

Polymorphic Variation in *TIRAP* Is Not Associated with Susceptibility to Childhood TB but May Determine Susceptibility to TBM in Some Ethnic Groups

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Abstract

Host recognition of mycobacterial surface molecules occurs through toll like receptors (TLR) 2 and 6. The adaptor protein TIRAP mediates down stream signalling of TLR2 and 4, and polymorphisms in the TIRAP gene (*TIRAP*) have been associated with susceptibility and resistance to tuberculosis (TB) in adults. In order to investigate the role of polymorphic variation in *TIRAP* in childhood TB in South Africa, which has one of the highest TB incidence rates in the world, we screened the entire open reading frame of *TIRAP* for sequence variation in two cohorts of childhood TB from different ethnic groups (Xhosa and mixed ancestry). We identified 13 SNPs, including seven previously unreported, in the two cohorts, and found significant differences in frequency of the variants between the two ethnic groups. No differences in frequency between individual SNPs or combinations were found between TB cases and controls in either cohort. However the 558C→T SNP previously associated with TB meningitis (TBM) in a Vietnamese population was found to be associated with TBM in the mixed ancestry group. Polymorphisms in *TIRAP* do not appear to be involved in childhood TB susceptibility in South Africa, but may play a role in determining occurrence of TBM.

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Introduction

Activation of host inflammatory responses are fundamental to containment of *Mycobacterium tuberculosis* (MTB) following initial infection [1]. The majority of individuals who are exposed to MTB successfully contain the infection and remain asymptomatic but latently infected throughout life. TB disease develops in a minority of those infected, either following the primary infection or due to reactivation of latent disease many years later [2]. Differences in immune response genes are believed to be important in determining whether an individual successfully contains the infection or develops disease [3,4,5], but the genes responsible remain largely unknown.

Children not only have an increased risk of developing progressive disease following exposure [6], but have a much greater risk of developing disseminated forms of the disease including TBM [7,8]. The ability to rapidly activate innate immune responses is likely to be critical in the containment of mycobacteria during primary infection in childhood, as evidenced by the unique susceptibility to mycobacteria in patients with Mendelian defects in interferon gamma (IFN γ) and interleukin 12 (IL-12) pathways [9,10,11,12].

Innate immune recognition of mycobacterial surface molecules including lipoarabinomannan, are believed to occur predominantly through toll-like receptor (TLR) 2 [13] with TLR6 as its co-receptor [14], and possibly TLR4 [15]. Binding of the ligand initiates a signalling cascade leading to activation of proinflammatory responses [16]. The TIR-domain-containing adapter like protein (TIRAP) is a cytoplasmic protein which is 221 amino acids in length and is important in both the TLR2 and TLR4 mediated signalling pathways [17,18]. Binding of the ligand to either receptor leads to the recruitment of several molecules to the receptor including the TIR-domain-containing adaptor molecules such as the myeloid differentiation primary response gene 88 (MyD88) and TIRAP [18]. This complex recruits other molecules including IL-1R kinases 1, 2, 3 and 4 (IRAK1, 2, 3 and 4) and TNF receptor associated factor 6 (TRAF6) [19] which dissociate and bind a further complex that consists of transforming growth factor- β -activated kinase 1 (TAK1) and TAK-1-binding proteins 1, 2 and 3 (TAB 1, 2, 3). TAK1 activates the inhibitor of NF κ B kinase (IKK) via IKK γ (also called NEMO). IKK causes the phosphorylation of the inhibitor of NF κ B (I κ B), which leads to its degradation and thereby allows NF κ B to translocate to the nucleus and promote the transcription of proinflammatory genes.