

Review article

Atopic eczema/dermatitis syndrome – a genetically complex disease. New advances in discovering the genetic contribution

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Due to recent developments in molecular genetics great progress has been achieved in understanding the etiology of human genetic diseases. Presumably, most causative genes for monogenic diseases will be known within the next few years. However, this progress is mainly limited to the rare monogenic diseases. Since Cloninger (1) – searching for genes predisposing to schizophrenia – stated a complex hypotheses about the inheritance of schizophrenia, a shift within medical genetics started, from the focus on monogenic diseases to genetically complex diseases.

Still, in most contexts, talk about being postgenomic seems a little premature. Post-Mendelian seems more accurate as we move from an era in which genetics has been rooted in monogenic diseases with high penetrance to a greater awareness (but limited understanding) of polygenic diseases and traits often with relatively low penetrance.

The etiology of complex diseases is multifactorial and based on several interacting genetic mechanisms and additional environmental factors. Today, many diseases like arterial hypertension, diabetes mellitus, inflammatory bowel disease, epilepsy, schizophrenia, migraine, psoriasis, asthma and atopic eczema/dermatitis syndrome (AEDS) are seen as genetically complex. Generally, they have a much higher population prevalence than the rare monogenic diseases, hence an improved understanding of the pathology of complex diseases is highly relevant in socioeconomic terms.

The present review is aimed to focus on research results on AEDS as a complex disease with a multifactorial

pathophysiologic background. The nomenclature of allergic diseases is used according to the EAACI Nomenclature Position Paper (2).

Atopic dermatitis – a complex disease

Atopic eczema/dermatitis syndrome (AEDS) is a common chronic inflammatory skin disorder that is regarded as a typical multifactorial disease. The etiology is complex and the disease is caused by concerted actions of environmental and genetic factors. A unifying causal and formal pathogenetic concept of AEDS has still not been established (3). The interactions between genetic and environmental mechanisms are largely unknown (4). Linkage of AEDS, allergic asthma, allergic rhinitis, and total serum IgE levels to several different chromosomal regions have been described extensively, but little is known about the contributing gene loci and their variants.

Like allergic asthma and allergic rhinitis AEDS became one of the most frequent diseases in populations of civilized countries (5, 6). In the past three decades an increasing prevalence was observed especially in industrialized populations (7, 8). This cannot be explained on the basis of genes alone (9), but reveals a multifactorial pathogenetic concept characteristic for complex diseases, depending on both environmental and genetic factors (10). Environmental allergen levels are probably the major determinant of whether sensitization of genetically predisposed individuals occurs. Increased exposure to sensitizing allergens and reduced stimulation of the immune system during critical periods of

development (11) are seen as the main factors driving the rising prevalence of allergic diseases. The IgE-mediated antigen presentation of (aero-) allergens has been recognized as a key event in the pathogenesis of AEDS (12).

There may be several genetic factors varying in different populations because there is not one single gene responsible for the disease like in monogenetic illnesses. In addition, imprinting, e.g., parent of origin effects may play a role in etiology, and have been observed in a number of population studies (13).

Epidemiological background

AEDS affects up to one in 10 children. Onset is usually in the first weeks and months of life and, while most affected people enter spontaneous remission, the dermatitis may persist into adult life. The condition causes major impairment of quality of life. Epidemiological studies show that parental AEDS confers a higher risk of atopic dermatitis to offspring than parental allergic asthma or allergic rhinitis (14). These findings indicate the existence of genes specific for AEDS.

To give an example of a European country, Schäfer et al. (15) found a prevalence of AEDS of 10.4% in Germany. The prevalence was found to be significantly higher in East (12.9%) as compared to West (8.2%) Germany. This is explained by an increase of the intrinsic form of AEDS (see below), that was almost twice as high in the East with 8.5% as compared to 4.7% in the West (15). The differences, however, are decreasing.

Von Mutius et al. (16) compared the prevalence of asthma in schoolchildren from the cities of Munich and Leipzig in the reunified Germany. The level of pollution was far higher in Leipzig. Surprisingly, there was significantly less allergic disease in the more heavily polluted city of Leipzig than in Munich. In addition, the prevalence of atopy has risen steadily in East Germany since lifestyle and environment have become more westernized. This suggests that the increase in the prevalence of allergic disease is probably due to factors associated with a western lifestyle (16).

Schultz-Larsen et al. (17) determined the increased prevalence of AEDS in Northern Europe by a cross-sectional questionnaire study. They found a frequency of AEDS of between 9% and 16% in 7-year-old-school children in Denmark, Germany and Sweden.

Comparing their results with previous studies, Schultz-Larsen et al. (18) found a rising cumulative incidence rate of atopic eczema/dermatitis syndrome: In children born before 1960 it was 2% to 3%, during the 1960s it rose to 4% to 8%. In the 1970s, rates from 9% to 12% were recorded, and for those born in the 1980s, at least 15% to 20% might develop AEDS during childhood as stated in 1986. This continuously increasing frequency of AEDS during the past 30–40 years suggests that widespread environmental factors originating from the industrialized

world are operating in genetically susceptible persons (18).

Genetic background of atopic eczema/dermatitis syndrome

So far, genome-wide scans for genes predisposing to allergic diseases have been performed mostly focussing on asthma and phenotypes characterized by high IgE levels (see below). Concerning atopic eczema/dermatitis syndrome (atopic eczema: OMIM *603165), the role of genetic factors in this disease is demonstrated by twin studies, which consistently showed a higher concordance rate in monozygotic (MZ) twins compared to dizygotic (DZ) twins. However, disease concordance in MZ twins is far from complete, a fact which highlights the substantial role of environmental factors acting on the basis of genetic susceptibility.

However, contrary to frequent belief, interpretation of twin studies is not unequivocal, due to different concepts and methodological approaches and their limitations (method of ascertainment and its associated bias, proband or pair-wise concordance rates, environmental variance components in MZ and DZ, etc.). Whereas all twin studies essentially show the same pattern of concordance rates, additional criticism can be directed against older studies since they were based on either ill-defined twin populations (19, 20), or did not address specifically AEDS (21, 22). A careful and targeted twin study from Denmark (18) demonstrated pairwise concordance rates of 0.77 in MZ and 0.15 in DZ twins, and subsequently, on a similar cohort some years later (23), 0.72 and 0.23, respectively. The decrease in MZ concordancy, and the concomitant increase in DZ concordance rate, may reflect the gain of exogenous factors, which by the same token is responsible for the gain in overall prevalence of the disease. The cumulative incidence rate for a seven year period was 0.03 for the birth cohort 1960–64, and 0.12 for the cohort 1975–79 (23).

The importance of genetic factors in AEDS is underlined by the finding that a positive parental history is the strongest risk factor for AEDS; the incidence rate is doubled if AEDS is present in one parent, and tripled if both parents are affected (24). In order to determine the relative contribution of genetic and the environmental factors on the occurrence of atopic diseases, Diepgen and Blettner (25) performed a family study on AEDS showing an odds ratio (OR) of 2.16 (95% CI 1.58–2.96) for AEDS if no distinction was made between the degree of relationship and an OR of 3.86 (95% CI 2.10–7.09) for siblings of an affected index case. The odds ratio describes the association between categorical or binary variables such as presence or absence of a disease between groups. In our context, an odds ratio greater than 1 reflects familial aggregation. Another study examined the OR in German families where one parent is also suffering from AEDS. Then the disease risk shows an OR between 3.4 (95% CI 2.6–4.4) and 6.2 (95% CI 3.3–11.5) (26, 27).

Gene mapping studies

Gene Mapping studies of familial atopy have identified several chromosomal regions containing genes predisposing to atopy. However, the data for candidate regions do not show consistency, which may presumably be due either to genetic heterogeneity or to clinical (phenotypic) heterogeneity, or to both. This is a common finding in complex diseases, and additionally may be due to the multicomponent nature of this genetic etiology (28).

Studies in patients with allergic asthma

Several candidate loci and genes for atopy have been suggested on the bases of family studies with patients suffering from allergic asthma. Evidence for inheritance through maternally transmitted alleles and atopy at different loci has been reported, including chromosomes 4q35.2, 11q13, 16q24.1 (29). An early set of studies searching for evidence of atopy and asthma-associated genes in several different populations exists for chromosome 5q31-q35, a region containing multiple candidate genes for allergy and asthma, including a clustered family of cytokine genes, i.e., IL4, which play important interactive roles in the allergic inflammatory response. In the Pennsylvania Amish population, evidence for linkage of total IgE, but not specific IgE, was found within the 5q31.1 region (30). Further studies suggested that IL4 and/or nearby genes in 5q31.1 regulate IgE production in a noncognate fashion (31). Linkage of total IgE to 5q31-q35 is supported by studies of Meyers et al. (32).

Malerba et al. (33) showed significant allele sharing for the locus of the high affinity IgE receptor beta chain (chromosome 11q13) in affected sib-pairs with positive skin prick test who were suffering from bronchial hyperresponsiveness. In the examined population of atopic children in Italy the commonly reported Ile181Leu mutation (34) was not replicable. These findings suggest that different genetic factors might vary within and between different populations.

A genom-wide screen in positive skin prick test Hutterites, a founder population in the USA with European ancestry, provided evidence for at least three atopy-susceptibility loci on chromosomes 1, 6 and 16 (1p32-31, 6p21, 16p12.1) (35). In the same Hutterite population, five regions showed possible linkage to asthma phenotypes (5q23-31, 12q15-24.1, 19q13, 21q21 and 3p24.2-22, the latter reported for the first time in the Hutterites) (36). In a single center study of multicase asthma families the role for HLA class II polymorphism in influencing allergen-specific and nonspecific IgE production was supported (37). Grasemann et al. (38) suggest that variants of the NOS1 gene located on chromosome 12q24 may be one source of genetic risk for asthma and atopy, whereas a genomewide screen for asthma susceptibility loci in three U.S. populations showed evidence for linkage at 1q32, 6p21 and 11q21

for the Hispanic, the European American and the African American, respectively (39).

Maternal/paternal inheritance

Linkage of atopy to a genetic marker on 11q13 was reported by Cookson et al. (40). The beta chain of the high-affinity receptor for IgE (FCER1B, OMIM*147138) was localized to the same region, and polymorphism with the gene related to atopy (41). Variants of this gene seem to exert a regulatory effect on IgE production and show significant association with positive IgE responses in a random patient sample (34). Cookson et al. (42) provided the first evidence for a maternal effect to atopy at the 11q13 marker for the β subunit of the high affinity IgE receptor *FcεRI*. In their study, a gene was assigned for atopy to chromosome 11q by linkage to the marker D11S97. These results show a significant sharing of maternally inherited alleles in region 11q13 in sib-pairs with atopic IgE responsiveness. Here, the transmission of atopy at the chromosome 11q locus is detectable only through the maternal line, because no excess sharing of paternally derived alleles was seen. The pattern of inheritance is consistent either with paternal genomic imprinting or with maternal modification of developing immune responses (42).

In a very recent study, evidence for linkage of AD (AEDS) to chromosome 3q21 near marker D3S3606 was detected (43). It was only under the assumption of paternal imprinting that significant evidence for linkage of allergic sensitization was detected to this locus, indicating that this trait is predominantly transmitted by the mother (43).

However, atopy seems to be inherited paternally in some families, and the offspring of two atopic parents have a greater chance of atopy than children of a single affected parent (44).

Coleman et al. (45) proved the reported genetic linkage between atopic respiratory disease and chromosomal region 11q13 in families with patients suffering from AEDS. In this study, a major susceptibility locus for atopy in the 11q13 region was excluded by linkage analyses. In some of the examined families, maternal imprinting seemed to be demonstrated, therefore here the possibility of a paternal influence on the inheritance of atopy cannot be excluded.

Cox et al. (46) tested several polymorphisms within the high-affinity receptor b chain gene FCER1B (11q13) for association to AEDS and confirmed association of FCER1B *RsaI* polymorphisms with the disease. The association was demonstrated only with maternally derived alleles.

These controversial linkage findings between atopy and markers at chromosome 11q13 were discussed by Folster-Holst et al. (47) who in their study of 12 families support the findings of the IgE high-affinity receptor gene FCER1B at 11q13.

Another coding variant of the FCER1B gene (Gly237-Glu) is associated with atopic asthma and very high total serum IgE levels (48). From a pathophysiological point of view, it is difficult to consider FCER1B as a crucial element since *FcεRI* expressing antigen presenting cells (APC) – which are suspected to play a dominant role in this disease – lack this receptor subunit (12).

IgE responsiveness

In order to identify relevant genes of IgE responsiveness, a positional cloning approach was started by the German asthma genetics group (49). The results showed that it is likely that the factors for genetic up-regulation of IgE responsiveness cannot be described by the action of a single major gene as several linkage regions were identified for each examined specific IgE (e.g., for Dermatophagoides pteronyssinus-IgE linkage regions on chromosomes 1, 2, 4, 5, 10, 12, 16 and 21). Genes seem to be more likely to influence the general IgE responsiveness at the amplification level rather than at the level of differentiation into fine specificity of antibodies (50).

Küster et al. (51) isolated, characterized and sequenced the gene for the human γ -chain of the IgE receptor *FcεRI* (FCER1G, OMIM*147139) on chromosome 1q23. Comparison between the DNA sequence of the γ -chain of the T-cell receptor indicates that these genes have evolved from a common ancestor by duplication and that they define a new gene family. In addition to being localized on the same chromosome, both genes show an analogous organization of their exons. A high level of homology is found in three of their respective exons, and the splice sites between them are identical. Furthermore, γ - and δ -chains are essential for surface expression of their respective receptors. Therefore, γ -chains of T-cell receptors may also define a new family of functionally related polypeptides (51).

The chromosome segment 5q31.1

Forrest et al. (52) studied families with multiple cases of early onset AEDS for involvement of genes from the candidate regions on chromosomes 5q31 (IL gene cluster), 11q13 (high-affinity IgE receptor *FcεRI*), 14q11.2 (mast cell chymase), and 16p12 (IL-4 receptor α -chain, IL4RA gene). A major locus that causes a general predisposition to atopy was found at 5q31; the authors postulated that this chromosomal region contains a gene predisposing to AEDS. Additionally, there are different genes that – combined with environmental factors – determine whether atopy manifests as eczema, asthma, or rhinitis. The elsewhere reported linkage to 11q13 could not be supported by the findings of this study. Furthermore, association with candidate polymorphisms in the mast cell chymase and IL4RA genes were not found here (52).

Studying chromosomal regions previously implicated in AEDS, Sönderhäll et al. found in a more recent study evidence for linkage in the region of 14q11 as

well as in the 11q13 and the 5q31–33 region in Swedish families with at least two siblings affected with AEDS (53).

The chromosome segment 5q31.1 contains the interleukin-4 cytokine-gene cluster which includes several important cytokine genes such as IL13, IL4, IL5, IL3, and CSF2. Rosenwasser et al. (54) showed that an IL4 promoter polymorphism, a C to T change at position –590 bp, is associated with elevated serum IgE levels in atopic families.

Elliott et al. studied polymorphisms within the promoter region of IL4 and tested their association with AEDS. The new polymorphism –34 C/T was identified and investigated with the known polymorphism –590 C/T. None of the polymorphisms predisposed to early onset AEDS by itself, but the study revealed suggestive linkage for the [–590C; –34C] haplotype (55).

Evidence for linkage and allelic association for AEDS in German and Swedish families was observed for markers on chromosome 13q12–14 in the Swedish, on both 13q12–14 and 5q31–33 in the German population (56).

Interleukin-4 receptor gene, IL4RA

The IL4RA gene on chromosome 16p12 was also suggested as a candidate gene for atopic diseases. A novel interleukin-4 receptor α allele was identified and found to be associated with atopy by Khurana-Hershey et al. (57). The relative risk of atopy among persons positive for a mutant allele was 9.3. Deichmann et al. (29) employed a sib-pair analysis to detect maternal inheritance of a gene in the chromosome 16p12 region which increases the risk for enhanced IgE responsiveness. The most obvious candidate gene in this region is the gene for the interleukin-4 receptor IL4RA. This IL-4 receptor consists of an alpha chain and the common gamma chain. Six missense polymorphisms have been reported: Ile50Val, Glu375Ala, Cys406Arg, Ser411Leu, Gln551Arg and Ser761Pro. Among these, Ile50Val and Gln551Arg were found to be of functional significance. The Ile50Val variant has been reported to up-regulate receptor response to IL-4, and increased proliferation of lymphocytes and IgE production (58). Moreover, the Ile50Val variant of IL-4R was associated with the development of atopic asthma. The up-regulation of the receptor response results in increased activation of the signal transducer activators of transcriptions 6 (STAT6 58). Noguchi et al. (60) studied families with asthmatic children and found no association with allelic variants of the IL4RA gene, whereas polymorphisms in the interleukin-4 receptor alpha chain have been reported to be associated with adult AEDS in Japan by Oiso et al. (61) who sequenced a locus for atopy on chromosome 16p11-p12 and proved the reported associations of Ile50Val and Gln551Arg variants in the IL4RA gene. They stated this gene should be considered a compelling

candidate gene for AEDS. It should also be noticed that IL-4 is a crucial cytokine for the induction of the synthesis of the α -chain of the high affinity IgE receptor in APC (*Fc ϵ RI*) (62) and thus may also be of importance in the current pathophysiological concept of AEDS.

Chromosome 12

On chromosome 12, the presence of the genes for interferon-gamma (*IFNG*) and stem cell factor (also known as mast-cell growth factor or KIT-ligand, *KITLG*) makes this region an attractive candidate for atopy susceptibility loci (4). Evaluating this statement, one has to take into consideration that our current pathophysiological understanding does no more support mast cells being the major cell type in the pathophysiology of AEDS.

Using markers in chromosome 12q21-q24.1, evidence was found for linkage of high total IgE by both sib-pair and transmission disequilibrium analyzes. Applying the transmission disequilibrium test to unrelated children of German ethnicity with persistently high IgE and their parents, a study of high IgE responsiveness provided further evidence for linkage of high IgE with 12q21-1q24.1 (31).

The German multicentre allergy study revealed genetic markers of atopy in infancy on chromosome 12q15-q24 as well as on chromosomes 5q31-q33 and 13q12-q14 (63).

The RANTES gene

A functional mutation in the proximal promoter of the RANTES gene (RANTES = small inducible cytokine A5, gene: *SCYAS*, # 17q11.2) has been identified (64). Up-regulation of C-C chemokine expression via C-C chemokine receptor 5 (gene: *CCR5*, # 3p21) characterizes allergic inflammation and AEDS. The mutation of the RANTES gene results in a new consensus binding site for the GATA transcription factor family. The point mutation at base pair -401 is strikingly more frequent in individuals of African descent compared to Caucasian subjects (64).

Genetic linkage to psoriasis susceptibility loci

Recently Cookson et al. published the results of a genome screen for childhood AEDS with elevated serum IgE concentration (geometric mean 880 IU/l, CI 637–1.230 IU/l), in which linkage to AEDS on chromosomes 1q21, 17q25 and 20p was identified. Surprisingly, these regions correspond very closely to known psoriasis loci, as does the previously described AEDS locus on chromosome 3q21 (65). The results indicate that AEDS is influenced by genes with general effects on skin inflammation.

In this context it is of interest that other immune disorders locate to the same chromosomal regions. Inflammatory bowel disease for example locates to

chromosomes 2, 7, 12 and 16 in a very similar interval to asthma-associated loci (66).

Nonallergic AEDS

Approximately 20% of patients suffer from a skin disease which clinically resembles the skin lesions and distribution pattern of allergic AEDS, but is not associated with elevated total serum-IgE levels and lacks sensitization towards environment or food allergens. Therefore, the pathogenesis of this nonallergic AEDS [called intrinsic atopic dermatitis by Wüthrich, (67)] seems to be different from the disease known as classical allergic form of AEDS (extrinsic atopic dermatitis). According to Schmid-Grendelmeier, Wüthrich et al. (68), diagnostic criteria should run as follows: (i) a clinical phenotype AEDS, fulfilling the diagnostic criteria of Hanifin and Rajka (69) (ii) low total serum-IgE levels (< 200 kU/l) in combination with negative *in-vitro* IgE-screening for aeroallergens and food allergens (e.g., negative SX1-RAST and SX-5 RAST) as well as negative prick test results for standard aero- and food-allergens (iii) absence of other atopic diseases such as allergic rhinoconjunctivitis or allergic bronchial asthma. Hence, patients may initially be considered having a nonallergic AEDS, but during the allergologic workup they may need to be reclassified as allergic AECS and vice versa. While nonallergic is clinically similar to allergic AEDS, the inflammatory microenvironment in these conditions seems to be different from classical allergic AEDS and can be clearly distinguished by phenotyping of epidermal dendritic cells (70).

Some authors suggest that the presence of allergen-specific IgE should be a mandatory criterium for the diagnosis of AEDS and that the nonallergic form should be diagnosed as constitutional eczema without referring to atopy (71).

For the nonallergic AEDS a sensitization against environmental allergens is not found. To date, the pathogenesis still remains to be examined in detail. Akdis et al. (72) investigated 1151 patients that fulfilled the criteria of Hanifin and Rajka. Of these, 116 patients with nonallergic AEDS were identified. Accordingly, 10% of all AEDS patients belonged to the nonallergic group.

AEDS, at least when the nonallergic subform is concerned, should be distinguished from the broad and comprehensive phenotype of atopic hypersensitivity associated with IgE hyperresponsiveness (OMIM *147050).

The strikingly different molecular pathogenesis of nonallergic AEDS suggests a different etiology, i.e., other genetic factors, most likely residing at different chromosomal positions as evidenced by linkage or linkage disequilibrium studies involving allergic AEDS patients. Since the distinction between allergic and nonallergic AEDS is a rather new concept (67), not much is known about epidemiological parameters and formal genetics.

Table 1. Candidate genes of atopy found in the studies discussed

Chromosomal region	Candidate gene	Phenotype (S)
1q21	Unknown	Childhood AEDS
1p32–31	Unknown	Positive skin prick test
3q21	Unknown	AEDS
3p24.2–22	Unknown	Atopy/allergic asthma
4q35.2	Unknown	Atopy/allergic asthma
5q23–35	IL-4 cytokine gene cluster	AEDS/allergic asthma/high total IgE
6p21	MHC class II/TNF- α	allergic asthma/specific IgE
11q13	β -chain of <i>FcϵRI</i> (FCER1B)	AEDS/high total IgE/positive skin prick test/bronchial hypersensitivity
11q21	unknown	Allergic asthma
12q15–24.1	IFNG, KITLG, NOS1	allergic asthma/high total IgE
13q12–14	Unknown	AEDS
14q11.2	Mast cell chymase/T-cell receptor	AEDS
16q12	IL-4 receptor α -chain	allergic asthma/AEDS/positiv skin prick test
16q24.1	Unknown	atopy/allergic asthma
16p12.1	IL-4 receptor α -chain (IL4RA)	allergic asthma/AEDS/high total IgE
17q11.2	SCYAS ('RANTES'-gene)	AEDS
17q25	Unknown	Childhood AEDS
19q13	Unknown	Allergic asthma/high total IgE
20p	Unknown	Childhood AEDS
21q21	Unknown	atopy/allergic asthma

However, both forms being distinct nosological entities would imply, that these phenotypes, however, overlapping, do run in families. Yet, there are no twin studies specifically directed towards nonallergic AEDS, and hence the degree of genetic causation is unknown in this subform. Preliminary personal observations tend to show a lesser degree of clustering in families and have led to the notion nonallergic AEDS being a sporadic subform. This impression, if taken for fact, does not necessarily imply a lesser degree of genetic causation, since recessive components will lead to a low parent-offspring recurrence risk, while a sibling recurrence risk may be substantial. Just to the contrary, arguments along the lines of conventional wisdom in genetic epidemiological reasoning will strongly argue in favor of genetic factors in nonallergic as compared to allergic AEDS, or atopic hyperresponsiveness. In the absence of exogenous factors, intrinsic factors will have to exert a relatively stronger effect. In the case of the nonallergic form of AEDS, genetic factors most obviously are these intrinsic factors. This reasoning is along the lines of the theory of multifactorial causation (73). However, it remains to be seen whether this theory holds in case of nonallergic AEDS. There is no reason *a priori* to believe that genetic factors play a lesser role in nonallergic than in allergic AEDS.

Conclusions

Atopy and the atopic disorders are likely to result from multifactorial causation, with interaction between several genetic and environmental factors. A number of candidate genes have been proposed and linkage has been

found between atopy and some chromosomal regions characterized by genetic markers (see Table 1). The genetic studies on atopic diseases (not restricted to the phenotype of AEDS) have provided almost contradictory results about numerous linkages to various chromosomal regions, a few of which could be reproduced in more than one study (e.g., 5q: cytokine cluster, 11q: β -chain of *Fc ϵ RI*). However, repetition of results in linkage analysis of complex disease do follow special rules and logic (28), and hence a lack of reproduction is not evidence for a false positive result. The genetic findings in atopy may be very different according to ethnic and local characteristics, and they must be carefully verified in different population samples.

The central problem of complex genetics is to map single members of an oligogenic ensemble for disease susceptibility prior to sequencing. With reasonable type I and II errors several hundred, and may be thousand affected sib pairs would be required to detect a locus accounting for 1/10 of the genetic effect on AEDS (74). Localization of oligogenes by linkage and linkage disequilibrium requires international collaboration to reach the necessary sample size (75). Meanwhile databases have been developed to provide an online resource for access to data on the genetics of asthma and allergy where detailed descriptions of linkage studies, gene expression studies and links to relevant patents are available at <http://cooke.gsf.de> (76).

Hence, there is still a great need for understanding the complex genetic background on which environmental threats interact to trigger AEDS, for an understanding of pathogenesis paves the way for rational therapy and possibly prevention.

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