Clinical Genetics of Atopic Eczema 23

F. Schultz Larsen

23.1 Introduction

The history of the inheritance of atopic eczema has been told in detail earlier [36, 38]. It has been known at least since the 1960s that atopic eczema falls into the category of what is today called a complex genetic disorder, i.e., a disease with genetic etiology but without Mendelian inheritance attributed to a single gene locus. It is the interaction between susceptibility genes and environmental triggers or influences that determines the initiation of symptoms and the natural course of the disease, including severity [38].

Twin studies are a helpful first step in determining whether a disease has a measurable genetic component. The outcome of twin studies in atopic eczema was reviewed in the first edition of this book, and in short, there is no doubt that genetic susceptibility plays a decisive role in the development of atopic eczema [36, 37, 40]. Even though twin studies cannot provide further evidence for the mode of inheritance, it might be highly informative to thoroughly investigate discordant monozygotic twins and twins reared apart. Without going into detail, but simply to gain some of the necessary tools to interpret genetic studies, some of the concepts should be mentioned.

23.2 Methods for Mapping Complex Diseases

Many monogenic Mendelian diseases have been identified by linkage analysis, which is based on the process of inheritance of stretches of adjacent genes or the tendency for alleles (variants of genes) close together on the same chromosome to be transmitted as an intact unit. The gene with the unknown position can then be localized by detection of linkage between the gene and the marker with a known position (also called positional cloning). Genetic linkage studies mostly use polymorphic microsatellites, which are very short repeated DNA sequences that vary among individuals and are distributed at known locations throughout the entire genome.

However, in complex diseases there is no simple or straightforward relation between genotype and phenotype. Multiple genes interact with each other and with environmental factors. The chance of discovering true positive linkage is hampered by the degree of penetrance (or expressivity) and epistasis, i.e., when penetrance is suppressed by other genes. Furthermore, the chances of a successful outcome is greatly influenced by the existence of genetic heterogeneity (the phenomenon that one phenotype can be caused by different genes), which very likely is the case in the phenotype we call atopic eczema or atopic dermatitis.

23.3 Atopic Eczema/Dermatitis Syndrome

This brings us to another area of concern and controversy. In most, if not all the newer genetic studies, the diagnosis of atopic eczema is based on the Hanifin-Rajka criteria [17]. The criteria are in accordance with prevailing clinical concepts. However, they are not formally validated, but they ensure, if properly used, a specificity of nearly 100 %. However, this insistence on specificity may result in findings that are primarily applicable on the moderate and severe spectrum of atopic eczema, but in many population-based studies these cases constitute only a minority.

Recently, a position paper has been published on nomenclature for allergic disorders [18]. In order to

standardize the definition in the field of allergy, the task force suggested using the term "atopic eczema/dermatitis syndrome" (AEDS) to what is currently called atopic eczema/dermatitis and to subdivide the syndrome into two subgroups: allergic and nonallergic AEDS. The allergic group is further divided into IgE-associated AEDS and another group of non-IgE-associated allergic AEDS that include cell-mediated forms, for example, cases characterized by positive atopy patch to aeroallergens in the absence of IgE sensitization. The term "nonallergic" AEDS should replace the previous term "intrinsic" variants of atopic eczema, which in my and many others' opinion covers the majority of patients with AEDS. The matter is further complicated by the fact – and named as such in the new nomenclature – that some nonallergic AEDS may shift over time to allergic AEDS and vice-versa [28, 48]. The pros and cons of redefining and dividing atopic eczema has recently been debated in the *British Journal of Dermatology* [4, 16]. In genetics, any phenotypic misclassification severely threatens the validity of any study, and from that standpoint it is highly desirable to make use of clearly defined subgroups, for example IgE-associated AEDS (ideally without respiratory atopy) and nonallergic AEDS. In the investigations mentioned below on the genetics of atopic eczema, most materials include about two-thirds of AEDS patients with elevated IgE and/or respiratory atopy, which is about the average proportion in any hospital group, and only one study deals with intrinsic atopic eczema [44].

What about the genetics of nonallergic AEDS? The classical twin method permits an evaluation of the relative importance of genetic and environmental factors. In conducting the earlier twin study on atopic eczema, care was given in the clinical examination as to whether the probands and co-twins had respiratory atopy, positive prick test to common allergens, and/or elevated serum IgE level (>100 U/ml) [40]. This population-based material reveals that that 31/48 (65%) or two-thirds of the twins (considered as singletons) had nonallergic AEDS, and the concordance rates can be calculated as shown in Table 23.1 (Table 5.1 from [35]).

The figures for the pair-wise concordance rates in nonallergic AEDS is of exactly the same level as in the total AEDS twin material (MZ =0.77 vs DZ =0.15) [40]. Thus, the degree of genetic causation in allergic and nonallergic AEDS seems to be nearly equal, but, of course, the same gene may not be involved, and it might even be anticipated, in the absence of exogenic factors resulting in inhalant allergy and elevated IgE, that the genetic component might have an even greater weight on the phenotypic expression of non-AEDS. It may also mean that inhalant allergy and factors associated with raised IgE have a rather limited, if any influence at all on the development of both allergic and nonallergic AEDS [25].

Table 23.1. Number of concordant and discordant twin pairs with nonallergic AEDS and the concordance rates for the two types of zygosity

	Zygosity Monozygotic (MZ)	Dizygotic (DZ)
Concordant twin pairs	11 (20)	2 (2)
Discordant twin pairs	4 (4)	14 (14)
Pair-wise concordance rate	0.73*	0.13
Proband concordance rate	0.83	0.13

In brackets: number of clinical probands
* $p<0.001$

23.4 Linkage Studies

The problems of genotype and phenotype are not the only obstacle in detection of genetic loci. In addition, there are disputable aspects in analyzing and interpretation of the evidence for linkage and the more precise mapping of genes. The traditional segregation studies and Lod score calculation (assuming the presence of a major disease locus with a special mode of inheritance) is not considered very powerful [47]. Today, the preferred technique is the affected sib-pair design, which tests for marker similarity in affected sib-pairs and makes no a priori requirement about the mode of inheritance. The method is more informative, when it is possible to marker-type the parents (for calculation of the identity-by-descent allele). The higher risk the siblings run (lambda s) in relation to the incidence rate in the population, the stronger the genetic effect, and it is easier to find linkage in diseases with a high lambda s. However, this is not the case in atopic eczema in which the siblings' risk ratio may not be higher than 2–4 [11, 39].

23.5 Statistics of Linkage Analysis

Just a few words on the issue of the statistics of linkage analysis. The Lod score (log of the odds) is a measure of the probability of linkage and is derived from the relative likelihood (the odds) of obtaining the observed data when two loci are linked in comparison with a situation in which they are not linked. The Lod score statistic is dependent on gene frequency, penetrance, and the recombination fraction. If the two loci are close together, then the crossover between them in meiosis will be rare, for example 1%–2%, but if the loci are completely unlinked the recombination fraction rises to 50%. The value at which the Lod score is accepted as the best estimate is called the maximum likelihood estimate, and that estimate is at the same time the recombination fraction and a measure of the distance between the two loci (in centiMorgan, cM). Here, it should be noted that the average spacing between two microsatellite markers in a genome-wide search is in the region of 10 cM, and 1 cM covers about 1 million base pairs (bp). By convention, a Lod score of more than 3 indicates linkage (a LOD score of 2.3 corresponds to $p = 0.001$). However, as a substantial proportion of the linkage claims from the 1980s could not be replicated, it has been suggested that a more stringent standard is required for reporting linkage in genome-wide scans (Table 23.2; [22])

As can be anticipated, linkage studies very often are suggestive at best, and the researcher has to narrow the region of interest by typing more markers in the area and/or add more affected sib-pairs to the study, and it has been a common practice in the second stage of the investigation to use at least two markers "flanking" each marker with an elevated statistic. Finally, the results from linkage analysis might be confirmed in association studies as a case–control design, ideally in isolated and/or inbred populations or families, such as the Amish and the Hutterites (which may also ensure a relatively uniform environmental exposure). However, the region in which reproducible evidence of linkage has been identified may still contain hundreds of genes.

Table 23.2. Criteria for mapping loci underlying complex disorders in sibs and half-sibs in genome screens

Category	Range of approximate *p* values	Range of approximate Lod scores
No linkage	1.00 – 0.0008	0.0 – 2.1
Suggestive linkage	0.0007 – 0.00003	2.2 – 3.5
Significant linkage	0.00002 – 0.0000004	3.6 – 5.3
Highly significant linkage	< 0.0000003	> 5.4
Confirmed linkage	Significant linkage in an initial study, confirmed in an independent study	

23.6 Candidate Gene

After confirmed linkage, the strategy is to apply directed genomic screening or the candidate gene approach, which means investigating certain areas/genes or loci of interest based on knowledge from previous studies or educated guesses for the phenotype being studied. The candidate gene studies rely on testing the frequency of polymorphisms (DNA sequences that vary among individuals) in known genes in cases and controls. Thus, the statistics is simpler, and the examination of polymorphisms in candidate gene studies is much more powerful statistically than linkage tests. A candidate gene may show association even when genetic linkage to a region has been sought, but not detected in the same data [32]. The candidate genes include the many abnormally or inappropriately functioning biochemical markers that participate in the pathogenesis of atopic eczema (Table 23.3). However, this approach ignores the potential contribution of unknown loci

Table 23.3. Candidate genes in linkage and association studies on atopic eczema

Chromosome	Candidate gene in the region
1q21	Epidermal differentiation genes
3q21 – 22	CD80/CD86
4q35	Interferon regulatory factor 2 (IRF-2)
5q31 – 32	Interleukin cluster, Netherton gene (SPINK)
6p21 – 23	MHC class I and II, TNF-alfa
11q13	High-affinity IgE-receptor, beta-chain
13q12-14	IgE-dependent histamine-releasing factor
14q11	Mast cell chymase (MCC), T cell receptor
16p11-12	IL-4 receptor
17q11-12	C-C chemokine cluster, RANTES
19q13	CD22, transforming growth factor (TGF), beta1
Xp11.23	Wiskott-Aldrich Syndrome (WAS) gene

that may be important. In order to enhance the power from association studies and maintain some of the advantage of linkage studies, conducting transmission disequilibrium testing (TDT) has recently been suggested, which includes assessing the frequency with which the disease-causing allele is transmitted to an affected offspring from either parent [31].

In the field of allergy in general, the most reproducible linkages are the IL-4 gene cluster on chromosome 5q31-33, the immune response gene in the HLA-DR region on 6p21, and the region that encodes the high-affinity IgE-receptor on 11q13 (Table 23.3).

23.7 Genome Screens in Atopic Eczema

Just a few genome-wide searches in atopic eczema have been reported. In the year 2000, Lee and co-workers conducted a genome scan with 380 microsatellite markers in 199 nuclear, mainly German families and detected highly significant linkage on chromosome 3q21 near marker D3S3606 ($p < 0.0000008$) under the assumption of paternal imprinting [23]. The CD80 and CD86 antigens have been mapped in this region. They are involved in the stimulatory signals for T cell activation and have been implicated in the activation of TH2 cells.

A second screen has been carried out with 385 microsatellite markers in 148 nuclear families recruited through children attending a tertiary referral hospital (Great Ormond Street Hospital in London) [9]. They found suggestive evidence for linkage to 1q21 (D1S498, $p < 0.001$) and 17q25 (D17S784, $p < 0.001$), but the study could not replicate the above-mentioned continental findings [23]. The authors found it remarkable that these putative loci closely overlap regions observed to contain psoriasis susceptibility genes and speculate that these shared regions of suggested linkage may contain genes with a general effect on dermal inflammation and immunity. However, they did not find any linkage to the major locus for psoriasis susceptibility PSORS1. This locus has been narrowed down to a 200-kb region in the centromeric part of the MHC class I on chromosome 6p21 [2].

Recently, a third scan has been reported from Sweden [6]. Initially 5,000 inpatients and outpatients with atopic eczema from Stockholm were contacted by a mailed questionnaire, and after a clinical examination by the same dermatologist, families with at least two affected siblings were included irrespective of the parental atopic status. By means of 367 microsatellite markers in 109 familis, suggestive linkage of atopic eczema to chromosome region 3p24-22 (D3S1768, $p < 0.001$) was detected together with some weaker evidence for linkage. In 62 of the families, the siblings had elevated specific IgE (IgE-associated AEDS). They showed suggestive linkage to chromosome 18q21 (D18S851, $p < 0.001$). In passing, it should be noted that 94 % of the IgE-associated AEDS had respiratory atopy. In addition, in the severity score study in the 109 pedigrees, suggestive linkage was indicated to chromosomes 3q14 (D3S2459, $p < 0.00007$), 13q14 (D13S325, $p < 0.00007$), 15q14-15 (D15S118, $p < 0.00007$), and 17q21 (D17S1290, $p < 0.00007$). The authors express the view that these chromosome regions provide a platform from which the search for atopic eczema genes may proceed.

23.8 Candidate Genes in Atopic Eczema

23.8.1 14q11

One of the first studies specifically exploring candidate gene and atopic eczema was published in 1996 [24]. Mao and co-workers conducted an association study in which they recruited 100 Japanese patients with "pure" atopic eczema, and an equal number of patients with respiratory phenotypes of atopy and controls [24]. They found a significant association between atopic eczema and a polymorphism encoding for the pro-inflammatory serine protease mast cell chymase (MCC) on chromosome 14q11 (p=0.009), but there was no association to the other phenotypes. Interestingly, approximately 98 % of dermal mast cells produce MCC, whereas only about 7 % of pulmonary mast cells produce the same protease. However, the results were not replicated in other Japanese, Australian, and Italian studies [15, 20, 30]. Evidence for linkage to the region was obtained in a Swedish study, but there was neither linkage nor association to the mast cell chymase 1 (CMA1) gene on 14q11 [41].

23.8.2 5q31-32

The chromosome segment 5q31-32 contains the interleukin-4 (IL-4) cluster, which includes several important cytokines in the pathogenesis of atopic eczema. The first study was reported from 88 Japanese families and 215 controls [20]. Using five markers, affected sib-pair analysis and a subsequent case–control comparison, the studies resulted in a weak association between the TT genotype of the –590C/T polymorphism of the IL-4 gene and atopic eczema ($p = 0.01$). However, the authors were aware that the are racial differences in the IL-4 allele frequencies, and that the T allele is particularly high in the Japanese population.

Using five markers, Forrest and co-workers [15] found linkage in 50 Australian families to a region on chromosome 5q31 (D5S404, $p = 0.006$) situated about 11 cM from the IL-4 cluster, but they did not find support for linkage to 11q13 and the MCC region of chromosome 14q11 [15]. The lack of evidence for linkage to chromosome 11q13 is consistent with the suggestion that this region is merely involved in IgE production (and bronchial hypersensitivity) rather than in atopic eczema.

In a joint communication from Germany (192 children with atopic eczema) and Sweden (40 families), evidence for allelic association was reported to D5S436 ($p = 0.007$) in an analysis of nine markers to region 5q31 [3]. Likewise, evidence in favor of linkage to the microsatellite marker D5S458 and the single nucleotide polymorphism –590C/T ($p < 0.005$) for the variable severity of atopic eczema was found by initially applying five markers to the region in 406 Swedish families [41, 42]. The authors suggest that the IL-4 gene may be important for the severity of atopic eczema. However, it has previously been shown that the –590C/T polymorphism is associated with elevated IgE in asthmatic families [33], and it might be that the findings merely reflect the increased IgE in severe atopic eczema, as there was no linkage to the phenotype atopic eczema.

Recently, a study from Japan focused on a polymorphism (1188 A/C) of the IL-12 p40 subunit in 164 patients with atopic eczema, 143 psoriasis patients, and 100 healthy individuals [45]. The A allele was slightly decreased in atopic eczema ($p = 0.03$) and increased in psoriasis ($p = 0.04$) compared with controls. IL-12 is a Th1 cytokine that has the ability to suppress IgE production and switch Th0 cells to Th1 cells and cytokines; the authors suggest that this polymorphism is associated with susceptibility to both psoriasis and atopic eczema by interference with the Th1/Th2 imbalance in these predominantly and respectively, Th1- and Th2-driven diseases.

There have also been negative studies in the area. In an extension of the aforementioned Australian study [15], in a cohort of 101 families there was no association with the –590C/T (and –34C/T) IL-4 polymorphism [13], and in a study from Japan, no significant association to the polymorphisms of the –589C/T of the IL-4 gene on 5q31was detected, either in 190 patients with atopic eczema or in 61 atopic eczema patients with "normal" IgE levels (< 500 IU/ml) [44].

23.8.3 11q13

A 1998 study explored the possibility of an association between atopic eczema and the region that encodes the beta chain of the high-affinity IgE receptor gene (FceR1beta) on 11q13 [10]. Using the TDT method on two groups (60 and 88 families of about 90 % Caucasians from the Great Ormond Street Hospital), the studies indicated linkage to two of four polymorphisms in the region ($p = 0.002$, $p = 0.003$). However, the association was only present with maternally derived alleles. The same year, Fölster-Holst and co-workers, in their study of 12 German families in a screening of 15 markers, found a weak association to D11S903 ($p = 0.02$) in close proximity to the high-affinity receptor gene [14]. Furthermore, their analysis as well as earlier twin studies indicated that there is likely to be genetic heterogeneity in the susceptibility within different families [14, 36].

An interesting paper on the Netherton's disease gene was published from the Oxford group, partly based on patients from the Great Ormond Street Hospital [10, 46]. Netherton's disease is a rare recessive skin disorder characterized by ichthyosiform erythroderma, bamboo hair, and atopic symptoms, including atopic eczema. The Netherton gene (SPINK5) has been localized to chromosome 5q31, near the IL4 cluster, and comprises 33 exons. The gene encodes a serine proteinase inhibitor (LEKTI), which is expressed in the outermost layers of the skin (and in mucosal surfaces and in the thymus), and may have a protective role against allergens that are serine proteases. In two panels of children (254 and 70 children with atopic ecze-

ma), they identified six polymorphisms in SPINK5, and the Glu420-Lys on exon 14 showed significant association with atopic eczema (and atopy) in both panels ($p < 0.005$). Recently, the same line of investigation was followed in 124 Japanese adults with atopic eczema and 110 healthy individuals [19]. They examined eight polymorphisms in exons 13 and 14 encoding the peptide HF7665, which exhibits an inhibitory function against serine protease. They found association between seven of these polymorphisms, including Glu420-Lys. The frequency of the genotype GG in Glu420-Lys was significantly less frequent in the atopic eczema group than in controls ($p = 0.02$), and the authors suggest that these amino acid changes (from Glu to Lys) might reduce its immunosuppressive function and play a role in the disturbed barrier function in atopic eczema.

23.8.4 16p12-11

The IL-4 receptor (IL-4R) gene on chromosome 16p is another candidate gene for atopic diseases. In the alfa-chain of IL-4R, six polymorphisms have been detected, and it has been demonstrated that two of them (Gln551-Arg and Ile50-Val) have functional significance. The Arg551 variant upregulates the receptor response to IL-4. In a study of 27 mainly severely affected Japanese patients with atopic eczema and 28 nonatopic physicians and nurses, six of the patients were heterozygous (Glu/Arg) at the 551 allele, while this was not the case in any of the controls ($p = 0.01$) [29]. It was stated that studies examining a larger population are needed to confirm this association, and recently 1,051 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) were genotyped for the 551 allele; a significant association was seen between the polymorphism and flexural eczema in children up to 6 months of age who had not been given antibiotics ($p = 0.02$), but not in children who had been given antibiotics [7]. The authors suggest that the effect of the 551 polymorphism may be restricted to early life and that the findings lend support to the hygiene hypothesis [43].

23.8.5 17q11-12

Chemotactic cytokines or C-C chemokines, are small signaling proteins that play an important role in attracting and stimulating leukocytes in allergic and infectious diseases. RANTES (regulated on activation of normal T cell expressed and secreted) is mainly produced in dermal fibroblasts and found in high levels in the scales of atopic eczema patients. The RANTES gene has been localized to the C-C chemokine cluster on 17q11-12. In a German multicenter study (MAS-90), 188 children with atopic eczema and 98 controls were genotyped for a polymorphism in the RANTES promotor region –401G/A. There were no differences in the distribution of the genotypes, but the –401A allele was slightly more frequent in the AD patients ($p = 0.04$) [26]. This finding has recently been challenged in 188 Hungarian children with atopic eczema and 303 without allergic disorders with a negative result for two polymorphisms (–403G/A and –28C/G) that affect the transcription of the RANTES gene [21].

23.8.6 Xp11.23

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder characterized by immunodeficiency, thrombocytopenia, and a rash indistinguishable from atopic eczema, which makes the previously identified WAS gene on Xp11.23 an interesting candidate gene. A study of the WAS gene was carried out in 406 Swedish families by four microsatellite markers to the region. One marker (MAOB) localized approximately 3 cM centromeric of the WAS gene showed linkage to the severity score of atopic eczema ($p < 0.05$), but not to the other phenotypes (atopic eczema, elevated IgE) [5]. It is suggested that either the WAS gene or another gene in the area may contribute to the severity of atopic eczema.

23.9 Other Chromosomes

In the aforementioned joint study from Germany and Sweden, a significant association was found between atopic eczema and the marker D13S218 on chromosome 13q12-14 in the German children ($p = 0.0008$) [3]. One of the candidate genes that maps in the region is the IgE-dependent histamine-releasing factor.

In a study from England in 68 children with atopic eczema and 50 controls, the data provided evidence that a certain polymorphism at position +915 of the transforming growth factor beta1 (TGF-β1) gene at

chromosome 19q13 is associated with a significantly higher risk of atopic eczema, and that the strongest association was found in the 35 most severely affected children ($p = 0.002$) [1]. Among other things, the TGF-β1 inhibits the activity of antigen-presenting cells.

An analysis of the interferon regulatory factor (IRF-2) gene on chromosome 4q35 in 49 Japanese families showed that the haplotype GA8 was transmitted preferentially to children with atopic eczema ($p = 0.03$) [27].

At the time of writing, these investigations have not been replicated.

23.10 Maternal Effect and Genomic Imprinting

In recent years, there has been an increasing awareness that mothers transmit atopic disorders more frequently than fathers. The first studies to explore the influence of maternal atopy on the development of atopic eczema was published in 1992 [12, 34]. In the large-scale population-based study of the genetic risk of atopy in school children in Germany, the tables reveal that in families with mothers with atopic eczema, the risk for children developing atopic eczema was increased in comparison to families with paternal atopic eczema [12]. Moreover, the same tendency has been reported from the southern part of Germany [11]. This maternal effect might be explained in several ways. It might be assumed that mothers and children share a higher degree of home environment, and/or that environmental influence affects the fetus in utero. Furthermore, recall bias from informant mothers may underestimate paternal atopy. In one of the studies from Germany, 80 % of the questionnaires were filled out by the mothers [12]).

However, the presence of increased maternal influence raises the possibility of what is called genomic imprinting, which implies that genetic material (in our case, paternal genes) is modified and suppressed during spermatogenesis. This modification is neither a mutation nor an allele of the particular gene, but rather a temporary change in the function, which, however, may have a profound, long-lasting effect for the individual in question. A popular explanation or hypothesis is that another layer of meaning – an imprint – is added to the genes. It has been known for some years that the severity of von Recklinghausen's disease (NF 1) is increased with maternal transmission, but so far there has been no clear evidence for imprinting in complex diseases. However, on the basis of IgE measurements and the affected sib-pair method, in 1992 the Oxford group showed that the transmission of high IgE was detectable only when the affected sib-pairs shared the maternal 11q13 allele (marker D11S97) [8], and they proposed that the results could be due to paternal genomic imprinting. In one of the genome-wide screens on atopic eczema, evidence for linkage was detected at chromosome 3q21 (marker D3S3606) only under the assumption of paternal imprinting [23].

23.11 Conclusions

The task of unraveling the genetic component of atopic eczema is obviously complicated. The work has definitely begun, but is still in its infancy. This survey has provided an opportunity to emphasize the necessity of repetition of the many inconsistent and almost contradictory results, and great effort should be directed in ways that encourage greater international collaboration in case finding and collection of family data, preferably of the same racial background. Still, there is a long way to go. The mapping gene of a complex disease such as atopic eczema is laborious, time-consuming, and resource-demanding, but may prove to be of crucial importance in our understanding of the nature of this engrossing disease.

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