Genetics of Atopic Eczema

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Young-Ae Lee, C. Söderhäll, U. Wahn

25.1 Genetic Epidemiology

Atopic dermatitis is a chronic inflammatory skin disease that is characterized by intense pruritus. In the industrialized countries the prevalence of atopic dermatitis is approximately 15 % with a steady increase over the last decades [1, 2]. Along with asthma and allergic rhinitis, atopic dermatitis is an important manifestation of atopy that is characterized by the formation of allergy antibodies (IgE) to environmental allergens. Atopic dermatitis is commonly the first clinical manifestation of allergic disease. Onset of disease is observed during the first year of life in 57 % and during the first 5 years in 87 % of patients [3]. For the majority of affected children atopic dermatitis heralds a lifetime of allergic disease. The development of atopic disease often follows an age-dependent pattern that is known as the „atopic march" [4]. A susceptible child commonly passes a characteristic sequence of transient or persistent disease stages that begins with atopic dermatitis and food allergy in the young infant and continues with the development of respiratory airways disease later in childhood and adulthood. Epidemiological studies have documented the impact of a decline of childhood infections [5] as associated with „western" lifestyle [6], small family size [7], and improved hygiene. There is emerging evidence that, in the susceptible individual, pivotal programming events of the immune system leading to promotion of or protection against atopic disease occur within the first 2 – 3 years of life.

A strong genetic component in atopy and allergy was recognized almost a century ago. Cooke and van der Veer first reported that the relatives of patients are at significantly increased risk of developing allergic disease [8]. The observed familial clustering is consistent with a genetic component of disease etiology. The strongest evidence for the importance of genetic factors in atopic disease stems from twin studies. The concordance rate for atopic dermatitis among monozygotic twins of about 80 % far exceeds the concordance rate of 20 % observed among dizygotic twins [9, 10]. These data clearly indicate that the genetic contribution to the expression of atopic dermatitis is substantial. In addition, studies on the vertical transmission of atopic dermatitis and atopic disease show that children are more likely to inherit these disorders if the mother is affected (parent-of-origin effect) [11]. The predominance of maternal inheritance may be due to environmental factors such as uterine milieu or breast feeding, but they may also arise due to genetic mechanisms such as parent-specific gene expression (genomic imprinting) [12]. Parent-of-origin effects should therefore be taken into account in the search for atopic dermatitis genes.

Atopic dermatitis and atopic disorders are complex genetic traits, as the inheritance pattern does not follow a Mendelian mode of inheritance. Presumably, the interaction of several major and minor disease susceptibility genes with environmental factors determines the manifestation and severity of atopic dermatitis. The data are consistent with an immune etiology shared by all atopic diseases and a congenital target organ defect, the penetrance of which is modified by multiple environmental factors acting in positive and negative ways during different stages of development.

Genetic investigations of atopic disease may prove important in dissecting the clinical entities of atopic disorders that we currently recognize clinically, thus providing novel guidelines for their classification. Identification of genes underlying atopic dermatitis and atopy has the capacity to define primary physiologic mechanisms, thereby clarifying disease pathogenesis, identifying pathways and targets for therapeu-

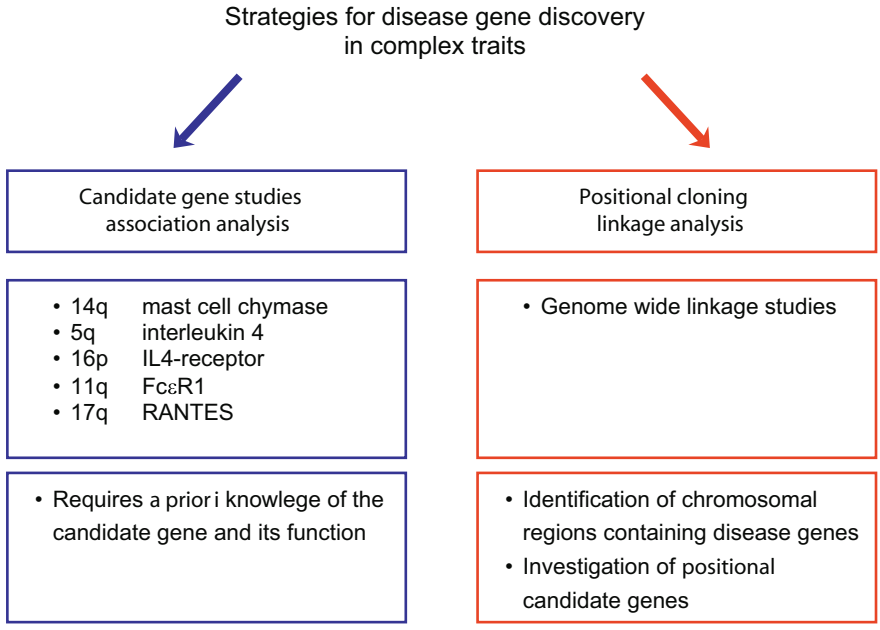

Fig. 25.1. Strategies of disease gene discovery for atopic dermatitis in man are summarized

tic intervention, providing opportunity for preclinical diagnosis, and allowing treatment tailored to underlying abnormalities in individual patients.

25.2 Approaches to the Genetic Analysis of Atopic Eczema

Genetic complexity is said to be present when there is no simple correlation of the disease phenotype with the genotypic constitution. The phenotype expression cannot be predicted using Mendel's laws of segregation [13]. Typically, there is wide variability in the expression of the disease phenotype. Moreover, disease allele carriers may themselves remain unaffected by disease (incomplete penetrance) because manifestation of the disease may require or be facilitated by the interaction with other genetic or environmental factors. The heritable component of atopic dermatitis can be regarded as the cumulative effect of multiple disease alleles. The number of genes that influence the trait and the magnitude of the effect imparted by any single locus remains a matter of conjecture. Furthermore, the combination of disease causing alleles is likely to vary among and even within different ethnic groups (genetic heterogeneity). To identify disease genes for complex traits such as atopic dermatitis by genetic approaches the investigation of hundreds to thousands of affected families is required. Major strategies of disease gene identification for atopic dermatitis in man are summarized in Fig. 25.1.

25.2.1 Candidate Genes

Initially, the only feasible approach to the analysis of complex traits in humans were candidate gene studies. For this approach candidate genes are selected based on their known function in the pathophysiology of atopic dermatitis. Based on the hypothesis that variants in these genes alter gene function or expression and may confer susceptibility to the disease, the gene is then screened for sequence variants and the frequency of these variants compared between groups of patients and controls. In a case-control study, spurious associations may arise from unrecognized population substructure resulting in different allele frequencies at markers that are unrelated to the disease phenotype. To address this problem, family-based association tests, such as the transmission disequilibrium test (TDT), have been developed (Reviewed in [14]). The classical TDT requires family triads consisting of a patient and the parents. The transmission of a putative disease

Table 25.1. Results of association studies for atopic dermatitis and associated phenotypes

Gene	Chromosomal location	Polymorphism	Population	Phenotype	Refs.
Mast cell chymase	14q11	-1903A/**G**	Japanese	AD	[16]
		-1903A/**G**	Japanese	Intrinsic AD	[17]
		-1903A/G	Japanese	No association	[18]
		-1903A/G	Italian	No association	[19]
		-1903A/G	Swedish	No association	[20]
IL4	5q31	-589C/**T**	Japanese	AD	[22]
		-589C/T	Japanese	No association	[23]
		-589C/T	Swedish	No association	[24]
		-589C/ -34C haplotype	Australian	AD	[25]
αIL4R, IL4 receptor	16p11	Q576**R**	US	Atopy	[26]
		Q551**R**	Japanese	AD	[27]
FcεRI		RsaI_in2, RsaI_ex7	British	AD	[29]
		FcεRI microsatellite	Swedish	AD	[20]
RANTES	17	-401G/**A**	German	AD	[31]
		-401G/A, -28G, -2518G	Hungarian	No association	[32]

from heterozygous parents to an affected offspring is observed. At a locus that is unrelated to the disease the marker alleles will be transmitted with equal probability, whereas a disease allele would be expected to be transmitted more frequently to an affected child. Modifications of this test for different family structures and certain modes of inheritance have been developed.

A number of candidate genes for atopic dermatitis have been explored and are summarized in Table 25.1. Most of the candidate genes explored were initially investigated for atopy and asthma. Those candidate genes that have been explored in at least two independent studies have been included.

25.2.1.1 Mast Cell Chymase

Mast cell chymase is a proinflammatory serine protease that is abundantly expressed by dermal mast cells. The expression of mast cell chymase is decreased in nonlesional skin of atopic dermatitis patients and further decreased in lesional skin, suggesting a role of mast cell chymase in suppressing skin inflammation [15]. The gene encoding mast cell chymase (chromosome 14q11) was investigated as a candidate gene for atopic dermatitis. Two noncoding polymorphisms were studied in four Japanese patient groups with atopic dermatitis, atopic asthma, nonatopic asthma, allergic rhinitis, each comprising 100 individuals, as well as a group of 100 healthy controls. One of the polymorphisms was associated with atopic dermatitis, and not allergic asthma or allergic rhinitis in a Japanese case control study [16]. The same polymorphism was evaluated comparing Japanese patients with atopic dermatitis alone, and those with atopic dermatitis and allergic airways disease. The association was confirmed in a small subgroup of 47 patients with atopic dermatitis alone and serum IgE-levels of <500 IU/L [17]. It was suggested that this variant may predispose to nonatopic eczema. However, further investigations failed to replicate the association in other Japanese [18], Italian [19], and Swedish [20] populations.

25.2.1.2 The Cytokine Gene Cluster and Cytokine Receptors

The chromosomal region harboring the cytokine gene cluster on chromosome 5q31-33 contains a number of functional candidate genes for atopic dermatitis and atopy including IL4, IL13, IL9, IL5, as well as CD14. This chromosomal region has been well studied for linkage and association with atopic disorders. Evidence for linkage of total serum IgE levels to a marker close to the IL4 gene was first demonstrated in 170 affected sib-pairs originating from 11 Amish families [21].

The cytokine interleukin 4 (IL4) plays a key role in the regulation of humoral and allergic responses. IL4 controls the differentiation of naïve T helper cells into T helper 2 (Th2) effector cells. It induces the expression

of TH2 cytokines like IL-5, IL-6, and IL-9, and class switching to IgE. Markers flanking the IL4 gene showed positive evidence for linkage with atopic dermatitis in a 88 Japanese families. In the same study group, promoter polymorphism in the IL4 gene, -589C/T, was investigated for association using the TDT. Significant overtransmission of the T allele to affected children (0.001) was observed [22]. This association, however, was not confirmed by a larger Japanese study comprising 302 atopic dermatitis patients and 120 controls [23]. The -589C/T promoter polymorphism gave positive evidence for linkage to the semiquantitative trait „severity score of atopic dermatitis" ($P < 0.005$) in a Swedish study investigating 406 affected sibling families [24]. In the Swedish study, two qualitative phenotypes, atopic dermatitis per se and specific sensitization, were not linked or associated with the genetic markers tested. The authors concluded that this chromosomal region influences the severity of atopic dermatitis.

Finally, promoter polymorphisms within the IL4 gene were investigated for association with childhood atopic eczema in an Australian cohort of 76 nuclear families and 25 triads. In addition to the -590C/T polymorphism (identical to -589C/T), a newly identified polymorphism, -34C/T, was studied. On its own, each polymorphism showed no association with atopic dermatitis. The two polymorphisms were used to generate haplotypes, and an association of the -590C/-34C haplotype with atopic dermatitis was detected. However, after Bonferroni correction for multiple testing, the association became nonsignificant. Neither polymorphism predisposes to early-onset atopic eczema by itself, but suggestive association was found for the -590C/-34C haplotype in this study [25].

The effects of IL4 are mediated by the IL4 receptor, a heterodimer consisting of an α-subunit (αIL4R) and either a γc subunit (type 1 receptor) or an IL-13Ra1 unit (type 2 receptor). The gene encoding the α-subunit of the interleukin 4-receptor (αIL4R) is located on chromosome 16p. Söderhäll et al. typed two highly polymorphic microsatellite markers closely flanking the αIL4R gene in 406 families with at least two children with atopic dermatitis. They conducted linkage analysis for these markers with atopic dermatitis and specific sensitization and reported no evidence for linkage for either trait. Linkage to this chromosomal region was excluded with $\lambda s = 2$ for atopic dermatitis and $\lambda s = 3$ for specific sensitization [24]. Similarly, linkage analysis in 100 nuclear families of the Danish ITA cohort (Inheritance of Type I Allergy) excluded the region of the αIL4R gene with $\lambda s = 2$ for atopy and atopic dermatitis. The cDNA of αIL4R was screened for sequence variants in 10 patients with severe atopic dermatitis or hyper-IgE-syndrome and a mutation was identified in position 1902 of the gene leading to an amino acid exchange (Q576R). This mutation was shown to induce enhanced expression of the low affinity IgE receptor (CD 23) in vitro. A significant association of this variant with atopy was detected in a small case control study comprising 30 atopic individuals and 30 controls [26].

Oiso et al. genotyped six known polymorphisms in the IL4-receptor α chain (IL 4R gene) in 27 patients with atopic dermatitis and 29 nonatopic controls and reported a positive association of the Gln551Arg polymorphism with atopic dermatitis ($P = 0.01$) [27]. However, this association was not confirmed in a larger study group of the same ethnic origin [23].

25.2.1.3 The High-Affinity IgE receptor

The high-affinity IgE receptor (FcεRI) is expressed on mast cells, basophils, and antigen-presenting cells and mediates allergic reactions by crosslinking with IgE. In humans FcεRI is expressed either as a trimer or a tetramer. The β subunit functions as a amplifier of FcεRI surface expression and signaling. The gene encoding the β subunit of FcεRI was investigated as a candidate gene for atopic dermatitis, as polymorphisms within the gene had previously been shown to be associated with asthma and atopy. Furthermore, the gene is located on chromosome 11q in a region that has been shown to be linked to asthma and atopy.

Two noncoding sequence variants in intron 2 and exon 7, and a coding polymorphism in exon 7 (E237G) of the FcεRI gene were examined in two independent family cohorts of 60 and 88 families respectively. Since the investigators had previously established a maternal pattern of inheritance of atopy at this locus [28], they tested for an overtransmission of the maternal allele using the TDT. A significant association of the two noncoding variants with atopic dermatitis was detected in both study groups [29]. How these polymorphisms modify the gene function of the high affinity IgE receptor is under investigation. In a study of 12 extended pedigrees from Germany, positive evidence

for linkage of atopic dermatitis with an intragenic microsatellite marker was reported [30]. Studying a large study sample of 406 nuclear families with siblings affected with atopic dermatitis, linkage on 11q was not confirmed, but a positive association of one of the most common alleles of the FcεRI microsatellite marker was found [20].

25.2.1.4 RANTES

The chemokine RANTES was explored as another candidate gene for atopic dermatitis. As a chemoattractant for eosinophils, lymphocytes, monocytes, and basophils, RANTES plays an important role in allergic inflammation. A functional variant in the promoter region (-401G/A) of the RANTES gene was shown to result in an additional consensus site for the GATA transcription factor family and in increased transcriptional activity of the promoter. This variant showed a positive association with atopic dermatitis in a case control study of 188 children with AD and 98 controls [31]. The same polymorphism, as well as two additional promoter polymorphisms -28G and -2518G were investigated for association with atopic dermatitis and atopy in 128 children with atopic dermatitis, 102 allergic children without atopic dermatitis, and 303 age-matched children without allergic disorders. No association of RANTES promoter polymorphisms with atopic dermatitis, total IgE levels, white blood cell count, or eosinophil cell count was detected in this cohort of Hungarian children [32].

Overall, the results of candidate gene studies vary enormously, and associations found in one study are often not replicated in others. While this summary is focused on association studies for atopic dermatitis, the results of association studies for related phenotypes such as asthma in the same and numerous other candidate genes have yielded conflicting results. For a complex disease such as atopic dermatitis, one would expect some variability to occur; however, it is difficult to assess whether they represent true associations or type I errors. An association may be detected if the gene polymorphism is indeed functionally relevant and is involved in the development of AD. However, a positive association may also be observed with a marker polymorphism that is in linkage disequilibrium with a true functional variant. Finally, spurious associations may occur if the patient or control populations have unrecognized substructure resulting in different allele frequencies at loci that are unlinked to true disease loci.

The following standards have been proposed for a good association study: Positive associations should be based on large sample sizes and small P values. The study design should include an initial study as well as an independent replication, as well as both family-based and population-based studies. Furthermore, the putative disease allele should affect gene function in a disease-relevant way [33]. Since the evaluation of strong functional candidate genes for a complex disease across the whole genome may include as many as 5,000 tests, a nominal P value of 10^{-5} (0.05/5,000) was proposed to provide a low type 1 error rate. Even more stringent parameters were suggested for genome-wide tests in the absence of convincing functional candidacy or prior evidence of linkage [34].

25.2.2 Mendelian Diseases

An alternative approach has been the investigation of rare Mendelian forms of atopic disease in which mutations in single genes impart large effects on phenotype expression. This approach may be particularly well suited to atopic dermatitis and atopy, as the functional consequences of single gene disorders are easier to explore and may define fundamental pathways which, when altered, also affect more common forms of atopic disease.

The first Mendelian disorder investigated was Wiskott-Aldrich syndrome (WAS). WAS is a rare X-linked recessive immunodeficiency disorder characterized by severe eczema, thrombocytopenia, recurrent infections, and susceptibility to autoimmune disease and lymphoreticular malignancies. The eczema observed in WAS usually presents within the first few months of life and is clinically indistinguishable from atopic dermatitis. Mutations in the gene encoding WAS protein (WASp) on chromosome Xp23 have been shown to cause WAS. The WAS gene region was investigated for linkage and association with atopic dermatitis. Four polymorphic microsatellite markers flanking the WAS gene were typed in a Swedish study group comprising 406 families with at least two siblings affected with atopic dermatitis. Three phenotypic traits were investigated: atopic dermatitis, severity score of atopic dermatitis, and atopy defined as raised allergen-specific

IgE. Positive evidence for linkage was reported at marker MAOB with a maximum lod score of 1.68 ($p < 0.05$) to the severity score of atopic dermatitis. Association of genetic markers in this region could not be seen with atopic dermatitis nor with elevated allergen-specific serum IgE antibodies using the transmission disequilibrium test. Our results indicate that either the WAS gene or another gene in the area contributes to the severity of atopic dermatitis.

Recently, the gene underlying the Mendelian disorder Netherton syndrome has been explored for atopic disorders. Netherton Syndrome is a rare autosomal recessive disease characterized by congenital erythroderma and ichthyosis, sparse brittle hair with a specific hair shaft defect (trichorrhexis invaginata), and atopic manifestations, including high levels of serum IgE, eczematous rashes, asthma, hay fever, angioedema, and eosinophilia. Susceptibility to systemic infections and hypernatremic dehydration cause high postnatal mortality. Netherton syndrome was mapped to chromosome 5q32 distal of the cytokine gene cluster [35]. The underlying disease gene was identified to be SPINK5, a serine protease inhibitor [11]. While the disease mechanisms are unclear, the clinical phenotype of Netherton syndrome clearly points to a critical role of SPINK5 in epidermal structure and barrier function and in the development of atopic manifestations. The SPINK5 gene was therefore explored as a candidate gene for atopic diseases [36]. The coding sequence consisting of 33 exons was resequenced and six coding polymorphisms were identified, four of which were genotyped in a panel of 148 families recruited through a child with active atopic dermatitis. Using the TDT test significant overtransmission of the maternal allele of two polymorphisms, Asn368Ser in exon 13 and Glu420Lys in exon 14, was observed for the phenotypes atopic dermatitis, specific sensitization and elevated total serum IgE. The association with the Glu420Lys polymorphism was replicated for the phenotypes atopic dermatitis, specific sensitization, elevated total serum IgE, and asthma in a second group of 73 families. An independent replication was attempted in a Japanese study of 124 patients with atopic dermatitis and 110 healthy controls. Two polymorphisms in Intron 12, three polymorphisms in exons 13, and one polymorphism in exon 14 were genotyped. Association analysis of the Asn368Ser and Glu420Lys polymorphisms did not show an association with the putative disease allele suggested by the original study. For the two intronic polymorphisms a weak association with atopic dermatitis was detected. The disparate results of the studies may reflect differences of the study populations in terms of ethnic origin, age, and the study design. Parent-of-origin effects could not be investigated in the Japanese study where the parents of the probands were unavailable.

25.2.3 Whole Genome Linkage Studies

As the number of plausible candidate genes are legion, an alternative approach to the identification of atopic dermatitis susceptibility genes are genome-wide linkage studies. The goal of a linkage study is to identify disease genes by finding their chromosomal location first. This approach is therefore referred to as positional cloning. This strategy allows the identification of disease genes without prior knowledge of putative disease mechanisms. Positional cloning of atopic dermatitis genes relies on chromosomal mapping/localization by linkage analysis, narrowing of the candidate region by linkage disequilibrium mapping, and finally characterization of sequence variants and their effect on gene function and disease pathogenesis. It is this approach that has revealed some exciting results.

In a genetic linkage study, many families, usually hundreds, are investigated in which the trait of interest, atopic dermatitis, segregates. To scan the genome, every proband is genotyped using several hundred genetic markers evenly spaced along all chromosomes. Usually, highly polymorphic „microsatellite markers“ are used that allow one to trace the inheritance of each chromosomal segment from parents to offspring. One would expect a chromosomal segment containing an atopic dermatitis gene to be shared among affected family members more often than regions that have no effect on disease susceptibility.

Ten previous genome scans focusing on asthma and elevated IgE levels had been conducted in different ethnic groups and had yielded numerous linkage findings in different chromosomal regions throughout the genome. The major coincident linkage findings on asthma were located on chromosomes 1p, 4q, 5p, 5q near the cytokine gene cluster, 6p near the major histocompatibility complex, 7p, 11q near the β chain of the high affinity IgE receptor, 12q, 13q, and 16q [37].

In view of the diverse findings for asthma, the first genome-wide scan for atopic dermatitis was per-

formed employing a stringent patient selection strategy. To enhance the contribution of genetic factors in the study group, only families with at least two children with atopic dermatitis with an early age of onset (before the second birthday) and severe disease expression were included. 199 complete families originating from Germany, Italy, Sweden, and the Netherlands were ascertained [38]. Highly significant evidence for linkage was detected in a single chromosomal region on chromosome 3q21. Further analysis revealed that a large estimated proportion of 40 % of the families contributed to the linkage score. As parent-of-origin effects are suspected to play an important role in the development of allergic diseases, an additional analysis was conducted computing linkage scores for both paternal and maternal imprinting. There was no evidence for imprinting effects for atopic dermatitis. However, for the phenotype atopy, significant evidence for linkage was detected under the assumption of maternal inheritance. Thus, linkage of two closely associated traits, atopic dermatitis and allergic sensitization, to the same locus on chromosome 3q21 was found, however, under two distinct genetic models. This indicates either the presence of two genes in the same chromosomal region influencing each trait respectively, or the pleiotropic effect of a single gene that may be imprinted in a time- or tissue-specific manner. As functional candidate genes for atopic dermatitis and atopy, two type I membrane proteins of the immunoglobin superfamily, CD80 and CD86, are located in this region. Both CD80 and CD86 are expressed on antigen-presenting cells and interact with CD28 to provide costimulatory signals for T cell activation. It has been suggested that CD80 and CD86 provide distinct signals for the differentiation of Th2 cells that are thought to play a pivotal role in mediating allergic inflammation[39].

Notably, the locus on chromosome 3q21 was distinct from any previous linkage reports for asthma or atopy phenotypes. This finding suggested that distinct genetic factors predispose to atopic dermatitis.

The second genome-wide scan was conducted in the UK and included 148 families recruited through a child with active AD [40]. The linkage finding on chromosome 3q was not replicated. Rather, additional linkages for atopic dermatitis on chromosome 1q21 and 17q25, and for atopic dermatitis with asthma on chromosome 20p were reported. Interestingly, all three loci as well as the one previously described on chromosome 3q closely overlap with linkage findings for another chronic inflammatory skin disease, psoriasis. This finding further supported the notion that skin-specific susceptibility factors exist. While atopic dermatitis and psoriasis are distinct clinical entities that show no epidemiological association, the newly identified candidate regions may contain genetic variants specific to skin barrier function and immunity and may thus facilitate the identification of the underlying disease genes. The candidate region on chromosome 1q21 contains the epidermal differentiation complex and that on chromosome 17q the keratin type I gene cluster. Mutations in a number of genes located in either region have been demonstrated to cause different monogenic disorders of epidermal differentiation and function (reviewed in [41]).

A third genome-wide linkage study investigating atopic dermatitis families from Sweden was published recently [42]. Here, 109 families with at least two affected siblings were included; all probands were genotyped using 367 microsatellite markers and linkage analysis was carried out for three qualitative phenotypes, atopic dermatitis, extrinsic atopic dermatitis, and severe atopic dermatitis, as well as one semiquantitative phenotype, severity of atopic dermatitis. Suggestive evidence for linkage was reported for atopic dermatitis on chromosome 3p24-22, and for atopic dermatitis combined with raised allergen-specific IgE levels (extrinsic AD) as well as for severe atopic dermatitis on chromosome 18q21. For the semiquantitative phenotype severity score of atopic dermatitis, suggestive evidence for linkage was found in four regions on chromosomes 3q14, 13q14, 15q14-15, and 17q21. The final analysis revealed two findings on 3q and 17q that replicate and confirm linkages from the two previous genome scans.

The results of the published genome scans are summarized in Table 25.2. All three studies demonstrate that multiple disease genes predispose to atopic dermatitis. There is only partial overlap with linkage findings for asthma confirming epidemiological data that suggested the existence of shared genetic susceptibility for all atopic diseases and organ-specific genetic susceptibility.

25.2.4 Animal Models

Gene mapping by linkage analysis in animal models offers several advantages such as reduced genetic heterogeneity in inbred strains and the possibility to gen-

Table 25.2. Results of genome screens for atopic dermatitis and its associated phenotypes

Population	Number of families	1q21	3p22–24	3q15–21	13q14	15q14	17q25	18q21	20p	Refs.
Germany, Sweden, Italy, the Netherlands	199			3q21 AD Atopy						[38]
UK	148	1q21 AD					17q25 AD		20p AD with asthma	[40]
Sweden	109		3p22–24 AD	3q15 Severity of AD	13q14 Severity of AD	15q14 Severity of AD	17q21 Severity of AD	18q21 Severity of AD		[42]

erate large numbers of offspring in short generation times. Furthermore, animal experiments can be conducted under conditions of tight environmental control. Thus, inbred animal strains provide the ideal setting for the investigation of gene-environment interactions.

Inbred mouse models with susceptibility to atopic dermatitis-like disease and atopy have been used in backcrosses with disease-resistant strains for gene mapping. The NOA (Naruto Research Institute Otsuka Atrichia) shows an ulcerating dermatitis with accumulation of mast cells and increased serum IgE. A susceptibility locus for dermatitis was mapped to a region on mouse chromosome 14 [43] that is syntenic to human chromosome 13q14 where linkage of total serum IgE levels and asthma has been reported [44, 45]. Two additional modifier loci on mouse chromosomes 7 and 13 have been identified [46]. The respective syntenic regions on human chromosome 11q13 and 5q13 have repeatedly been linked to atopic phenotypes [37].

A second genetic model, the NC/Nga mouse (NC) has been explored. This mouse is characterized by severe dermatitis with epidermal hyperplasia and increased numbers of mast cells and eosinophils, as well as elevated serum IgE. A locus for the atopic dermatitis skin-like lesions was located on mouse chromosome 9 in a region syntenic to human chromosomes 11q22-23 and 15q21-25 [47]. The latter region has shown linkage to the severity score of atopic dermatitis in Swedish families [42]. Fine mapping of the proposed atopic dermatitis loci in the mouse and disease gene identification is pending. Gene discovery by positional cloning in mouse models is facilitated by the availability of breeding strategies such as congenic substitution mapping [48]. The orthologs of genes within a defined mouse chromosome interval are strong candidates for human disease loci and are expected to reveal disease-relevant pathways that can be explored further in human populations.

25.3 Conclusion

Atopic dermatitis and atopy are multifactorial disorders that are under polygenic control. Improved methods of genetic analysis and the availability of the sequence of the human genome have led to remarkable progress in identifying chromosomal regions and candidate genes linked to atopic dermatitis. Functional evaluation of these variants including their predictive value in human populations and possible interactions with environmental factors will require the examination of large numbers of clinically well-characterized patients and families.

Genetics provides the basis for the host response to environmental stimuli. It is possible that many gene variants that predispose to atopic dermatitis and atopy have evolved as determinants of natural host resistance to infectious disease. The overlapping linkage findings for atopic dermatitis and other chronic inflammatory skin conditions favor genes that determine skin-specific disease mechanisms. Genetic investigations of atopic dermatitis and atopic disorders are aimed at the dissection of the underlying biological pathways. They are expected to point to molecular targets for the development of new diagnostic and interventional strategies.

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