

IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma

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Background: IgE production, a hallmark of asthma and atopic disease, may be under genetic control. Genes of the IL-4 and IL-13 pathway, central for IgE regulation, have so far only been assessed in studies of single gene effects.

Objective: Here we analyzed combined extended haplotypes involving *IL-4*, *IL-13*, their shared receptor chain *IL-4Rα*, and the intracellular signal transducer and activator of transcription, *STAT6*, to assess the combined effect of single nucleotide polymorphisms in this important immunological signaling pathway.

Methods: We genotyped a large cross-sectional population of 1120 children age 9 to 11 years for 18 polymorphisms in the respective genes of the IL-4/IL-13 pathway. One polymorphism per gene was selected because of its putative functional role, and extended haplotypes were built in a stepwise procedure where gene-by-gene interactions were assessed by using a Cordell model.

Results: Combining polymorphisms in all 4 major pathway genes in a stepwise procedure, the risk for high serum IgE levels increased 10.8-fold ($P = .02$) and the risk for the development of asthma increased by a factor of 16.8-fold ($P = .005$) compared with the maximum effect of any single polymorphism. Significant interactions in a model with additive and dominant effects, for both pair and triplet combinations for asthma (lowest $P = .005$), and for pairs of polymorphisms in IgE regulation were observed (lowest $P = .054$).

Conclusion: These data indicate that only the combined analyses of genetic alterations in the IL-4/IL-13 pathway reveal its actual significance to the development of atopy and childhood asthma. (J Allergy Clin Immunol 2006;117:269-74.)

Key words: Asthma, IgE, IL-4, IL-13, pathway, polymorphism

Abbreviations used

IL-4Rα: IL-4 receptor α
IL-13Rα: IL-13 receptor α
ISAAC: International Study of Asthma and Atopy in Childhood
OR: Odds ratio
SNP: Single nucleotide polymorphism
STAT: Signal transducer and activator of transcription

The switching of immunoglobulin production from immunoglobulin class M to E in activated B lymphocytes, which is largely influenced by the activation of the IL-4/IL-13 cytokine pathway, is the key biological feature common to helminth infection and atopic diseases.¹ Both IL-4 and IL-13 signal through a common pathway.² On the surface of T cells, binding of IL-4 and IL-13 is facilitated through a heterodimeric receptor composed of the IL-4 receptor α (IL-4Rα) chain and either the common γ chain (for binding IL-4 and IL-13) or the IL-13 receptor α (IL-13Rα) chain (for exclusive IL-13 binding). Hence, intracellular signaling is initiated through the Janus tyrosine kinase mediated phosphorylation of signal transducer and activator of transcription (STAT) 6. Once phosphorylated, STAT6 molecules form homodimers, which in turn penetrate the nucleus, activating the transcription of target genes inducing IgE switching (Fig 1). In addition to IgE switching, IL-4 and IL-13 are involved in several immunoregulatory and proinflammatory activations inducing, enhancing, and controlling features of atopic inflammation and asthma, as reviewed by Corry and Kheradmand.³

By systematic screening approaches, 7 single nucleotide polymorphisms (SNPs) in the *IL-13* gene, 16 SNPs in *IL-4*, approximately 15 SNPs in *IL-4Rα*, and 13 SNPs in the *STAT6* gene have been identified.⁴⁻⁸ Because single gene studies showed inconsistent effects of SNPs on asthma and atopy outcomes,⁴⁻¹¹ it was hypothesized that the presence of a single SNP in only 1 of the genes involved in the IL-4/IL-13 pathway may not be sufficient to result in profound changes in IgE regulation or asthma susceptibility. Moreover, gene by gene interaction, also called *epistasis*, may modify the effects of SNPs in the IL-4/IL-13 signaling pathway. The nature of these interactions has not been studied in detail for asthma and atopy

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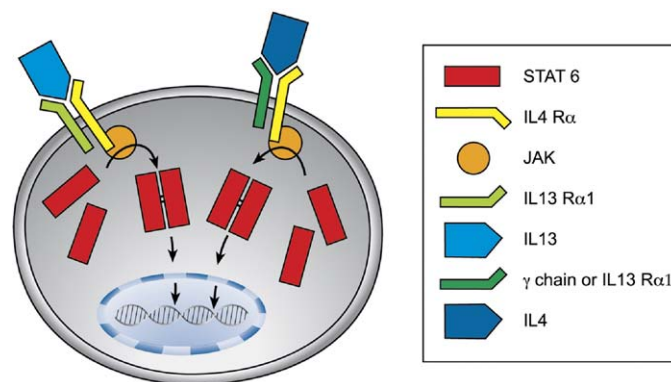


FIG 1. Schematic depiction of the IL-4/IL-13 pathway. Activation of receptors containing *IL-4R α* by *IL-4* or *IL-13* led to the phosphorylation (by Janus kinases [JAK]) and transduction of *STAT6* into the nucleus, inducing IgE production via target genes.

so far. Therefore, the effects of gene-by-gene interactions between the 4 major molecules of the IL-4/IL-13 pathway were studied by using an extended haplotype analysis in a population of 1120 German children from the cross-sectional International Study of Asthma and Atopy in Childhood (ISAAC) II.

METHODS

Between 1995 and 1996, cross-sectional studies were conducted in Munich (ISAAC II), southern Germany, and Leipzig, eastern Germany, to assess the prevalence of asthma and allergies in school children age 9 to 11 years.¹² For the purpose of this genetic analysis, only children of German origin who had both DNA and IgE data available were included (total, $n = 1120$; Munich, $n = 528$; Leipzig, $n = 592$). Informed written consent was obtained from all parents, and all study methods were approved by the ethics committee of the University of Leipzig and the Bavarian medical council. No significant differences between study populations from both cities were found with respect to population characteristics⁵ and genotype frequencies. Because the study population and the study methods have been described in detail before,^{4,5,13,14} only methods pertaining to this analysis are given here.

Standardized parental questionnaires for self-completion according to the ISAAC guidelines were sent through the schools to the families. Children whose parents reported a doctor's diagnosis of asthma or recurrent spastic or recurrent asthmatic bronchitis were classified as having asthma. Children underwent skin prick testing for 6 common aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria tenuis*, cat dander, and mixed grass and tree pollen) using highly standardized extracts and lancets (ALK, Hørsholm, Denmark). Serum IgE was measured by using the Insulite system (DPC Biemann, Bad Nauheim, Germany). On the basis of all available German study subjects at the age of 9 to 11 years with existing IgE measurements in our data set ($N = 3063$), IgE percentiles were calculated. For this haplotype analysis, the 90th percentile (457 IU/mL) for total serum IgE was used as an outcome variable correlating with highly elevated serum IgE levels.

Genotyping of 18 polymorphisms in the respective genes was performed as previously described^{4,5} using allele-specific PCR, restriction enzyme-based assays, solid phase oligonucleotide ligation assay (Variom Biotech Inc, Berlin, Germany), and the MASSARRAY system (Sequenom, San Diego, Calif). All genotyping details including primers and assay conditions are given in the

respective references^{4,5,13,14} in Table I and are also available in Table E1 (see the Online Repository of this article at www.jacionline.org).

Haplotype frequencies were estimated by using the expectation-maximization algorithm.¹⁵ To evaluate associations with traits, haplotype trend regressions were estimated, where the estimated probabilities of the haplotypes are modeled in a logistic regression as independent variables.^{16,17} In addition to the haplotype analyses, the Cordell model for epistasis was used to test for statistically significant interactions in models with both additive and dominant effects and respective interaction terms.¹⁸ Epistasis, the interaction between genes, is tested by using a global test for interaction of the model with interaction terms versus the null model without interaction terms. This method identifies combinations of genes showing interaction, but does not identify individual haplotypes causing the interaction. Because the power for tests of interaction is poor in comparison with tests for main effects (genotypes), a significance level of .10 was used for the global test of interaction. All statistical analyses were performed by using the SAS statistical software package (version 8.2; SAS Institute GmbH, Heidelberg, Germany), whereas the haplotype analyses were implemented by using the SAS/Genetics module.¹⁷

RESULTS

For the analysis presented here, only common polymorphisms leading to functionally relevant alterations in the respective genes *IL-4*, *IL-13*, *IL-4R α* , and *STAT6* were selected from a total of 18 SNPs initially genotyped in all subjects. SNP C-589T in the proximal promoter region of *IL-4* was chosen for this analysis, because it alters the binding of a transcription factor.¹⁹ For *IL-13*, the promoter polymorphism C-1112T was selected, because it changes binding of STAT transcription factors and influences the expression of IL-13 in T cells.⁴ In the *IL-4R α* gene, SNP A148G was included in the analyses, because it alters an amino acid in the extracellular part of the receptor (I50V), which leads to an increased downstream activation of STAT6 and increased IgE production in B cells.²⁰ In *STAT6*, the polymorphism C2892T, located in a potential nuclear factor- κ B-dependent, highly conserved cis-regulatory element, was studied.¹³ Genotyping was successful in 92.6% to 98.7% of cases (Table I), and

TABLE I. Description of the investigated IL-4/IL-13 pathway SNPs, assay conditions, and allele frequencies

Gene and position from ORF	rs number	Alleles	Genotyping method	Minor allele frequency	PCR primer	Extension primer/restriction enzyme	Call rate (%)
IL4-589	rs 2243250	C/T	Restriction assay	0.32	CACTAAACTTGGGAGAACATGGT GAAGGGAGAGGCCACAGGGGT	AVA II	97.59
IL13 -1112	rs 1800925	C/T	Restriction assay	0.46	GGAATCCAGCATGCCTTGTGAGG	BstUI	92.58
IL4Ra 148	rs 1805010	A/G	Allele specific PCR	0.43	GTCGCCTTTTCCTGCTCTTCCCGC GCCTCCGTTGTTCTCAGGTAT	GCCTC CGTTG TTCTCA GGTAC	97.50
STAT6 2829	rs 324011	C/T	MALDI-TOF	0.37	ATCCTTGGTGCATGTGGTAAG GCTTATACCCCTCTTCCCCAC ACGCCCTCGTCATCGCAG ACGTTGGATGAGAAACAGGAA GGAAGGTCC ACGTTGGATGTATGGTTCGAC TGAGTCCAC	CTGAG TCCAC ACTCC CCTG	98.68

ORF, Open reading frame.

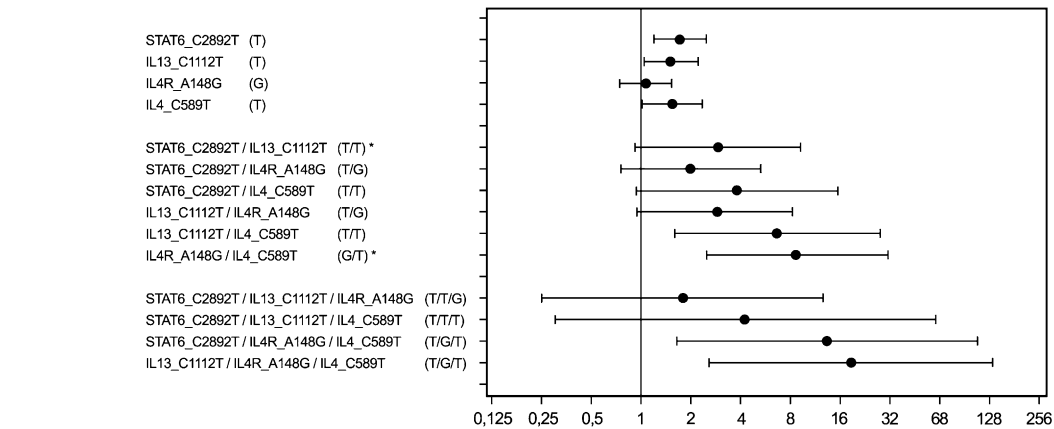


FIG 2. Combinations of alleles in the IL-4/IL-13 pathway increase the risk to develop elevated serum IgE levels (90th percentile). In the *upper panel*, effects of single SNPs are shown. In the *middle panel*, haplotype pairs, and in the *lower panel*, haplotype triplets are presented. *Haplotypes from genotype combinations showing statistically significant epistatic interactions.

complete information on all 4 SNPs was available in 856 subjects, of whom 8.6% had asthma and 7.6% had elevated IgE levels beyond the 90th percentile. Geometric means of IgE stratified by asthma are shown in [Table E2](#) (see the Online Repository of this article at www.jacionline.org).

According to its biological function, the effects of SNPs in the IL-4/IL-13 pathway on 2 main outcomes were studied: the regulation of serum IgE levels and the development of childhood asthma. First, the effects of single SNPs on these 2 variables were tested independently of the effects of polymorphisms in any of the other genes. Thus, the isolated effects of single alleles of the respective SNPs on the development of highly elevated serum IgE (90th percentile) are shown in the upper panel

of [Fig 2](#). In a second step, pairs of SNPs in the IL-4/IL-13 pathway were formed, and finally, triplets were analyzed. According to the stepwise introduction of SNPs, the risk for elevated serum IgE levels increased from the maximum single effect of odds ratio (OR) 1.73 (95% CI, 1.21-2.47) for *STAT6* C2892T to a maximum of 18.73 (95% CI, 2.59-135.46) for the triplet interaction among *IL-13* C-1112T, *IL-4Rα* A148G, and *IL-4* C-589T.

In a second analysis, genetic effects on asthma were studied according to the same stepwise procedure ([fig. 3](#)). The maximum observed OR for the effect of any single SNP was 1.60 (95% CI, 1.06-2.41) and increased to a maximum of 4.55 (95% CI, 1.59-12.97) for the interaction between *STAT6* C2892T and *IL-13* C-1112T and again to 26.81 (95% CI, 3.05-236.62) when SNP *IL-4* C-589T was

Mechanisms of asthma and allergic inflammation

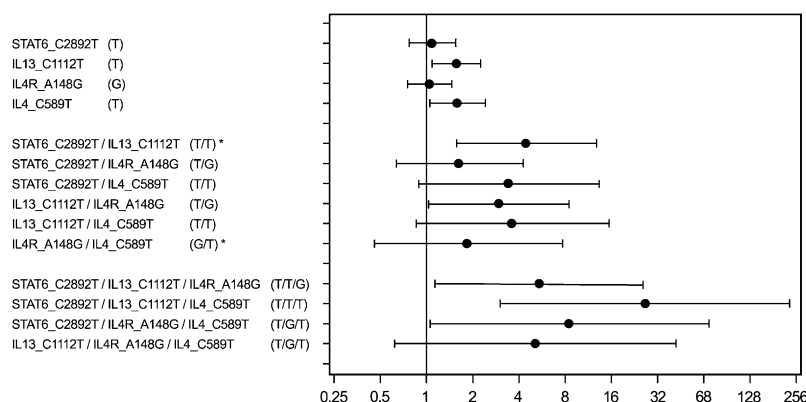


FIG 3. Single SNPs and combinations of SNPs in the IL-4/IL-13 pathway increase the risk of developing asthma. In the *upper panel*, effects of single SNPs are shown. In the *middle panel*, haplotype pairs, and in the *lower panel*, haplotype triplets are presented. *Haplotypes from genotype combinations showing statistically significant epistatic interactions.

added to the model. As indicated by increasingly large CIs, the informative proportion of the study population decreased with the stepwise addition of SNPs (2.5% to 4.2% carriers of the 3 SNPs risk allele combination), and the analysis of 4 SNP interactions could not be performed confidently because of low numbers. Epistatic interaction effects on the 2 main outcomes were estimated by using the Cordell case-control epistatic model,¹⁸ and in several cases, departures from expected ORs caused by combined additive and dominant effects resulted in statistically significant epistatic interactions as indicated in Figs 2 and 3 (the expected OR for the presence of a pair of SNPs, for example, is the product of the ORs for the 2 modeled as main effects under the assumption of an additive model for the log odds).

DISCUSSION

These data suggest that an interaction between different polymorphisms in the IL-4/IL-13 pathway composed of *IL-4*, *IL-13*, *IL-4Rα*, and *STAT6* significantly influence the genetic control of serum IgE levels and the development of asthma. Although variable effects of single SNPs have been observed in our and other populations, the combined effects of the 4 polymorphisms tested here exceeded the single effects by far. Even though the population tested here was relatively small for a study of multiple interaction terms, the effects were strong enough to reach statistical significance for epistatic interactions in the Cordell epistatic case-control models, indicating their importance in those individuals affected by the presence of multiple SNPs in the IL-4/IL-13 pathway. Several plausible possibilities of interaction effects between SNPs exist according to epistasis theory: (1) When several SNPs (with individual effects) are combined, an additive effect could occur and the OR would increase accordingly (additive). (2) Individual SNPs may actually interact with each other in a biological way. This would lead to a more

than additive effect on a logarithmic scale (equivalent to a more than multiplicative effect). (3) Individual SNPs may show association with the disease only by chance, and a combination of these SNPs with other SNPs in the pathway would not influence the outcome. (4) The combinations of different SNPs would level out each other in that combinations of different SNPs in the pathway would not increase above the effect observed with a single SNP. This would be the case if a threshold existed at which SNPs would be able to influence the system only to a certain degree. In our study, we observed effect 2, showing interactions exceeding the additive effect on a logarithmic scale. In biological terms, this is the most intriguing result possible, because this may indicate that putatively functional SNPs are distributed over the pathway and that a combined occurrence leads to interaction between these effects.

All 4 SNPs tested in the IL-4/IL-13 pathway are suspected to alter the function of the respective gene they occur in. For *IL-4* C-589T, located in the proximal promoter region of the *IL-4* gene, it was shown that the binding of a transcription factor is increased by the presence of the polymorphic T allele.¹⁹ In the light of previously published association studies, it can be hypothesized that this SNP may lead to an overexpression of the *IL-4* gene and thus increases the strength of any IL-4-dependent immunological reaction. However, at least 2 other SNPs in the *IL-4* gene have been shown to be in almost complete linkage disequilibrium with C-589T, and it can not be determined at this point which of these polymorphisms may be causally related to the observed association.

In the *IL-4Rα* gene, SNP A148G was included in the analyses, because it alters an amino acid in the extracellular part of the receptor (Ile50Val), which in turn leads to an increased IL-4-mediated downstream activation of STAT6 and an increased IgE production in B cells in the presence of the A (Ile) allele.²⁰ In a previous investigation of the isolated effects of *IL4Rα* polymorphisms in our study population, this SNP had only minor effects on

atopic outcomes per se. Overall, the associations between IL4R α polymorphisms and asthma as well as IgE levels were only weak. However, in this combined analysis, this SNP seems to amplify effects of other polymorphisms in the signaling pathway.

We selected the C-1112T polymorphism in *IL-13* because this SNP showed significant and persistent associations with asthma and elevated serum IgE levels in German populations. Furthermore, phylogenetic shadowing (data not shown) showed a high degree of conservation in this area, indicating a putative functional role. Located within the extended matrix of a STAT binding site in the *IL-13* promoter, first results from gene expression studies and transcription factor binding analysis by electrophoretic mobility shift assay with the *IL-13* C-1112T site strongly support a functional role of this SNP altering *IL-13* gene expression in the presence of the T allele in cell lines and committed T_H2 cells.²¹ On the basis of these data, it can be speculated that this site may be involved in a STAT6-dependent regulatory loop in the signaling pathway.

Signal transducer and activator of transcription 6, the intracellular transcription factor that transfers the effects of the activation of the IL-4/IL-13 pathway to target genes, not only may be involved in the regulation of its own pathway but is also a key regulatory element of the T_H2 immune response, activating several T_H2 specific gene promoters. Our previous studies and those of others have consistently shown that the T allele of SNP C2892T in the second intron of the *STAT6* gene is associated with elevated serum IgE levels.^{6,13,22} The T allele at position 2892 disrupts a putative nuclear factor- κ B site, which may very well have regulatory effects on the *STAT6* gene because it is located in a putative cis-regulatory region.

Out of the 4 SNPs tested, *IL-13* C-1112T and *STAT6* C2892T seem to be overrepresented in those extended haplotype combinations that conferred the greatest risk for elevated IgE and/or asthma. This may indicate that these 2 polymorphisms are key in the deviation of the IL-4/IL-13 pathway, whereas other SNPs further modify IL-4/IL-13-dependent outcomes. Taken together, a complex picture of cross-regulation on a genetic level evolves around SNPs in the IL-4/IL-13 pathway. Of interest, those individuals that did not have any of the tested polymorphism in the IL-4/IL-13 pathway and thus could be labeled as “supernormals” concerning the IL-4/IL-13 pathway were significantly less likely to show elevated serum IgE or present with a diagnosis of asthma (data not shown). Although the IL-4/IL-13 pathway may influence the development of asthma mainly through its effect on IgE regulation, our results indicate that this may not exclusively be the case, as revealed by the results in Figs 2 and 3, which go in the same direction but are not identical. Thus, it may be speculated that some of the SNPs tested here may have additional, not IgE-mediated effects on the development of asthma.

This analysis may help us understand better the complex nature of gene-by-gene interactions or epistasis in

common diseases of complex genetic traits. Because IgE switching is fundamental for human immunity and survival, the regulation of IgE is delicate and in part redundant, which may be a common observation in biologically important pathways. Thus, it can be deduced that a certain amount of genetic variance (maybe in combination with certain environmental factors) is necessary in these pathways to overwhelm the system and to result in a profound, clinically measurable expression of a disease. However, statistical interaction alone does not prove biological interaction, only hints to it. It may therefore be necessary to establish biological interaction between these SNPs in the IL-4/IL-13 pathway in functional assays *in vitro* and *in vivo*.

The observations presented here may, however, have implications of practical clinical relevance. A combined analysis of SNPs in the IL-4/IL-13 pathway may prove valuable as a predictor of atopy and asthma in children. Even though the prevalence of children carrying SNPs in 3 or more genes of the pathway is low, the extremely elevated risk to develop asthma in carriers may predict the disease in those individuals. On the other hand, children who do not show any alterations in the pathway seem to be protected against the exaggerated production of serum IgE. How valuable SNPs in the IL-4/IL-13 pathway are as disease predictors and whether they could be used as screening tools for the development of asthma in childhood still remain to be tested, and further replication studies are necessary.

Michael Kabesch participated in the development of the study design, collection of data, genotyping, data analysis, and manuscript preparation; David Carr performed data analysis and participated in manuscript preparation; Michaela Schedel and Bernd Woitsch participated in genotyping, data analysis, and manuscript preparation; Christian Fritzsche collected data; and Stephan Weiland and Erika von Mutius contributed to the development of the study design, collection of data, and manuscript preparation.

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