Commentary

The gene encoding interleukin-13: a susceptibility locus for asthma and related traits

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Abstract

Asthma is a complex inflammatory disorder controlled by both genetic and environmental influences. Multiple genetic analyses have identified the T helper type 2 (Th2) cytokine gene cluster on chromosome 5q as a susceptibility locus for asthma. Recently, the Th2 cytokine interleukin-13 has been shown to be a critical mediator of the asthma phenotype in murine models. In this commentary we discuss several recent studies that have identified polymorphisms in the gene encoding interleukin-13. The consistent genetic associations of interleukin-13 with asthma and related traits across diverse ethnic populations in these studies provides strong support for the candidacy of this cytokine as a susceptibility locus for asthma and atopy on chromosome 5q31.

Keywords: asthma, atopy, genetics, interleukin-4 receptor, interleukin-13

Asthma is a complex inflammatory lung disease controlled by both environmental and genetic factors. Although the exact genes controlling susceptibility to asthma have not been identified, several genome-wide searches have provided evidence for the linkage of asthma or asthma-related traits (serum IgE levels, skin test reactivity, bronchial hyper-responsiveness, blood eosinophils) to loci on multiple autosomal chromosomes [1–6]. Of particular interest is the 5q31–33 region, which contains the T helper type 2 (Th2) cytokine gene cluster [interleukin (IL)-4, IL-13, IL-5 and IL-9] and has been linked to asthma or related phenotypes in many studies [2–8]. In addition to the linkage data, many human and animal studies have implicated these cytokines, either individually or in concert, in the pathophysiology of asthma. Of the Th2 cytokines in this chromosomal region, IL-4 has been extensively studied because it is known to be important in the differentiation of T cells into Th2 cytokine-producing cells. A polymorphism has been identified in the promoter of this gene (–590C/T) [9] which was initially associated with elevated serum IgE levels. This polymorphism has been associated with asthma in some studies [10,11] but not in others [12–14]. Thus attention has turned to other genes in this region. Recent studies in animal models that support the dominance of the gene encoding IL-13, which resembles IL-4, in the allergic response have spurred an extensive study of this molecule in susceptibility to asthma [15–17].

The gene encoding IL-13 is located only 25 kilobases upstream of the gene for IL-4 and in the same orientation,

AHR = airway hyper-responsiveness; IL = interleukin; IL-4R = IL-4 receptor; IL-13R = IL-13 receptor; IRS = insulin receptor substrate; NFAT = nuclear factor of activated T cells; STAT = signal transduction and transactivation; Th2 = T helper type 2.

leading to the speculation that these genes arose as a duplication event during evolution. In addition to their structural similarities they share considerable functional similarities. They are both known to have a number of actions relevant to the asthmatic diathesis such as the regulation of isotype class switching in B cells to IgE synthesis, induction of the expression of major histocompatibility complex II and CD23, the induction of adhesion molecule expression on endothelial cells (vascular cell adhesion molecule-1), chemokine production (eotaxin), the activation of mast cells and eosinophils, and the inhibition of proinflammatory gene expression (IL-1, tumor necrosis factor and IL-6). This overlap in function is due to the sharing of a receptor chain in their individual multimeric receptor complexes (for review see [18]).

The unique IL-4 receptor (IL-4R), which is expressed primarily on cells of hematopoietic origin, is made up of the common γ chain (γc) and the IL-4RA chain. The functional IL-13 receptor complex is a heterodimer composed of the IL-4RA chain and the IL-13RA1 chain. There is an additional IL-13-binding protein referred to as IL-13RA2. This receptor chain binds IL-13, but not IL-4, with very high affinity but does not seem to be important in signaling. At present it is thought to serve as a decoy receptor, because it has been found in soluble form *in vivo*. Interestingly, the receptor complex formed by IL-4RA and IL-13RA1 also serves as a receptor for IL-4 in cells lacking the γc chain.

Ligation of this complex results in tyrosine phosphorylation of several signal transduction molecules including insulin receptor substrate (IRS)-1 and IRS-2, and a member of the signal transduction and transactivation (STAT) family, STAT6. STAT6 is phosphorylated by Janus kinases (JAK1 or JAK3), followed by its dimerization and translocation to the nucleus, where it binds to specific consensus sequences found within the promoter regions of genes regulated by IL-4 and IL-13. Sharing of the IL-4RA and IL-13RA1 receptor complex explains many of the redundancies observed between these two molecules but does not explain the accumulating evidence that these two cytokines have unique actions *in vivo* [15,16,19,20]. One hypothesis is that the relative distribution of the four receptor chains might dictate the importance of each of these two cytokines on any given cell type. For example, it is known that T cells do not express the IL-13RA1 chain, thus explaining the lack of effect of IL-13 on T cell differentiation. Furthermore, the presence of the γc chain has been shown to decrease the binding of IL-13 to the receptor complex [21]. It will be of interest to determine whether the presence of the IL-13RA2 chain favors IL-13 binding over IL-4.

Recent murine studies have identified IL-13 as a critical mediator in the effector phase of the allergic airway response [15–17]. Specifically, several groups have shown that blockade of endogenous levels of IL-13 in sensitized mice by the administration of a soluble form of the IL-13RA2, which binds only IL-13, reverses airway hyperresponsiveness (AHR) and pulmonary mucous cell hyperplasia [15,17], whereas the neutralization of IL-4 does not [22]. Furthermore, when IL-13 is delivered as a recombinant cytokine to naive mice or is overexpressed in the lungs of mice they develop a phenotype very similar to that observed in human asthma (ie AHR, eosinophilic inflammation, mucous cell hyperplasia and subepithelial fibrosis) [15–17]. In contrast, IL-4 transgenic mice do not develop AHR or subepithelial fibrosis [23]. Taken together, these studies suggest that, whereas IL-4 might be essential for the initial differentiation of CD4 T cells into cells producing Th2 cytokine, once IL-13 has been produced it is capable of eliciting the entire allergic phenotype. This contention is supported by the finding that IL-13 induces allergic responses in mice lacking functional T cells [16]. Together these findings demonstrate that IL-13 is a critical mediator of the effector phase of allergic asthma in experimental models. The importance of IL-13 in human asthma is supported by numerous reports of elevated IL-13 levels in the lungs of asthmatic patients with or without atopy [24,25].

In support of the notion that IL-13 is a central mediator of asthma, several groups have recently reported associations of polymorphisms in the IL-13 gene with various features of the asthmatic phenotype [13,14,26]. First, Van der Pouw Kraan *et al* [26] described a C-to-T nucleotide exchange at position −1055 in the putative IL-13 promoter. Comparison of the genotype at −1055 in an atopic asthmatic group ($n = 101$) with that of a non-atopic control group ($n = 107$) revealed a significantly higher frequency ($P = 0.002$) of homozygous −1055 T carriers in the atopic asthmatic group in comparison with the non-atopic controls. In contrast, they found no association of this polymorphism with total or specific IgE levels or bronchial hyperresponsiveness in the patient group.

In an effort to determine the functional relevance of this polymorphism, Van der Pouw Kraan *et al* examined the association of the genotype at −1055 in IL-13 with IL-13 protein levels measured *in vitro*. They demonstrated that subjects homozygous for −1055 T had significantly different levels of IL-13 from those in the −1055 CC or CT genotypes ($P = 0.0016$ and $P = 0.0002$), respectively. As this region contains a putative binding site for nuclear factor of activated T cells (NFAT), they examined whether altered binding of nuclear proteins to this region could explain the differences in IL-13 promoter activity. They report that the C to T change at −1055 results in increased binding of nuclear proteins to this region of the IL-13 promoter. Interestingly, different NFAT proteins have been shown to regulate IL-4 and IL-13 gene expression differentially. In particular, NFAT-c is thought to be a positive regulator, whereas NFAT1 and NFAT4 might act as repressors

of Th2 cytokine production [27]. It will be of interest in the future to determine whether in fact the expression of this variant influences the relative binding of the individual NFAT proteins. If this variant does indeed lead to the overexpression of IL-13, it could be an important susceptibility locus for asthma; however, it would not explain the overexpression of the other Th2 cytokines because IL-13 is not thought to influence Th2 differentiation. Despite the evidence for association of atopic asthma with this polymorphism, it is still entirely possible that this variant might be in linkage disequilibrium with other regions of the IL-13 gene or surrounding genes on chromosome 5q.

In a screen of more than 200 atopic subjects, Heinzmann *et al* [13] identified a single variant (A4464G) in the terminal coding region of the gene for human IL-13 that results in a predicted amino acid change in residue 110 (Gln110→Arg). To test for a genetic association with clinical asthma and IgE they conducted case control studies in a British population (150 young adults with asthma and atopy, and 150 controls) and a Japanese population (100 young adults with asthma and atopy, 100 subjects with non-atopic asthma, and 100 controls). In the British subjects, Gln110 was significantly associated with asthma ($P = 0.014$), whereas Gln110 was associated with both atopic asthma ($P = 0.033$) and non-atopic asthma ($P = 0.047$) in the Japanese population. Interestingly, they did not find an association between this genotype and serum IgE levels in either population (British, $P = 0.10$; Japanese, $P = 0.508$). These results suggest that Gln110 is associated with asthma rather than atopy; however, the inclusion of an atopic, non-asthmatic group in the analysis might be needed to clarify this issue. In a follow-up population-based survey of genotype frequency in Japanese schoolchildren aged 12–13 years ($n = 290$) they found a significantly higher frequency of Gln110 in asthmatic children than in non-asthmatic children. When they examined the association between serum IL-13 levels and Gln110 they found that children homozygous for Gln110 had significantly higher levels of IL-13 than did those homozygous for Arg110. To begin to understand the biological activity of the Gln110 variant of IL-13, they conducted computer-modeling studies based on the assumed homology between the IL-4 and IL-13 proteins.

The results of the modeling studies suggest that the Arg130→Gln variant occurs (resides) in a site crucial for ligand–receptor interactions. Thus Heinzmann *et al* hypothesize that the expression of this variant might result in a protein with enhanced binding affinity for its receptor. However, so far they have no direct evidence for this hypothesis. If their assumption is correct, enhanced activity of IL-13 at its receptor could theoretically account for many of the features of the allergic phenotype (IgE, AHR, hypersecretion of mucus, eosinophilic inflammation). It is also possible that this polymorphism could alter the stability of the IL-13 message or the metabolism of the IL-13 proteins because it was associated with higher protein levels in the serum.

In a detailed analysis of the gene encoding IL-13, Graves *et al* [14] identified seven polymorphisms in the human gene for IL-13 in a screen of 30 unselected volunteers. They report two promoter polymorphisms (–1512 and –1112), one of which is the same (–1112) as that described by van der Pouw Kraan *et al*. In addition, they found five other variants in the IL-13 gene, one in the third intron (+1923) and three in the 3′ untranslated region (+2525, +2580 and +2749). They also identified the variant described by Heinzmann *et al*, which they refer to as Arg130→Gln. In an initial genotyping experiment of 286 white children enrolled in a longitudinal study of asthma and allergy in Tucson, Arizona, they found that all of the polymorphisms in the gene encoding IL-13 were in tight linkage disequilibrium with Arg130→Gln. In a subsequent study they assessed the relationship between total serum IgE and Arg130→Gln and the two polymorphisms in the IL-13 promoter (–1112 and –1512) in three separate study populations of children (Tucson, $P = 0.0023$; Leipzig, $P = 0.0081$; Munich, $P = 0.0069$); when all subjects were considered, they found stronger associations in subjects with a negative skin test.

These findings were in contrast with the study by Heinzmann *et al*, in which association of Gln110→Arg was found with total serum IgE levels in either of the populations studied. The reason for the discrepancy between these studies is not entirely clear, but Heinzmann *et al* did not examine skin test reactivity as a variable in their analysis. These results also differ from those of the Dutch group in that they reported no association of the –1055T polymorphism with IgE levels, although their patient population was selected as an atopic asthmatic group. Furthermore, Graves *et al* [14] studied children, whereas the other two studies were conducted with adults. Because IgE levels change with age, this might have weakened the ability to detect associations with IgE levels. The fact that Graves *et al* found significant linkage disequilibrium between the independent polymorphisms in the gene encoding IL-13, including those examined in the studies by both van der Pouw Kraan *et al* and Heinzmann *et al*, suggests that it will be problematic to discern which, if any, of the polymorphisms described so far contribute to asthma and related traits. Interestingly, one consistent finding in the above studies was the lack of association of asthma [13] or total serum IgE [14] with the previously identified IL-4 polymorphism (–590C/T). Furthermore, both studies reported that there was no linkage disequilibrium between the –589 polymorphism in IL-4 and polymorphisms in the gene for IL-13 [13,14]. A possible explanation for the previous reports of associations of the IL-4 promoter polymorphisms with IgE is that IL-4 –589 is simply a marker for the

polymorphisms in the gene encoding IL-13 or another enhancer element.

Polymorphisms in the genes for both IL-4RA and IL-13RA1 have been identified [13,28–31]. In fact, the gene encoding IL-4RA is located on chromosome 16p12, a region that has been linked to atopy and asthma in several populations [29,30]. It was originally reported that a polymorphism at position Q576R of the gene for IL-4RA resulted in enhanced activity of the receptor [28]; however, more recent studies suggest that the altered receptor activity in cells from asthmatics might be due to either a different polymorphism or a combination of polymorphisms within the gene [30–32]. Defects in the gene encoding IL-4RA that result in an enhanced capacity to signal could have a major effect on the immune response as this receptor is necessary for the signaling of both IL-4 and IL-13. Specifically, enhanced activity of this receptor could mediate both the IL-4-dependent differentiation of Th2 cells and the IL-13-dependent processes mediating the effector phase of the response.

In contrast with IL-4RA, little is known about the role of IL-13RA1, on chromosome Xq13, in susceptibility to atopy and asthma. Heinzmann *et al* [13] have identified three single-nucleotide polymorphisms in the IL-13RA1. An analysis of the most common single-nucleotide polymorphism, A1398G, showed a marginal association with high IgE levels ($P = 0.021$) but not with asthma in the British population described above. In contrast, no association was seen with either high IgE levels or asthma in the Japanese population. Because males are hemizygous at IL-13RA1, the authors calculated adjusted odds ratios by sex in the British population. The odds ratio for males was 3.39 ($P = 0.015$) and 1.10 in females ($P = 0.680$) for atopy. Of particular interest is the demonstration that both the IL-13RA1 chains are expressed on airway epithelial cells and bronchial smooth muscle cells, suggesting that these cytokines might have direct actions within the airways [13]. A determination of the importance of this variant in asthma pathogenesis awaits additional studies. The IL-13RA2 chain is also located on the X chromosome; however, to my knowledge no polymorphisms in this gene have been identified. One might envision that polymorphisms in both the gene encoding IL-13 itself and its two receptor chains (IL-4RA, IL-13RA1) could affect the severity of the disease.

In summary, the consistent genetic associations of IL-13 with asthma and related traits across diverse ethnic populations provides strong support for the candidacy of IL-13 as a major locus for asthma and atopy on chromosome 5q31. Importantly, these associations seem to be independent of polymorphisms in the neighboring similar gene, that encoding IL-4. However, owing to the significant level of linkage disequilibrium between the polymorphic sites in this gene, the contribution of surrounding genes on chromosome 5q (CD14 [33] or CNS-1[34]), or other as yet unidentified polymorphisms within the gene for IL-13, cannot be ruled out. Because asthma is a complex polygenic disease, it still remains to be determined whether expression of the various IL-13 variants alone contributes significantly to susceptibility to asthma or whether interactions with other genes (those encoding IL-4RA or IL-13RA1) are required to alter function significantly. Taken together with the accumulating biological evidence of the importance of IL-13 in the pathogenesis of asthma, these results support the contention that IL-13 might be involved in promoting bronchial asthma in humans. The identification of variants of IL-13 signaling in the development of asthma and atopy in humans provides a focus for the development of novel diagnostic and therapeutic strategies for asthma. It is certain that these intriguing findings will fuel continued studies into the specific pathways controlling susceptibility to asthma in the foreseeable future.

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