Polymorphisms Not Found in the IL-13 Gene Promoter

In their recent report (1), M. Wills-Karp et al. describe the critical role of interleukin-13 (IL-13) in the expression of murine asthma. This observation is substantiated by the fact that concentrations of IL-13 are elevated in tissues from the airways of asthmatic patients (2).

In their discussion, Wills-Karp et al. refer to the fact that although polymorphisms in the IL-4 gene are well recognized, the IL-13 gene has yet to be examined. The presence of polymorphisms has also been suggested by the observation of marked inter-individual variation in IL-13 production (3) and by areas of discrepancy in the sequences deposited in the GenEMBL database. We have examined the IL-13 promoter region from −1039 to +80 base pairs relative to the transcriptional start site (4) by single-strand conformation polymorphism analysis, which includes the region −940 to +48, which has previously been shown to be sufficient to confer transcription of a reporter gene (4). We analyzed this region in four smaller overlapping sections, in 129 individuals from a population in the United Kingdom comprising 96 patients with minimal-change nephropathy (which is associated with atopy, raised IgE and a T-helper 2 cytokine bias and might be predicted to show a disease association) and 33 healthy people (serving as controls). We found identical single-strand conformation polymorphism patterns in every case, indicating an absence of polymorphisms in this region. The identity of 11 of the amplified products was confirmed by biologic function in vivo and in vitro and by association in population studies for these changes to be considered as disease modifying markers (6).

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Response: In our report (1), we demonstrated that IL-13 is a critical effector molecule in the allergic airway response. Although a number of investigators have shown that IL-13 is overexpressed in the lungs of asthmatic individuals, little is known about the underlying mechanisms governing IL-13 overexpression (2). Possible mechanisms include polymorphisms in the gene itself, coordinate regulation of IL-13 gene expression by other cytokines or factors as yet undescribed, and polymorphisms in downstream receptor and signaling molecules. Several groups of investigators have shown linkage of atopic symptoms to regions of human chromosome 5q31-33, which encode genes for a number of cytokines including IL-13, IL-4, IL-3, IL-9, granulocyte-macrophage– colony-stimulating factor, IL-12B, and IL-5 (3). Several years ago, these genes were examined for sequence variants within a population of asthmatic individuals from families that had been collected and ascertained for asthma. The results of our findings, examining in detail the 5′-regions of gene structure for these seven cytokine genes, revealed significant population-based promoter polymorphisms within the cytokine genes for IL-3, IL-4, and IL-9 (4). Our examination of similar 5′-regions with putative promoter activity for all of the other cytokine genes, including IL-13, yielded no significant population-based polymorphisms (5). Our studies included heteroduplex analysis via single-stranded conformation polymorphisms followed by sequencing of variants.

Other areas within the coding or intronic regions as well as the 3′-regions of these cytokine genes remain potential candidates for identifying polymorphisms and, in fact, in a number of the genes in which no 5′- or promoter polymorphisms were identified, or other structural and intronic polymorphisms have been identified. Furthermore, variation in the expression of some of these cytokine genes may be dependent not only on promoter-based regulation, but also on message stability, coordinate activation and regulation by common transactivators such as transcription factors.

We agree with Anderson, Mathieson, and Gillespie that the IL-13 promoter as a susceptibility locus is not a likely target for genetic control, but other important targets may exist that can provide genetic variation to the expression of IL-13, including coordinate regulation from other cytokines such as IL-4 and IL-9, as well as genetic variations in downstream receptor (IL-4Ra) and signaling molecules such as Janus-activated kinase 1 and 3 (JAK1 and 3) and STAT6. The relation of molecular variants in gene structure to asthma, atopy, or any disease must be confirmed by biologic function in vivo and in vitro and by association in population studies for these changes to be considered as disease modifying markers (6).

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