Association of polymorphisms in IL-12/IFN-gamma pathway genes with susceptibility to pulmonary tuberculosis in Indonesia

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Upon infection with mycobacteria the IL-12/IFN-gamma axis plays an essential role in the activation of cell-mediated immunity required for the elimination of pathogens. Mutations in genes of the IL-12/IFN-gamma axis are known to cause extreme susceptibility to infection with environmental mycobacteria, and subtle variations in these genes may influence susceptibility to more virulent mycobacteria. We analyzed the distribution of polymorphisms in four essential genes from the IL-12/IFN-gamma axis, IL12B, IL12RB1, IFNG and IFNGR1, in 382 pulmonary tuberculosis patients and 437 healthy controls from an endemic region in Jakarta, Indonesia. The IL12RB1 gene was sequenced in a subset of individuals. Nine known single nucleotide polymorphisms (SNPs) and two new silent variations, 135G>A and 1056C>T, were detected in IL12RB1. Six functional SNPs (-2C>T, 467G>A, 641A>G, 1312C>T, 1573G>A, 1781G>A) in IL12RB1, an IL12B promoter insertion/deletion polymorphism and CA repeats in IFNG and IFNGR1 were analyzed in the cohort. The IFNGR1 allele CA(12) (p=0.004) and genotype CA(12)/CA(12) (p=0.01; OR 0.5) were associated with protection from pulmonary tuberculosis. Interestingly, IL12B promoter heterozygosity was associated with protection from tuberculosis in BCG-vaccinated individuals (p=0.03; OR=0.6). This new finding supports the role that IL-23-of which IL12B encodes a subunit-plays in generation of memory T cells.