

## Review Article

## Genetic and environmental factors of atopy

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## ABSTRACT

Atopy is a common immune disorder characterized by raised IgE levels, which lead to clinical disorders (i.e. primarily bronchial asthma, atopic dermatitis and allergic rhinoconjunctivitis). Interleukin (IL)-4 and IL-13, derived from T-helper cell type 2 (Th2) subsets, are central in mediating IgE production and development of immediate hypersensitivity. Atopy is also characterized by Th1/Th2 skewing that derives from genetic and environmental factors. The prevalence of atopy has increased in recent decades, especially in developed countries among children and young adults. In the present review, we first discuss the relationship between the Th1/Th2 imbalance and the recent rise of allergy. Second, we present evidence that human genetic variation is also a key factor responsible for atopy.

**Key words:** allergy, asthma, atopy, FcεRIβ, interleukin-4, interleukin-13, Th1/Th2 imbalance.

## INTRODUCTION

Allergy is a multifactorial disease and there has been little discussion regarding the mechanisms by which identified genetic mutations interact with each other. Atopic diseases were rare a few decades ago but, today, constitute an increasingly severe public health problem.<sup>1</sup> The prevalence of atopic diseases in developed countries is estimated to exceed 30%.<sup>2</sup> The genes that cause atopic diseases must reside in the common human gene repertoire; several environmental factors could cause the

overexpression of some constitutive genes, which would then lead to the development of atopic diseases.<sup>2</sup>

In the present review, we first discuss the reason why the incidence of atopic diseases has increased recently. Second, we introduce the present situation of genetic analysis of atopy and asthma.

## REDUCED FREQUENCY OF BACTERIAL AND VIRAL INFECTIONS

Viral infections generally induce a strong cell-mediated immune response; an immune response that is mainly driven by T helper 1 (Th1) cells and interferon (IFN)-γ. Intracellular bacteria, such as mycobacteria, have the same ability: therefore, it has been assumed that early infections with, in particular, *Mycobacterium tuberculosis* could protect against the development of allergic diseases in later life.<sup>1</sup> Our study<sup>3</sup> supports this assumption. From a population of approximately 1000 12–13-year-old schoolchildren attending the 18 junior high schools in Wakayama Prefecture, Southern Honshu, Japan, in 1995, we studied 867 children by complete retrospective examination of the records of their tuberculin responses.<sup>3</sup> The children responded to a questionnaire documenting atopic symptoms and social and environmental variables and we measured IgE serum levels, as well as Th1 and Th2 cytokine profiles.<sup>4</sup> These data were analyzed in relation to the record of tuberculin responses.<sup>3</sup> A strong inverse association was found between positive tuberculin responses at both 6 and 12 years of age and a range of atopic characteristics, including allergic symptoms at any age and IgE levels, and Th2 cytokine profiles assayed at 12 years of age (Tables 1,2).<sup>3</sup> Asthmatic symptoms were one-half to one-third as likely in positive tuberculin responders as in negative responders (Table 2).<sup>3</sup> Moreover, remission of atopic symptoms between 7 and 12 years of age was six- to ninefold as likely as in positive tuberculin responders. Serum IgE levels, both total and allergen specific, were also lower

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Accepted for publication 10 June 2002.

**Table 1** History of infectious diseases, atopic symptoms, IgE levels and cytokine profiles in subjects grouped according to tuberculin reactivity

Measurement	Group 1 (n = 290)	Group 2 (n = 289)	Group 3 (n = 213)	Group 4 (n = 75)	Total (n = 867)
Tuberculin response					
At 6 years of age	–	–	+	+	
At 12 years of age	–	+	+	–	
Positive antiviral immunity (%)					
Measles (history + vaccine)	83.4	87.2	84.5	81.3	84.3
Chicken pox (history + vaccine)	86.9	82.3	82.2	82.7	83.9
Mumps (history + vaccine)	62.8	60.9	60.1	57.3	61.0
No. subjects with IgE to <i>Ascaris</i>	2	2	2	1	7
Symptoms (%)					
Atopy (past + present)	46.8	33.9 <sup>##</sup>	25.8 <sup>##</sup>	38.7	36.6
Atopy (present)	32.1	7.9 <sup>###</sup>	9.8 <sup>###</sup>	30.7	18.5
Asthma (past + present)	13.4	4.1 <sup>##</sup>	3.7 <sup>##</sup>	6.8	7.4
Rhinitis (past + present)	16.2	4.8 <sup>##</sup>	8.6 <sup>†</sup>	14.6	10.4
Eczema (past + present)	22.7	12.8 <sup>##</sup>	12.2 <sup>##</sup>	16.0	16.2
Geometric mean IgE (IU/mL)	208	149 <sup>**</sup>	98 <sup>***</sup>	178	154
Positive ASE (%)	55.8	43.9 <sup>##</sup>	41.8 <sup>##</sup>	53.3	48.2
Atopic (high IgE or positive ASE; %)	65.5	54.0 <sup>##</sup>	49.2 <sup>##</sup>	61.3	57.3
Median cytokine level (pg/mL)					
IL-4	1.88	0.96 <sup>†</sup>	0.92 <sup>†</sup>	1.66	1.22 (10.2–UD)
IL-13	18.3	10.2 <sup>###</sup>	7.8 <sup>###</sup>	19.1	14.2 (45.6–UD)
IL-10	5.9	3.1 <sup>##</sup>	2.9 <sup>##</sup>	5.9	3.9 (10.2–UD)
IL-12	UD	UD	UD	UD	UD
IFN $\gamma$	7.8	11.0 <sup>##</sup>	13.2 <sup>##</sup>	6.4	10.5 (23.2–UD)
Positive family history within three generations (%)	54.1	49.8	49.8	48.0	51.0
Mean BMI (kg/m <sup>2</sup> )	21.1	22.0	21.9	21.2	21.6

Data in parentheses show the maximum–minimum values.

<sup>\*\*</sup>*P* < 0.01, <sup>\*\*\*</sup>*P* < 0.001 compared with group 1 (Student's *t*-test); <sup>†</sup>*P* < 0.05, <sup>##</sup>*P* < 0.01, <sup>###</sup>*P* < 0.001 compared with group 1 (median test); <sup>†</sup>*P* < 0.05, <sup>##</sup>*P* < 0.01, <sup>###</sup>*P* < 0.001 compared with group 1 ( $\chi^2$ -test).

ASE, allergen-specific IgE; IL, interleukin; IFN, interferon; BMI, body mass index; UD, undetectable.

**Table 2** Odds ratios for atopy and for the occurrence and remission of atopic symptoms in positive compared with negative tuberculin responders according to age

Tuberculin response	Atopy	Odds ratio	
		Occurrence	Remission
Conversion to positive up to 6 years of age	0.50 (0.29–0.83)*	Asthma: 0.31 (0.22–0.45)* Eczema: 0.50 (0.33–0.91)*	Asthma: 8.2 (6.0–9.8)** Eczema: 1.6 (1.0–2.2)*
Conversion to positive between 6 and 12 years of age	0.43 (0.25–0.83)**	Asthma: 0.42 (0.24–0.56)*	Asthma: 6.0 (2.8–10.3)*** Eczema: 6.7 (4.8–11.4)*** Rhinitis: 9.0 (6.2–14.2)***

Multiple logistic analysis was conducted with the SPSSX package, version 2.2 (SPSS Inc., Chicago, IL, USA).

In all models, allowance was made for dichotomized variables, including sex, lifestyle, nutritional status, environmental factors and family history. Only significant values are shown (<sup>\*</sup>*P* < 0.05, <sup>\*\*</sup>*P* < 0.01, <sup>\*\*\*</sup>*P* < 0.005 compared with negative conversion of tuberculin response). Figures in parentheses are the 95% confidence intervals.

in positive tuberculin responders.<sup>3</sup> A plot of the logarithm of total serum IgE against the diameter of tuberculin response showed an inverse linear relationship, with  $r = -0.492$ .<sup>3</sup> A strong inverse association between delayed hypersensitivity to *M. tuberculosis* and atopy was observed;<sup>3</sup> positive tuberculin responses predicted a lower incidence of asthma, lower serum IgE levels and cytokine profiles biased towards the Th1 type.<sup>3</sup> It is suggested that exposure and response to *M. tuberculosis* may, by modification of immune profiles, inhibit atopic disorders.<sup>3</sup>

In addition to *M. tuberculosis*, an inverse relationship between the prevalence of atopy and a single virus, such as the hepatitis A virus, has been observed.<sup>5</sup> Because infection with the hepatitis A virus is a strong marker of poor hygiene,<sup>6</sup> the association between poor hygiene and protection against atopy is clear.<sup>7</sup>

Although we found no relationship between a history of measles infection and atopy in our study, epidemiological data from Guinea-Bissau show that a history of childhood measles infection around the time of an epidemic was associated with a one-half reduction in the rate of positive atopic skin tests.<sup>8</sup> It is likely that a set of specific infections that strongly promote Th1 immunity have the potential to inhibit atopic disorders by repression of Th2 immunity.<sup>3</sup>

## THE TH1/TH2 IMBALANCE

Atopic allergy is characteristically associated with an imbalance between various types of T cells and, consequently, an increased synthesis of IgE.<sup>1</sup> Early studies revealed a T cell imbalance that was found to be present in all the important types of childhood atopic diseases, such as bronchial asthma, hay fever and atopic dermatitis.<sup>9</sup> In 1986, Mosmann *et al.* reported that most cloned lines of murine CD4<sup>+</sup> T cells could be classified into two groups, Th1 and Th2, based on the cytokines they produced and their related functional activities.<sup>10</sup> The Th1 cells are now defined by their production of interleukin (IL)-2 and IFN- $\gamma$  and the Th2 cells are defined by their production of IL-4, IL-5, IL-6, IL-10 and IL-13; both cell types produce IL-3, tumor necrosis factor (TNF)- $\alpha$  and granulocyte-macrophage colony stimulating factor (GM-CSF).<sup>2</sup> Atopic diseases are characterized by an imbalance between these cytokines, so that type 2 cytokines are provided in abnormally high concentrations relative to the type 1 cytokines.<sup>1</sup> The Th2 cells also induce the local influx of eosinophils, which release toxic

products that contribute to tissue damage.<sup>11</sup> In addition, the Th2 cell releases key cytokines, particularly IL-4, which are essential for the maturation of CD4<sup>+</sup> naive T cells towards Th2 cells and the production of IgE,<sup>12,13</sup> and IL-5, which regulates activation and tissue recruitment of eosinophils.<sup>14</sup> This is known as the 'Th2 hypothesis in allergy'.<sup>11</sup> Among the factors that control the differentiation of T lymphocytes, IFN- $\gamma$  plays pivotal roles in promoting the differentiation of CD4<sup>+</sup> naive T lymphocytes towards Th1 effector cells.<sup>15</sup> The Th1 and Th2 subsets are subject to cross-regulation, such that Th2 development is inhibited by IFN- $\gamma$ , whereas Th1 development is inhibited by IL-4.<sup>15</sup> An imbalance between IL-4 and IFN- $\gamma$  may lead to an abnormally high production of IgE and of the various mediators that give rise to allergic symptoms.<sup>1</sup> The reliable predictive marker for atopic disease known today is perhaps a decreased ability of cord-blood lymphocytes to produce IFN- $\gamma$ .<sup>1</sup> A reduced ability to produce IFN- $\gamma$  in the neonatal period has been shown to be closely correlated with an increased tendency to develop allergic sensitization and atopic diseases in later life.<sup>16-18</sup>

## DOMINANT EFFECT OF THE ILE50VAL VARIANT OF THE HUMAN IL4 RECEPTOR $\alpha$ -CHAIN IN IGE SYNTHESIS

Interleukin-4 is a pleiotropic cytokine that plays a crucial role in IgE-dependent atopic disorders;<sup>19</sup> it is central to B cells switching to IgE antibody production. Human IL-4 operates through the IL-4 receptor (IL-4R) and, thereby, activation of STAT6 (signal transducer and activator of transcription 6).<sup>20</sup> An Ile50Val (numbering for mature peptide) variant that is the extracellular variant of human IL-4R<sup>21</sup> has been identified.<sup>22,23</sup> To test whether the Ile50Val variant promotes dysregulation of IgE synthesis, we first conducted a genetic association study for serum IgE levels in a Japanese population.<sup>24</sup> There was a significant difference in Ile/Val 50 genotype frequencies between control and atopic subjects; Ile50 was associated with atopic asthma, but not with non-atopic asthma; Ile50 was specifically and significantly associated with raised total serum IgE levels and mite-specific IgE.<sup>24</sup> The association with atopy was especially strong in children.<sup>24</sup> The high frequency of Ile50 homozygotes (approximately 60%) in the childhood atopic asthma group described here and the significant skewing from Hardy-Weinberg equilibrium ( $P < 0.0001$ ) suggest a largely recessive genetic effect for Ile50 on atopy.<sup>24</sup>

Second, we investigated the relative activation of the transcription factor STAT6.<sup>24</sup> The Ile50 variant augmented STAT6 activation 1.8-fold compared with the Val50 variant in both mouse (BF-GETP) and human (J-GETP) B cell lines.<sup>24</sup> Therefore, these data from both the mouse and human cell lines strongly suggest that the Ile50 variant of IL-4R significantly upregulates receptor response to IL-4, with a resultant increase in the activation of STAT6 and, hence, increased cell proliferation and increased IgE production.<sup>24</sup> In contrast, another variant of human IL-4R $\alpha$  carrying arginine (Arg) at 551 (numbering from the start of the mature protein) instead of glutamine (Gln) has also been identified and shown to be correlated with hyper-IgE syndrome and severe atopic eczema and to cause upregulation of CD23 expression and dissociation with the tyrosine phosphatase SHP-1.<sup>25</sup> Based on these studies, two possibilities arise. One is that these two substitutions act independently to cause atopy. In this case, an individual bearing both variants would belong to a higher-risk group than an individual who carries each single variant. The other possibility is that these two polymorphisms are in linkage disequilibrium. In this case, either of these variants simply represents a marker of the other variant. It is important to address this point in order to estimate the quantity of risk of contracting atopic asthma.<sup>26</sup> We analyzed responsiveness to IL-4 of transfectants with four kinds of IL-4R $\alpha$  carrying either Val or Ile at 50 and either Gln or Arg at 551.<sup>26</sup> The substitution of Ile for Val augmented STAT6 activation, proliferation and transcription activity of the I $\epsilon$  promoter by IL-4, whereas substitution of Arg for Gln did not change these IL-4 signals. Arg<sup>551</sup> was not associated with atopic asthma in the Japanese population.<sup>26</sup> Taken together, substitution of Arg<sup>551</sup> does not enhance the IL-4 signal for generation of germline transcript, whereas the substitution of Ile50 contributes to enhancement of IgE synthesis.<sup>26</sup>

### GENETIC VARIANTS OF IL-13 SIGNALING AND ASTHMA AND ATOPY

Atopy is a key predisposition to bronchial asthma between the ages of 3 and 20 years.<sup>12,27</sup> Bronchial hyper-responsiveness (BHR), an exaggerated bronchospastic response to specific and non-specific substances, represents a physiological hallmark of asthma induced by Th2 cytokines such as IL-4, -5, -9, -10 and -13.<sup>12,27</sup> Recent animal model data suggest that IL-13 is a central cytokine in promoting asthma, through the stimulation of

bronchial epithelial mucus secretion and smooth muscle hyper-reactivity.<sup>28</sup> Interleukin-13 is a 12 kDa protein product and shares several biological profiles with IL-4,<sup>12,27</sup> including IgE production, CD23 and major histocompatibility complex (MHC) class II expression, inhibition of antibody dependent cell-mediated cytotoxicity with downregulation of IgG type I receptor (Fc $\gamma$ RI), and suppression of type I IFN. Although IL-4 and IL-13 possess many similar biological activities,<sup>12,27</sup> IL-13 shows some unique activities. Unlike IL-4-deficient mice, IL-13-null mice fail to generate goblet cells, responsible for mucus overproduction in asthma, fail to recover basic IgE levels after stimulation with IL-4 and fail to expel helminths.<sup>29</sup> Interleukin-13 operates through IL-13R, a heterodimer of IL-4R $\alpha$  and IL-13R $\alpha$ 1 chains.<sup>12,13,27</sup> Interleukin-13 is crucial for allergen-induced BHR in experimental animals and may be relevant to human asthma.<sup>30,31</sup> Significantly higher IL-13 levels have been found in asthmatic patients with and without atopy.<sup>32,33</sup> A novel variant of human IL-13, Gln110Arg, on chromosome 5q31 was found to be associated with asthma rather than IgE levels in case-control populations from Britain and Japan (peak odds ratio (OR) = 2.31, 95% confidence interval (CI) 1.33–4.00); the variant also predicted asthma and higher serum IL-13 levels in a general Japanese pediatric population.<sup>28</sup> Immunohistochemistry demonstrated that both subunits of IL-13R are prominently expressed in bronchial epithelium and smooth muscle from asthmatic subjects.<sup>28</sup> Detailed molecular modeling analyses indicate that residue 110 of IL-13, the site of the charge-modifying variants Arg and Gln, is important in the internal constitution of the ligand and crucial in ligand–receptor interaction.<sup>28</sup> A non-coding variant of IL-13R $\alpha$ 1, namely A1398G, on chromosome Xq13 was found to be associated primarily with high IgE levels (OR = 3.38 in males, 1.10 in females) rather than asthma.<sup>28</sup> Thus, certain variants of IL-13 signaling are likely to be important promoters of human asthma.

### CHROMOSOME 11q13, Fc $\epsilon$ RI $\beta$ AND ATOPIC ASTHMA

The first genetic region reported to show linkage to atopy was chromosome 11q13.<sup>34,35</sup> The evidence for genetic linkage was confounded by the existence of a maternal pattern of inheritance.<sup>35,36</sup> A significant portion of atopic asthmatic families in Caucasian and Japanese populations may be linked to chromosome 11q13

through the maternal line.<sup>35,36</sup> The  $\beta$ -subunit of the high-affinity IgE receptor (Fc $\epsilon$ RI $\beta$ ) gene has been mapped to chromosome 11q13.1<sup>37-41</sup> and is a candidate gene for atopy because of its important role in initiating a type I allergic reaction by mast cells and basophils.<sup>42</sup> A recent large-scale population-based linkage study by sib-pair methodology in an Australian population affirms linkage of asthma with microsatellite repeats of Fc $\epsilon$ RI $\beta$ , but not with other markers on 11q13.<sup>43</sup>

The *Fc $\epsilon$ RI $\beta$*  gene is composed of seven exons and six introns, spanning approximately 11 kb.<sup>44</sup> Eight variants of this gene have been identified, including three coding and five non-coding variants; three coding polymorphisms within the *FCERB1* are Ile181Leu, Val183Leu<sup>45-47</sup> and Glu237Gly.<sup>48,49</sup> A strong association was seen between the 181Leu allele and measures of atopy in a small random sample of 13 subjects.<sup>50</sup> Similarly, in a set of unrelated nuclear families with allergic asthmatic probands, strong association with atopy was found with a maternal pattern of inheritance.<sup>50</sup> The 181Leu/183Leu allele was found at high frequency (72%) in Kuwaiti Arabs and was associated with asthma.<sup>51</sup> In a study of South African blacks and whites, 181Leu was detected at a high frequency<sup>52</sup> and an association of 181Leu in white South African asthmatics was seen.<sup>50</sup>

A third coding polymorphism in the *FCERB1* gene, called Glu237Gly, has been found at a low frequency (5%) in a number of populations.<sup>48,49</sup> In Caucasians, significant associations between 237Gly with BHR and skin test responses to grass and house dust-mite allergies have been reported.<sup>48</sup> The 237Gly allele occurs at a high frequency in Japanese asthmatics (20%)<sup>49</sup> and is associated with atopic asthma, in particular, childhood asthma, as well as with high total serum IgE levels.<sup>50</sup>

Two additional polymorphisms that alter the amino acid sequence of the protein have also been identified within these genes (*RsaI*\_in2<sup>53</sup> and *RsaI*\_ex7<sup>54</sup>). They have shown strong associations with atopic eczema and asthma in a study of families recruited through a child affected with eczema.<sup>55,56</sup> Therefore, a number of studies implicate the *FCERB1* gene as having an influence on the pathogenesis of allergic disease.<sup>50</sup>

The second locus for asthma on 11q13.1 is close to D11S480/D11S1883, approximately 5 cM telomeric to Fc $\epsilon$ RI $\beta$ .<sup>50</sup> Strong linkage with clinical symptoms (e.g. asthma) at D11S480 in 40 British asthmatic families has been found (M Dubowitz *et al.*, unpubl. data, 1995).<sup>50</sup> Recently, a strong genetic association was found between childhood asthma and *CC16*,<sup>57</sup> 1 cM centromeric to

D11S480 on 11q13.1. The gene for Clara cell secretory protein, *CC16*, is a plausible candidate because of its involvement in the control of airway inflammation.<sup>50</sup> Protein studies have revealed significant differences in levels of *CC16* between asthmatics and healthy controls.<sup>50</sup> Another candidate is *CHRM1*,<sup>58</sup> a muscarinic receptor on airways; however, no association was found in our population.<sup>42</sup> A third atopic asthma locus on 11q13.1 has been reported telomeric to *FGF3*, more than 10–12 cM away from Fc $\epsilon$ RI $\beta$ . Genetic linkage or association for atopic asthma has been found on 11q13.1 with other markers, including *FGF3*,<sup>59</sup> D11S534<sup>60</sup> or D11S97,<sup>61</sup> in relation to total serum IgE levels, or D11S527<sup>60</sup> in relation to asthma or BHR.

## CONCLUDING REMARKS

We have provided evidence that human genetic variation and exposure to certain infections in early childhood are key influences of allergy. The overall picture emerging from the genetic and functional analyses provides increasing evidence that there are major loci for asthma and atopy in relation to signaling of IL-4 and IL-13 through IL-4R $\alpha$ –STAT6. Interleukin-4R $\alpha$  and STAT6 are essential for the action of both cytokines and for the development of asthma and atopy. These findings are of immediate importance in the planning of new drug therapies (personalized medicine) in atopic disorders.

It is clear that the recent rapid rise in atopic disorders has been in certain environments, where exposure to infection has fallen swiftly due to improved hygiene. In a large population of Japanese children from Wakayama, exposure to the tuberculosis microorganism in early life very strongly predicts less asthma and atopy in later childhood. It was proposed that such infections in early life program the immune system in a way that is antagonistic to the development of atopic disorders. There is some evidence from other researchers that confirms that tuberculosis organisms may prevent experimental allergy in mice. These findings lay the foundation for developing vaccines that mimic the exposure to tuberculosis and that need to be trialled for preventing asthma and atopy. There is an urgent need for a more fundamental understanding of the origins of allergy in order to plan more effective treatment and prevention.

Allergy is multifactorial disease affected by interacting genetic and environmental factors. However, it remains unknown how environmental and relevant variants interact. Thus, it is necessary to develop a model to analyze

the relationships between the complicated genetics and to develop a 'model' to clarify the effects of environmental factors.

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