

Sabine Hoffjan · Jörg T. Epplen

The genetics of atopic dermatitis: recent findings and future options

Received: 23 February 2005 / Accepted: 8 April 2005 / Published online: 18 May 2005
© Springer-Verlag 2005

Abstract Atopic dermatitis (AD) is a chronic pruritic skin disease affecting up to 15% of children in industrialized countries. AD belongs to the group of allergic disorders that include food allergy, allergic rhinitis, and asthma. A multifactorial background for AD has been suggested, with genetic as well as environmental factors influencing disease development. Genome-wide screens for AD have been completed in four different populations to date. Interestingly, the susceptibility regions identified for AD

show little overlap with asthma susceptibility regions, suggesting that, at least in part, separate genes might be involved in the pathogenesis of the different atopic disorders. Instead, some of the identified regions overlap with susceptibility regions for psoriasis, another chronic skin disease. Thus, genes expressed in the skin might play an important role in AD pathogenesis, in addition to genes influencing atopic diatheses. Although no veritable “AD gene” has been identified by positional cloning to date, examples from other complex genetic disorders such as asthma show that this goal is likely to be reached in the near future. Candidate gene studies, on the other hand, have identified 19 genes that were shown to be associated with AD in at least one study. The results of genome-wide screens as well as candidate gene studies are evaluated here in detail.

Keywords Atopic dermatitis · Multifactorial · Polymorphism · Genetic association · Review

Abbreviations AD: Atopic dermatitis · CE: Cornified envelope · EDC: Epidermal differentiation complex · IgE: Immunoglobulin E · MHC: Major histocompatibility complex · SNP: Single nucleotide polymorphism · Th2: T helper lymphocyte type 2



SABINE HOFFJAN received an M.D. degree from the University of Düsseldorf in 2001. After a two-year postdoctoral fellowship at the Department of Human Genetics, University of Chicago, she now works at the Department of Human Genetics in Bochum. Her research interests include the genetics of multifactorial disorders, in particular the genetics of atopic diseases



JÖRG T. EPPLEN heads the department of Human Genetics at the Ruhr-University of Bochum. His research interests cover a spectrum of monogenic neurodegenerative diseases as well as the genetic predispositions to selected multifactorial disorders in addition to behavioural genetics

Introduction

Atopic dermatitis (AD), also referred to as atopic eczema, is a chronic inflammatory disease of the skin that affects up to 16% of children in some countries [1]. Symptoms include pruritus and chronic or relapsing eczematous lesions that are typically localized in the face and at the extensor sides of the extremities in children and at the flexural sides in adults [2]. The disease usually presents with acute lesions in infancy or early childhood and, for most affected children, enters spontaneous remission over time. Alternatively, symptoms can persist into or even start in adulthood only [2]. Chronic AD is characterized by lichenification and excoriations.

S. Hoffjan (✉) · J. T. Epplen
Department of Human Genetics, Ruhr-University,
Universitätsstrasse 150,
44801 Bochum, Germany
e-mail: sabine.hoffjan@ruhr-uni-bochum.de
Tel.: +49-234-3223823
Fax: +49-234-3214196

AD belongs to the group of allergic disorders characterized by the development of immunoglobulin E (IgE) antibodies to ubiquitous, nonpathogenic allergens; this group also includes food allergy, allergic rhinitis, and asthma. A genetic background for AD as well as the other allergic disorders has long been proposed because these diseases tend to cluster in families [3]. AD as the cutaneous manifestation of atopy often represents the beginning of the so-called atopic “march”, which leads to the development of asthma and allergic rhinitis in many afflicted patients [4]. However, the underlying inflammation in patients suffering from AD is not always mediated by IgE antibodies. For example, skin symptoms without IgE-mediated sensitization are common in preschool children, with prevalences as high as 45–64% [5, 6], and even in adults, prevalences as high as 40% of those affected have been reported [7]. Although these patients used to be classified as having “intrinsic atopic dermatitis” (compared to the extrinsic, IgE-dominated type) [8], a revised nomenclature for allergic disorders suggests the use of such as terms “atopic dermatitis” or “atopic eczema” only for patients with IgE-mediated eczema [9].

Interestingly, children whose parents suffer from AD have a higher risk of developing AD than children of parents with asthma or allergic rhinitis, suggesting that separate or additional genes might influence AD development [10]. Twin studies also point to a strong genetic component for AD: concordance rates for monozygotic twins have been estimated between 72 and 86%, compared to 21–23% for dizygotic twins [11, 12]. Still, unraveling the genetic basis of AD is challenging because—unlike monogenic disorders which are caused by mutation in a single gene—AD belongs to the group of complex, multifactorial diseases believed to arise from a complex interaction of several genetic background and environmental factors. For AD, it is not yet clear whether a large amount of the genetic contribution will be explained by variation in a limited number of genes, as has been postulated recently [13].

Incomplete concordance for AD among monozygotic twins (see above) points to elusive nongenetic factors. The relevance of environmental factors for the pathophysiology of allergic diseases is also reflected in the fact that the prevalence of AD, asthma, and allergic rhinitis has been rising in industrialized countries for several decades [14–16]. The main reason(s) for this increase may relate to our modern environment because the gene pool has not changed substantially over this relatively short period of time. It has been postulated in the so-called hygiene hypothesis that the lack of microbial products in our comparatively clean microenvironment might result to decreased stimulations of the immune system in early infancy, giving way for allergies to arise [17–20]. Yet, although environmental factors clearly play an important role, exploring the genetic background of AD and the complex interaction between genes and the environment may offer a better understanding of the pathophysiology and potentially facilitate diagnostic and treatment options.

Current status of the genetic studies for atopic dermatitis

In order to identify susceptibility genes for AD, two general approaches have been used: genome-wide screens followed by positional cloning on the one hand and candidate gene association studies on the other. So far, in genome-wide linkage screens, several hundred markers spaced evenly throughout the genome have been typed in families with the disease phenotype. Markers that are located close to the disease gene will be coinherited (i.e., linked) with the disease. Following genome-wide screens, positional cloning techniques can be used to identify the gene influencing disease susceptibility in the linked region. This approach can theoretically identify all genes that have a measurable effect on AD susceptibility, without prior knowledge about the gene function. Yet, for complex traits such as AD, linkage studies are usually statistically not very powerful and often produce a variety of modestly significant linkage peaks across the genome, making the interpretation of the results difficult.

In candidate gene association studies, on the other hand, variations in known genes whose biological functions implicate them in the pathophysiology are compared between unrelated cases and controls. Significantly higher frequencies of alleles at candidate loci in cases compared with controls may indicate a causal relationship between the marker allele and the disease. In general, association studies are easier to perform than genome-wide screens because they do not require the collection of family material. Furthermore, they have a greater power to detect common alleles with modest effect on disease susceptibility than linkage studies [21]. Yet, candidate gene association studies rely on having chosen the right gene(s) based on biological hypotheses, and there are also various potential problems associated with this approach, e.g., population stratification, false positive results, and the necessity for correcting for multiple testing (reviewed in detail in [22]). The results of both types of genetic studies for AD are discussed below.

As a new approach, genome-wide association studies, assessing several hundred thousand single nucleotide polymorphisms (SNPs) over the whole genome for an association with common diseases and complex traits, are already theoretically feasible [23]. This approach could potentially make use of the advantages of association studies without the necessity of choosing genes based on knowledge about their biological function. Yet, there is still ongoing debate about the number of SNPs that would have to be typed to provide sufficient coverage of the whole genome (assessments range between a few hundred thousand and a million SNPs per person), the statistical methods to analyze the data, and other financial and practical concerns [23]. So far, no truly genome-wide association study has been carried out, and the above-mentioned difficulties will probably prevent their actual execution for another couple of years [23, 24].

Results of genome-wide screens for atopic dermatitis

Genome-wide screens for AD have been completed in four different populations to date (Table 1). Overall, there is no substantial overlap between the results of these studies, which could be due to differences in ascertainment schemes, sample and marker panel sizes or statistical methods. Furthermore, the definition of the phenotype AD varies substantially between studies, also reflecting the changes in classification and nomenclature for this disease over the past few years [9]. Nevertheless, regions on chromosomes 3q, 3p, 17q, and 18q showed suggestive evidence for linkage in at least two studies, indicating promising candidate regions for AD (Fig. 1). For example, suggestive evidence for linkage to AD was found for a region on chromosome 3q21 in European families [25], which is in close proximity to the region linked to the severity score of AD in a genome screen in Swedish families (3q14) [26]. Furthermore, the region on chromosome 3p24-22 showing suggestive evidence for linkage in the Swedish screen [26] might correspond to the region linked to the more restricted phenotype "AD plus specific IgE" in Danish families (3p26-24) [27]. A third region, spanning approximately 20 cM, on chromosome 18q showed evidence for linkage to the same phenotype "AD plus specific IgE" in both the Swedish (18q21) and the Danish genome screen (18q11-12) [26,

27]. Finally, a region on chromosome 17q25 that showed suggestive evidence for linkage to AD in a genome scan in the British population [28] might correspond to the region on 17q21 linked to the semiquantitative phenotype "severity score of AD" in the Swedish population [26]. Yet, although these regions between the highest linkage peaks span only about 20–30 cM, they are still large (~20–30 Mbp, including up to several hundred genes) and need to be further defined for positional cloning. Some of these regions might also contain more than one susceptibility gene.

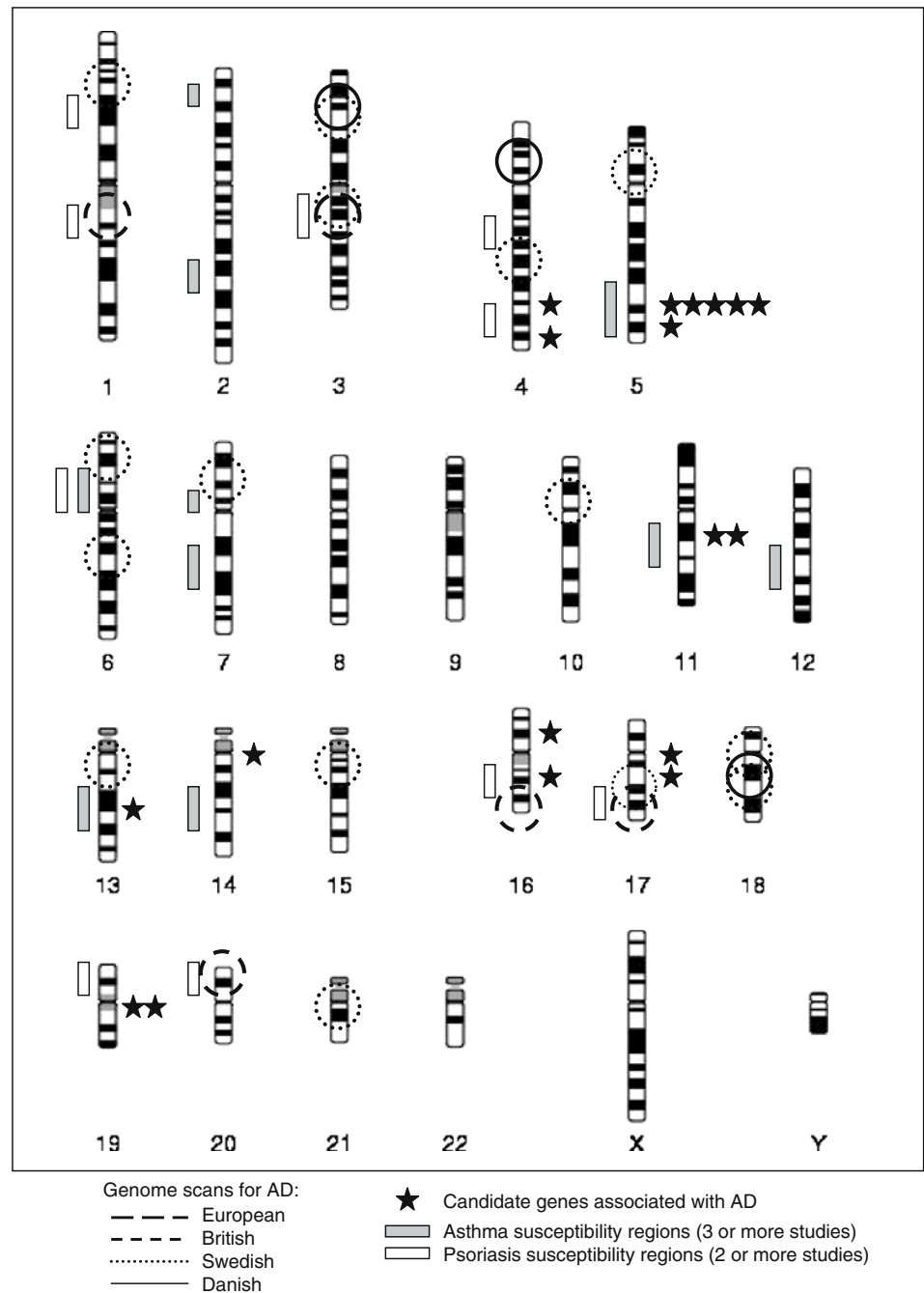
Figure 1 summarizes the results of the genome-wide screens for AD in comparison with genome-wide linkage results for related diseases. Interestingly, out of the four major regions identified for AD (see above), only two (3p and 17q) have shown suggestive evidence for linkage to asthma or related phenotypes in more than one study [29]. Furthermore, the regions most consistently linked to asthma or related phenotypes, including the cytokine cluster region on chromosome 5q, the major histocompatibility complex (MHC; in man *HLA*) region on chromosome 6p and regions on 13q and 12q [29], did not show substantial evidence for linkage to AD in the four genome screens, indicating that separate genes might be important for susceptibility to AD.

Table 1 Genome-wide screens for AD

Reference	Study population	Sample	Phenotypes	Regions of highest linkage
Lee et al. 2000 [25]	European	199 families with ≥ 2 affected siblings	AD Allergic sensitization	3q21 ($p=8.42 \times 10^{-6}$) 3q21 ($p=6.7 \times 10^{-4}$)
Cookson et al. 2001 [28]	British	148 nuclear families recruited via children with active AD	AD AD plus asthma Σ serum IgE	1q21 ($p=0.0005$) 17q25 ($p=0.0004$) 20p ($p=0.0005$) 16q-tel ($p=0.0007$) 5q31 ($p=0.004$)
Bradley et al. 2002 [26]	Swedish	109 families (197 affected full-sib pairs, 9 affected half-sib pairs)	AD AD plus specific IgE Extreme AD Severity score of AD	3p24-22 ($p<0.001$) 5p13 ($p<0.005$) 6q16 ($p<0.01$) 10p13-12 ($p<0.01$) 18q21 ($p<0.001$) 4q24-26 ($p<0.005$) 6p ($p<0.005$) 1p32 ($p<0.01$) 18p ($p<0.005$) 21q21 ($p<0.005$) 7p14 ($p<0.005$) 13q14 ($p<7.41 \times 10^{-4}$) 15q14-15 ($p<7.4 \times 10^{-4}$) 17q21 ($p<7.4 \times 10^{-4}$) 3q14 ($p<7.4 \times 10^{-4}$)
Haagerup et al. 2004 [27]	Danish	23 affected sib-pair families	AD plus specific IgE	3p26-24 ($p \leq 0.001$) 4p15-14 ($p \leq 0.0126$) 18q11-12 ($p=0.004$) 18q11-12 ($p \leq 0.004$)

AD Atopic dermatitis, IgE immunoglobulin E

Fig. 1 Results of genome-wide screens and association studies for atopic dermatitis. Regions on chromosomes 3q, 3p, 17q, and 18q showed suggestive evidence for linkage to AD in at least two genome-wide screens (*overlapping circles*). AD regions identified on chromosomes 1q, 3q, 17q, and 20p overlap with psoriasis loci (*white bars*; loci linked to psoriasis in at least two different populations), while there is little overlap with regions consistently linked to asthma (*grey bars*; loci linked to asthma and related phenotypes in at least three studies or showing genome-wide evidence for linkage in at least one study; adapted from [29]). Candidate genes that have been associated with AD so far (*stars*) are generally not located in the AD regions identified by linkage studies, but rather in regions linked to asthma and atopy (e.g., 5q and 11q)



In fact, some of the regions relevant for AD overlap with regions showing linkage to psoriasis, another chronic skin disorder that is characterized by thickened, silvery-scale patches [30]. AD and psoriasis are the two most common chronic inflammatory skin diseases; however, their mechanisms for skin inflammation are quite different. Whereas in AD, the immune response is predominated by T helper (Th)2 cytokines [such as interleukin (IL)-4, IL-5, and IL-13] and eosinophilia, the immune response in psoriasis is Th1-mediated and associated with local neutrophil infiltration [31]. Ten genome screens for psoriasis have been completed to date [32, 33]. It has long been recognized that the *HLA* region on chromosome 6p21 harbors the main

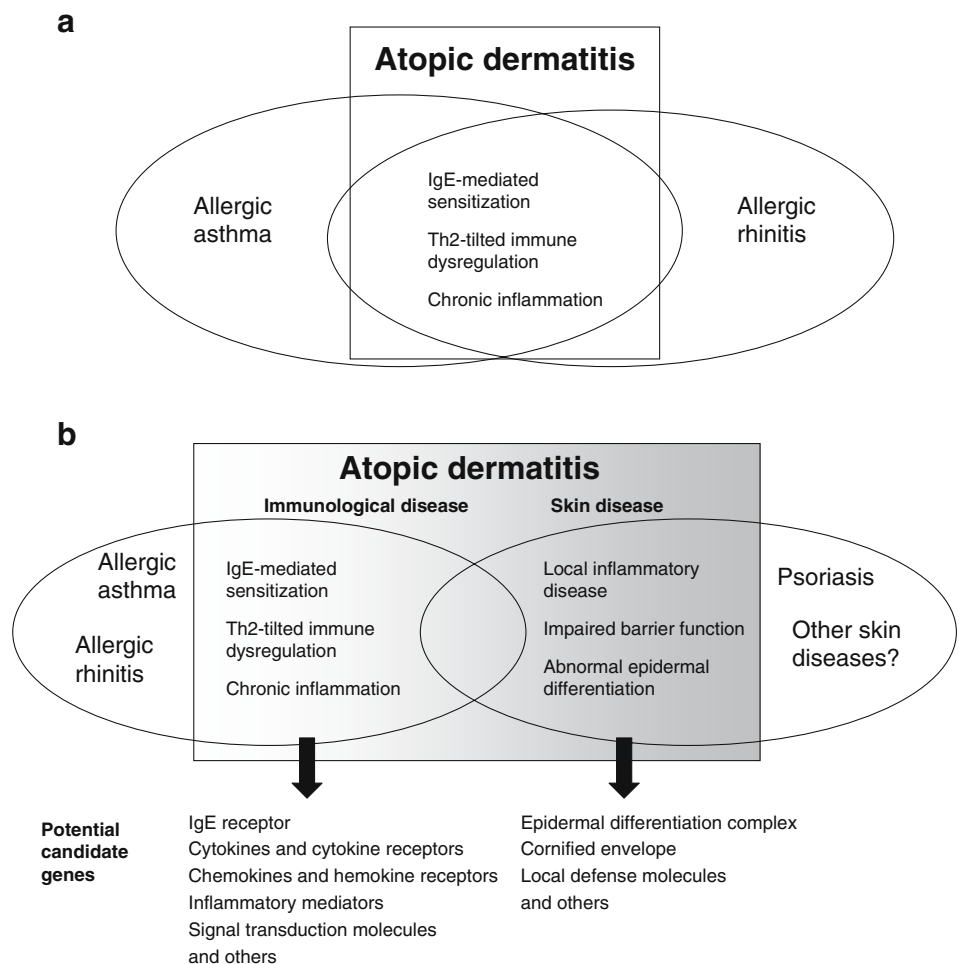
determinant conferring psoriasis susceptibility (*PSORS1*) [34]. Besides the *HLA* region, several other susceptibility loci for this disease have been described: *PSORS2* to *PSORS9*. The AD region on chromosome 17q (see above) overlaps with *PSORS2* (17q25), the AD region on chromosome 3q overlaps with *PSORS5* (3q21), and two additional regions showing suggestive evidence for linkage to AD or AD with asthma in the British genome screen (1q21 and 20p) overlap with psoriasis susceptibility loci [28]. Thus, genes that are expressed in the skin might play an important role in AD pathogenesis, in addition to genes influencing atopic diatheses.

Figure 2 illustrates the changing concept for AD pathophysiology: although AD was previously mainly classified as part of the spectrum of allergic disorders with IgE-mediated sensitization and Th2-tilted immune dysregulation as major characteristics, the results of the genetic studies suggest that AD is also partly a local skin disease that shares important features—such as abnormal epidermal differentiation and defective skin defense mechanisms—with other skin diseases, e.g., psoriasis. For example, the 1q21 locus that was linked to both AD and psoriasis houses a cluster of genes known as the epidermal differentiation complex (EDC) which encode proteins involved in keratinocyte terminal differentiation [35]. The importance of the EDC for AD pathophysiology is further highlighted by the result of genome-wide gene expression studies. EDC genes were found to be differentially expressed in psoriasis as well as in AD [36–38]. Precisely, when comparing the expression of 23,000 genes in skin biopsies from 17 patients with AD in relation to healthy controls, four of the ten genes with the greatest differences in expression were EDC genes [38]. Several of the proteins encoded by EDC genes are part of a specialized protective barrier structure in the skin, the so-called cornified envelope (CE) [39]. Another CE gene that showed high expression in AD, the Keratin 16 gene, is located within the region linked to AD

on chromosome 17q21 [38]. Taken together, these results highlight the potential importance of genes expressed locally in the skin in the pathogenesis of AD.

Following a genome-wide screen, positional cloning techniques are used to identify the gene(s) influencing disease susceptibility in the linked region. Although no AD gene has been identified by positional cloning yet, there are promising results for related complex diseases. In asthma, for example, four genes have been positionally cloned so far. The *ADAM33* (a disintegrin and metalloprotease 33) on chromosome 20p was the first “asthma gene” to be discovered in 2002 [40]. Other groups later reported the *DPP10* (dipeptidyl peptidase 10) [41], *PHF11* (plant homeodomain Zink finger 11 protein) [42] and *GPRA* (G protein-coupled receptor for asthma susceptibility) [43] genes on chromosomes 2q, 13q, and 7p, respectively, as positionally cloned asthma genes. Similarly, for Crohn’s disease, an inflammatory bowel disorder, the *CARD15*, *SLC22A4*, and *DLG5* genes have been identified after positional cloning [44–46]. Although it is likely that many more genes may be discovered, which overall seem to contribute only moderately to disease susceptibility, these examples show that the positional cloning approach can be successful for complex and heterogeneous diseases. Thus, it is possible (and likely)

Fig. 2 Changing concept for AD pathophysiology: although AD was for a long time mainly classified as part of the spectrum of allergic disorders with IgE-mediated sensitization and Th2-tilted immune dysregulation as major characteristics (a), the results of the genetic studies suggest that AD is also partly a local skin disease that shares important features, like abnormal epidermal differentiation and defective skin defense mechanisms, with other skin diseases, e.g., psoriasis (b). Thus, two different sets of possible candidate genes for AD can be evaluated



that susceptibility genes for AD will be discovered with this approach in the near future as well.

Results of candidate gene studies for atopic dermatitis

Several candidate gene association studies for AD have been reported to date, most of which have focused on genes thought to play a role in allergic disorders in general, e.g., genes in the cytokine gene cluster region on chromosome 5q31 (Fig. 1). Variations in 19 genes have shown significant association with AD in at least one study (Table 2). These studies vary substantially with respect to design and specific phenotypes. Overall sample sizes are small (less than 100 cases in most studies), and relatively few positive findings have been replicated. Yet, variations in three genes have been associated with AD in at least four different studies.

Interleukin 13 (*IL13*) gene

Interleukin-13 is a Th2 cytokine that is believed to play an important role in the pathogenesis of allergic disorders (reviewed in [47]). In subacute and chronic AD lesions, IL-13 mRNA is up-regulated, suggesting that IL-13 is a crucial cytokine in lesioned skin [48]. The gene encoding IL-13 is located in the cytokine gene cluster region on chromosome 5q31. Two functional SNPs have been identified in this gene to date. A C/T SNP in the promoter region at position -1112 was associated with increased IL-13 production and increased binding of nuclear proteins to this region [49]. Furthermore, a coding SNP in exon 4 (G4464A) that results in an amino acid exchange from arginine to glutamine at position #130 (Arg130Gln) was shown to influence binding of IL-13 to the IL-13 receptor $\alpha 2$ chain, leading to slower clearance as well as enhanced stability in plasma [50]. The Arg130Gln variation was associated with AD in Canadian [51], Japanese [52], and German populations [53]. The promoter SNP was associated with AD in a Dutch cohort [54]; however, it did not show association with AD in the Japanese sample [52]. Yet, these two SNPs in the interleukin 13 gene are among the variations most consistently associated with allergic phenotypes in general, including asthma [49, 55, 56], bronchial hyper-responsiveness [56], total IgE levels [53, 57], and atopy [58], suggesting that the *IL13* gene may indeed represent an atopy susceptibility locus in the 5q31 chromosomal region.

Interleukin 4 receptor alpha (*IL4RA*) gene

The receptors for IL-13 and IL-4, another important Th2 cytokine, share a common α -chain, encoded by the *IL4RA* gene on chromosome 16p12. Ten amino acid substitutions have been described in the coding regions of the *IL4RA* gene on chromosome 16p12, three of which were shown to

be functional (Ile50Val, Ser478Pro, and Gln551Arg). Out of these variations, the Gln551Arg substitution showed association with severe AD in a small American sample [59] and with adult AD in a Japanese population [60]. Interestingly, Callard et al. [61] described an interaction between genotype at this locus and infection in early infancy on the susceptibility for AD, suggesting gene/environment interplay (see below). The Gln551Arg variation was not associated with AD with normal IgE levels in a Japanese cohort [62]. Recently, a promoter SNP was identified at position -3223 (C/T) that was associated with decreased levels of soluble IL-4 receptor protein [63]. This SNP was found to be associated with extrinsic AD in Germans [64], but did not show association with AD in a Japanese sample [65].

These somewhat conflicting results for AD regarding the *IL4RA* locus reflect the results of association studies between the *IL4RA* gene and allergic phenotypes in general. Although many studies report significant associations with one of the known variations in this gene with asthma or atopy [66–68], the associated alleles differ substantially between studies and populations. Therefore, in recent studies on asthma, several to multiple SNPs were investigated simultaneously in the form of haplotypes, and this approach was found to be more informative than an examination of isolated SNPs [69–71]. Thus, investigation of *IL4RA* haplotypes might reveal deeper insights into the role of this gene in AD susceptibility in the future.

Serine protease inhibitor Kazal-type 5 (*SPINK5*) gene

Netherton's syndrome is a rare autosomal recessively transmitted disease characterized by elevated IgE levels with atopic manifestations and ichthyotic skin, including characteristic hair abnormalities [72]. Mutations causing Netherton's disease have been identified in the *SPINK5* gene on chromosome 5q31, encoding LEKTI, a 15-domain serine protease inhibitor expressed in epithelial and mucosal surfaces and the thymus [73]. Walley et al. [74] recently screened the coding sequence of this gene for variation in patients with AD and identified six coding polymorphisms [74]. The Glu420Lys substitution was associated with AD and atopy in two different cohorts of British families. Interestingly, a parent-of-origin effect was seen, with an increased risk for atopy when the Asn368 and Lys420 alleles were maternally inherited [74]. Polymorphisms in the same gene subsequently showed an association with AD in two independent Japanese studies [75, 76], with asthma in combination with AD in a large German cohort [77], and with disease severity and food allergy in Japanese children with AD [78]. One hypothesis for the role of LEKTI polymorphisms in the pathophysiology of AD reflects that it might influence the inhibition of many allergens that are also serine proteases [74]. Yet, the exact manner of how LEKTI influences AD and allergic disease remains to be unraveled.

Table 2 Candidate gene studies for AD; genes that have been associated with AD in at least one study

Gene	Gene name	Location	Variant	Phenotype	Population	Association?	Reference
<i>TLR2</i>	Toll-like receptor 2	4q32	Arg753Gln	Severe AD	German	Yes	[82]
<i>IRF2</i>	Interferon regulatory factor 2	4q35	−467 G/A	AD	Japanese	Yes	[87]
<i>CSF2</i>	Colony-stimulating factor 2	5q31	−677 A/C	AD	British	Yes	[88]
			3606 T/C, 3928 C/T	AD at 12 and 24 months	Canadian	Yes	[89]
<i>IL4</i>	Interleukin-4	5q31	−590 C/T	AD	Japanese	Yes	[90]
				Extrinsic AD	German	Yes	[64]
				AD	Australian	No	[91]
				Intrinsic AD	Japanese	No	[62]
<i>IL13</i>	Interleukin-13	5q31	Arg130Gln	AD	Canadian	Yes	[51]
				AD	Japanese	Yes	[52]
				AD	German	Yes	[53]
			−1111 C/T	AD	Dutch	Yes	[54]
				AD	Japanese	No	[52]
<i>IL5</i>	Interleukin-5	5q31	−703 C/T	Blood eosinophilia in AD	Japanese	Yes	[92]
<i>CD14</i>	Monocyte differentiation antigen CD14	5q31	−159 C/T	AD (interaction with dog ownership)	American	Yes	[80]
				AD	German	No	[93]
<i>IL12B</i>	Interleukin-12B	5q31-33	1188 A/C	AD, Psoriasis	Japanese	Yes	[94]
<i>SPINK5</i>	Serine protease inhibitor, Kazal-type 5		Glu420Lys	AD	British	Yes	[74]
				AD	Japanese	Yes	[75]
				AD	Japanese	Yes	[76]
				Asthma with AD	German	Yes	[77]
				Disease severity and food allergy in AD	Japanese	Yes	[78]
<i>FCER1B</i>	High affinity IgE receptor, beta chain	11q13	Rsalin2, RsaIex7	AD	British	Yes	[95]
<i>GSTP1</i>	Glutathione <i>S</i> -transferase, P1	11q13	Ile105Val	AD	Russian	Yes	[96]
			Haplotypes	AD	Russian	Yes	[97]
<i>PHF11</i>	Plant homeodomain Zink finger 11 protein	13q14	T/C intron3, G/A 3' UTR	Childhood AD	Australian	Yes	[98]
<i>CMA1</i>	Mast cell chymase	14q11	BstXI	AD	Japanese	Yes	[99]
				AD	Japanese	Yes	[100]
				AD	Japanese	No	[101]
				AD	Italian	No	[102]
			−1903 G/A	IgE levels in AD	British	Yes	[103]
<i>IL4RA</i>	Interleukin 4 receptor α chain	16p12	Gln551Arg	Severe AD	American	Yes	[59]
				Adult AD	Japanese	Yes	[60]
				AD (interaction with infection)	British	Yes	[61]
				Intrinsic AD	Japanese	No	[62]
			−3223 C/T	Extrinsic AD	German	Yes	[64]
				AD	Japanese	Yes	[65]
<i>CARD15</i>	Caspase recruitment domain- containing protein 15	16q12	2722 G/C	AD	German	Yes	[104]
<i>RANTES</i>	Regulated upon activation, normally T cell expressed + secreted	17q11-q12	−403 A/G	AD	German	Yes	[105]
				AD	Hungarian	No	[106]
<i>EOTAXIN</i>	Eotaxin	17q21	−426 C/T, −384 A/G	IgE levels in AD	Japanese	Yes	[107]
<i>TGFB1</i>	Transforming growth factor β 1	19q13.1	Arg25Pro	AD	British	Yes	[108]
<i>SCCE</i>	Stratum corneum chymotryptic enzyme	19q13	AACCins	AD	British	Yes	[109]

AD Atopic dermatitis, IgE immunoglobulin E

Gene/gene and gene/environment interactions

Since AD belongs to the group of complex and heterogeneous disorders, gene/gene as well as gene/environment interactions are suspected to play an important role for disease inception. Very few genetic studies have incorporated such comprehensive analyses so far. For example, interaction was reported between genotypes of the IL-4 and thromboxane A2 receptors (*IL4RA* and *TBXA2R*) on serum IgE levels in Japanese patients with AD [79]. Patients with both *TBXA2R* 795TT and *IL4RA* Ile50/Ile50 genotypes showed the highest IgE concentrations [79].

Callard et al. [61] found a significant association between the Gln551Arg variation of the *IL4RA* gene and flexural eczema at the age of 6 months only in children who had not had an infection requiring antibiotics, suggesting gene/environment interaction. Furthermore, interaction between the *CD14* genotype (encoding part of the endotoxin receptor) and persistent dog contact was reported on the risk for AD at the age of 1 year in a cohort of children at high risk for developing allergic disease [80]. These latter results are particularly interesting with respect to the hygiene hypothesis, indicating that the complex interplay between genes and environment (in this case, microbial stimuli in early childhood) plays an important role in the development of allergic diseases.

The receptor system that constitutes the first, innate immune response to microbial stimuli consists of the family of Toll-like receptors (TLRs), highly conserved receptor complexes that recognize pathogen-associated molecular patterns. Recently, a potential role of genetic variation in *TLR* genes in human disease was suggested (reviewed in [81]), but little is known about the role of these genes in AD so far. A coding variation in *TLR2* was associated with a severe form of AD in one study [82]. Yet, we could neither replicate an association of this coding variation nor of a promoter polymorphism (−16934 A/T) in *TLR2* with AD in a German cohort (unpublished results, 2005). Similarly, polymorphisms in the *TLR6* (Ser249Pro) and *TLR4* (Asp 299Gly) genes did not show association with AD (unpublished data). Yet, incorporating analyses on potential gene/environment interactions (e.g., stratifying by level of endotoxin exposure or else) might be a promising approach to evaluate the role of these innate immunity genes in the pathogenesis of AD. Examples from association studies for related phenotypes such as asthma [83–85] emphasize that incorporating gene/gene and gene/environment interactions in genetic studies could contribute profoundly to understanding the complex genetic background underlying susceptibility for multifactorial diseases.

Conclusions and future prospects

There is initial evidence that the genetic background for AD and related allergic diseases such as asthma is less similar than expected and that genes expressed locally in the skin, e.g., genes encoding proteins for the cornified envelope and local defense mechanisms, might be crucial

for AD development. These findings pave the way for different categories of candidate genes to be examined for AD.

Following genome-wide screens, positional cloning efforts for AD will certainly be conducted in the near future. Additionally, association studies on a genome-wide level are likely to become feasible within a few years, and genome-wide expression studies are also starting to improve the current knowledge about the genetic background of AD. Combining these different techniques will eventually reveal more genes that are important for the pathophysiology of AD.

Identifying genetic variation that influences the development of AD can have important clinical implications. First, knowledge about genetic susceptibility allows us to identify at-risk individuals very early in life and to develop specific prevention strategies. Second, genetic variation can influence treatment response to certain pharmaceuticals (as described for variation in the gene encoding the β_2 -adrenoceptor and treatment with β_2 -adrenoceptor agonists in asthma patients [86]). Thus, specific treatments for genetically different individuals might be developed. And third, a better understanding of the complex genetic and molecular background that underlies AD, with the incorporation of gene/gene and gene/environment interactions, should lead to the development of new diagnostic and therapeutic strategies in the future.

Acknowledgements This work was supported by the “Forschungsförderung der Ruhr-Universität Bochum (FoRUM)”, grant F377-03.

References

- Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, Asher I, Beasley R, Bjorksten B, Burr M et al (1999) Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. *J Allergy Clin Immunol* 103:125–138
- Leung DY, Bieber T (2003) Atopic dermatitis. *Lancet* 361:151–160
- Kaiser HB (2004) Risk factors in allergy/asthma. *Allergy Asthma Proc* 25:7–10
- Spergel JM, Paller AS (2003) Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 112:S118–S127
- Bohme M, Lannero E, Wickman M, Nordvall SL, Wahlgren CF (2002) Atopic dermatitis and concomitant disease patterns in children up to 2 years of age. *Acta Derm Venereol* 82:98–103
- Cabon N, Ducombs G, Mortureux P, Perromat M, Taieb A (1996) Contact allergy to aeroallergens in children with atopic dermatitis: comparison with allergic contact dermatitis. *Contact Dermatitis* 35:27–32
- Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wuthrich B (2001) Epidemiology, clinical features, and immunology of the “intrinsic” (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). *Allergy* 56:841–849
- Novak N, Bieber T (2003) Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol* 112:252–262
- Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J et al (2004) Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 113:832–836

10. Dold S, Wjst M, von Mutius E, Reitmeir P, Stiepel E (1992) Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. *Arch Dis Child* 67:1018–1022
11. Schultz Larsen FV, Holm NV (1985) Atopic dermatitis in a population based twin series. Concordance rates and heritability estimation. *Acta Derm Venereol Suppl* (Stockh) 114:159
12. Larsen FS, Holm NV, Henningsen K (1986) Atopic dermatitis. A genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 15:487–494
13. Farrall M (2004) Quantitative genetic variation: a post-modern view. *Hum Mol Genet* 13(Spec no. 1):R1–R7
14. Schultz Larsen F, Hanifin JM (1992) Secular change in the occurrence of atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh) 176:7–12
15. Burr ML, Butland BK, King S, Vaughan-Williams E (1989) Changes in asthma prevalence: two surveys 15 years apart. *Arch Dis Child* 64:1452–1456
16. Isolauri E, Huurre A, Salminen S, Impivaara O (2004) The allergy epidemic extends beyond the past few decades. *Clin Exp Allergy* 34:1007–1010
17. Martinez FD (2001) The coming-of-age of the hygiene hypothesis. *Respir Res* 2:129–132
18. Gehring U, Bolte G, Borte M, Bischof W, Fahlbusch B, Wichmann HE, Heinrich J (2001) Exposure to endotoxin decreases the risk of atopic eczema in infancy: a cohort study. *J Allergy Clin Immunol* 108:847–854
19. Weiss ST (2002) Eat dirt—the hygiene hypothesis and allergic diseases. *N Engl J Med* 347:930–931
20. Flohr C, Pascoe D, Williams HC (2005) Atopic dermatitis and the ‘hygiene hypothesis’: too clean to be true? *Br J Dermatol* 152:202–216
21. Risch N, Merikangas K (1996) The future of genetic studies of complex human diseases. *Science* 273:1516–1517
22. Hoffjan S, Nicolae D, Ober C (2003) Association studies for asthma and atopic diseases: a comprehensive review of the literature. *Respir Res* 4:14
23. Hirschhorn JN, Daly MJ (2005) Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet* 6:95–108
24. Wang WY, Barratt BJ, Clayton DG, Todd JA (2005) Genome-wide association studies: theoretical and practical concerns. *Nat Rev Genet* 6:109–118
25. Lee YA, Wahn U, Kehrt R, Tarani L, Businco L, Gustafsson D, Andersson F, Oranje AP, Wolkertstorfer A, v Berg A et al (2000) A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. *Nat Genet* 26:470–473
26. Bradley M, Soderhall C, Luthman H, Wahlgren CF, Kockum I, Nordenskjold M (2002) Susceptibility loci for atopic dermatitis on chromosomes 3, 13, 15, 17 and 18 in a Swedish population. *Hum Mol Genet* 11:1539–1548
27. Haagerup A, Bjerke T, Schiotz PO, Dahl R, Binderup HG, Tan Q, Kruse TA (2004) Atopic dermatitis—a total genome-scan for susceptibility genes. *Acta Derm Venereol* 84:346–352
28. Cookson WO, Ubhi B, Lawrence R, Abecasis GR, Walley AJ, Cox HE, Coleman R, Leaves NI, Trembath RC, Moffatt MF et al (2001) Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. *Nat Genet* 27:372–373
29. Hoffjan S, Ober C (2005) Genetic factors. In: Lenfant C (ed) *Lung biology in health and disease*. Marcel Dekker, NY (in press)
30. Loudon BA, Pearce DJ, Lang W, Feldman SR (2004) A Simplified Psoriasis Area Severity Index (SPASI) for rating psoriasis severity in clinic patients. *Dermatol Online J* 10:7
31. Biedermann T, Rocken M, Carballido JM (2004) TH1 and TH2 lymphocyte development and regulation of TH cell-mediated immune responses of the skin. *J Investig Dermatol Symp Proc* 9:5–14
32. Sagoo GS, Cork MJ, Patel R, Tazi-Ahnini R (2004) Genome-wide studies of psoriasis susceptibility loci: a review. *J Dermatol Sci* 35:171–179
33. Sagoo GS, Tazi-Ahnini R, Barker JW, Elder JT, Nair RP, Samuelsson L, Traupe H, Trembath RC, Robinson DA, Iles MM (2004) Meta-analysis of genome-wide studies of psoriasis susceptibility reveals linkage to chromosomes 6p21 and 4q28–q31 in Caucasian and Chinese Hans population. *J Invest Dermatol* 122:1401–1405
34. Bowcock AM, Cookson WO (2004) The genetics of psoriasis, psoriatic arthritis and atopic dermatitis. *Hum Mol Genet* 13(Spec no. 1):R43–R55
35. Mischke D, Korge BP, Marenholz I, Volz A, Ziegler A (1996) Genes encoding structural proteins of epidermal cornification and S100 calcium-binding proteins form a gene complex (“epidermal differentiation complex”) on human chromosome 1q21. *J Invest Dermatol* 106:989–992
36. Bowcock AM, Shannon W, Du F, Duncan J, Cao K, Aftergut K, Catier J, Fernandez-Vina MA, Menter A (2001) Insights into psoriasis and other inflammatory diseases from large-scale gene expression studies. *Hum Mol Genet* 10:1793–1805
37. Nomura I, Gao B, Boguniewicz M, Darst MA, Travers JB, Leung DY (2003) Distinct patterns of gene expression in the skin lesions of atopic dermatitis and psoriasis: a gene microarray analysis. *J Allergy Clin Immunol* 112:1195–1202
38. Sugiura H, Ebise H, Tazawa T, Tanaka K, Sugiura Y, Uehara M, Kikuchi K, Kimura T (2005) Large-scale DNA microarray analysis of atopic skin lesions shows overexpression of an epidermal differentiation gene cluster in the alternative pathway and lack of protective gene expression in the cornified envelope. *Br J Dermatol* 152:146–149
39. Kalinin AE, Kajava AV, Steinert PM (2002) Epithelial barrier function: assembly and structural features of the cornified cell envelope. *BioEssays* 24:789–800
40. Van Eerdewegh P, Little RD, Dupuis J, Del Mastro RG, Falls K, Simon J, Torrey D, Pandit S, McKenny J, Braunschweiger K et al (2002) Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature* 418:426–430
41. Allen M, Heinzmann A, Noguchi E, Abecasis G, Broxholme J, Ponting CP, Bhattacharyya S, Tinsley J, Zhang Y, Holt R et al (2003) Positional cloning of a novel gene influencing asthma from chromosome 2q14. *Nat Genet* 35:258–263
42. Zhang Y, Leaves NI, Anderson GG, Ponting CP, Broxholme J, Holt R, Edser P, Bhattacharyya S, Dunham A, Adcock IM et al (2003) Positional cloning of a quantitative trait locus on chromosome 13q14 that influences immunoglobulin E levels and asthma. *Nat Genet* 34:181–186
43. Laitinen T, Polvi A, Rydman P, Vendelin J, Pulkkinen V, Salmikangas P, Makela S, Rehn M, Pirskanen A, Rautanen A et al (2004) Characterization of a common susceptibility locus for asthma-related traits. *Science* 304:300–304
44. McGovern DP, van Heel DA, Ahmad T, Jewell DP (2001) NOD2 (CARD15), the first susceptibility gene for Crohn’s disease. *Gut* 49:752–754
45. Peltekova VD, Wintle RF, Rubin LA, Amos CI, Huang Q, Gu X, Newman B, Van Oene M, Escoson D, Greenberg G et al (2004) Functional variants of OCTN cation transporter genes are associated with Crohn disease. *Nat Genet* 36:471–475
46. Stoll M, Corneliussen B, Costello CM, Waetzig GH, Mellgard B, Koch WA, Rosenstiel P, Albrecht M, Croucher PJ, Seegert D et al (2004) Genetic variation in DLG5 is associated with inflammatory bowel disease. *Nat Genet* 36:476–480
47. Wills-Karp M (2004) Interleukin-13 in asthma pathogenesis. *Immunol Rev* 202:175–190
48. Tazawa T, Sugiura H, Sugiura Y, Uehara M (2004) Relative importance of IL-4 and IL-13 in lesional skin of atopic dermatitis. *Arch Dermatol Res* 295:459–464
49. van der Pouw Kraan TC, van Veen A, Boeije LC, van Tuyl SA, de Groot ER, Stapel SO, Bakker A, Verweij CL, Aarden LA, van der Zee JS (1999) An IL-13 promoter polymorphism associated with increased risk of allergic asthma. *Genes Immun* 1:61–65

50. Arima K, Umeshita-Suyama R, Sakata Y, Akaiwa M, Mao XQ, Enomoto T, Dake Y, Shimazu S, Yamashita T, Sugawara N et al (2002) Upregulation of IL-13 concentration in vivo by the IL13 variant associated with bronchial asthma. *J Allergy Clin Immunol* 109:980–987
51. He JQ, Chan-Yeung M, Becker AB, Dimich-Ward H, Ferguson AC, Manfreda J, Watson WT, Sandford AJ (2003) Genetic variants of the IL13 and IL4 genes and atopic diseases in at-risk children. *Genes Immun* 4:385–389
52. Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Kakinuma T, Fujita H, Asano N, Tanida Y, Wakugawa M et al (2002) Interleukin-13 gene polymorphism G4257A is associated with atopic dermatitis in Japanese patients. *J Dermatol Sci* 30:100–107
53. Liu X, Nickel R, Beyer K, Wahn U, Ehrlich E, Freidhoff LR, Bjorksten B, Beaty TH, Huang SK (2000) An IL13 coding region variant is associated with a high total serum IgE level and atopic dermatitis in the German multicenter atopy study (MAS-90). *J Allergy Clin Immunol* 106:167–170
54. Hummelshoj T, Bodtger U, Datta P, Malling HJ, Oturai A, Poulsen LK, Ryder LP, Sorensen PS, Svejgaard E, Svejgaard A (2003) Association between an interleukin-13 promoter polymorphism and atopy. *Eur J Immunogenet* 30:355–359
55. Heinzmann A, Mao XQ, Akaiwa M, Kreomer RT, Gao PS, Ohshima K, Umeshita R, Abe Y, Braun S, Yamashita T et al (2000) Genetic variants of IL-13 signalling and human asthma and atopy. *Hum Mol Genet* 9:549–559
56. Howard TD, Whittaker PA, Zaiman AL, Koppelman GH, Xu J, Hanley MT, Meyers DA, Postma DS, Bleeker ER (2001) Identification and association of polymorphisms in the interleukin-13 gene with asthma and atopy in a Dutch population. *Am J Respir Cell Mol Biol* 25:377–384
57. Graves PE, Kabesch M, Halonen M, Holberg CJ, Baldini M, Fritzsch C, Weiland SK, Erickson RP, von Mutius E, Martinez FD (2000) A cluster of seven tightly linked polymorphisms in the IL-13 gene is associated with total serum IgE levels in three populations of white children. *J Allergy Clin Immunol* 105:506–513
58. Leung TF, Tang NL, Chan IH, Li AM, Ha G, Lam CW (2001) A polymorphism in the coding region of interleukin-13 gene is associated with atopy but not asthma in Chinese children. *Clin Exp Allergy* 31:1515–1521
59. Hershey GK, Friedrich MF, Esswein LA, Thomas ML, Chatila TA (1997) The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. *N Engl J Med* 337:1720–1725
60. Oiso N, Fukai K, Ishii M (2000) Interleukin 4 receptor alpha chain polymorphism Gln551Arg is associated with adult atopic dermatitis in Japan. *Br J Dermatol* 142:1003–1006
61. Callard RE, Hamvas R, Chatterton C, Blanco C, Pembrey M, Jones R, Sherriff A, Henderson J (2002) An interaction between the IL-4R alpha gene and infection is associated with atopic eczema in young children. *Clin Exp Allergy* 32:990–993
62. Tanaka K, Sugiura H, Uehara M, Hashimoto Y, Donnelly C, Montgomery DS (2001) Lack of association between atopic eczema and the genetic variants of interleukin-4 and the interleukin-4 receptor alpha chain gene: heterogeneity of genetic backgrounds on immunoglobulin E production in atopic eczema patients. *Clin Exp Allergy* 31:1522–1527
63. Hackstein H, Hecker M, Kruse S, Bohnert A, Ober C, Deichmann KA, Bein G (2001) A novel polymorphism in the 5' promoter region of the human interleukin-4 receptor alpha-chain gene is associated with decreased soluble interleukin-4 receptor protein levels. *Immunogenetics* 53:264–269
64. Novak N, Kruse S, Kraft S, Geiger E, Kluken H, Fimmers R, Deichmann KA, Bieber T (2002) Dichotomic nature of atopic dermatitis reflected by combined analysis of monocyte immunophenotyping and single nucleotide polymorphisms of the interleukin-4/interleukin-13 receptor gene: the dichotomy of extrinsic and intrinsic atopic dermatitis. *J Invest Dermatol* 119:870–875
65. Hosomi N, Fukai K, Oiso N, Kato A, Ishii M, Kunitomo H, Nakajima K (2004) Polymorphisms in the promoter of the interleukin-4 receptor alpha chain gene are associated with atopic dermatitis in Japan. *J Invest Dermatol* 122:843–845
66. Mitsuyasu H, Izuhara K, Mao XQ, Gao PS, Arinobu Y, Enomoto T, Kawai M, Sasaki S, Dake Y, Hamasaki N et al (1998) Ile50Val variant of IL4R alpha upregulates IgE synthesis and associates with atopic asthma. *Nat Genet* 19:119–120
67. Izuhara K, Yanagihara Y, Hamasaki N, Shirakawa T, Hopkin JM (2000) Atopy and the human IL-4 receptor alpha chain. *J Allergy Clin Immunol* 106:S65–S71
68. Sandford AJ, Chagani T, Zhu S, Weir TD, Bai TR, Spinelli JJ, Fitzgerald JM, Behbehani NA, Tan WC, Pare PD (2000) Polymorphisms in the IL4, IL4RA, and FCER1B genes and asthma severity. *J Allergy Clin Immunol* 106:135–140
69. Bottini N, Borgiani P, Otsu A, Saccucci P, Stefanini L, Greco E, Fontana L, Hopkin JM, Mao XQ, Shirakawa T (2002) IL-4 receptor alpha chain genetic polymorphism and total IgE levels in the English population: two-locus haplotypes are more informative than individual SNPs. *Clin Genet* 61:288–292
70. Ober C, Leavitt SA, Tsalenko A, Howard TD, Hoki DM, Daniel R, Newman DL, Wu X, Parry R, Lester LA et al (2000) Variation in the interleukin 4-receptor alpha gene confers susceptibility to asthma and atopy in ethnically diverse populations. *Am J Hum Genet* 66:517–526
71. Risma KA, Wang N, Andrews RP, Cunningham CM, Ericksen MB, Bernstein JA, Chakraborty R, Hershey GK (2002) V75 R576 IL-4 receptor alpha is associated with allergic asthma and enhanced IL-4 receptor function. *J Immunol* 169:1604–1610
72. Smith DL, Smith JG, Wong SW, deShazo RD (1995) Netherton's syndrome: a syndrome of elevated IgE and characteristic skin and hair findings. *J Allergy Clin Immunol* 95:116–123
73. Chavanas S, Bodemer C, Rochat A, Hamel-Teillac D, Ali M, Irvine AD, Bonafe JL, Wilkinson J, Taieb A, Barrandon Y et al (2000) Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet* 25:141–142
74. Walley AJ, Chavanas S, Moffatt MF, Esnouf RM, Ubhi B, Lawrence R, Wong K, Abecasis GR, Jones EY, Harper JJ et al (2001) Gene polymorphism in Netherton and common atopic disease. *Nat Genet* 29:175–178
75. Kato A, Fukai K, Oiso N, Hosomi N, Murakami T, Ishii M (2003) Association of SPINK5 gene polymorphisms with atopic dermatitis in the Japanese population. *Br J Dermatol* 148:665–669
76. Nishio Y, Noguchi E, Shibasaki M, Kamioka M, Ichikawa E, Ichikawa K, Umebayashi Y, Otsuka F, Arinami T (2003) Association between polymorphisms in the SPINK5 gene and atopic dermatitis in the Japanese. *Genes Immun* 4:515–517
77. Kabesch M, Carr D, Weiland SK, von Mutius E (2004) Association between polymorphisms in serine protease inhibitor, kazal type 5 and asthma phenotypes in a large German population sample. *Clin Exp Allergy* 34:340–345
78. Kusunoki T, Okafuji I, Yoshioka T, Saito M, Nishikomori R, Heike T, Sugai M, Shimizu A, Nakahata T (2005) SPINK5 polymorphism is associated with disease severity and food allergy in children with atopic dermatitis. *J Allergy Clin Immunol* 115:636–638
79. Tanaka K, Roberts MH, Yamamoto N, Sugiura H, Uehara M, Mao XQ, Shirakawa T, Hopkin JM (2002) Genetic variants of the receptors for thromboxane A2 and IL-4 in atopic dermatitis. *Biochem Biophys Res Commun* 292:776–780
80. Gern JE, Reardon CL, Hoffjan S, Nicolae D, Li Z, Roberg KA, Neaville WA, Carlson-Dakes K, Adler K, Hamilton R et al (2004) Effects of dog ownership and genotype on immune development and atopy in infancy. *J Allergy Clin Immunol* 113:307–314
81. Cook DN, Pisetsky DS, Schwartz DA (2004) Toll-like receptors in the pathogenesis of human disease. *Nat Immunol* 5:975–979

82. Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, Klotz M, Werfel T, Herz U, Heeg K, Neumaier M, Renz H (2004) The toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol* 113:565–567
83. Baldini M, Vercelli D, Martinez FD (2002) CD14: an example of gene by environment interaction in allergic disease. *Allergy* 57:188–192
84. Colilla S, Nicolae D, Pluzhnikov A, Blumenthal MN, Beaty TH, Bleecker ER, Lange EM, Rich SS, Meyers DA, Ober C et al (2003) Evidence for gene–environment interactions in a linkage study of asthma and smoking exposure. *J Allergy Clin Immunol* 111:840–846
85. Howard TD, Koppelman GH, Xu J, Zheng SL, Postma DS, Meyers DA, Bleecker ER (2002) Gene–gene interaction in asthma: IL4RA and IL13 in a Dutch population with asthma. *Am J Hum Genet* 70:230–236
86. Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, Deykin A, Fagan JK, Fahy JV, Fish J et al (2004) Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 364:1505–1512
87. Nishio Y, Noguchi E, Ito S, Ichikawa E, Umebayashi Y, Otsuka F, Arinami T (2001) Mutation and association analysis of the interferon regulatory factor 2 gene (IRF2) with atopic dermatitis. *J Hum Genet* 46:664–667
88. Rafatpanah H, Bennett E, Pravica V, McCoy MJ, David TJ, Hutchinson IV, Arkwright PD (2003) Association between novel GM-CSF gene polymorphisms and the frequency and severity of atopic dermatitis. *J Allergy Clin Immunol* 112:593–598
89. He JQ, Ruan J, Chan-Yeung M, Becker AB, Dimich-Ward H, Pare PD, Sandford AJ (2003) Polymorphisms of the GM-CSF genes and the development of atopic diseases in at-risk children. *Chest* 123:438S
90. Kawashima T, Noguchi E, Arinami T, Yamakawa-Kobayashi K, Nakagawa H, Otsuka F, Hamaguchi H (1998) Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. *J Med Genet* 35:502–504
91. Elliott K, Fitzpatrick E, Hill D, Brown J, Adams S, Chee P, Stewart G, Fulcher D, Tang M, Kemp A et al (2001) The –590C/T and –34C/T interleukin-4 promoter polymorphisms are not associated with atopic eczema in childhood. *J Allergy Clin Immunol* 108:285–287
92. Yamamoto N, Sugiura H, Tanaka K, Uehara M (2003) Heterogeneity of interleukin 5 genetic background in atopic dermatitis patients: significant difference between those with blood eosinophilia and normal eosinophil levels. *J Dermatol Sci* 33:121–126
93. Sengler C, Haider A, Sommerfeld C, Lau S, Baldini M, Martinez F, Wahn U, Nickel R (2003) Evaluation of the CD14 C-159 T polymorphism in the German multicenter allergy study cohort. *Clin Exp Allergy* 33:166–169
94. Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Fujita H, Asano N, Kishimoto M, Tanida Y, Kakinuma T et al (2002) Interleukin-12 p40 gene (IL12B) 3'-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris. *J Dermatol Sci* 30:161–166
95. Cox HE, Moffatt MF, Faux JA, Walley AJ, Coleman R, Trembath RC, Cookson WO, Harper JI (1998) Association of atopic dermatitis to the beta subunit of the high affinity immunoglobulin E receptor. *Br J Dermatol* 138:182–187
96. Safronova OG, Vavilin VA, Lyapunova AA, Makarova SI, Lyakhovich VV, Kaznacheeva LF, Manankin NA, Batyckho OA, Gavalov SM (2003) Relationship between glutathione S-transferase P1 polymorphism and bronchial asthma and atopic dermatitis. *Bull Exp Biol Med* 136:73–75
97. Vavilin VA, Safronova OG, Lyapunova AA, Lyakhovich VV, Kaznacheeva LF, Manankin NA, Molokova AV (2003) Interaction of GSTM1, GSTT1, and GSTP1 genotypes in determination of predisposition to atopic dermatitis. *Bull Exp Biol Med* 136:388–391
98. Jang N, Stewart G, Jones G (2005) Polymorphisms within the PHF11 gene at chromosome 13q14 are associated with childhood atopic dermatitis. *Genes Immun*
99. Mao XQ, Shirakawa T, Yoshikawa T, Yoshikawa K, Kawai M, Sasaki S, Enomoto T, Hashimoto T, Furuyama J, Hopkin JM et al (1996) Association between genetic variants of mast-cell chymase and eczema. *Lancet* 348:581–583
100. Mao XQ, Shirakawa T, Enomoto T, Shimazu S, Dake Y, Kitano H, Hagiwara A, Hopkin JM (1998) Association between variants of the mast cell chymase gene and serum IgE levels in eczema. *Hum Hered* 48:38–41
101. Kawashima T, Noguchi E, Arinami T, Kobayashi K, Otsuka F, Hamaguchi H (1998) No evidence for an association between a variant of the mast cell chymase gene and atopic dermatitis based on case-control and haplotype-relative-risk analyses. *Hum Hered* 48:271–274
102. Pascale E, Tarani L, Meglio P, Businco L, Battiloro E, Cimino-Reale G, Verna R, D'Ambrosio E (2001) Absence of association between a variant of the mast cell chymase gene and atopic dermatitis in an Italian population. *Hum Hered* 51:177–179
103. Iwanaga T, McEuen A, Walls AF, Clough JB, Keith TP, Rorke S, Barton SJ, Holgate ST, Holloway JW (2004) Polymorphism of the mast cell chymase gene (CMA1) promoter region: lack of association with asthma but association with serum total immunoglobulin E levels in adult atopic dermatitis. *Clin Exp Allergy* 34:1037–1042
104. Kabesch M, Peters W, Carr D, Leupold W, Weiland SK, Von Mutius E (2003) Association between polymorphisms in caspase recruitment domain containing protein 15 and allergy in two German populations. *J Allergy Clin Immunol* 111:813–817
105. Nickel RG, Casolaro V, Wahn U, Beyer K, Barnes KC, Plunkett BS, Freidhoff LR, Sengler C, Plitt JR, Schleimer RP et al (2000) Atopic dermatitis is associated with a functional mutation in the promoter of the C–C chemokine RANTES. *J Immunol* 164:1612–1616
106. Kozma GT, Falus A, Bojszko A, Krikovszky D, Szabo T, Nagy A, Szalai C (2002) Lack of association between atopic eczema/dermatitis syndrome and polymorphisms in the promoter region of RANTES and regulatory region of MCP-1. *Allergy* 57:160–163
107. Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Fujita H, Asano N, Tanida Y, Kakinuma T, Wakugawa M et al (2002) Eotaxin gene single nucleotide polymorphisms in the promoter and exon regions are not associated with susceptibility to atopic dermatitis, but two of them in the promoter region are associated with serum IgE levels in patients with atopic dermatitis. *J Dermatol Sci* 29:222–228
108. Arkwright PD, Chase JM, Babbage S, Pravica V, David TJ, Hutchinson IV (2001) Atopic dermatitis is associated with a low-producer transforming growth factor beta(1) cytokine genotype. *J Allergy Clin Immunol* 108:281–284
109. Vasilopoulos Y, Cork MJ, Murphy R, Williams HC, Robinson DA, Duff GW, Ward SJ, Tazi-Ahnini R (2004) Genetic association between an AACC insertion in the 3' UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis. *J Invest Dermatol* 123:62–66