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Variable functional phenotypes of inherited IL-12 receptor variants in patients with Mendelian Susceptibility to Mycobacterial Disease

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Abstract

Purpose: In high TB burden countries such as South Africa, individuals with Mendelian Susceptibility to Mycobacterial Disease (MSMD) are prone to developing severe, persistent, unusual or recurrent (SPUR) TB. Several genes have been associated with MSMD, all resulting in the disruption of the IL-12-IFN-γ cytokine axis, which is essential for the effective control of mycobacterial infections. The aim of this study was to assess the immunological phenotypes (relating to the IL-12-IFN-γ cytokine pathways) in four patients with likely disease-causing variants identified in the IL-12 receptor genes (IL12RB1 or IL12RB2)and their unaffected family members using a set of in-house functional profiling assays.

Methods: Novel, plausible disease-causing variants were identified in the genes coding for the IL-12 receptor in all four MSMD patients included in the study: IL12RB1 for P1 and P2; P3 had variants in both IL12RB1 and IL12RB2; while P4 had a variant identified in IL12RB2. IL-12Rβ1 and IL-12Rβ2 expression was assessed through standard flow cytometric phenotyping and IL-12 receptor signalling was assessed by means of phospho-specific flow cytometry, which detects phosphorylated STAT4 following in vitro stimulation. IL-12-induced IFN-γ production was determined by Luminex following 48-hour IL-12 and PHA or BCG co-stimulation.

Conclusion: The four patients had varying degrees of immune dysfunction, which deviated from the controls as well as from their unaffected family members. This emphasises the importance of in vitro assessment of genetic variants in patients and their family members to determine functional penetrance of particular gene variants. An accurate molecular diagnosis for MSMD allows for appropriate intervention and treatment for affected individuals.