A structural variant of the human interferon-gamma gene

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The first structural *IFNG* variant, G54D (c.287G>A, ss105106770), located in the second exon, was identified.

Interferon-γ (IFNγ) is the hallmark cytokine of Th1 immune responses. It is secreted by Th1 cells, cytotoxic T cells, dendritic cells and natural killer (NK) cells and modifies transcription in up to 30 genes, inducing a variety of complex cellular responses. Major immunoregulatory properties of IFNγ include the increase of antigen presentation and lysosomal activity of macrophages, suppression of Th2 immune responses, expression of class II human leukocyte antigen molecules and the induction of NK cell activity (1). In addition, IFNγ promotes adhesion in migration of leukocytes and differentiation of Th1 cells.

The IFN-γ gene (*IFNG*, 12q24.1, OMIM *147570) comprises four exons encoding 146 amino acids and three introns. *IFNG* exhibits limited genetic variability, and structural variants have not been identified so far (2; www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId = 3458). Intron 1 contains a polymorphic CA microsatellite repeat. Allele 2 causes high levels of IFNγ production *in vitro* (3), which appears to be because of the almost perfect linkage of allele 2 with the +874 variant. *IFNG* + 874 variability has been implicated in

differential susceptibility to rheumatoid arthritis (4) and to other conditions.

In the course of studies on human genetic factors in Ghana, West Africa, we have re-sequenced the *IFNG* gene in 69 DNA samples. In addition to the known extraexonic variability, we found the yet unidentified structural variant G54D (GenBank reference NM_000619.2, c.287G>A, ss105106770) in the second *IFNG* exon. The variant was confirmed by fluorescence resonance energy transfer genotyping in 28 individuals in a total of 4208 individuals. The allele occurred heterozygously only.

Our observation of the exonic G54D variant is not consistent with earlier studies reporting perfect exonic *IFNG* conservation (2). Alignments of equine, bovine, murine and rat *IFNG* sequences show that the identical G>D substitution that we found occurs in other vertebrate species as well as (5; http://www.pantherdb.org/). An *in silico* prediction of functional effects of human single nucleotide polymorphisms (http://genetics.bwh.harvard.edu/pph/) suggested that the G54D variant does not cause any major structural modification.

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