatives of P0 spoke of premarital screening as one way they could get rid of FXS in their family.

> *Thank you because this research allowed me to learn that there is a laboratory test we must do before getting married, and for us who have already given birth, this test will help us to know if our children are carriers of FXS or not. And if they are carriers, we will have to advise our children to include this in their prenuptial test for them and their husbands to break this chain so that it does not last. **(IDI, Family Female 7)***

The majority of people who spoke about premarital diagnosis were unwilling to let their children or other relatives get married if they found out that the couple they want to form would likely have offspring with the FMR1 gene mutation. This was mainly associated with the challenges that are related to raising a child with a developmental delay.

4.3.4 Discussion

This study reports on the effects of receiving a genetic diagnosis for Fragile X Syndrome in a rural Cameroonian family, and to our knowledge, constitutes the first such study from Africa. Most interviewees in this family expressed a combination of relief and guilt, which was associated with receiving a genetic diagnosis for FXS. This could be accounted for by the fact that they were grieving for long and receiving a diagnosis brought diagnostic closure and the possibility of becoming resilient. Joy and social acceptance following diagnostic closure appear to have significantly contributed to the wellbeing of the family – which is in line with evidence described by Lloyd et al. (2008), who evaluated psychological variables that could affect the maternal adjustment to having children with intellectual disabilities and found that mothers who accepted the condition encountered fewer psychological challenges and a better overall quality of life (Lloyd & Hastings, 2008). Similarly, Wheeler et al. (2018) suggested that interventions that focus on improving acceptance could promote the health and wellbeing of mothers with children suffering from FXS (Wheeler et al., 2018). Other scholars like Visootsak et al. (2012), Bailey et al. (2003) and McConkie-Rosell et al. (1997), also concluded that participants in their studies were emotionally relieved when they knew the cause of mental disability in their family which could occur weeks or days after receiving the diagnosis (Bailey

D. B. et al., 2014; Bailey D. B. et al., 2003; McConkie-Rosell et al., 1997; Visootsak et al., 2012).

In contrast to relief, guilt is reportedly a common reaction for carriers of heritable diseases like FXS and was expressed by some participants in our study. We identified two types of guilt, which are the "genetic guilt" related to those with carrier status and "survivor guilt" towards other relatives. McConkie Rosell et al. (1997) and Anido et al. 2005 in their studies also found that some mothers who did not have affected children but had a family history of FXS were likely to express survivor guilt (Anido et al., 2005; McConkie-Rosell et al., 1997). Moreover, James et al. (2006), while studying families with X- linked and autosomal recessive conditions, found that there was a strong association between having a child affected by an inherited condition and feelings of genetic guilt (James et al., 2006). In a systematic review of 20 relevant articles, guilt was closely related to gender, mode of inheritance, and having affected children (Lewis et al., 2011). In our study in Cameroon, we also found genetic guilt and survivor guilt to be an important factor in how individuals make sense of their family history of FXS.

We also explored the communication of genetic risk to extended family members. Our data suggest that the chronic occurrence of mental disabilities in this family fashioned skills in parents that were important to counsel their offspring about this phenomenon in the family. Some scholars support that this family involvement is crucial for coping after the diagnosis is revealed (Forrest et al., 2003; Gaff et al., 2007; McConkie-Rosell et al., 2011). Gaff et al. (2007) highlighted in a systematic review that parents play a crucial role in explaining genetic risk. After the diagnosis, the communication of genetic risk to other relatives was through either proactive or more subtle communication, which were often used interchangeably during family reunions. However, challenges and conflicts may arise if these communication styles are not consciously used. Lee et al. (2014) and Beal et al. (2001) argue that it is challenging to gather people in the same place for a massive communication about genetic risk and opts for the use of phone and website communication to transmit genetic risk information (Beall, 2001; Lee et al., 2014). Bailey et al. (2003) reported on research that intended to communicate genetic risk for FXS in the USA. They reported cases where pre-existing family conflicts were exacerbated by an attempt to communicate genetic risk.

4.3.5 Practical implications

Health care workers in clinical and genetic counselling services should pay attention to the complex psychosocial experiences that may be encountered by individuals receiving a genetic result. The African family described in this paper had a long-standing belief that ID was due to

a ‘curse’ from the founder of this family, who occupied an influential position in society. Diagnosis of FXS has started shedding some doubts on the curse narrative and brought through a new way of explaining the disease in this community (Kengne et al., 2021). A pertinent finding from our study is that returning the result of a genetic test to a patient with a relevant family history of FXS or undiagnosed mental disorder can create feelings of guilt in the patient and also in their relatives. Over time, these families can develop coping mechanisms that revolve around preparing the future generation about the risk of having FXS. This risk adjustment strategy can then lead to a positive reaction following diagnosis.

Moreover, the psychological effect of receiving a genetic diagnosis mirror that of the western population characterized by the high access in health care services. Health care workers and counsellors should be aware of these psychological issues and address them during pre- and post- counselling sessions. Also, inviting patients to communicate this genetic risk with extended family members actively is crucial in counselling. However, to minimize conflict that can arise or exacerbate pre-existing family conflicts, health care workers or people who are comfortable with the subject should serve as intermediaries for affected families by connecting them with resources that are easy to navigate and sensitive to their needs.

4.3.6 Study limitations

In this study, our sample size was relatively small since we focused on the experience of P0 and her extended family members who knew the diagnosis and accepted to share their experiences. Furthermore, the family that we conducted our research with has a long history of mental disorders, and they have found ways of coping with this condition. This may not be the case for other families. Our sampling technique constituted a limitation in not gathering experiences from other family members who could have contributed to the overall discussion.

4.3.7 Research recommendation

This paper is the first study to examine the experiences of a large family affected with FXS in Cameroon. Given that FXS is a rare disease and based on the communication challenges encountered in this study, we suggest that future studies should focus on designing innovative tools to enhance the process of connecting family members together once they receive the FXS diagnosis. This may help bridge the gap in the communication barriers that often exist between the main person who receives the diagnosis and the extended relatives. This information should be made accessible to the general public and, where possible, translated into local languages. These messages could best be communicated using Participatory Visual Methods during community engagements.

4.3.8 Conclusion

The findings from this paper provide an insight into the psychological impact of receiving a genetic diagnosis as well as the communication strategies that are used by a Cameroonian family to cope with the occurrence of FXS and undiagnosed mental disabilities. Two main themes emerged from the interviews relating to psychological adaptation and communication of FXS genetic risk. First, the happiness and relief that is associated with diagnostic closure. Next, the genetic guilt, survivor guilt, and frustrations associated with a family history of FXS and taking care of developmentally delayed children. Finally, the research highlighted the communication styles used by this family to convey genetic risk to extended relatives and promote resilience. Understanding the complex interaction which occurs during the return of genetic findings will help improve the quality of pre and post counselling practices and hence minimize the risks of conflicts. With the limited number of genetic counselling services in Africa, the involvement of other family members in the discourse of genetic risk is a great asset.

Author Contributions

KKK: Design, data collection, interpretation, and writing

NSM: Interpretation, writing.

SN, JDV, AW: design, interpretation, writing.

KKK, JDV and AW confirm that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of Interest

The authors declare that they have no competing interests.

The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Human studies and informed consent

The study was performed following the Declaration of Helsinki. Ethical approval for the study was obtained from the Institutional Committee for Health Research (no. 698/CIERSH/DM/2018) in Yaoundé, Cameroon, and the University of Cape Town's Faculty of Health Sciences' Human Research Ethics Committee (HREC: 782/2017). Written informed consent was obtained from all participants who were all legal adults, including permission to publish photographs. Administrative authorizations were obtained from the local authorities (District Medical Officer and the village chief).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

4.4 Negotiating political power and stigma around Fragile X Syndrome in a rural village in Cameroon: a tale of a royal family and the community

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Synopsis

In this paper, I describe the public and associative stigmas between a Cameroonian royal family with a high incidence of FXS and her community. I also describe the different stereotype labels used in this community before describing the stigma-power dynamic between the community members and the royal family. From my observations, I conclude that the primary role of stigma in this community is to keep people away from FXS or keep them down through domination and exploitation.

Author contributions:

Kengne Kamga Karen (KKK): Study design, data collection, interpretation; wrote the first draft of the article, and incorporated comments from co-authors; responded to all reviewer comments.

Nchangwi Syntia Munung (NSW): Assisted in the interpretation of study findings and in the writing process.

Séraphin Nguefack (SN), Jantina de Vries (JdV), Ambroise Wonkam (AW): Assisted in the design and interpretation and commented on various drafts of the manuscript.

Negotiating political power and stigma around Fragile X Syndrome in a rural village in Cameroon: a tale of a royal family and the community

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Abstract

Background: Fragile X Syndrome (FXS) is a neurogenetic condition that significantly impacts the lives of affected individuals and their families due to its association with intellectual disability (ID) and stigma. In 2011, a royal family from a Western rural region of Cameroon received a genetic diagnosis for FXS through one of their daughters, who had two affected male children.

Method: In this paper, we present the findings of an ethnographic study in the community of the patient who received the genetic diagnosis. This study builds on an earlier data set from 28 participants related to the royal family and 58 from the community who elaborated on stigma through 20 in-depth interviews and nine focus group discussions.

Results: From our dataset, we identified two types of stigma in this community: public stigma directed towards the royal family and courtesy stigma experienced by the royal family members. We outlined the stereotyped labels used in this locality before describing the stigma-power dynamic between the community members and the royal family. Firstly, most interviewees believe that people from the royal family should have a unique way of addressing FXS children from the chieftaincy because of their position in society. Secondly, due to their

social position, the royal family uses their status to negotiate marriages with community members. From these observations, we suggest that the primary role of stigma in this community is to keep people away from FXS and keep them down through domination and exploitation.

Conclusion: We advocate that other researchers examine if the same pattern exists in other inheritable forms of ID and conduct more qualitative research on FXS in Africa.

Keywords: Fragile x syndrome, stigma

4.4.1 Introduction

Fragile X syndrome (FXS) is a neurodevelopmental condition that is genetically known as the leading cause of Intellectual Disability (ID) and Autism Spectrum Disorder (ASD)(Crawford et al., 2001). Individuals with intellectual and developmental disabilities face stigma, prejudice, and significant obstacles that restrict their human rights (Mitter et al., 2018). People suffering from FXS and other forms of ID are also susceptible to developing significant mental health problems due to other factors like social deprivation (Dykens, 1999; Pattison, 2005). While social and other adaptive issues might be why people are marginalized, a distinction must be made between people's actual disabilities and the social barriers arising from stigma and discrimination. Stigma occurs when a person differs from dominant social norms and is negatively evaluated by others. Hence, the person's whole identity is defined by that dimension, and the person is dehumanized, to a degree, by those who hold such views (Goffman, 1963; Link Bruce G & Phelan, 2001).

Stigma has a significant impact on the lives of individuals living with ID. In many communities, people with disabilities are stigmatized. Their disability has been associated with curses, disease, dependence, and helplessness, resulting in social avoidance, stereotyping, and discrimination (Eddey & Robey, 2005; Goffman, 1963). Cooley in 1992 described "the looking glass self-theory," which elaborates on the processes wherein individuals base their sense of self on how they believe others view them. Using social interaction as a type of "mirror," people use the judgments they receive from others to measure their worth, values, and behavior (Cooley, 1992). In this light, people with disabilities may manage their condition in ways that protect them from being stigmatized by people in their surroundings (Morris et al., 2014). If this is not managed correctly, it can result in emotional problems such as anxiety and depression (Gilbert, 2007; Jahoda A. & Markova, 2004). Tajfel et al. in their book "human groups and social categories," describe challenges associated with dealing with people who have a mental disorder. In this narrative, taking care of disabled individuals, especially those

with severe mental illness, is thought to be a contribution to bring some social normalization, which is achieved through belonging to groups and establishing a policy for the society (Tajfel, 1981). Many people with mental illnesses are in a situation where they experience a conflict between the positive value of belonging to a group of other patients and the danger of stigmatization resulting from being identified with them (Hall & Cheston, 2002). The impasse between the need to belong and the danger of stigmatization is accentuated in small communities (Ekeland & Bergem, 2006). However, people who live in groups can easily cope with their situation through social and political actions, which can change social norms such as complaining to the authorities that they are being bullied (Jahoda Andrew et al., 2010). Other scholars have shown that people with intellectual disabilities can focus on non-stigmatizing personal characteristics to cope (Dagnan & Sandhu, 1999; Finlay & Lyons, 2000). In 2001, Link and Phelan conceptualized a process by which stigma develops (Link Bruce G & Phelan, 2001). Diverting from considering stigma as merely a mark (Goffman, 1963), they imagined stigma as a process through which society navigates. They defined stigma as the association or co-occurrence of labelling, stereotyping, loss of status, and discrimination. Link and Phelan also pointed out that the social representations of groups can be stigmatizing, and that these social representations are often well understood by members of stigmatized groups themselves. People with ID and those with other forms of stigmatizing disabilities can cultivate positive social interactions like having employment, being a member of a church group, or self-advocating for their condition, which will help buffer the emotional damages of stigma (Dagnan & Sandhu, 1999).

Intellectual Disability and inheritance patterns have long been described in African cultures, but very few works have associated genetic concepts with current understanding in the African population (Raghavan & Small, 2004). In most African cultures, inherited forms of ID like FXS is usually attributed to interesting ancestral stories that follow an inheritance pattern. They may be related to stigma, gendered blame, or a curse (de Vries et al., 2020; Meilleur et al., 2011). The return of a FXS genetic diagnosis to a Cameroonian family in the rural part of the country unveiled several explanatory beliefs concerning the understanding of FXS and other forms of inherited intellectual disability in this community. To understand the stigma power dynamic around FXS in Cameroon, we think it is necessary to examine the beliefs of people living with FXS and their social position. In this light, the current exploratory study attempts to provide an insight into the dynamic relationship of stigma between families with FXS and the community in which they live. In this paper, we present findings from a rural community in Cameroon's western region formally described as having a high ID incidence and where a FXS genetic cluster was identified in the royal family (Kengne et al., 2020). We then elaborate

on the different forms of stigma identified in this community and evaluate the strategies that community members and family members use to cope with stigma.

4.4.2 Methodology

4.4.2.1 Ethical compliance

Before starting this study, we obtained ethical approval from the Institutional Committee for Health Research (no. 698/CIERSH/DM/2018) in Yaoundé, Cameroon, and the University of Cape Town's Faculty of Health Sciences' Human Research Ethics Committee (HREC: 782/2017). Written informed consent was also obtained from all participants who were legal adults, including permission to publish photographs. Then, administrative authorizations were obtained from the local traditional and medical authorities. Our study builds on a more extensive study, which aims at exploring the impact of giving back a genetic result in a rural community. In this paper, we shall be focusing on the stigma component.

4.4.2.2 Site and population

In this paper, we report on the stigma experiences of 86 participants who were either relatives of P0 or her community members. P0 is our initial patient, a mother of 3 children who received a diagnosis of FXS for her two kids in 2011 at the child neurology unit of the Yaoundé Gynaeco-Obstetric and Paediatric hospital, Cameroon. Information shared during her first consultation revealed that in the village P0 originates from, her children's condition was associated with a curse directed at the founder of her family, a royal chief. The community of P0 is found in a rural region of western Cameroon. This rural community is characterized by poor access to health services and severe economic limitations. With a population of approximately 2000 inhabitants, this rural area is historically known to be a locality with a high ID incidence. In 2020, 46 subjects from the royal family were clinically evaluated and screened for FXS, and 18 of them had a mutation on *FMR1* (OMIM:309550) (Kengne et al., 2020). Intrigued by the co-existence of traditional narratives to explain the inheritance of this severe condition and a modern genetic diagnosis, we sought P0's permission to conduct a qualitative study with her family and members of the community, to better understand how people in a rural African setting make sense of genetics and inheritance, and how this condition had affected the family and the community.

Of the 86 participants, 58 were community members, while 28 were members of P0's extended family – which is the royal family in this village. Two selection criteria were used to include participants in the study. Firstly, individuals 18 years and above who were either resident of the community of P0 or members of her extended family were included in the study. Secondly,

individuals who were knowledgeable about either FXS or the issues surrounding ID in the village were recruited. The demographic characteristics of the family and community groups are shown in the table below.

Table 4.5: Socio-demographic characteristics of participants

		Family	Community	Summary
Number		28	58	86
Sex	**Male**	11	16	27
	Female	17	42	59
Mean age		47.8 years	38.4 years	41.5 years
Age range		28- 69 years	18 – 81 years	18 – 81 years
Indepth interviews		16	4	20
Focus group discussion		3	6	9

4.4.2.3 Procedure

We used a semi-structured questionnaire to guide the conversations with all the different participants through 20 in-depth interviews and 9 Focus Group Discussions (FGDs). Before scheduling an in-depth interview, the first author spent several hours with the participants, either in their homes or workplaces, to gain confidence and let the interviewee know that private information will be treated in strict confidentiality. In addition to building a trust relationship, the first author thus also obtained insight into the participants' way of seeing life, which provided a better understanding of the data context and how to facilitate dialogue flow. On the other hand, participants for focus group discussions were recruited after participating in a family reunion organized by the family of P0. Moreover, announcements were passed in churches and marketplaces to sensitize and inform community members that a research team was in the community to discuss issues relating to inheritable diseases like FXS/ID in their community. Snowball sampling was used to recruit all the participants in the FGDs and IDIs. Most of the FGDs organized with the community (5/6) were organized in the church premises of the community of P0, where we could secure a room for the purpose. On the other hand, FGDs with family members were conducted either in their residences (1/3) or in a conference room (2/3) in the city where they resided.

The first author, who conducted all the interviews, had a list of topics to cover while promoting dialogue and allowing the participants to raise issues that they saw as necessary. The interviews were conducted either in French or English, depending on the interviewee's first language. However, in certain circumstances, some participants could not express themselves in any of

the official languages preferring instead to speak Ngombale, the local language. Where this was the case, one of the research assistants who is a member of the community translated to English. With regard to the data presented here, the interviews covered participants' views on FXS, experiences of stigma, and coping strategies. We did not approach sensitive issues directly; instead, we used terms primarily accepted by the community and family members as less stigmatizing. "Alienate" was the term used to represent people with ID and FXS during our interviews. The IDI and FGDs lasted between 27 and 90 minutes. All the interviews were audio-recorded and transcribed verbatim.

4.1.1.4 Analysis

All the transcribed interviews were imported in NVivo 12 (QSR International, 2020). The first step of the data analysis was a content analysis of the interviews to identify what the participants reported regarding their experiences of stigma and discrimination. Then these transcripts were analysed qualitatively through the identification of themes (Braun & Clarke, 2012). This involved producing a summary of the views each participant expressed about stigma. The transcripts were then examined to establish the main themes that emerged regarding how the community and the royal family manage to cohabitate in the face of stigma directed towards FXS.

4.4.3 Results

In our study, we encountered public and associative stigma relating to FXS. These stigmatizing beliefs and behaviours could be articulated either between P0's family and her community or remained solely within the family. In this light, stigma manifested partly in descriptions of the labels given to the parents of children with FXS or even to the royal family as a whole. We also observed stigmatizing behaviours through the interactions which members of the royal family had with their peers or the community. In the following, we shall illustrate the stigmatizing events in this community before describing the complex stigma power dynamic that exists between the community and the royal family.

4.4.3.1 Associative Stigma as experienced by members of the royal family

Few participants in our study described courtesy stigma. An associative stigma is a form of prejudice that people with FXS or families with FXS direct to themselves. Some participants described instances where they were discriminated against, or one of their children who has FXS had discriminatory treatment from others. A family member reports a discriminatory treatment that her sister lived with her children. She quoted:

> *I went to Yaoundé a year ago, the alienated child [child with FXS] took a rubber band and tied it on the cat's neck. The father of this child whipped him properly. What caught*

my attention was that my sister was in tears because her husband had beaten the son. She confides to me with great sadness that she did not choose to have insane children and went on to say that despite their condition, she still loved them. Her husband had more preference for the cat than for his child. **(IDI family female 8)**

Other healthy family members could associate with children who were suffering from FXS. Several royal family members described situations where they were marginalized in society just because they come from the royal family. More interestingly, during an IDI with a male informant from the family, he sorrowfully elaborated on the fact that FXS is affecting several generations of the royal family. He followed by saying he could have been happy if the condition was limited only to earlier generations and not passed onto the grandchildren. He reported:

There are several insults coming from others in the community. When you hear these insults, you can be demoralized, and it makes you uncomfortable to hear and see these situations. What have we not done up to date in our family to put an end to this evil? Unfortunately, it could still be limited in our circle, but it is not good when it crosses to go to the grandchildren. It hurts. **(IDI, family male 6)**

4.4.3.2 Public stigma directed at the royal family by the villagers

Labels given to the royal family and people with FXS in the community

In the community where P0 lives, community members use specific labels to address people with FXS. These labels are collectively agreed upon and can quickly generate impressions and expectations of individuals who belong to families affected by FXS. Most of these labels describe the characters of people who have to be isolated due to their behaviour or physical appearance. For instance, one mother who has two children with FXS reported that people in the community refer to her as "mother of fools." The common understanding of being a fool is that of a person who cannot think properly and cannot obey simple commands. This mother recounted her experience:

I would start with the negative effects of FXS. I have gone through a lot because of the stigma with which the society gives to such a situation, I have gone through it. Like people who call me "mother of fools, "mamy foul-foul," [mother of fools] meaning that I have given birth to fools. The stigma has been too much **(IDI family female 1)**

Another name that is used to describe the royal family colloquially is "la'an Kuate", translated as "the descendants of Kuate". Kuate was the royal families' founding father, who is believed to have cursed his daughters because they did not assist him in mourning one of his

intellectually disabled servants. Hence 'la'an Kuate' equates to 'being cursed' – a powerful epithet in African communities that often signals stigma. Several community members recognize this label, and members of the royal family are conscious of this fact. One of P0's relatives describes how people use this label:

> *You know that is kind of thing that the whole village, my village people, and then my husband's people know that we have those kinds of children from my mother's family. So, there is a way to refer to my mother's family as far as those kinds of children are concerned. In the dialect, we say "La'an kuaté" [the descendants of Kuate*] **(IDI family female 3)**

Some participants also described that others may use the term "Joujou" to describe individuals with FXS and ID. To them, "Joujou" is a representation of a frightful totem which is generally used during traditional ceremonies to scare children. This label is mostly related to the physical appearance of people with FXS and ID in the community. A community member during a FGD enlightened us on this character. He recounted:

> *It all starts with the mentality because when some children see this type of person, they can call him "Joujou," and they run away. I think that often when we see people with FXS for the most part, they are always dirty, and when we see them, we always say that they are crazy.* **(FGD 5, community, male)**

Stigma dynamics between the community and members of the royal family

Although villagers used stereotyped labels for people with ID and FXS, most interviewees believe that FXS children from the chieftaincy should be addressed differently than non-royal children with ID because of the former's position in society. During one of our focus group discussions with the community, we noticed a dynamic for how people named children from the royal family. The intellectually disabled children of the royal family were termed "rheureuh" while the term used to describe other children with ID was "Peuh." "Rheureuh" and "Peuh" are used in the vernacular language to address individuals with intellectual disabilities, with Rheureuh being used to describe a milder form of ID. We were subsequently obliged to adopt this appellation because the members of the FGD categorically dissociated themselves from calling children of the royal family "Peuh" or fools. We followed up on this discussion with other community members and recorded our observations in our field notes.

> *In the local language, "rheureuh" means a child who is an Alienate [child who is different from others], while "Peuh" means madness or fools. Informants reported that their children are not mad but somewhat alienated. They preferred that we used "rheureuh" in subsequent interviews. This is because "rheureuh" is "better" than*

"peuh" since you can take care and support a "rheureuh" until he/she even gets married while you cannot do anything for a mad man. This community respects traditional customs and will not like the royal family's name to be tarnished. Before adopting the name "rheureuh" for ID in the royal family, we had a harsh discussion with the informants up to a point where they threatened to withdraw their consent if we continue to use labels that can undermine the moral status of members of the chieftaincy. "Rheureuh" [alienate] was finally adopted as the term which will be used in subsequent interviews **(Field notes 15 October 2018)**

Many people in the community would love to be part of the royal family. This could explain the fact that nearly all the women in this family are married. During an early conversation with a member of the royal family, he argued that "*they are not marginalized at all, and if that was the case, then there could have been several single princesses who are 30 years and above, and this is not the case"* **(IDI, family male 5)**.

This royal family also uses its position in society to arrange marriages for their male children with community members, even when they know that the match is disadvantageous for the marital partner. Several family members are conscious of this situation. One of them described a circumstance that led to the marriage of one of their relative who is known to have FXS. She recounts:

The week we were in the village for the meeting, he [brother with FXS] saw a girl and the girl interested him; he told his mother that he liked this pretty girl. This is how we went to negotiate with her parents. With us in the chiefdom, so many parents who are not of this line would like to be in the royal family. When anyone from the royal family asks for their daughter's hand, they are immensely proud to join the royal family. So that is what this is about. **(IDI Family Female 8)**

Furthermore, parents of children with FXS will tend to actively seek a wife for their male children because they do not want their in-laws to notice that their child has a disability. In most marriages with this royal family, the disability is mostly discovered only after marriage. According to local custom, it is difficult to untie a bond that has been made traditionally because of the shame that could occur. A family member recounted a situation that is known by several community members:

It seems that the marriage of the one [relative with FXS] who is here in Douala was arranged between the parents from the village. The girl did not know exactly how the guy was. He got married, and his wife left shortly after. It seems that it was the parents who arranged the marriage. The girl did not know how the guy was. When she got to him, she saw that he did not have all his senses, and they did not get along. So, she

started threatening members of the royal family that she was going to leave. She could not leave because we had spent a lot to make her the wife of the insane guy. We endowed her; we did everything. She was ashamed to get up suddenly and leave after all the expenses that his family had made. And the girl's parents could not accept her coming back. **(IDI family Female 7)**

Despite the advantages that one can obtain by getting into the royal family, another stigma power dynamic was noticed between the royal family and the community members where the community members were seeking to have the upper hand over the royal family. Some interviewees from the royal family described instances in which a suitor in order to save-face sought to tarnish her and her family by describing them as a family where many children are developmentally delayed. Two females in the family quoted:

There is a gentleman who walked behind her [the elder sister of the informant] for a wedding ... you often know when your heart does not accept a thing, you also have to make manners to go away. Later, to explain why it had not worked with my sister, the gentleman said that he had even been told that we give birth only to the insane in our family, which is why he left **(IDI, Family Female 7).**

When I was still a student, I was engaged to a guy; in the meantime, I realized that I do not want to be with him, and I stopped the relationship. Later in the informal conversations, he said he broke up because he noticed that there are so many mentally ill people in our family. **(IDI, family female 8)**

One way of understanding these quotes is that stigma is used as a means to gain some form of domination over (some members of) the royal family by people who are excluded from its power. For instance, in the case of the snubbed suitor, his inability to be part of the royal family could have led him to use stigma in an attempt to maintain domination over the girl. In other cases, family members described a perception that people seem to be of the impression that the girls from the royal family are easy to get as wives because they do not think. In our focus groups, we observed that when community members cannot be part of the royal family, they downplay family members.

Stigma-power dynamic in the family

Importantly, we found evidence not only of stigma directed to the royal family by community members but also within the family. There were a few instances where family members emphasized their superiority to other family members with a lower IQ. A family male describes a situation that happened in their family.

Often when we pass, people say that the chief's sons are only insane. There was a time, one of the sons of the founder of the royal family insulted his brother by saying: "there are many alienates here in the chiefdom, but there are other alienated who think they are normal and who are well dressed." **(IDI, family, male 5)**

This shows how stigma-power dynamics can occur in this family. This behavioral modification is to show their kin that they are superior to them. On another note, in families with many FXS children, parents discriminate amongst them by treating them better than those with ID, as previously reported.

4.4.4 Discussion

In this African community, people suffering from FXS have a double challenge. On the one hand, they struggle with symptoms and disabilities that result from FXS. On the other, they are challenged by the stereotypes and stigma resulting from the explanatory beliefs of FXS. Our findings summarize some characteristics of stigma relating to FXS in a rural community of western Cameroon, which appears to be a FXS genetic cluster similar to what has been reported in Colombia by Saldarriaga et al., 2018. We outlined the stereotyping labels used in this locality before describing the stigma-power dynamic between the community members and the royal family.

In this community, the royal family is seen as politically powerful, and many people from the community may want to be part of this family. This creates a stigma-power dynamic between the royal family and her community. According to Link (2014) and Phelan (2008), power is a key feature of how stigma occurs and is maintained. Arguably the main aim is to push people down and out of society, thereby maintaining the current social order and preserving power. Phelan et al. (2008) argue that stigma keeps people in a socially subordinate position where they are compelled to accept low pay, sub-standard housing, or inefficient health services, and is more effective when it is covert or implicit (Phelan et al., 2008). Link et al. in 2014 suggested that when there is no rapport of power; it merely means there is no stigma (Link B. G. & Phelan, 2014). We described that given the royal family's position, several community members seek to challenge or erode the royal family's power when they cannot be part of the royal family. Others articulated that this royal family should be given the respect they deserve by providing less derogative labels to affected princes and princesses from the chiefdom. One way this strategic function of stigma in the community is evidenced is through the different terms community members applied to ID occurring in the royal family – which they named 'RheuRheu' – and ID occurring outside of the royal family – which was called "Peuh." Some participants described that the first condition was less stigmatized than the latter, which could

suggest that, in this case, the community tried to affirm the political power vested in the royal family.

On another note, the royal family, to maintain their social position, use their status to negotiate marriages with community members. Several observations reveal that the family needs to resort to 'tricks' to get spouses for its affected males, actively bringing to bear the strong incentive for people to marry into the royal family because of the access to power and privilege that it brings.

4.4.4.1 Clinical Implications

Phelan et al. (2008) suggested that to reduce stigma, we must have a thorough understanding of stigma's function, which in our case was to either keep people away from FXS or keep them down through domination and exploitation. Concerning disease-related stigma, this can be nurtured by automatic emotional reactions. However, familiarizing with the condition can reduce this stigma. This may be associated with desensitization, which can be seen after being exposed to evolutionary phobias as reported by Kolodziej et Johnson 1996 who support this argument by suggesting that personal contact with people with the disease is a decisive factor in the reduction of stigma (Kolodziej & Johnson, 1996). Papadopoulos in 2016 argued that experience stigma could be minimized by focusing on reducing associative and internalized stigma (Papadopoulos, 2016). Thus, the identification of stigma is essential because the stigmatized individuals develop coping strategies to become resilient. The coping strategies can be improved by the education of the people surrounding them. We can argue that knowing the cause of a condition may bring relief from stigma, especially when the disease in question is not contagious, like in the case of FXS. Also, offering early genetic counselling for FXS and psychotherapy services through peer support groups to families at risk of experience stigma can provide emotional support. In these groups, caregivers will share their experiences, which can be regarded as an early form of intervention.

4.4.4.2 Conclusions

In our concluding note, we can say that our work has made progress in understanding FXS associated stigmas and its interaction in an African rural community. This was through the description of the public stereotypes translated through discriminatory behaviours in this rural African community with a high incidence of ID. At the same time, we have described a complex stigma-power dynamic between the community members and the royal family. Given that this is the first qualitative study exploring stigma related to FXS in Cameroon, we advocate that other researchers examine whether the same pattern exists in other inheritable forms of ID and conduct more qualitative research on FXS in Africa.

4.4.5 Study Limitations

In our study, we focused on the views of participants about stigma in the community. We rarely interrogated participants' perceptions of the social structure that makes up their society. Besides, understanding society's social customs and the meaning participants give to these norms are essential components when exploring stigma in a complex society like in our study. In this light, researchers should think of introducing this component in their interview guides.

Conflict of Interests

The authors declare that they have no competing interests.

The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

KKK: Design, data collection, interpretation, and writing

NSM: Interpretation, writing.

SN, JDV, AW: design, interpretation, writing.

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Chapter 5: Summary, Discussion and Conclusions

5.1 Introduction

This thesis was framed around four research questions, which were (1) to identify other family members who were carriers of FXS in an African setting where there is a high incidence of ID and determine the pattern of transmission, (2) determine the effects of receiving a genetic diagnosis of FXS on the lives of the indicator family, and how this genetic diagnosis affected (relations with) other family members and the community, (3) explore the different explanatory models used by the family and the community to explain the high prevalence of ID in their village and (4) establish the role of stigma/power in the face of FXS and ID. To help provide an answer to these research questions, I used three methodological approaches. Firstly, I conducted a scoping literature review of the lived experiences of FXS caregivers. After this, I developed a plan to conduct cascade counselling testing for FXS in a rural Cameroonian village with is high incidence of ID. Then, I used qualitative methods to explore the impact of receiving a FXS diagnosis, explanations for FXS in the community, and the stigma associated with FXS.

5.2 Summary of the thesis

In the first part of my thesis, through a scoping review, I showed that there is limited African qualitative literature on FXS and other inheritable conditions. This review established common challenges reported for living with FXS, which informed the design of my empirical work. I summarised findings according to four major themes: grief experiences, challenges of living with FXS, coping mechanisms, and the need to plan for the future of children affected with FXS. Adults described the need for a good relationship with their health care providers, to be treated with respect and as a whole person, a need for understandable information about the diagnosis, and valued health professionals who could assist whenever needed. York et al. (1999) reported the limited knowledge that educators and health caregivers taking care of children living with FXS had. After the literature review, I elaborated on the procedure used to conduct cascade counselling and testing in a rural African setting where the molecular diagnosis may not be accessible to the population. I then presented my results in the form of a family pedigree (Chapter 4.1). The family's pedigree analysis revealed that this family's traditional head was probably a normal transmitting male carrier.

The rest of my results elaborates on the qualitative component of my thesis. I reported what people in a community and members of an affected family in Cameroon perceive as the causes of Fragile X Syndrome and inherited forms of ID. The study results indicated four different

explanatory models for this syndrome used by community members: The curse model, spiritual model, socioeconomic model, and a genetic model (Chapter 4.2).

In Chapter 4.3 of my thesis, I interrogated the experiences of receiving a genetic diagnosis of family members who participated in cascade testing. Two main themes emerged from the interviews relating to psychological adaptation and FXS genetic risk communication. Firstly, I described the happiness and relief that is associated with diagnostic closure. Next, I described genetic guilt, survivor guilt, and frustration associated with a family history of FXS and taking care of developmentally delayed children. Finally, I highlighted the communication styles used to convey genetic risk to extended relatives and promote resilience. I argued that joy and social acceptance following diagnostic closure significantly contributed to the family's well-being. This argument was also brought forward by Lloyd & Hastings (2008), who evaluated psychological variables that could affect the maternal adjustment to having children with intellectual disabilities. They found that mothers who accepted the condition encountered fewer mental challenges and had a better overall quality of life (Lloyd & Hastings, 2008). Similarly, Wheeler et al. (2018) suggested that interventions that focus on improving acceptance could promote mothers' health and well-being with children suffering from FXS.

Other scholars like Visootsak et al. (2012), Bailey et al. (2003) and McConkie-Rosell et al. (1997), also concluded that participants in their studies were emotionally relieved when they knew the cause of mental disability in their family, which could occur weeks or days after receiving the diagnosis. My data also suggests that the chronic occurrence of mental disabilities in this family has fashioned skills in parents that were important to counsel their offspring about this phenomenon. Some scholars support the idea that this family involvement is crucial for coping after the diagnosis is revealed (Forrest et al, 2003; Gaff et al, 2007; McConkie-Rosell et al, 2011).

I concluded my results section by presenting the complex stigma-power between a royal family with a high ID prevalence in their lineage and the rural community. It was revealed that the presence of this ID in the family had genetic origins, FXS. The names used to refer to children with ID have been reported in other African countries, like Ghana (Avoke, 2002; Opare-Henaku & Utsey, 2017), but these studies refer to common names that translated to 'being stupid or a fool' for describing these children. Similarly, my study showed two names, "Rheurheu" and "Peuh", where "rheurheu" is an inherited and milder form of ID which is more accepted by the community, while "peuh" could be associated with severe forms of ID.

5.3 Practical Implications

Many African countries have adopted practices, decisions, and ideas from the Western world. Mindful of the cultural perception Africans give to disease, it becomes evident that genomic researchers need to consider African health beliefs when designing and implementing their research strategies. Due to high poverty levels in many African countries, several individuals cannot receive adequate health care services and may rely on alternative medicine. In some instances, individuals may enrol in genomic research because they seek a monetary reward or obtain some particular benefit from the research – this may have been the case in our study. However, knowing whether the study participants believe in the explanatory genetic model as the cause of FXS is a pertinent issue. This thesis communicated on the absence of qualitative African literature for FXS. Also, in this Cameroonian rural community where there is a high incidence of FXS, several non-biomedical causal models explain the high prevalence of FXS in the royal family, who have a complicated stigma-power relationship with their community. This relationship is thought to be a mechanism of coping with FXS through domination and avoidance.

The return of a positive genetic result for FXS in this rural Cameroonian community led to the relief and acceptance of this condition in the family. This also created awareness of the different interventions that could be done for FXS, which would help prepare the next generation to be free from this inheritable condition. Inviting patients to actively communicate their genetic risk with extended family members is crucial in counselling. However, to minimise conflict that can arise or exacerbate pre-existing family conflicts, health care workers or people who are comfortable with the subject should serve as intermediaries for affected families by connecting them with resources that are easy to navigate and sensitive to needs. Thus, health care providers should try to understand their patients' lived experiences and their relatives. This may influence their counselling approach and facilitate the grief process that follows the return of results and subsequent therapy for patients. Health care workers in genetic services should also pay attention to the complex and variable psychosocial experiences encountered by individuals receiving a genetic result.

Furthermore, an awareness of the different explanatory models creates an opportunity for health care workers to negotiate the biomedical explanation for FXS while simultaneously creating a common ground between the patient and researcher. The return of a genetic diagnosis for FXS in this family induced a drive from the non-biomedical explanation to the genetic explanation for FXS. Despite this, the community members still have a non-biomedical

explanatory model for the cause of FXS. Some scholars like Naanyu (2009) and Matshabane et al, (2020) reported that participants in their study rarely mentioned only biomedical explanations (i.e., genetic attribution) to disease, and most often, participants establish a relation of causality with non-biomedical explanatory models. Moreover, Kleinman et al. (1978) argued that significant health problems do not fit with biomedical explanations in cross-cultural. Hence, anthropologic concepts can provide an alternative framework for identifying issues requiring resolution. Though the explanatory genetic model for FXS is still an emerging model in this community, I believe that with proper counselling and education, other family members can curb the psychosocial stress related to FXS in the community and reduce out-of-pocket spending for unnecessary consultations and therapies.

Culture and context play an important role in understanding the dynamics of disease mechanisms in a community and should not be disregarded when designing and conducting genomic research. This thesis presented several stigmatising labels that were used for people with FXS in this Cameroonian community. The use of these labels had either the purpose of keeping the royal family member away or keeping them down. Besides this, the privileged position occupied by the royal family in the village put members in a place where they can claim certain privileges. This creates a stigma-power dynamic that I described in Chapter 4.4 of this thesis. From these observations, I can confidently suggest that social realities and disease attribution to causal explanations play a significant role in how people experience stigma.

5.4 Strengths and Limitations

The population presented in this thesis represents only a small fraction of the affected people in this family. Although this thesis presented participants' views, we acknowledge that due to my focus on the experience of P0 and her extended family members who knew the diagnosis and accepted to share their experiences, the views expressed do not capture the entire scope of family members regarding their understanding of FXS and the return of FXS genetic diagnosis in relation to traditional beliefs. The thesis' qualitative component was also limited by recall bias since the explanatory model for FXS was mainly based on the participants' ability to recall the different events that had happened. Other limitations and strengths of the study are presented below.

As described in this thesis' methods section (Chapter 2), being a bilingual physician with origins from the west region of Cameroon facilitated rapport building, engagement, and

understanding of participants enrolled in my study. One of the main challenges was to engage with participants who could not express themselves in any of the two official languages of Cameroon, English, and French. Another difficulty was that some genetic terms and concepts (such as heredity, stigma, genetic counselling) were difficult to translate in the participants' mother tongue. However, a strength of this study was that two research assistants who were fluent in English, French, Ngombalé (the native language of the people in this region) were recruited and also had a conceptual understanding of qualitative research.

Most participants in the FGDs had low literacy levels, with some of them having low English or French proficiency. Hence, most of them needed assistance from the researcher or the research assistant to understand the consent and information sheet and complete the demographical information form. This extra time used to assist the participants resulted in a prolonged time allocated for every FGD session. During the FGDs, some participants did not respect the ground rules instituted at the beginning of the session. The most common example was the tendency of participants to interrupt and speak over other participants. This could have resulted in the discouragement of other participants in responding to some questions. Hence, some participants may have answered questions in agreement with the dominant speakers in the group, or individuals may have opted not to respond to the items already extensively answered by others. This could constitute a limitation to the voices and views expressed in the FGDs.

5.5 Recommendations

The findings reported in this thesis adds to the literature on African genomics and provides insight into how an African population understands inheritable conditions like FXS. Before this work, no qualitative studies reporting on the experiences of living with FXS on the African continent existed. Given the lack of qualitative studies in Africa, there is an urgent need to conduct more research on FXS in Africa. After the cascade testing and analysis of the qualitative data obtained from this family in rural Cameroon, future studies should focus on designing innovative tools to enhance the process of connecting family members together once they receive the FXS diagnosis. This may help bridge the gap between the communication barriers, the main person who gets the diagnosis and the extended relatives. This information should be made accessible to the general public and, where possible, translated into local languages. These messages could best be communicated using Participatory Visual Methods during community engagements.

Moreover, genomic researchers and health care professionals who work with inheritable diseases like FXS should be aware of the diverse and complex causal models that patients hold about their condition. This is important because it affects how, when, and why they choose to adhere to Western medicine provided in local health facilities. Therefore, it is essential that when the opportunity arises, patients are engaged sensitively. Lastly, researchers must develop theories that consider the African cultural belief models concerning the theory. In this light, cultural elements such as curse, bewitchment, and idioms commonly used in a particular language can be considered in developing approaches used in future studies.

5.6 Conclusions

Overall, there are three main insights from this thesis that could inform future scholarship around issues of ethics, in social sciences, and genetics. These are the community engagement practices, the centrality of the patient voice, and feedback of genetic findings. As discussed throughout my thesis, community engagement activities were prominent in how this research was conducted. Building on my field experience, two main observations stand out that merit discussion. In the literature on community engagement in the African continent, the emphasis is repeatedly placed on the importance of entering the community by engaging with traditional community leaders and opinion leaders first (Collier, 2014; Tindana et al, 2011; Tindana et al, 2007). Taking guidance from this literature, I had initially adopted the same strategy and sought to enter the community from the top levels. However, what I learned during this project was that coming in from the top level does not guarantee community participation in a rural village in Cameroon and that, perhaps, sometimes engagement from the bottom level might be as important because those from the bottom will lead you to the top.

A second and associated observation relates to how the researchers' personal and professional status impacts on their ability to engage with community members. As described in the methods chapter, I derived status both from my medical qualification and from having grown up in a Chief's household. As a medical doctor, my training emphasised certainty (in terms of diagnosis conditions) and engendered a perception that medical knowledge may be superior to other forms of knowledge about health and disease. In my original approach to the research, I explicitly brought the status to bear by associating myself with the local health care centre and offering my services as a medical doctor, thinking that this would help the community to get to know and trust me. What I found was quite the reverse. Bringing my status into the conversation or to the relationship with the community meant that people already did not see me as their equal, and that impacted the way they were willing to engage with me, approach

my research, and participation when responding to my questions. When I became conscious of this fact, I started employing strategies that significantly reduced the immediate visibility of my status by not introducing myself as a medical doctor, wearing similar clothes, and eating and living with them. This then opened up opportunities for more equal exchanges with community members.

Several key relationships with community leaders were built on a primary interaction with other community members, who then brought me to their community leaders. This was the case of the relationship I built with one of the religious leaders of the community. This suggested that the overemphasis in the literature around community engagement in health research on the African continent, an engagement that starts with community leaders, needs to be questioned or challenged because of the existing power dynamic between community members and their leaders. Pratt & de Vries (2018) articulated the importance of designing community engagement interventions that specifically take into account the power disparity that exists between community members and their leaders. My research has shed some practical light on the importance of this suggestion.

Current literature contains many suggestions for how people should share genetic findings, and there is some emphasis on whether and how people affected by heritable diseases such as FXS should share their genetic findings with their relatives (Bredenoord et al, 2011; Marsh et al, 2013; McConkie-Rosell et al, 2005). With regards to FXS specifically, some authors have suggested that it will be desirable, especially in the face of scarce medical genetic resources, for family members to share their diagnostic results because it will be cost-effective and promote active diagnosis for diseases (McConkie-Rosell et al, 2005). Yet, my research demonstrated that sharing results within the family context is not straightforward, and in fact, there might be compelling reasons why it does not happen. For instance, in this particular project, the index patient, years after receiving her diagnosis, had only shared her diagnostic result with five other people in her family despite the high prevalence of FXS in their family, as described in Chapter 4.1.

The problem of sharing FXS genetic results with relatives was related to fear of reputational damage and status loss within the family, as described in Chapters 4.3 and 4.4. To address these challenges whilst still promoting the sharing of medical genetic diagnostic results within families, my recommendation is that when providing feedback of a genetic result during follow-up visits, emphasis should be placed on the importance of organising a family information session, which was found to be important in this project. My thesis has shown that

how genetic information is interpreted by those receiving it is not neutral but rather understood and interpreted in ways that match people's pre-existing disease explanatory beliefs and frameworks. This knowledge is an essential starting point for understanding the complex social interactions and establishing a collaborative platform where health professionals, educators, and policymakers can significantly contribute to developing and evaluating culturally and sensitive patient-friendly interventions. One way to ensure this is to focus more on community engagement programmes based on participatory activities, which can provide effective community participation.

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Addendum 1

Topic guide

Title: Return of a Fragile X Syndrome Genetic Result: Exploring the feedback of Individual genetic findings and their relation to traditional knowledge in a village in Cameroon

This document is a guide to the principal themes and issues to be covered. Questions can be modified and followed up in more detail as appropriate.

1. Introduction (for the interviewer)

- Introduce yourself and thank them for receiving you or answering your appointment.
- Share an outlook of the project with them and inform them that the interview will last for about 45 mins
- Remind them that participation is optional
- Establish ground rules

2. Confidentiality

- Your names will not be tagged in the interview. You should feel free while sharing your opinions with us. If you feel like not answering any questions, you are free not to.
- We would prefer to record the interview as this helps us capture exactly what you said. Are you comfortable with that?

(Ask for verbal confirmation that they understand the purpose and confidentiality of the research and that they are happy to take part)

3. Understanding of FXS in the village (use an opening question or an ice breaker to get the participant comfortable):

- Can you please tell me what you know about FXS in the village? (use the name that is common in the village)?
- Do you know if many people in the village have it? If yes
    - Do you know how they contracted it?
    - What could be the possible explanation for the causes of (use the name common in the village) in your community?
- Can you please give us a few narratives or stories around this phenomenon? (follow up)
    - What about the story behind this belief? (use the name that is common in the village)?
    - Do you have family members or relatives or friends with this condition (use the name common in the village)? (follow up)
    - Can you please share with us your experience with them?

- How did they get this condition? (follow up)
- Are there other explanations for the high prevalence of this condition in the village?

3. Diagnostic experience (for participants who received a FXS genetic test result)

- Tell us about your diagnosis experience, starting from when you first recognized any problems to when you got the diagnosis of fragile X syndrome for your child.
- What were some of the first symptoms that you noticed?
- What doctor gave you the diagnosis of FXS?
- What part of the whole process of receiving a diagnosis did you think went the smoothest?
- What part of the process was the most challenging?
- How did you feel when your child was given a diagnosis of fragile X syndrome?
- Tell us about any support you received when you first got the diagnosis?
    - What role did your family play in the support you received?
    - What role did your friends play in the support you received?
    - Did you receive support from other types of organized groups?
- If you could change anything about the process of getting a diagnosis of fragile X syndrome, what would you change?
- Is there anything else you would like to tell us about your experience that might help us assist other families in the future?

5. Diagnostic closure

- What made you go for a diagnostic test?
- What was it like when you first received the genetic results that your children had fragile x syndrome?
- What was the care given to the children before you knew about the medical test results? (follow up)
- How are they taken care of now?
- Did you inform other family members about genetic testing and results? Why do you think it was (or was not) important to let them know?
- (if we do a test and discover that there is fragile x syndrome (use the name that is common in the village) in your family, would you like us to tell you about the results? (Follow up) Why (why not)?

6. Sigma and gender blame

- How have you been living with this condition? (use the name common in the village)
- How were peoples in the village react to people who have FXS? (use the name common in the village)

- Can you please give us some examples?

- How has this condition affected your relationship with relatives, other members of the community, or with the affected families?

7. Closing notes

- Is there anything that we have did not address that you want to add?

- Thank you for your time

Addendum 2

INFORMATION SHEET FOR THE FILM

Title of the Study: Return of a Fragile X Syndrome Genetic Result: exploring the feedback of Individual genetic findings and their relation to traditional knowledge in a village in Cameroon.

Introduction and summary

We are hoping to make a film about a condition called Fragile X syndrome (FXS). FXS is an inheritable condition, meaning that it can be transmitted in families from generations to generations, due to some changes (mutation) in a specific gene, which causes mental retardation in mostly boys and men. In FXS, children that are affected will be delayed in their capacity to learn and will not be able to attend normal school and will not verbally communicate well with people and could also have some autistic behaviour ("living in their own world" and having some inappropriate repetitive actions). The film will explore how learning that FXS is a genetic condition has impacted on the lives of people that are affected, their families and their communities and the village. The film is part of a study exploring how giving back to people (feedback) a genetic diagnosis impacts on the lives of these people affected by this disease. This study that is being conducted in Cameroon is part of a larger study, called *IFGeneRA*, looking at how best to feedback individual genetic research findings to people and communities in Africa. Other countries involved are South Africa and Botswana.

Objective

We hope to use this film as educational material to inform others about the impact that a genetic diagnosis may have, specifically in a rural community, and the way Cameroonians experience this condition, specifically in Babadjou village. The film will help educate the broader public about the disease – Fragile X Syndrome – but also about genetics more broadly. The film will be used in Cameroon but also in other African countries, and will be available on the internet.

The researchers

This project is led by Prof Wonkam who is a geneticist. Other members include Prof Jantina de Vries a bioethicist, Prof Nguefack a neuro paediatrician, and Dr Kengne K Karen a physician. They work together with an international team of researchers based in Botswana, South Africa, Ghana, Kenya and the United States.

Participants

We are involving individuals from families that have been affected by Fragile X Syndrome and who have received a genetic diagnosis. This includes patients, their family members, and members of the wider community in the village.

Methods

If you agree to participate, we will have a discussion with you about the Fragile X Syndrome, and the genetic diagnosis that you received. We will ask questions about how the disease and diagnosis have affected your life. We will film the entire discussion but will use only short fragments from the discussion in the film.

We will speak to many people for this film, and we will use short fragments from each of the discussions we will have. When you see the final film, you may find that you appear only very shortly – this is because we spoke to many people. On the other hand, you may also find that you appear often, but we won't know until we have finished preparing the film.

Risks and Benefits

When you appear in the film, others will know who you are and will know your story. You may never have told people about Fragile X Syndrome in your family, and how it has affected you. You may feel shy talking about this on camera, and others may tease you afterwards. If you feel insecure or do not want to share your story, then please know that there is no pressure for you to participate.

On the other hand, once we have the film, it will help us educate others about Fragile X Syndrome, genetics, and about how a genetic diagnosis may help people that have diseases that are in the genes. This could help reduce the stigma related to this disease, and help other people understand genetics better.

Do I have to participate in this film?

It is entirely up to you whether you want to share your story on film or not. We completely understand if you are uncomfortable with being filmed and there are no consequences if you do not want to be filmed.

Will I be recognized?

When we film you, others will be able to know who you are when they see the film. But it is also possible for you to participate but not appear in the film in a way that others can recognize you. For instance, we can film you from the back or you could wear clothes that make it difficult for others to know who you are (for instance, a wig and glasses). Please let us know whether you would like to participate in a way that others will not be able to recognize you.

What will happen with the film?

Once we have filmed everyone, we will start to put together the film. Before we finish the film, we will come to show you and get your feedback. At that stage, we can still take out fragments that you are worried about. Following that, we will finalize the film and come show it to you again. You will receive a DVD with the film on it. We will share the film widely with other people conducting genomic research in Africa, including on the internet. By sharing the film, we ensure that it reaches as many people as possible.

We will give DVDs with the film to members of the local community, to doctors and nurses involved with caring for patients with Fragile X Syndrome, to future patients, to other researchers at conferences and meetings, and to any other person who may benefit from having a copy.

Withdrawal

You are free to stop the discussion and the filming at any time. If you have agreed to be filmed but have changed your mind and would not like to participate any longer, please contact us as soon as possible so that we can destroy the video and not use it in the film. However, once we have created the final film, it will not be possible for us to remove fragments from it anymore. We will make available the video open access (meaning other people all over the world can have access to the video), for use by the H3Africa Consortium and other researchers in genetics and genomics

Compensation

We would like to thank you for the time that you took to be part of our study. We will pay for the cost of your transport and telephone calls that you have made.

Contact Information

If you have any questions or comments about this project, or if you want to speak more about the project, you can contact:

CIERSH: Bp 4362, tel:+237 222212433, Fax:+237 222212430;

Human Research Ethics Committee (HREC), Room E53-4& Old Main Building Groote Schuur Hospital, Observatory 7925, Telephone [021] 406 6626, Email: shuretta.thomas@uct.ac.za Website: www.health.uct.ac,za/fhsfresearchfbumanethlcslfonns;

Professor Ambroise Wonkam Private Bag X3, Rondebosch, 7701 , South Africa , Barnard Fuller Building, Anzio Road, Observatory, Cape Town, Tel: +27 (0) 21 406-6633 Fax: +27 (0) 21 447-8955 , E-mail: ambroise.wonkam@uct.ac.za, research.health@uct.ac.za, Internet: www.uct.ac.za .

Dr Kengne Kamga karen, Tel: +237 675112107/ +237965965225 email: krnken003@myuct.ac.za

INFORMED CONSENT SIGNATURE SHEET

*"*Return of a Fragile X Syndrome genetic result: exploring the feedback of individual genetic findings and their relation to traditional knowledge in a village in Cameroon*."*

Date: _____

Venue: _____

1. □I,_____, agree to take part in a film about my experience of Fragile X Syndrome and of a genetic diagnosis;
2. □ I understand that the discussion will be videotaped;
3. □ I give permission for this video material to be made into a short educational film to be shown to other people;
4. □ I understand that this video will be put on selected websites where they can be used by others who want to educate people about Fragile X Syndrome and genetics;
5. □ I understand that whilst the research team will not put the video on public websites such as YouTube and Facebook and other Social Media platforms, we cannot guarantee that others will not do this;
6. □ I understand that people may recognize me in the video. If that happens, they may find out something about me or my family that I didn't tell them personally. I understand that I can use props such as wigs and hats to disguise myself;
7. □ I have read, or have been read, the accompanying information sheet in my own language. I understand this consent form and the information sheet. Any questions I had have been answered.
8. □ I understand that I may withdraw my consent at any time until the final film has been produced.

Signed in _____ (place) on _____ (day) of _____ (month) 20__ (year)

Signature_____

INFORMATION SHEET FOR IN-DEPTH INTERVIEWS AND FOCUS GROUPS

Title of the Study: Return of a Fragile X Syndrome Genetic Result: exploring the feedback of Individual genetic findings and their relation to traditional knowledge in a village in Cameroon.

Introduction and summary

We are hoping to make a film about a condition called Fragile X syndrome (FXS). FXS is an inheritable condition, meaning that it can be transmitted in families from generations to generations, due to some changes (mutation) in a specific gene, which causes mental retardation in mostly boys and men. In FXS, children that are affected will be delayed in their capacity to learn and will not be able to attend normal school and will not verbally communicate well with people and could also have some autistic behaviour ("living in their own world" and having some inappropriate repetitive actions). The film will explore how learning that FXS is a genetic condition has impacted on the lives of people that are affected, their families and their communities and the village. The film is part of a study exploring how giving back to people (feedback) a genetic diagnosis impacts on the lives of these people affected by this disease. This study that is being conducted in Cameroon is part of a larger study, called *IFGeneRA*, looking at how best to feedback individual genetic research findings to people and communities in Africa. Other countries involved are South Africa and Botswana.

Objective

we will like to explore the impact of receiving a positive FXS results in the affected family in Cameroon and to explore the effect of this diagnosis on other family members affected by the same condition. We may also want to study community views on fragile x syndrome, the curse explaining patterns of inheritance, traditional knowledge of genetics and gendered blame.

The Researchers

This project is led by Prof Wonkam who is a geneticist. Other members include Prof Jantina de Varies a bioethicist Prof Nguefack a neuro paediatrician, and Dr Kengne K Karen a physician. They work together with an international team of researchers based in Botswana, South Africa, Ghana, Kenya and the United States.

Participants

We are seeking to involve individuals from families that have been affected by Fragile X Syndrome and who have received a genetic diagnosis. This includes patients, their family members, and members of the wider community in the village.

Methods

If you agree to participate, you will be asked to be part of the study through either interview and focus group discussions. The interviews and focus group discussions will take approximately 45 mins and 90 mins, respectively, of your time. All information will be kept or anonymous and confidential. This means that your name will not appear anywhere and no one except me will know about your specific answers. During focus group discussions, we will assign a number or a nickname to your responses, and only I will have the key to indicate which number or nick name belongs to which participant. In any articles we write or any presentations that we make, we will use a made-up name for you, and we will not reveal details, or we will change details about where you work, where you live, any personal information about you, and so forth.

Risks and Benefits

The benefit of this research is that you will be helping us to understand the effects to returning of fragile x result and their relation to the traditional knowledge in a village of Cameroon. This information will help us to better understand the effect of giving back genetic results, the traditional understanding genetic results and the gender stigma associated to genetic neurodevelopmental conditions such as fragile x Syndrome.

The risks to you for participating in this study is the time that you will give us. These risks will be minimized by compensating you for your time and travel expenses to up to 5000 CFA. If you do not wish to continue, you have the right to withdraw from the study, without penalty, at any time.

Withdrawal

You are free to stop the discussion at any time. If you have agreed to be interviews but have changed your mind and would not like to participate any longer, please contact us as soon as possible so that we can destroy the audio and transcripts and not.

Compensation

We would like to thank you for the time that you took to be part of our study. We will pay for the cost of your transport and telephone calls that you have made.

Contact Information

If you have any questions or comments about this project, or if you want to speak more about the project, you can contact:

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Professor Ambroise Wonkam Private Bag X3, Rondebosch, 7701 , South Africa , Barnard Fuller Building, Anzio Road, Observatory, Cape Town, Tel: +27 (0) 21 406-6633 Fax: +27 (0) 21 447-8955 , E-mail: ambroise.wonkam@uct.ac.za, research.health@uct.ac.za, Internet: www.uct.ac.za .

Dr Kengne Kamga karen, Tel: +237 675112107/ +237965965225 email: krnken003@myuct.ac.za

INFORMED CONSENT SIGNATURE SHEET

Title: **"Return of a Fragile X Syndrome genetic result: exploring the feedback of individual genetic findings and their relation to traditional knowledge in a village in Cameroon."**

Date: _____

Venue: _____

1. □I,_____, agree to take part in a film about my experience of Fragile X Syndrome and of a genetic diagnosis;
2. □ I understand that the discussion will be audiotaped;

   6.
3. □ I have read, or have been read, the accompanying information sheet in my own language. I understand this consent form and the information sheet. Any questions I had have been answered.
4. □ I understand that I may withdraw my consent at any time.

Signed in _____ (place) on _____ (day) of _____ (month) 20__ (year)

Signature_____

INFORMATION SHEET FOR SAMPLE COLLECTION

Title of the Study: Return of a Fragile X Syndrome Genetic Result: exploring the feedback of Individual genetic findings and their relation to traditional knowledge in a village in Cameroon.

Introduction and summary

FXS is an inheritable condition, meaning that it can be transmitted in families from generations to generations, due to some changes (mutation) in a specific gene, which causes mental retardation in most boys and men. In FXS, children that are affected will be delayed in their capacity to learn and will not be able to attend normal school and will not verbally communicate well with people and could also have some autistic behaviour ("living in their own world" and having some inappropriate repetitive actions). We intend to provide a diagnosis for this condition in the community and precisely to people in the community who have a pass family history of intellectual disability. This study that is being conducted in Cameroon is part of a larger study, called *IFGeneRA*, looking at how best to feedback individual genetic research findings to people and communities in Africa.

Objective

We hope to provide ancillary care to this large family affected by fragile x syndrome by offering genetic testing since this may be the only time they may have access to a molecular diagnosis. we also plan to provide genetic counselling to the extended family as per the outcome of the result which is one of our duty as health care providers.

The researchers

This project is led by Prof Wonkam who is a geneticist. Other members include Prof Jantina de Vries a bioethicist, Prof Nguefack a neuro paediatrician, and Dr Kengne Kamga Karen a physician. They work together with the university of Yaoundé 1, the university of cape town and the united states of America through the NIH (national institute of health).

Participants

We are involving individuals from families that have been affected by Fragile X Syndrome and other community members who have a family pass history of intellectual disability with a heredity pattern.

Methods

If you agree to participate, we shall collect 10 ml of your blood which will be used to study something that we call genes. Genes are found in our body and we inherit it from our parents. There is a bad gene that causes FXS. We are going to be studying these bad genes that make people sick and check what other genes protect people from having signs. Once we have done the research that we are planning for this project, we would like to store your blood if you give us permission to do so.

Return of result

We will study samples of many people in your family or community. it may take several months before they know if the results have any meaning. When the results are available, it will be provided to you after an appropriate discussion about their meaning. We shall schedule a meeting with you in a health care facility to provide genetic counselling before the disclosure of the results. A follow-up meeting will then be scheduled at two months and 6 months after disclosure of results. We also intend to share the combined results from our research with other researchers through newsletters and other forms of communication.

Risks and Benefits

Most of the time when we take blood it is safe, but in rare cases people feel a bit faint or get a bruise where we took the blood. If this happens please let us know and you will be treated.
Another potential risk of participating in this study is that information about you may become known to people who should not have this information. We will treat all your data confidentially by using codes.
This study will help you know if you have the bad gene that causes fragile x syndrome then you will be offered genetic counselling in in relation to your results.

Withdrawal

It is your decision whether you take part in the study. In other words, it is up to you whether you want to participate in the study

Compensation

We would like to thank you for the time that you took to be part of our study. We shall compensate you with an amount equivalent to the cost of your transport.

Contact Information

If you have any questions or comments about this project, or if you want to speak more about the project, you can contact:

CIERSH: Bp 4362, Tel: +237 222212433, Fax: +237 222212430;

Human Research Ethics Committee (HREC), Room E53-4& Old Main Building Groote Schuur Hospital, Observatory 7925, Telephone [021] 406 6626, Email: shuretta.thomas@uct.ac.za Website: http://www.health.uct.ac,za/fhsfresearchfbumanethlcslfonns;

Professor Ambroise Wonkam Private Bag X3, Rondebosch, 7701, South Africa, Barnard Fuller Building, Anzio Road, Observatory, Cape Town, Tel: +27 (0) 21 406-6633 Fax: +27 (0) 21 447-8955, E-mail: ambroise.wonkam@uct.ac.za

Dr Kengne Kamga Karen, Tel: +237675112107/+237965965225 email:karenke@yahoo.co.uk

INFORMED CONSENT SIGNATURE SHEET

Title: *"*Return of a Fragile X Syndrome genetic result: exploring the feedback of individual genetic findings and their relation to traditional knowledge in a village in Cameroon*."*

Please read/listen to the following statements and tick the YES box if you agree. If you do not agree tick No.

	Yes	No
The information sheet has been read to me and I understand it / I have read and understand the information sheet		
I understand that the information regarding me that is collected will remain confidential.		
I understand that none of my results will be given to me and that I will not benefit financially from taking part.		
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. Deciding not to take part or to withdraw from the study will not affect the care that I or any of my family members is normally entitled to.		
I have had a chance to ask questions and have them answered.		

Please read/listen to the following statements and tick the YES box if you agree. If you say no, you can still participate in the study.

	Yes	No
I give permission for long-term storage and use of my blood for health-related laboratory tests and research purposes, and do not claim any rights to these samples.		

Name of participant/relative Date (dd/mm/yyyy) Signature or Thumbprint

_____ _____ _____

Name of the Witness Date (dd/mm/yyyy) Signature

_____ _____ _____