

## Association between the 1188 A/C polymorphism in the human *IL12B* gene and Th1-mediated infectious diseases

Dear Editor,

An association was found between an A-to-C exchange at position 1188 in the 3'-UTR of the *IL12B* gene and tuberculosis and salmonellosis in Russians. Both case-control and family-based association studies data suggest that this gene variant is a risk factor of common susceptibility to infection due to intracellular bacteria.

Interleukin-12 (IL-12) is the key cytokine of Th1-mediated immunity in humans. It is secreted by antigen-presenting dendritic cells and phagocytes and activates CD4+ T cells to differentiate to Th1, IFN- $\gamma$ -secreting cells, associated with cellular immune responses. IL-12 plays a crucial role in immunity to intracellular bacteria, such as *Mycobacterium* and salmonellae species. The whole p70 IL-12 is a heterodimeric protein comprised of p35 and p40 subunits encoded by two distinct genes (Jouanguy *et al.*, 1999). It is interesting to note that the p40 subunit is shared by IL-12 and IL-23, another cytokine which is thought to be important in cell-mediated anti-infectious immunity (Oppmann *et al.*, 2000). Because of the shared p40 subunit, IL-23 induces the same intracellular signals (Parham *et al.*, 2002), explaining the overlapping activities of IL-12 and IL-23. However, IL-23 seems to be less efficient than IL-12 at inducing IFN- $\gamma$  production and Th1-cell differentiation. Subunit p40 is encoded by the *IL12B* gene, located on chromosome 5q31. Impaired IL-12 secretion, as a consequence of rare mutations in this gene, has been associated with atypical disseminated infection due to poorly virulent mycobacteria and salmonella (Altare *et al.*, 1998). An A-to-C exchange has been found in the 3'-UTR of the gene, in position 1188 (Huang *et al.*, 2000) that correlates with decreased protein secretion (Stanilova & Miteva, 2005) and it might be a cause of common predisposition to Th1-mediated infectious diseases.

To clarify this hypothesis, we performed an association study of the *IL12B* 1188 A/C polymorphism in individuals with active tuberculosis and salmonellosis in Russians from the city of Tomsk. Three hundred and four tuberculosis, 49 salmonellosis and 129 control cases matched by age and sex were genotyped for the *IL12B* 1188 A/C polymorphism by the TaqI-RFLP (restriction fragment length polymorphism) method (Hall *et al.*, 2000). Control individuals have never been affected by tuberculosis and salmonellosis, and also have no previous histories of chronic Th1- or Th2-mediated diseases such as insulin-dependent diabetes mellitus or atopic disorders. In addition, 40 family trios with tuberculosis-affected offspring were studied by transmission/disequilibrium test (TDT) (Spielman *et al.*, 1993).

Genotypes distribution in the group of healthy individuals met Hardy-Weinberg equilibrium (A/A -85, A/C -43, C/C -1;  $P = 0.118$  by Fisher's exact test for HWE),

confirming relevance of the sample as control. The prevalence of the 1188C allele in tuberculosis ( $0.240 \pm 0.018$ ) and in salmonellosis ( $0.347 \pm 0.048$ ) was significantly higher than in controls ( $0.174 \pm 0.024$ ;  $\chi^2 = 4.075$ ,  $P = 0.044$  and  $\chi^2 = 11.264$ ,  $P = 0.001$ , respectively). Also, the 1188C allele was significantly more frequently transmitted from heterozygous parents to tuberculosis offspring as compared to the alternate (13 vs. 2 times; TDT = 8.067,  $P = 0.005$ ).

Thus, both case-control and family-based association data suggest that the *IL12B* 1188 A/C polymorphism is a factor of common susceptibility to Th1-mediated infectious disorders due to intracellular bacteria. This association may be because of the decreased expression of IL-12 associated with the 1188C allele as compared to the 1188 A (Stanilova & Miteva, 2005) or due to linkage disequilibrium of the 1188C allele with other common polymorphisms in *IL12B* that were recently found to be associated with tuberculosis (Tso *et al.*, 2004).

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