

The Hyper IgE Syndrome and Mutations in *TYK2*

The hyperimmunoglobulin E syndrome (HIES) is a rare primary immunodeficiency, characterized by the clinical triad of recurrent staphylococcal skin abscesses, recurrent respiratory-tract infections, and serum IgE concentrations of >2000 IU/mL. Autosomal dominant (AD) and autosomal recessive (AR) forms have been described (Grimbacher et al., 1999; Renner et al., 2004). The AR-HIES variant includes, in addition to this HIES triad, recurrent viral infections, extreme eosinophilia, and neurological complications but no skeletal symptoms.

In the November 2006 issue of *Immunity*, Minegishi et al. (2006) reported the first monogenetic defect in a single patient, from consanguineous parents, who was presented with some clinical features of autosomal-recessive HIES. The patient had a homozygous defect in the receptor-associated cytoplasmatic tyrosine kinase *TYK2*. However, the authors did not report whether they investigated *TYK2* in additional patients with AR-HIES. Thus, it remains an open question whether *Tyk2* deficiency might be a common cause of AR-HIES.

This prompted us to analyze *TYK2* in a collection of patients with the characteristic appearance of the autosomal-recessive HIES. All patients participating in this study were consented according to protocols approved by a local ethics-review board.

We screened a total of 15 autosomal-recessive families with HIES (seven of them from consanguineous marriages including three unrelated patients out of the initially six published families; see Renner et al. [2004]) by genotyping and linkage analysis. The affected individuals in five families were homozygous at marker D19S586 within 1 Mb of the *TYK2* gene. Four of

the five families had at least one unaffected child, and in three of these four, the genotype data were consistent with genetic linkage to the *TYK2* locus on chromosome 19. We subsequently performed sequence analysis on the genomic DNA of one patient from each of these five families, by using the primers for human *TYK2* kindly provided by Minegishi et al. (2006). We did not find any mutation in the coding regions of exons and the adjacent intronic sequences of *TYK2*. However, we did not analyze the full intronic regions and the promoter of the gene. We conclude that *Tyk2* deficiency is most likely not a common cause of the AR-HIES and suggest that human *Tyk2* deficiency is a distinct disease entity that is genetically and clinically different from the previously published patients with AR-HIES. This hypothesis is supported by atypical features in the clinical history of the patient described by Minegishi et al. (2006), such as a BCG lymphadenitis and a non-Typhi *Salmonella* infection. The susceptibility to these certain viral and intracellular bacterial infections may imply that human *TYK2* deficiency is clinically and pathophysiologically closely related to patients with particular defects in the interleukin-12-interferon axis as described by Casanova and Abel (2004). Therefore, it might be rewarding to analyze *TYK2* further in these cohorts in addition to patients with AR-HIES.

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