

Response: The Hyper IgE Syndrome and Mutations in *TYK2*

We would like to thank Woellner et al. for their thoughtful comments and additional data to our recent article (Minegishi et al., 2006).

Woellner et al. (2007) evaluated 15 families with autosomal-recessive hyper IgE syndrome (AR-HIES) and found that the affected individuals in five families are homozygous at marker D19S586 within 1 Mb of the *TYK2* gene, four of the five families have at least one unaffected child, and in three of these four, genotype data are consistent with genetic linkage to the *Tyk2* locus on chromosome 19. The results suggest that homozygous mutation in *TYK2* gene is responsible for their AR-HIES. Nevertheless, the authors performed sequence analysis on the genomic DNA, but only in the coding regions of exons and the adjacent intronic sequences of *Tyk2*, and with these data, the authors conclude that *Tyk2* deficiency is most likely to not be a common cause of the AR-HIES.

The sequence analysis of coding regions of exons and the adjacent intronic sequences of a given gene alone is not sufficient to identify all of the existing genetic alterations. Substantial

percentage of mutations with large insertions, inversions, and duplications, as demonstrated in human X-linked agammaglobulinemia (Rohrer et al., 1999), could be missed. Therefore, it may be too early to conclude from their analysis that *Tyk2* deficiency is not a common cause of the AR-HIES. More detailed studies on the genomic structure of the *TYK2* gene as well as the biochemical and functional analyses of *Tyk2* protein are needed to draw the conclusion.

Woellner et al. (2007) also claimed that human *Tyk2* deficiency is a distinct disease entity that is genetically and clinically different from the patients with AR-HIES on the basis of their experimental data. However, as described in our previous report (Minegishi et al., 2006), the patient with *Tyk2* deficiency displayed clinical features characteristic of AR-HIES, with clinical and laboratory scores high enough to diagnose as HIES according to the National Institutes of Health scoring system that was developed for HIES diagnosis (Grimbacher et al., 1999). In addition, the patient showed clinical features of Mendelian susceptibility to mycobacterial disease

(MSMD) (Casanova and Abel, 2004). Therefore, we think that *Tyk2* deficiency should be categorized as a disease entity having characteristic features of both AR-HIES and MSMD. Further genetic analyses of HIES patients including autosomal-dominant and sporadic forms should clarify this issue.

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