

An update on the genetics of atopic dermatitis: Scratching the surface in 2009

Kathleen C. Barnes, PhD *Baltimore, Md*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the JACI Web site: www.jacionline.org. The accompanying tests may only be submitted online at www.jacionline.org. Fax or other copies will not be accepted.

Date of Original Release: January 2010. Credit may be obtained for these courses until December 31, 2011.

Copyright Statement: Copyright © 2009-2011. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The

AAAAI designates these educational activities for a maximum of 1 *AMA PRA Category 1 Credit*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: *Authors:* Kathleen C. Barnes, PhD
Activity Objectives

1. To become familiar with traditional and newer methods used to identify candidate genes for atopic dermatitis (AD).
2. To recognize the role of the innate and adaptive immune response in the development of AD.
3. To understand the contribution of skin barrier gene dysfunctions in the susceptibility of AD.

Recognition of Commercial Support: This CME activity is supported by an educational grant from Merck & Co., Inc.

Disclosure of Significant Relationships with Relevant Commercial

Companies/Organizations: K. C. Barnes has received research support from the National Institutes of Health.

A genetic basis for atopic dermatitis (AD) has long been recognized. Historic documents allude to family history of disease as a risk factor. Before characterization of the human genome, heritability studies combined with family-based linkage studies supported the definition of AD as a complex trait in that interactions between genes and environmental factors and the interplay between multiple genes contribute to disease manifestation. A summary of more than 100 published reports on genetic association studies through mid-2009 implicates 81 genes, in 46 of which at least 1 positive association with AD has been demonstrated. Of these, the gene encoding filaggrin (*FLG*) has been most consistently replicated. Most candidate gene studies to date have focused on adaptive and innate immune response genes, but there is increasing interest in skin barrier dysfunction genes. This review examines the methods that have been used to identify susceptibility genes for AD and how the underlying pathology of this disease has been used to select candidate genes.

From the Johns Hopkins Asthma & Allergy Center.

Supported by the National Institute of Health (National Institute of Allergy and Infectious Diseases: HSN266200400029C).

Received for publication July 28, 2009; revised November 6, 2009; accepted for publication November 9, 2009.

Reprint requests: Kathleen C. Barnes, PhD, the Johns Hopkins Asthma & Allergy Center, 5501 Hopkins Bayview Circle, Room 3A.62, Baltimore, MD 21224. E-mail: kbarnes@jhmi.edu.

0091-6749/\$36.00

© 2010 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2009.11.008

Terms in boldface and italics are defined in the glossary on page 17.

Current challenges and the potential effect of new technologies are discussed. (*J Allergy Clin Immunol* 2010;125:16-29.)

Key words: *Atopic dermatitis, genetics, IgE-mediated response, innate immunity, skin barrier dysfunction, genetic association, gene-environment interaction, ethnicity*

More than 2,500 years ago, Hippocrates described a condition of an undetermined cause characterized as “itching over [a patient’s] whole body.”¹ During the 18th and 19th centuries, what was believed to be this nondescript pruritic state was termed “eczema” or “prurigo diathésique.”² The condition received increasing attention in the dermatologic literature in the late 19th and early 20th centuries, especially as a component of the allergic diathesis, as Coca noted that “every recognized category of allergic disease affects the skin,” suggesting that, “among the diseases of the skin the familial allergy (hay fever-asthma group) is represented by atopic eczema.”³ The term was ultimately replaced with the descriptive term “atopic dermatitis” (AD) by Coca.³

A common theme from the most ancient descriptions of this syndrome to more recent observations is that allergy in general and AD in particular has a profound capacity to run in families. That is, AD, even more so than other atopic disorders, is highly heritable. For example, in the Munich Asthma and Allergy Study, it was demonstrated that the risk of a child having AD if one or

Abbreviations used

AD:	Atopic dermatitis
cM:	Centimorgans
EDC:	Epidermal differentiation complex
FLG:	Filaggrin gene
GWAS:	Genome-wide association study
NOD:	Nucleotide-binding oligomerization domain
OR:	Odds ratio
SC:	Stratum corneum
SNP:	Single nucleotide polymorphism
TJ:	Tight junction
TLR:	Toll-like receptor

both parents have AD is higher (odds ratio [OR], 3.4; 95% CI, 2.6-4.4) compared with the risk if 1 or both parents have asthma (OR, 1.5; 95% CI, 1.0-2.2) or allergic rhinitis (OR, 1.4; 95% CI, 1.1-1.8),⁴ supporting the notion that although generic atopy genes might be responsible for the manifestation of AD, there are likely to be phenotype-specific genes as well. Early observations of a strong family history of allergy, eczema, and asthma^{5,6} contributed not only to an understanding of at least one of the underlying causes of AD (ie, an allergic response to “environmental inhalant factors” in addition to “hereditary factors”⁵) but also promoted the next stage of heritability investigations. A number of twin studies suggested wide ranges of concordance rates of between 0.23 and 0.86 for monozygotic twins and 0.15 and 0.5 for dizygotic twins.⁷⁻¹¹ These wide ranges can probably be explained in part by heterogeneity of the phenotype and phenotype definition across studies, but as suggested by the relatively low concordance in some studies, even for identical twins, the environment is also

influencing disease risk and manifestation. Parent-of-origin effects, or maternal heritability, has also been attributed to AD,¹² an observation that has subsequently been supported by genetic association studies (ie, maternally transmitted alleles in the Kazal-type serine protease inhibitor 5 [*SPINK5*] gene).¹³

Discovery of atopic dermatitis genes with traditional approaches: Genome-wide linkage and candidate gene association studies

Genome-wide linkage studies on AD. Given the long-standing recognition of the role of heritability in the manifestation of AD and the characteristic early age of disease onset, AD is a trait highly amenable to the genome-wide linkage approach for identifying novel genes. The genome-wide linkage method is a family-based approach relying on a collection of affected individuals (proband) and their parents (ie, case-parent trio design) or affected sibling pairs and their parents (and often additional family members) for which the inheritance pattern of a trait is compared with the inheritance pattern of chromosomal regions using highly polymorphic genetic (microsatellite) markers evenly spaced across all chromosomes (Fig 1, A). There are several advantages of genome-wide linkage mapping, such as that it is hypothesis independent because the entire genome is scanned without regard to specific candidates. Because of the polymorphic nature of microsatellite markers, genome-wide linkage mapping is cost-effective because it requires a relatively small number of markers (approximately 350); as a result, a significant linkage peak requires a much lower correction of the *P* value (eg, an LOD score of 3.6 or $P = 2 \times 10^{-5}$)¹⁴ compared with study designs involving thousands or tens of thousands of markers. Because linkage cannot detect genes

GLOSSARY

CD14: CD14 is the pattern-recognition receptor for LPS and is present on monocytes, macrophages, and neutrophils. Genetic polymorphisms in the *CD14* gene have been linked to gene-environment interactions, including dog ownership, house dust mite exposure, and tobacco exposure in asthmatic patients.

CLAUDIN, OCCLUDIN: Claudins and occludins are members of the TJs that are important for epithelial barrier integrity. Claudin-1 gene-deficient mice die shortly after birth and have significant transepithelial water loss.

EXPRESSION PROFILING: Expression profiling can assess the transcriptional activation of large sets of genes by using microarrays that identify the activity of target genes in control versus diseased populations. Sequence-based expression profiling can sequence any active gene rather than a defined target set of genes on a microarray.

FILAGGRIN: Filaggrin is a skin matrix protein that promotes keratin aggregation. Mutations in *FLG* have been associated with ichthyosis, eczema, and asthma.

GENOME-WIDE ASSOCIATION STUDY: Genome-wide association studies are used to find candidate genes linked to a disease of interest by using diseased and control patients. The screen uses bioinformatics to find associations between the disease and a haplotype block based on SNPs. Once a block is found, a candidate gene of interest that resides in the block can be studied to see associations with the disease of interest. A recent asthma GWAS found a new candidate gene, *ORMD3*.

HAPLOTYPE BLOCKS: Haplotype blocks are groups of SNPs that are statistically associated, such that the identification of a few alleles will define all of the polymorphisms in a given region of the chromosome.

HUMAN β -DEFENSINS: Innate antimicrobial peptides that are important as the first line of host defense, human β -defensin levels are decreased in the skin of patients with eczema and appear to predispose to cutaneous superinfections.

INVOLUCRIN, LORICIN: Loricin and involucrin (along with profilaggrin) are found in basophilic keratohyalin granules of granular keratinocytes. Release of granule contents into the intracellular space between the granular and cornified layers of the skin are essential for protection from transepidermal water loss.

LINKAGE DISEQUILIBRIUM: Linkage disequilibrium refers to the non-random association of 2 or more gene loci. The degree of linkage disequilibrium measures the frequency in the combinations of alleles in a population.

NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN: Nucleotide-binding oligomerization domain (NOD)-like receptor family protein members are members of the pattern recognition receptor family that includes TLRs. Mutations in NOD-like receptor genes have been implicated in a number of diseases, including Muckle-Wells syndrome, Crohn disease, and vitiligo.

PATTERN-RECOGNITION RECEPTORS: Pattern-recognition receptors are families of receptors in the innate immune system that recognize pathogen-associated molecular patterns and danger-associated molecular patterns, including peptidoglycan, RNA, muramyl dipeptide, and amyloid- β -peptide.

S100: The S100 proteins are a family of proteins that contain calcium-binding activity and regulate cell growth, cycling, and differentiation. There are 20 S100 protein family members, 14 of which reside on chromosome 1q21.

The Editors wish to acknowledge Seema Aceves, MD, PhD, for preparing this glossary.

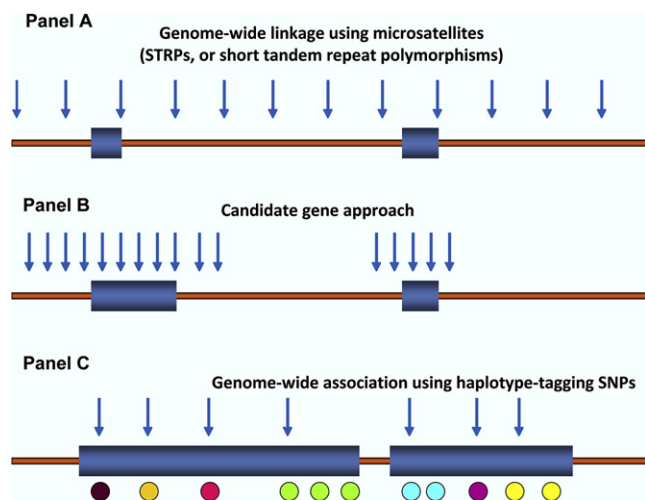


FIG 1. Methods for detecting disease susceptibility genes. **A**, Genome-wide linkage method relying on polymorphic microsatellites referred to as short tandem repeat polymorphisms (STRPs) evenly spaced across the chromosomes, typically including approximately 350 STRPs. **B**, Candidate gene approach whereby genetic markers, usually easily typed substitutions (ie, SNPs) or structural variants (ie, insertions/deletions), are selected within and flanking a candidate gene of interest. **C**, GWASs using hundreds of thousands and up to 1 million SNPs to fully cover a subject's genome represent a hypothesis-free systematic search across the genome to identify novel associations with common diseases using a set of haplotype-tagging SNPs (htSNPs), which are indicated as blue arrows. htSNPs represent a relatively small subset of SNPs of the potential 2.5 million SNPs in the public database (ie, needed to uniquely identify a complete haplotype). The premise behind htSNPs is the observation that when SNPs are in linkage disequilibrium with each other and form haplotypes, there is redundant information contained within the haplotype because several of the SNPs will always occur together. Thus a marker at one locus can reasonably predict a marker or markers that will occur at the linked locus nearby.

with minimal or modest disease effect, linkage peaks that reach statistical significance are generally indicative of a locus (loci) with substantial effect on disease risk.

To date, there have been 5 genome-wide linkage studies performed on AD, plus a genome-wide linkage screen originally designed for asthma with analyses repeated for the AD outcome (Fig 2). All but one of these screens were performed on families of European ancestry: (1) 199 German and Scandinavian,¹⁵ (2) 148 British,¹⁶ (3) 109 Swedish,¹⁷ (4) 100 Danish,¹⁸ and (5) 295 French¹⁹ families, of which 62 affected sib pairs for AD were available for reanalysis. The non-European study was performed on 77 Japanese families selected through 111 sib pairs with AD (287 individuals) and relied on a linkage mapping panel of 5,861 single nucleotide polymorphisms (SNPs) rather than the microsatellite panel traditionally used for linkage screens.²⁰

Underscoring the heterogeneity commonly observed in complex diseases, which, in addition to genetic heterogeneity, reflects heterogeneity of nongenetic factors, including differences in family ascertainment schemes, definition of the phenotype, and analytic approaches, there has been limited overlap of signals among these genome-wide linkage studies. Only the 3p24 locus has been truly replicated, with significant LOD scores observed for microsatellite markers in chromosome 3p24-p22 in the Swedish¹⁷ families and chromosome 3p26-p24 in the Danish¹⁸ families. Under a more relaxed threshold of a maximum distance of 25 centimorgans (cM) between linkage peaks, replication can be considered for the chromosome 3q13-q21 locus in the German/¹⁵

Scandinavian¹⁵ and Swedish¹⁷ samples and chromosome 18q11-q21 in the Danish¹⁸ and Swedish¹⁷ samples.

In the French study the linkage screen was originally designed to study asthma and allergic rhinitis in a sample of 295 families ascertained through asthmatic probands, but analyses were repeated for the outcome of eczema and demonstrated linkage at 5q13 and 11p14. Follow-up fine mapping of 8 markers in the 11p14 locus suggested a pleiotropic effect for the 3 allergic diseases of AD, asthma and allergic rhinitis. More recently, the Danish team followed up on their previous evidence for linkage at the 3 p, 4q, and 18q loci, in addition to previous evidence for linkage at 3q, in an independent sample of 130 AD sib-pair families and concluded the strongest evidence for linkage was to 3p34, 3q21, and 4q22.²¹ From these follow-ups, however, conclusions are speculative at best, given that each of the regions in which significant evidence of linkage has been identified contains multiple candidate genes. The best evidence for linkage in any one of these regions tends to extend over relatively large portions of the chromosome, rendering pinpointing of any specific locus (or gene) very difficult.

Although the genome-wide linkage approach represented one of the most sophisticated technologies in genetic epidemiology just over a decade ago, inherent challenges in this approach, including the considerable cost to follow-up genotyping of unwieldy and large chromosomal loci and the difficulties ascertaining sufficient numbers of complete families, has been, in part, an impetus for pursuing alternative approaches in gene hunting. After an initial genome-wide linkage analysis, positional cloning usually follows, whereby extra microsatellite markers at a density of 0.5 to 1.5 cM are genotyped over the linkage peaks that are suggestive or significant in the initial scan until the precise locus contributing to linkage is identified. However, even at this level of fine mapping, with an aim of localizing a gene to a region less than 1 cM (1 cM $\approx$ 1 million base pairs), the region of peak linkage score might still include hundreds of genes. In none of the AD genome-wide linkage studies shown in Fig 1 was a candidate gene identified with positional cloning.

Candidate genes in select pathways of AD. With the publication of initial efforts in sequencing the human genome²² (http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml), the opportunity to genotype markers directly in genes of interest was greatly expanded as polymorphisms were identified in the approximately 20,000 to 25,000 genes across the 3 billion chemical base pairs that make up human DNA. Relying on one of the simplest of these polymorphisms, SNPs, and relatively simple structural variants, such as insertions/deletions and repeats, this advancement allowed researchers to expand genetic studies beyond linkage toward the genetic association study design (Fig 1, B). Because many more biallelic markers are required compared with microsatellites to detect linkage and association across the genome, a candidate gene approach was adopted whereby investigators have focused on a specific gene or set of genes believed to be causally involved in the underlying pathology of a certain disease. An advantage of the candidate gene approach is that it is not limited to families and can be applied to case-control study designs, which possess certain advantages over family-based studies. For example, although association studies based on case-control designs are sensitive to confounding due to population stratification (ie, ethnic/racial admixture),²³ they are generally considered to be more powerful in detecting true associations once the gene has been identified.²⁴ Moreover,

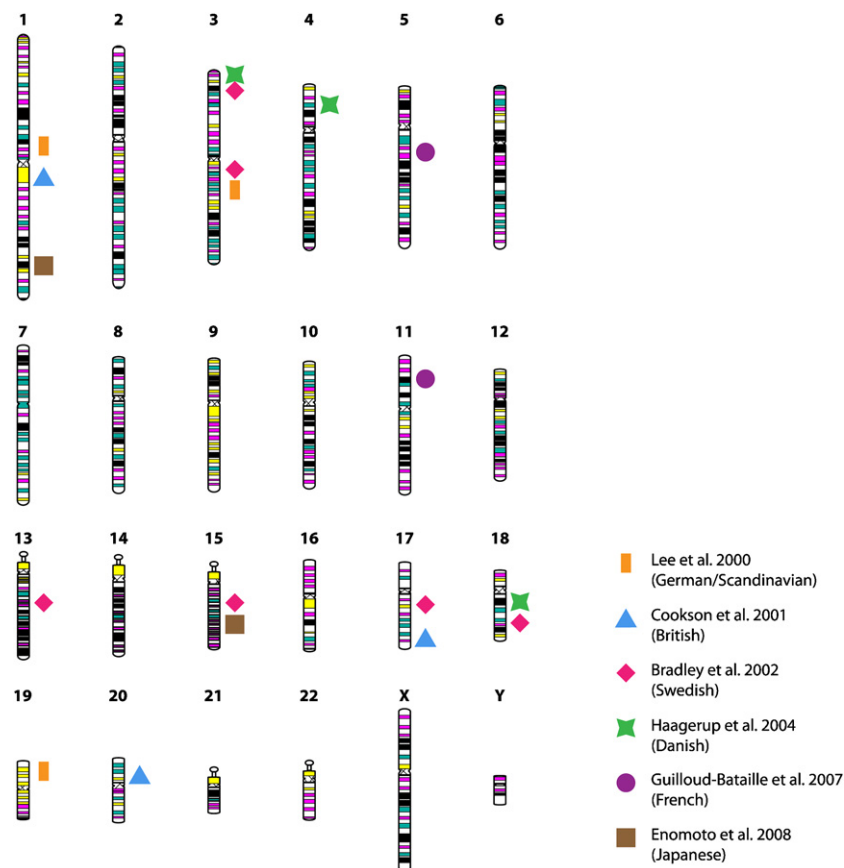


FIG 2. Summary of genome-wide linkage studies of AD: representation of the 23 human chromosomes, highlighting those loci for which genome screens have identified linkage to AD. Loci are mapped to short or long chromosomal arms and color coded according to the studies listed in the legend.¹⁵⁻²⁰ See Table E1 in this article's Online Repository for a complete summary of 111 published studies.

it is considerably easier (requires less effort and has lower costs in recruitment) to amass reasonably powered groups of patients with AD and healthy control subjects without AD than it is to collect complete case-parent trios or nuclear families.

For these reasons, there has been considerable effort in conducting association studies on AD and related phenotypes in independent populations in the post-genome-wide linkage era. In a search of the public database (<http://www.ncbi.nlm.nih.gov/pubmed/>) through June 2009, using key words including “association,” “atopic dermatitis,” “eczema,” “gene,” “polymorphism,” “mutation,” and “variant,” 111 studies were identified for which results of tests for association for AD were reported on a candidate gene (see Table E1 in this article's Online Repository at www.jacionline.org). The major outcome was limited to AD as a qualitative trait or AD severity. A significant association was defined liberally as any association at a *P* value of less than .05 without regard to effect size or weaknesses in the study design. Limitations in this exercise include the sometimes missing information on the precise variant for which association was (or was not) demonstrated and the unfortunate reality that negative association studies are rarely published and are therefore underrepresented in Table E1. In most instances the only information available on genes for which association was sought but for which the result was negative are those studies for which the negative results are included in manuscripts reporting positively associated genes/variants. In other words, there are undoubtedly more genes

for which associations have been tested but failed but for which the information is not available in the public arena.

It is critical to note that there are several biases in this summary. First, there is the bias of reporting associations in studies for which either type I error (false-positive result) or type II error (false-negative result) is possible (and in many cases likely) because of the limited power in the original study design. Other biases are related to potential study design weaknesses, such as a failure to adjust for population stratification in the case-control studies and consideration of Hardy-Weinberg proportions. There is a general assumption that for risk variants with common allele frequencies of greater than 20%, the ORs will range from 1.1 to 1.5, and for rarer risk allele frequencies (ie, <0.20), the ORs can be approximately 3.0. Based on these assumptions, there is a requirement of at least 1,000 cases and 1,000 control subjects to detect ORs of approximately 1.5 with at least 80% power, although the required sample size is dependent on multiple additional factors. Regardless, according to the summary in Table E1, in barely 2 dozen of the reported studies have sample sizes reached even 250 in each group. Another important consideration is the extreme heterogeneity of the phenotype definition from study to study, wherein some studies consider early-onset AD versus studies that combine pediatric populations with adult populations, variations in means for determining disease severity, and so on. Variation in the phenotype renders replication of associations especially difficult.

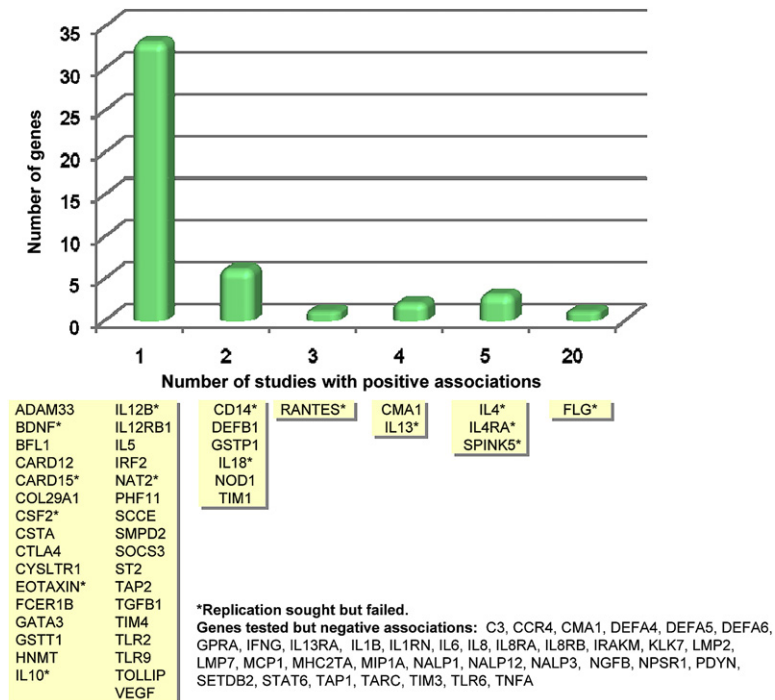


FIG 3. Genes associated with AD in at least 1 published study. Genes are grouped according to how many positive association studies have been reported (see Table E1 in this article's Online Repository for a complete summary of 111 published studies). The y-axis indicates the number of genes (corresponding to the yellow boxes) for each time that a positive association was reported.

A critical bias in this exercise is that replication was considered at the level of the gene rather than the specific variant/mutation. Elsewhere, there has been extensive discussion regarding the merit of this approach, including the comprehensive review of asthma genetics by Ober and Hoffjan,²³ in which the authors refer to advocacy of a gene-centric approach because the more conventional SNP-for-SNP approach is predicated on the assumption that allele frequencies and haplotype structure at a specific locus is identical in 2 (or more) populations, which is unlikely.²⁵ Elsewhere, the pitfalls of this "loose" replication have been cautioned.²⁶ However, a major outcome from the International Haplotype Map Project²⁷ is the observation that a large portion of the human genome is arranged into blocks of common polymorphisms (SNPs) in strong *linkage disequilibrium* with one another, and there is considerable diversity within these *haplotype blocks*. Because much of this diversity is driven by mutation and given our knowledge that the functional properties of protein products (eg, candidate genes) can depend on specific combinations of multiple polymorphisms within a gene or interactions with polymorphisms in other genes,²⁸ it is not surprising that a single-locus approach might fail to detect association *a priori*, much less fail to replicate across studies in different sets of populations. The recent report by Rogers et al,²⁹ wherein they combined SNP data from the Ober and Hoffjan review²³ supplemented by their own review of the asthma genetics literature with SNP data from their *genome-wide association study* (GWAS) on more than 1,000 asthmatic children and family members in the Childhood Asthma Management Program study and more than 500,000 SNPs, underscores the unlikely success in replication at the SNP level because the group only identified 10 significantly associated SNPs in 6 genes that were on the commercial

SNP chip and that overlapped with 160 SNPs in 39 genes previously associated with asthma in the literature.²⁹

Finally, another area of potential controversy has to do with common versus rare variants. A perspective on the scientific value of GWASs³⁰ suggested that (assuming currently available commercial chips capture the bulk of common genetic variation) SNPs with large effects might have already been discovered (implying there is no need for additional genome wide scans) and that the focus should therefore shift toward detailed search for rare variants. Although the application of both conventional candidate gene studies and GWASs has led to the discovery of hundreds of loci conferring risk of common diseases, it has been noted that the risk variants identified by GWASs in particular explain only a small fraction of the disease-specific heritability. One explanation that is beginning to emerge is that much of the remaining heritable disease risk is associated with rare variants (usually defined as those with a frequency of <5% to ≤1%).³¹ For example, rare alleles of at least 10 loci contribute to the risk for breast cancer, and more than 40 loci underlie the risk of type 1 diabetes. Importantly, in contrast to common variants, rare nonsynonymous variants in the human genome might be deleterious and therefore of significance because they influence protein function, phenotypic variation, or both. Most of these variants are probably only mildly deleterious, segregate at low frequencies, and are not pathogenic. However, a subset of these variants have more modest effects and are rare but could collectively explain a substantial fraction of the heritable variability of common disease phenotypes.

Although rare coding variants might have a greater functional effect than common variants, their analysis must consider the low frequency of any variant because it will reduce the power to infer statistical associations and therefore require very large

populations of cases and control subjects or affected families. This complication can be overcome by evaluating the collective frequency of rare nonsynonymous variants within 1 or more genes or for a pathway or pathways and the functional effect of the discovered variations. As described further below, however, with the exception of studies focused on mutations in the gene encoding *filaggrin* (*FLG*), few if any other studies in patients with AD have specifically focused on rare variants or have been designed with sufficient power to be able to detect rare variants.

Despite the biases and potential pitfalls described above, several interesting conclusions can be inferred from this comprehensive review of the literature on the genetics of AD. In the 14 years since the first published report on an association between a genetic variant and AD, more than a third of the studies have been reported in the past 2½ years, and already in the first half of 2009, more reports have been published than in all of 2008. From these 111 published studies, there are reports on 81 genes, of which more than half (46 genes) had at least 1 positive association study reported (Fig 3). Of these 46 genes, 15 studies failed to replicate associations, and 13 were positively associated in at least 1 other independent study. One of these genes, *FLG*, has been associated with AD in 20 different reports (details below). There are 35 additional genes studied for which there has been no evidence for a positive association to date.

Adaptive and innate immune response genes. The well-established comorbidities of the other 2 allergic diseases that constitute the atopic triad (ie, asthma and allergic rhinitis), in addition to the sensitization to common aeroallergens that is commonly observed in patients with AD, has guided researchers toward selection of candidate genes that fall within the broad category of dysregulation of the adaptive and innate immune response and a heightened IgE-mediated, systemic T_H2 response plus a combined T_H1 and T_H2 response in the skin. This selection bias is evident in Table E1.

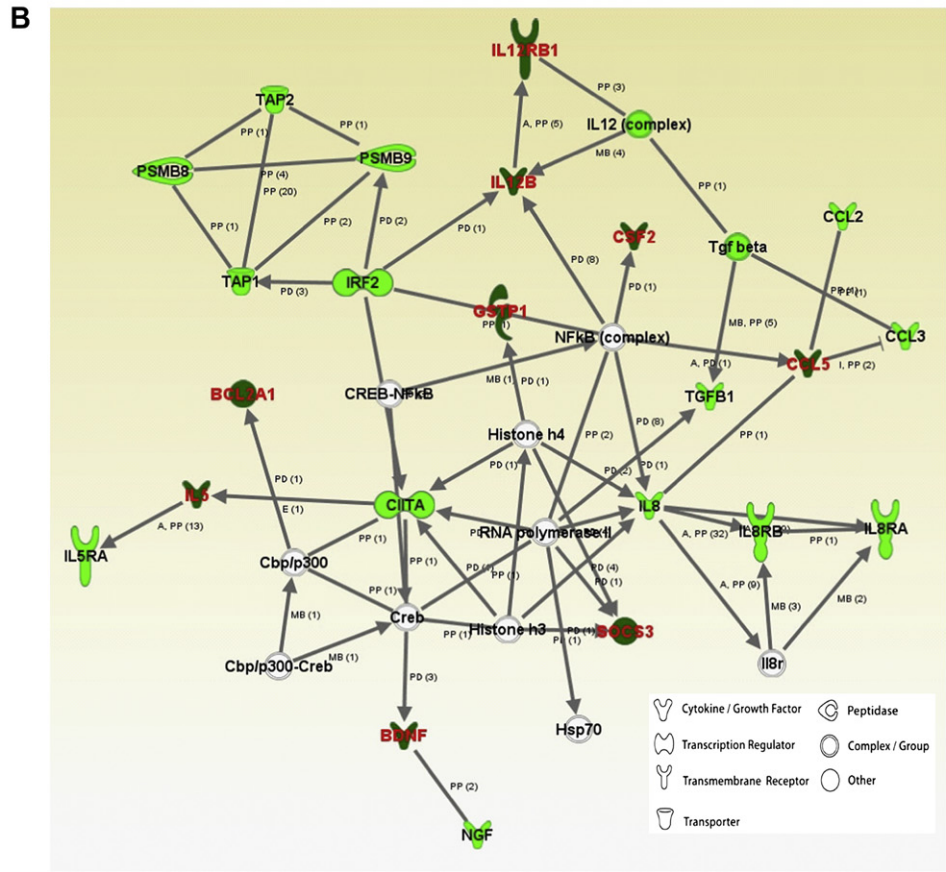
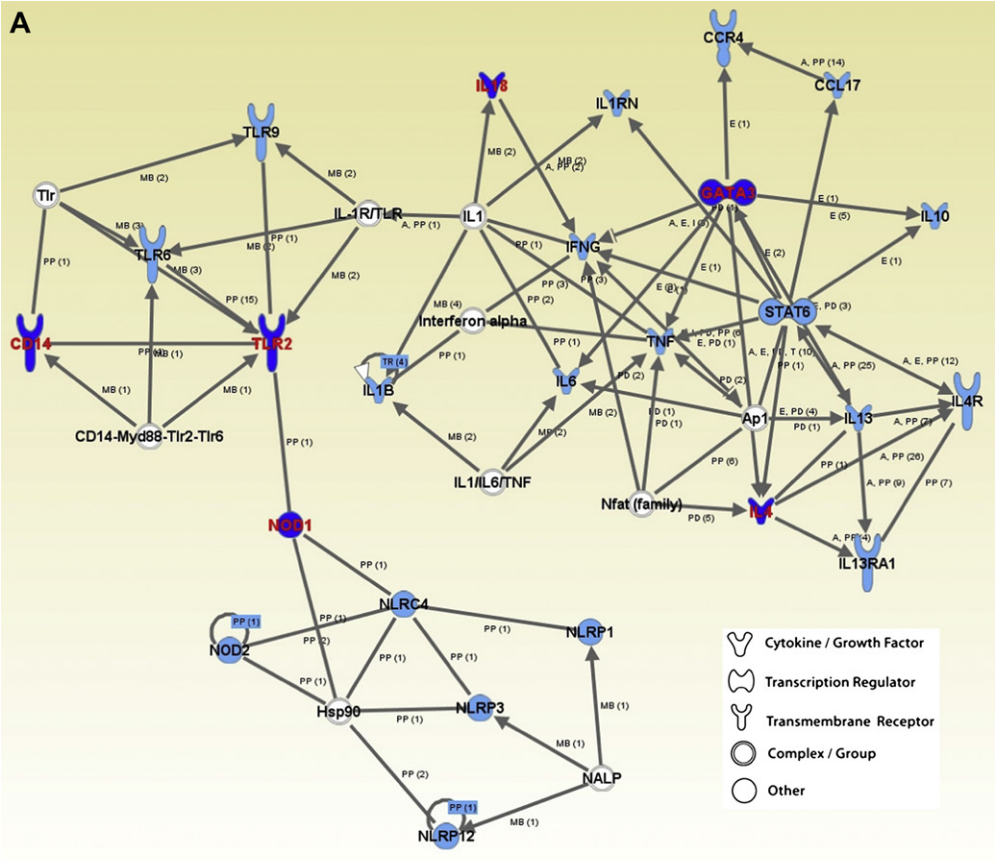
For complex diseases, such as AD, that involve a dense network of immune response proteins, it is anticipated that many genes will be involved and that multiple genetic variants will contribute to the alteration of gene function and expression. Because the effect of a single gene/polymorphism in a complex disease, such as AD, is anticipated to be relatively modest, it can be assumed that variants in multiple genes will cooperate in an additive or synergistic manner to affect disease risk, a phenomenon referred to as epistasis. A major difficulty in testing for epistasis is power: not only will fewer subjects in a sample possess both polymorphisms (or a set of polymorphisms) associated with risk of disease compared with the number of subjects with only 1 of the polymorphisms but also the correction factor for additional (multiple) comparisons (ie, tests for association) is quite large. Consider the example of 100,000 genetic markers, wherein there are a total of $5 \times 10^4 + 9$ 2-locus combinations, requiring a (Bonferroni) correction factor of $P = 1 \times 10^{-11}$ for a GWAS significance level of .05.³²

One approach toward characterizing potential gene-gene interactions and systematically evaluating the role of candidate genes/polymorphisms in AD susceptibility for which there is compelling evidence for association is to implement the program Ingenuity Pathways Analysis (Ingenuity Systems, Inc, Redwood City, Calif; www.analysis.ingenuity.com). The Ingenuity Pathways knowledge base is a Web-based entry tool developed by Ingenuity Systems, Inc, to characterize genes according to the

predefined canonical pathway or pathways into which they fit and also to investigate the extent to which genes are in shared networks and might cooperate in a synergistic or additive manner to affect the risk of disease. As a proof of concept, we evaluated the 81 genes summarized in Fig 3 using the Ingenuity Pathway Analysis. Slightly more than half ($n = 48$) of the 81 genes studied to date clustered in 2 major networks, both of which are associated with immune dysregulation, specifically the pathway associated with antigen presentation and cell-mediated and humoral immune response and the pathway associated with cell signaling and interaction, cellular movement, and hematologic system development and function. Six genes (monocyte differentiation antigen CD14 [*CD14*], GATA-binding protein 3 [*GATA3*], interleukin 4 [*IL4*], *IL18*, *nucleotide-binding oligomerization domain 1* [*NOD1*], and Toll-like receptor 2 [*TLR2*]), which have previously been significantly associated with AD, were clustered into the antigen presentation and immune response pathway, and 9 previously associated genes (BCL2-related protein A1 [*BCL2A1*], brain-derived neutrophilic factor [*BDNF*], Regulated upon Activation, Normally T-Expressed, and presumably Secreted [*RANTES*], colony-stimulating factor 2 [*CSF2*], glutathione S-transferase, 1 [*GSTP1*], *IL5*, interleukin 12 beta [*IL12B*], interleukin 12 receptor beta 1 [*IL12RB1*], and suppressor of cytokine signaling 3 [*Socs3*]) were clustered into the cell-signaling/movement pathway. Although the studies for which these candidate genes were evaluated did not specifically test for gene-gene interaction, this interrogation of the potential for interaction serves as an example of the power of this approach in selecting optimal candidates for genetic association studies.

In addition to immune dysregulation manifested as IgE-mediated sensitization to numerous allergens, AD is also characterized as a common, chronic, pruritic, inflammatory skin disease complicated by recurrent bacterial and viral skin infections (ie, *Staphylococcus aureus* and herpes simplex virus).^{33,34} More seriously, patients with AD are at greater risk for severe and generalized viral infections caused by herpes simplex virus (eg, eczema herpeticum), molluscum contagiosum virus (eg, eczema molluscum), and eczema vaccinatum, which occurs after exposure to the smallpox vaccine.³⁵

Increased susceptibility to infections and cutaneous colonization implicate several of the immune function genes listed in Fig 4, A, specifically those genes associated with a dysfunctional host defense (or innate immune) response. These candidates include the *pattern-recognition receptor* type I transmembrane, TLRs,³⁶ the NOD-leucine rich-containing protein family (NOD1 and NOD2),^{37,38} and CD14.³⁹⁻⁴¹ Antimicrobial peptides, including *S100* proteins, human defensin α and β , and sphingosine, exert potent antimicrobial activity by directly killing bacteria, fungi, and certain viruses.⁴² Natural killer cells, a critically important population of lymphocytes for innate immune responses against viral infection,⁴³ are dependent on transcription factors, such as IFN regulatory factor 2, for efficient cell development. (For an extensive review on innate immunity in AD, see McGirt and Beck⁴⁴ and De Benedetto et al.⁴⁵) Genetic association studies on AD to date in fact support a number of these candidates (ie, *TLR2*, *NOD1*, *NOD2*, *CD14*, and defensin beta 1 [*DEFB1*]; Fig 3). In addition to the direct effect of genetic modifications in innate immune response molecules and their role in susceptibility to infection, the attenuation of upregulation of the normal antimicrobial response to bacterial and viral stimuli because of an overabundance of T_H2 cytokines in the skin appears to be



especially relevant in patients with AD.^{46,47} For example, it has been demonstrated that increased T_H2 cytokine levels can inhibit mobilization of potent innate immunity molecules, such as *human* β -defensin 3, in epidermal keratinocytes.⁴⁸ Alternatively, persistent *S aureus* infections can also mediate inflammatory cascades by staphylococcal toxins acting in a superantigen-driven fashion to activate T cells⁴⁹ or by induction of a state of glucocorticoid resistance.⁵⁰ This observation further underscores the potential relevance of gene-gene interactions, as shown in Fig 4, A.

Notably, the candidates described above and summarized in Fig 4, as well as Table E1, are not all unique to AD; in fact, many AD candidate genes overlap with not only other atopic phenotypes (eg, asthma and allergic rhinitis) but also other diseases of inflammation and immune dysfunction. The common disease/common variant hypothesis⁴¹ has been put forth as one explanation for why many complex diseases are so common and why disease-associated variants occur at such a high frequency in the population. The common variant/multiple disease hypothesis, which is an extension of the common disease/common variant hypothesis, suggests that certain disease genes might not be disease specific and might contribute to related clinical phenotypes.⁵¹ One possibility is that the functional effects of certain alleles manifest in multiple disorders, presumably because they are involved in basic underlying immune regulatory pathways. Multiple examples of genetic association of the same gene (or allele) to diverse but related disorders abound (see the Genetic Association Database at <http://geneticassociationdb.nih.gov>). For example, in addition to AD, genetic associations have been observed in *DEFB1* for asthma,⁵² chronic obstructive pulmonary disease,⁵³ and infectious diseases, including HIV⁵⁴ and sepsis.⁵⁵ *NOD2* polymorphisms, in addition to AD, have also been associated with Crohn disease⁵⁶ and sarcoidosis.⁵⁷ Associations with *RANTES* polymorphisms are especially diverse, including phenotypes associated with immune response, infection, reproduction, and metabolic disorders (<http://geneticassociationdb.nih.gov>). Given the prominent role that certain pathways, such as host defense, play in susceptibility to AD, it is likely that many more coassociations will be observed in the near future.

Skin barrier dysfunction genes. It is increasingly appreciated that both genetic and environmental factors that affect skin barrier function contribute to AD susceptibility⁵⁸ and that barrier dysfunction is an essential feature of AD and allergic diseases in general.⁵⁹⁻⁶³ A disrupted barrier would allow penetration of microbes and allergens and other environmental insults, such as toxins, irritants, and pollutants, with consequences including inflammation, allergen sensitization, and bacterial colonization. This might explain why 55% to 90% of patients with AD are colonized with *S aureus* compared with only 5% of subjects without

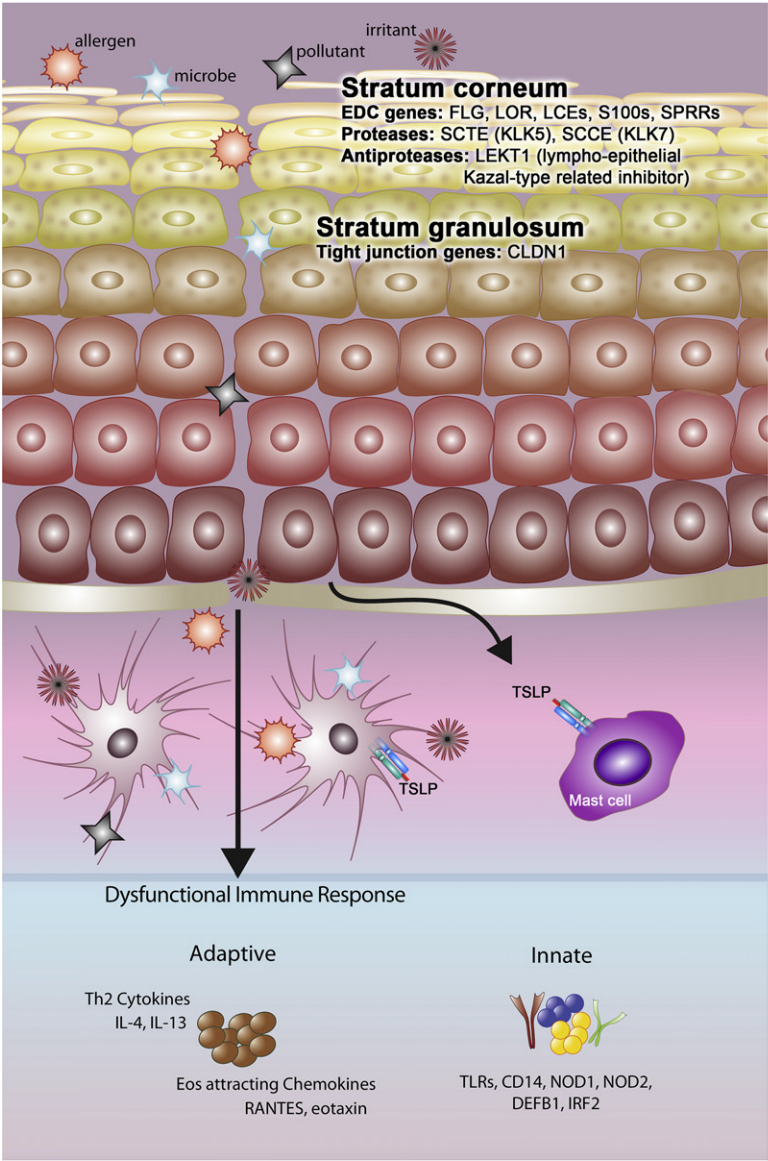
AD.⁶⁴⁻⁶⁸ Although the epidermis functions as the primary defense to the external environment, considerable barrier function is regulated by the stratum corneum (SC) and by the tight junctions (TJ), which reside at the level of the stratum granulosum. When the SC is compromised, either by reduced levels of SC lipids,²⁹⁻³¹ mechanical trauma resulting from extensive scratching that is precipitated by intensive itch (the hallmark of AD), or as a result of genetic defects in SC proteins (ie, FLG), TJs are the next line of defense. Currently, there is considerable interest in the more than 40 proteins that comprise TJs, which include the *claudin* family members, *occludin*, cingulin, tricellin, and the cytoplasmic plaque proteins,⁶⁹ which bind to actin and myosin,⁷⁰ and their role in human disease in general⁷¹ and specifically in AD.

As described earlier, linkage screens performed on AD to date have not elucidated specific candidate genes *per se*, but they have implicated loci harboring clusters of genes associated with skin barrier dysfunction. Specifically, one of the earliest screens indicated linkage at the epidermal differentiation complex (EDC) locus on chromosome 1q2116, which contains a very large and diverse family of genes associated with skin barrier dysfunction, including *loricrin*, *involucrin*, members of the S100 gene family, a large group of the late cornified envelope gene family, many of the small proline-rich proteins, peptidoglycan recognition proteins (ie, *PGLYRP3* and *PGLYRP4*) and, most notably, *FLG*.⁷² Linkage has also been reported in 17q2117, where the gene encoding one of the keratins (*KRT16*) is localized.

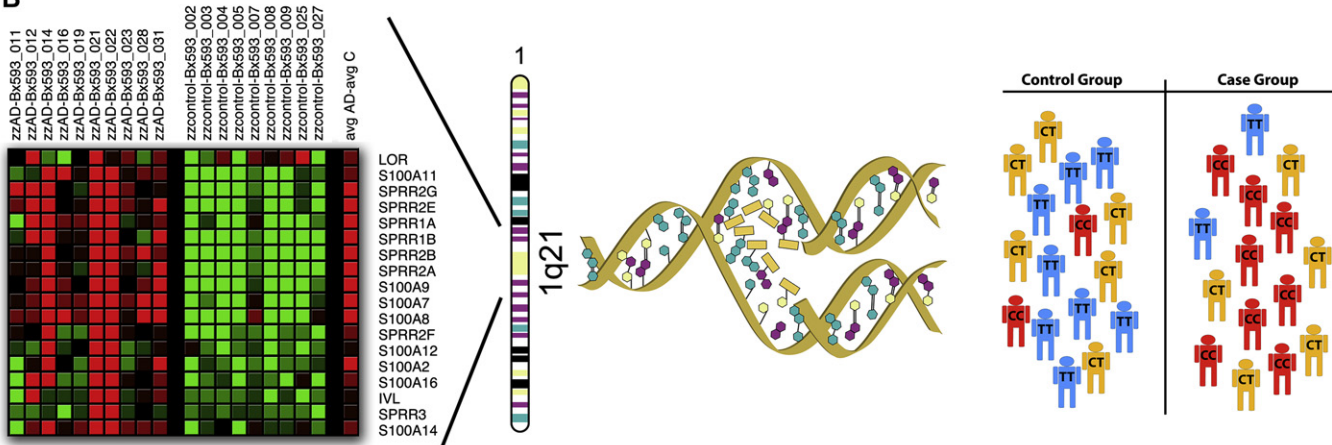
Association studies on genes related to the EDC cluster and other barrier dysfunction candidates have, to date, been largely restricted to *FLG*, also known as filament-aggregating protein, and within *FLG*, most associations have been limited to 2 null mutations (R501X and 2282del4). In fact, *FLG* is the most consistently associated gene with risk of AD⁷³; as shown in Fig 3, by mid-2009, there were 20 positive reports on genetic associations between *FLG* mutations and AD. The gene encoding human FLG was first cloned in 1989, when it was found to contain numerous tandem FLG repeats localized to chromosome 1q21, and because of its tight regulation at the transcriptional level in terminally differentiating epidermis, it was postulated to be an important candidate for disorders of keratinization.⁷⁴ It was subsequently evaluated for its function in the formation of the SC and found to be a critical protein involved in epidermal differentiation and in maintaining barrier function.⁷⁵ Smith et al⁷⁶ developed long-range PCR conditions for a 12-kb genomic fragment covering exon 3 of *FLG* and identified a homozygous nonsense mutation (R501X) near the start of repeat 1 and a second mutation (2282del4) that similarly stops protein translation within the first *FLG* repeat in 3 patients with ichthyosis vulgaris. They

FIG 4. Networks revealed through the Ingenuity Pathways Analysis based on 81 AD genes established in genetic association studies. Forty-eight genes clustered into 2 major networks associated with immune dysregulation. **A**, Antigen presentation and cell-mediated and humoral immune response pathway. Significantly associated genes are highlighted in dark blue. **B**, Cell signaling and interaction, cellular movement, and hematologic system development and function pathway. Significantly associated genes are highlighted in dark green. For both panels, genes or gene products are represented as nodes (*shapes*; see legend) that represent the functional class of the gene product. The relationship between genes is presented as solid lines with arrows (direct activation), and arrows point to the element on which an action is performed. All relationships (or lines) are supported by at least 1 reference (numbers of references in parentheses). Annotation of relationship (labels) between the nodes: A, Activation; E, expression; I, inhibition; MB, group/complex membership; PD, protein-DNA binding; PP, protein-protein binding. See Table E1 in this article's Online Repository for a complete summary of 111 published studies.

A



B



demonstrated that these relatively rare mutations (a combined allele frequency of approximately 4% in the European population studied) are semidominant, with heterozygotes exhibiting mild disease with incomplete penetrance. Shortly thereafter, the same group showed that these 2 loss-of-function variants were associated with AD⁷⁷ and that they are ancestral European variants carried on conserved haplotypes.⁷⁸

Full sequencing of the *FLG* gene by the same team has revealed multiple additional polymorphisms with varying frequency across ethnic groups⁷⁸; however, with a combined allele frequency among patients with AD of 18% and 48% for the R501X and 2282del4 mutations, respectively, the 2 null mutations represent the strongest and most compelling genetic risk factors for AD. In the largest meta-analysis performed thus far on the R501X and 2282del4 mutations, Rodriguez et al⁷⁹ analyzed data from 24 independent studies, which included 6,448 cases, 26,787 control subjects, and 1,993 families (all selected for AD) and determined that the effect size for risk of eczema caused by the 2 *FLG* null mutations is not dissimilar to previous reports at an OR of just over 3.

The *FLG* mutations have also been consistently associated with risk of other atopic traits, including asthma, hay fever, rhinoconjunctivitis, and allergen-specific IgE.⁷⁹⁻⁸⁶ Recently, Gao et al (unpublished data) evaluated whether *FLG* polymorphisms contribute to the serious complication of AD resulting from disseminated cutaneous herpes simplex virus infections (eczema herpeticum) and determined that the frequency of the R501X mutation was 3 times higher (24% vs 8%, respectively) and the relative risk for disease nearly double for patients with eczema herpeticum compared with those with AD without eczema herpeticum (OR, 11.8 vs 6.2; $P = .0008$). The authors speculate that the relationship between *FLG* null mutations and disease is most likely related to an increased propensity for disseminated viral skin infection resulting from skin barrier dysfunction rather than disease severity *per se* and provide the first insight into the genetic underpinnings of AD complications, such as viral dissemination.

New approaches on the horizon: The genome-wide approach. GWASs. A major limitation in the candidate gene approach is that selection of candidates is often based on limited knowledge,⁸⁷ and moreover, each potentially causal variant at each candidate gene can only make a modest contribution to overall heritability. Data from the Haplotype Map Project combined with more accurate approaches in selecting tagging markers sufficiently dense to capture most of the common variation in the

human genome (Fig 1, C) have recently allowed GWASs to replace candidate gene studies as an unbiased approach to search for genes controlling the risk for complex diseases. At the time of this review, results have been published on 1 GWAS for AD in which investigators in Germany genotyped a set of AD cases and control subjects and an independent set of 270 nuclear families on the Affymetrix Human mapping 500 K and 5.0 arrays (resulting in 342,303 successfully typed markers).⁸⁸ Although none of the markers analyzed were significantly associated with AD at the genome-wide significance level ($P < 1.46 \times 10^{-7}$), the group genotyped 54 SNPs associated with AD at a modest P value in an independent German group and observed replication in markers in chromosomal regions 1q21, 9p21, and 11q13, with further replication in an additional European group for a marker (rs7927894) in an intergenic region near chromosome 11 open reading frame 30 (*C11orf30*) on chromosome 11q13.5, which is the same marker that has been associated with Crohn disease.⁸⁹ An additional European-based GWAS is in the replication phase. It will be of interest to determine the extent to which the Esparza-Gordillo et al⁸⁸ findings will be replicated.

High-throughput gene profiling. Expression profiling of all known genes in the human genome is an ideal strategy for characterizing disease mechanisms and defining the transcriptome of complex diseases, such as AD. Indeed, genome-wide microarray technology has the potential to identify molecular signatures of clinical disease impossible to identify by using a gene-by-gene approach, and there are many examples whereby this technology can be highly predictive of clinical outcome. Although relatively few genome-wide expression studies have been performed for AD, which is likely due to the difficulties in ascertaining sufficient numbers of selected cell types of the epidermis and other relevant tissue samples, limitations related to the size of biopsied tissue, and challenges in ensuring collection of representative samples, it is anticipated that integration of this technology into gene discovery for AD will increase, especially as the cost for performing a genome-wide microarray continues to decrease.

Sugiura et al⁹⁰ performed high-throughput expression profiling of biopsy specimens from skin lesions of patients with AD compared with those from healthy control subjects and observed that several of the most significantly differentially expressed genes (ie, *S100A8* and *S100A7*, upregulated; *loricrin* and *FLG*, downregulated) were epidermal differentiation genes localized in chromosome 1q21, a region previously linked with AD. (Note: results were similar in comparisons between affected and unaffected skin among the patients with AD.) Similar

FIG 5. Genetic epidemiologic approaches toward identification of genes conferring AD susceptibility. In this summary of approaches used to date to identify candidate genes for AD, the first consideration is the complex pathology of AD (A), which includes defects and damage at the epithelial barrier and penetration of allergens, microbes, pollutants, and irritants into the epidermis and dermis, ultimately interacting with antigen-presenting cells (ie, Langerhans cells and dermal dendritic cells). The brick wall–like structure of the SC is compromised, possibly by defects in genes residing in the EDC, including *FLG*, *loricrin* (*LOR*), *LCEs*, *S100s*, *SPRRs*, *SCTE*, and *SCCE*. Additional candidates include TJs, proteins that constitute the “gate” to the passage of water, ions, and solutes through the paracellular pathway in the stratum granulosum (ie, *CLDN1*). A defective innate immune response (involving, for example, the *TLRs*, *CD14*, *NOD1*, *NOD2*, *DEFB1*, and *IRF2*) might contribute to a heightened, IgE-mediated, systemic T_H2 response. Combining a candidate gene approach with robust, genome-wide gene expression profiling has the potential of both elucidating novel candidates and validating suspected candidates, as shown in B, in which genes in the EDC on chromosome 1q21 are significantly differentially expressed in skin biopsy specimens taken from patients with AD compared with those from healthy nonatopic control subjects (courtesy of L. A. Beck). Candidate genes are selected, substitutions (ie, SNPs) and simple structural variants (ie, insertions/deletions and repeats) are genotyped in large populations selected for AD, and tests for association are performed.

findings have been observed by Beck et al (personal communication), who compared nonlesional skin of patients with extrinsic AD with the skin of nonatopic healthy control subjects (Fig 5, B). The Sugiura et al group also observed that keratin 16, localized on chromosome 17q21, another linkage hotspot, was upregulated. In addition to validating genes, high-throughput expression studies have led to novel discoveries. One example is the work by Lu et al,⁹¹ in which they relied on primary cultured keratinocytes from patients with AD and healthy control subjects to identify a number of novel candidates. Significant findings included 2 extracellular matrix-associated factors, matrix metalloproteinase 1 and 10, for which ELISA studies of sera from patients with intrinsic AD showed that both proteins were upregulated nearly 2-fold compared with levels seen in healthy subjects and patients with extrinsic AD. In a differentiated keratinocyte model, *FLG2* (or ifapsoriasin), also localized in the EDC, was identified, as well as 3 novel lipase genes, suggesting that these genes might also play a key role in the skin barrier and are worthy of further study.⁹² Thus, high-throughput expression profiling has already proved useful in supporting the hypothesis that defects in epidermal genes play a critical role in the development of AD, and it is also a tool for validating genetic findings and gene discovery.

Confounders and complexities

It's not all about the genes. The role of the environment.

In the same year that Watson and Crick reported their structure of the DNA molecule in the journal *Nature*,⁹³ Senior Registrar at the Manchester and Salford Hospital for Skin Diseases, Dr J. K. Morgan, made the following observation: "In theory, in every case in which there is an eczematous reaction in the skin, there are two prime factors involved. The first, and the more important, is a constitutional or internal factor, relating to the individual himself. The second in an external factor. It is upon the relative balance and interplay between these two that the appellation of the disease is based."⁹⁴

In the years of heritability studies that followed (described above), the consistent observation that concordance rates for AD among monozygotic twins raised together are higher than those among dizygotic twins supported the role of a genetic cause, but the relatively low concordance rates in both groups also supported the earliest suppositions that differences in exposure to certain environmental triggers might account for a considerable proportion of disease expression.

The challenge in the genetic epidemiology of AD in terms of interrogating gene-environment interactions is precisely which environmental factors should be considered. For example, at the core of the innate immune response are the ubiquitous fragments of bacterial LPS, or endotoxin, and many studies focusing on endotoxin exposure early in life suggest a protective effect in the development of allergic disease in general^{95,96} by skewing the T_H profile toward T_H1 , as purported by the hygiene hypothesis.⁹⁷ Interestingly, there is some support for the role of the hygiene hypothesis in susceptibility to AD.⁹⁸ Alternatively, the effect of exogenous substances, such as irritants (ie, soap and detergents), allergens (ie, exogenous proteases derived from house dust mites), and drugs (ie, topical corticosteroids) on patients with AD with genetic alterations in skin barrier genes has also been considered.⁵⁸

Very few of the genetic association studies summarized in Table E1 have considered evidence of association between

genetic polymorphisms in the context of exposure to certain environmental factors. Perhaps the best example is the study by Bisgaard et al,⁹⁹ in which it was hypothesized that a compromised skin barrier among patients with AD who are *FLG* deficient might enhance the effect of exposure to certain aeroallergens, such as house dust mite and pet allergen. The group confirmed previous observations that the risk of eczema was considerably higher among children with the *FLG* mutations (hazard ratio,¹⁰⁰ 2.26; $P = .0005$) but that the risk increased considerably if children were exposed to cat allergen at birth (hazard ratio, 11.11; $P < .0001$). Important considerations in similar studies performed in the future will be the ability to detect such interactions for variants with smaller effect sizes, the temporal relationship between environmental exposure and risk of disease (ie, perinatal exposure vs exposure later in childhood), and the generalizability of such findings across populations.

Ethnic diversity and underrepresentation. As described previously, failure to replicate associations between genetic markers and a complex trait, such as AD, in independent populations can be due to several factors, including chance, misclassification of the phenotype, environmental heterogeneity, inadequate sample sizes, and population stratification.¹⁰¹⁻¹⁰³ An important factor contributing to failure to replicate associations is also related to population diversity. For example, it is possible that certain genetic markers might contribute to disease risk in a particular (ie, ethnic or racial) population but not in others, either because of differences in frequencies of the risk allele or alleles or because of specific gene-gene interactions. It is difficult to evaluate the effect of ethnicity on genetic associations of AD, however, because there is relatively little diversity in the populations that have been studied thus far. As shown in Table E1, the overwhelming majority ($n = 70$) of association studies have been performed in populations of European descent, followed by 42 studies performed in Asian populations. A single study was performed in a Mexican cohort, and none of the reported studies have been performed in groups considered underserved minorities, such as African Americans. Sadly, this statistic does not reflect the actual prevalence of AD because African Americans and Asian/Pacific Islanders reportedly have more AD than US whites.¹⁰⁴

Perhaps the best example of a candidate gene for which ethnicity likely influences the extent to which a polymorphism confers risk is *FLG*. Palmer et al⁷⁷ observed differences in the R501X and 2282del4 *FLG* null mutation frequencies in diverse cohorts and suggested that different populations will have different *FLG* mutation profiles. Indeed, this group and others have demonstrated that in populations in which the R501X and 2282del4 mutations are not present, other mutations are prevalent and confer risk of AD, such as the 3321delA and S2554X mutations among Japanese patients.¹⁰⁵ In unpublished data our group observed a complete absence of the R501X mutation and very low frequency (1%) of the 2282del4 mutation among healthy African Americans compared with a frequency of 9% of the R501X mutation and 0% of the 2282del4 mutation among patients with AD. The low frequency and even absence of this mutation is not novel; elsewhere, the prevalence of the R501X mutation among subjects without AD has ranged from 0.8% to 3.0% among European populations and has been found to be absent in southern European (ie, Italian)¹⁰⁶ and Asian^{77,105} groups. In the only summary data available on the frequency of this mutation in African populations, it was absent in a cohort of 124 North Africans.⁷⁷ Collectively,

the distribution of these alleles suggests a latitude-dependent distribution with a decreasing north-south gradient of frequency and suggests that polymorphisms other than the relatively common R501X and 2282del4 mutations might be more important in non-Northern European groups.

SUMMARY

To recapitulate, AD is a chronic inflammatory disease of the skin characterized by dysregulation of the adaptive and innate immune response and a heightened IgE-mediated, systemic T_H2 response. Extreme T_H2 polarization and primary defects in the innate immune response, including epithelial barrier defects, in conjunction with mechanical damage to the epidermis as a consequence of the intense pruritus that is the hallmark feature of AD likely contribute to the more severe sequelae, including chronic bacterial colonization (ie, *S aureus* infection) and viral dissemination (ie, eczema herpeticum). This scenario can be summarized in Fig 5, whereby the damaged epidermal surface is penetrated by a host of exogenous substances, including allergens, irritants, microbes, pollutants, and even topical drugs. The brick wall-like structure of the SC, which normally creates a barrier that maintains water within the body and prevents the entrance of pathogens and allergens, is further compromised. The EDC, the DNA region in which a large number of genes encoding many of the cornified cell envelope precursor proteins, small proline-rich proteins, members of the S100 family, and intermediate filament-associated protein precursors (ie, profilaggrin) are localized, is an important target of candidate genes associated with barrier dysfunction at the level of the SC. The last line of defense is the stratum granulosum, containing TJs, proteins that constitute the “gate” to the passage of water, ions, and solutes through the paracellular pathway. Systemically, a dysfunctional immune response resulting in an imbalanced innate and adaptive milieu further aggravates the system. Early genome-wide linkage studies, association studies, and high-throughput expression profiling studies have supported the role of skin barrier dysfunction candidate genes in conjunction with innate and adaptive immune response genes. A comprehensive evaluation of all candidate gene studies published to date on AD shows the importance of both sets of genes, and a pathway analysis of the genes studied thus far supports a more thorough approach toward gene-gene and gene-environment interactions.

There are considerable challenges in the field: expanded analyses of skin barrier dysfunction genes to include not only those residing in the SC but also TJ genes at the level of the stratum granulosum; an expanded focus on both rare and common variants; expansion of population studies to include more ethnically diverse groups that are adequately powered; and a better integration of higher-throughput technology in addition to analyses that consider the interactive effects of common environmental factors. Each of these efforts will require greatly expanded sample sizes of carefully phenotyped patients and rigorous statistical approaches. None of these goals are achievable in the absence of a multidisciplinary approach, which will require the equal contributions of expert clinicians, geneticists, statistical analysts, and molecular biologists.

I thank Drs Li Gao, Peisong Gao, and Candelaria Vergara; Nicholas Rafaels; and Pat Oldewurtel for technical assistance and Mr Boyd Jacobson for his artistic contributions, as well as Drs Donald Leung and Stephan Weidinger for

invaluable discussions and comments. A special thanks to Dr Lisa A. Beck, who shared critical preliminary data and contributed to important discussions. I also acknowledge the contributions of the Atopic Dermatitis Vaccinia Network (ADVNet) in generating much of the data used in this review.

What do we know?

- It has long been recognized that there is a heritable component to the development of AD.
- Five genome-wide linkage studies have been performed on AD, plus a genome-wide linkage screen originally designed for asthma with analyses repeated for the AD outcome; however, there has been limited overlap of signals across studies, with only the 3p24 locus replicating.
- For the majority of candidate gene studies on AD to date, the focus has been on SNPs, which are relatively simple structural variants and include substitutions, insertions/deletions, and repeats.
- In a search of the public database for references through June 2009, there were 111 studies reporting on genetic association for 81 genes, of which more than half (46 genes) had at least 1 positive association.
- Mutations in *FLG* have been associated with AD in more than 20 different reports.
- By using a pathways analysis approach, slightly more than half ($n = 48$) of the 81 genes studied to date for AD cluster into 2 major networks: (1) antigen presentation and cell-mediated and humoral immune response and (2) cell signaling and interaction, cellular movement, and hematologic system development and function.
- There is increasing evidence that genes associated with skin barrier dysfunction, especially genes that reside in the EDC locus on chromosome 1q21, are associated with the risk of AD.
- The first GWAS on AD has been reported, and although none of the associations approached a genome-wide significance threshold, replication of modestly associated markers was observed in independent populations for a marker near *C11orf30* on chromosome 11q13.5, the same marker associated with Crohn disease.
- Expression profiling of all known genes in the human genome has been useful in validating several candidate genes, including several candidates in the EDC.

What is still needed?

- Interpretation of results from candidate gene studies of AD is difficult because of a variety of potential shortcomings, including the bias of journals in only reporting positive associations, power limitations in the original study design, and a failure to adjust for population stratification (ie, admixture of different ethnic/racial groups) in the case-control studies and consideration of Hardy-Weinberg proportions.
- It is generally believed that most polymorphisms will confer a relatively small effect on the risk of disease; however, most published studies to date on AD are insufficiently powered to detect an OR of approximately 1.5.

- It is increasingly believed that rare variants might contribute considerably to the risk of complex common diseases, such as AD, but very few studies to date have focused on the role of rare variants.
- Although environmental factors are believed to contribute greatly to the manifestation of AD, there is a dearth of information on the role of gene-environment interactions.
- Some polymorphisms might contribute to disease risk in one particular ethnic/racial group but not in others, but very few genetic association studies in nonwhite populations have been performed.

REFERENCES

- Smith WD. Hippocrates. Cambridge (MA): Harvard University Press; 1994.
- Besnier E. Premier note et observations preliminaire pour service d-introduction a letude des prurigos diathesiques. *Ann Dermatol Syphil* 1892;3:634-8.
- Coca AF. Specific diagnosis and treatment of allergic diseases of the skin. *JAMA* 1934;103:1275-7.
- Dold S, Wjst M, Mutius Ev, Reitmeir P, Stiepel E. Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. *Arch Dis Child* 1992;67:1018-22.
- Sneddon IB. The management of infantile eczema. *Med Press* 1951;226:329-33.
- Schaffer N. Atopic dermatitis in the older child. *J Asthma Res* 1966;3:189-91.
- Edfors-Lubs M-L. Allergy in 7000 twin pairs. *Acta Allergol* 1971;26:249-85.
- Schultz Larsen FV, Holm NV. Atopic dermatitis in a population based twin series. Concordance rates and heritability estimation. *Acta Derm Venereol Suppl* (Stockh) 1985;114:159.
- Larsen FS, Holm NV, Henningsen K. Atopic dermatitis. A genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1986;15:487-94.
- Strachan DP, Wong HJ, Spector TD. Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins. *J Allergy Clin Immunol* 2001;108:901-7.
- van Beijsterveldt CE, Boomsma DI. Genetics of parentally reported asthma, eczema and rhinitis in 5-yr-old twins. *Eur Respir J* 2007;29:516-21.
- Diepgen TL, Blettner M. Analysis of familial aggregation of atopic eczema and other atopic diseases by odds ratio regression models. *J Invest Dermatol* 1996;106:977-81.
- Walley AJ, Chavanas S, Moffatt MF, Esnouf RM, Ubhi B, Lawrence R, et al. Gene polymorphism in Netherton and common atopic disease. *Nat Genet* 2001;29:175-8.
- Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet* 1995;11:241-7.
- Lee YA, Wahn U, Kehrt R, Tarani L, Businco L, Gustafsson D, et al. A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. *Nat Genet* 2000;26:470-3.
- Cookson WO, Ubhi B, Lawrence R, Abecasis GR, Walley AJ, Cox HE, et al. Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. *Nat Genet* 2001;27:372-3.
- Bradley M, Soderhall C, Luthman H, Wahlgren CF, Kockum I, Nordenskjold M. Susceptibility loci for atopic dermatitis on chromosomes 3, 13, 15, 17 and 18 in a Swedish population. *Hum Mol Genet* 2002;11:1539-48.
- Haagerup A, Bjerke T, Schiotz PO, Dahl R, Binderup HG, Tan Q, et al. Atopic dermatitis—a total genome-scan for susceptibility genes. *Acta Derm Venereol* 2004;84:346-52.
- Guilloud-Bataille M, Bouzigon E, Annesi-Maesano I, Bousquet J, Charpin D, Gormand F, et al. Evidence for linkage of a new region (11p14) to eczema and allergic diseases. *Hum Genet* 2008;122:605-14.
- Enomoto H, Noguchi E, Iijima S, Takahashi T, Hayakawa K, Ito M, et al. Single nucleotide polymorphism-based genome-wide linkage analysis in Japanese atopic dermatitis families. *BMC Dermatol* 2007;7:5.
- Christensen U, Moller-Larsen S, Nyegaard M, Haagerup A, Hedemand A, Brasch-Andersen C, et al. Linkage of atopic dermatitis to chromosomes 4q22, 3p24 and 3q21. *Hum Genet* 2009;126:549-57.
- Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. *Science* 2001;291:1304-51.
- Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. *Genes Immun* 2006;7:95-100.
- Risch N, Merikangas K. The future of genetic studies of complex human diseases. *Science* 1996;273:1516-7.
- Neale BM, Sham PC. The future of association studies: gene-based analysis and replication. *Am J Hum Genet* 2004;75:353-62.
- Kabesch M. The art of replication. *Thorax* 2009;64:370-1.
- International HapMap Consortium. A haplotype map of the human genome. *Nature* 2005;437:1299-320.
- Morris AP. A flexible Bayesian framework for modeling haplotype association with disease, allowing for dominance effects of the underlying causative variants. *Am J Hum Genet* 2006;79:679-94.
- Rogers AJ, Raby BA, Lasky-Su JA, Murphy A, Lazarus R, Klanderman BJ, et al. Assessing the reproducibility of asthma candidate gene associations, using genome-wide data. *Am J Respir Crit Care Med* 2009;179:1084-90.
- Goldstein DB. Common genetic variation and human traits. *N Engl J Med* 2009;360:1696-8.
- Bodmer W, Bonilla C. Common and rare variants in multifactorial susceptibility to common diseases. *Nat Genet* 2008;40:695-701.
- Gayan J, Gonzalez-Perez A, Bermudo F, Saez ME, Royo JL, Quintas A, et al. A method for detecting epistasis in genome-wide studies using case-control multi-locus association analysis. *BMC Genomics* 2008;9:360.
- Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003;361:151-60.
- Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483-94.
- Beck LA, Boguniewicz M, Hata T, Schneider LC, Hanifin J, Gallo R, et al. Phenotype of subjects with atopic dermatitis with a history of eczema herpeticum. *J Allergy Clin Immunol* 2009;124:260-9, e7.
- Hashimoto C, Hudson KL, Anderson KV. The Toll gene of *Drosophila*, required for dorsal-ventral embryonic polarity, appears to encode a transmembrane protein. *Cell* 1988;52:269-79.
- Chamaillard M, Hashimoto M, Horie Y, Masumoto J, Qiu S, Saab L, et al. An essential role for NOD1 in host recognition of bacterial peptidoglycan containing diaminopimelic acid. *Nat Immunol* 2003;4:702-7.
- Girardin SE, Boneca IG, Carneiro LA, Antignac A, Jehanno M, Viala J, et al. Nod1 detects a unique muropeptide from gram-negative bacterial peptidoglycan. *Science* 2003;300:1584-7.
- Bazil V, Horejsi V, Baudys M, Kristofova H, Strominger JL, Kostka W, et al. Biochemical characterization of a soluble form of the 53-kDa monocyte surface antigen. *Eur J Immunol* 1986;16:1583-9.
- Durieux JJ, Vita N, Popescu O, Guette F, Calzada-Wack J, Munker R, et al. The two soluble forms of the lipopolysaccharide receptor, CD14: characterization and release by normal human monocytes. *Eur J Immunol* 1994;24:2006-12.
- Labeta MO, Durieux JJ, Fernandez N, Herrmann R, Ferrara P. Release from a human monocyte-like cell line of two different soluble forms of the lipopolysaccharide receptor, CD14. *Eur J Immunol* 1993;23:2144.
- Schroder JM, Harder J. Antimicrobial skin peptides and proteins. *Cell Mol Life Sci* 2006;63:469-86.
- Raulet DH. Natural killer cells. In: Paul WE, editor. *Fundamental immunology*. New York: Lipincott Williams-Wilkins; 2003. p. 365-91.
- McGirt LY, Beck LA. Innate immune defects in atopic dermatitis. *J Allergy Clin Immunol* 2006;118:202-8.
- De Benedetto A, Agniflohi R, McGirt LY, Bankova LG, Beck LA. Atopic dermatitis: a disease caused by innate immune defects? *J Invest Dermatol* 2009;129:14-30.
- Nomura I, Goleva E, Howell MD, Hamid QA, Ong PY, Hall CF, et al. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol* 2003;171:3262-9.
- Howell MD, Gallo RL, Boguniewicz M, Jones JF, Wong C, Streib JE, et al. Cytokine milieu of atopic dermatitis skin subverts the innate immune response to vaccinia virus. *Immunity* 2006;24:341-8.
- Kisich KO, Carspecken CW, Fieve S, Boguniewicz M, Leung DY. Defective killing of *Staphylococcus aureus* in atopic dermatitis is associated with reduced mobilization of human beta-defensin-3. *J Allergy Clin Immunol* 2008;122:62-8.
- Leung DY. Infection in atopic dermatitis. *Curr Opin Pediatr* 2003;15:399-404.
- Hauk PJ, Hamid QA, Chrousos GP, Leung DY. Induction of corticosteroid insensitivity in human PBMCs by microbial superantigens. *J Allergy Clin Immunol* 2000;105:782-7.
- Gao L, Grant AV, Rafaels N, Stockton-Porter M, Watkins T, Gao P, et al. Polymorphisms in the myosin light chain kinase gene that confer risk of severe sepsis are associated with a lower risk of asthma. *J Allergy Clin Immunol* 2007;119:1111-8.
- Levy H, Raby BA, Lake S, Tantisira KG, Kwiatkowski D, Lazarus R, et al. Association of defensin beta-1 gene polymorphisms with asthma. *J Allergy Clin Immunol* 2005;115:252-8.
- Matsushita I, Hasegawa K, Nakata K, Yasuda K, Tokunaga K, Keicho N. Genetic variants of human beta-defensin-1 and chronic obstructive pulmonary disease. *Biochem Biophys Res Commun* 2002;291:17-22.

54. Segat L, Milanese M, Boniotto M, Crovella S, Bernardon M, Costantini M, et al. DEFB-1 genetic polymorphism screening in HIV-1 positive pregnant women and their children. *J Matern Fetal Neonatal Med* 2006;19:13-6.
55. Chen QX, Lv C, Huang LX, Cheng BL, Xie GH, Wu SJ, et al. Genomic variations within DEFB1 are associated with the susceptibility to and the fatal outcome of severe sepsis in Chinese Han population. *Genes Immun* 2007;8:439-43.
56. Ferraris A, Torres B, Knafelz D, Barabino A, Lionetti P, de Angelis GL, et al. Relationship between CARD15, SLC22A4/5, and DLG5 polymorphisms and early-onset inflammatory bowel diseases: an Italian multicentric study. *Inflamm Bowel Dis* 2006;12:355-61.
57. Gazouli M, Koundourakis A, Ikononopoulos J, Gialafos EJ, Rapti A, Gorgoulis VG, et al. CARD15/NOD2, CD14, and toll-like receptor 4 gene polymorphisms in Greek patients with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2006;23:23-9.
58. Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, et al. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *J Allergy Clin Immunol* 2006;118:2-23.
59. Callard RE, Harper JJ. The skin barrier, atopic dermatitis and allergy: a role for Langerhans cells? *Trends Immunol* 2007;28:294-8.
60. Holgate ST. Epithelium dysfunction in asthma. *J Allergy Clin Immunol* 2007;120:1233-46.
61. Holgate ST. The epithelium takes centre stage in asthma and atopic dermatitis. *Trends Immunol* 2007;28:248-51.
62. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 2008;121:1337-43.
63. Hammad H, Lambrecht BN. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. *Nat Rev Immunol* 2008;8:193-204.
64. Higaki S, Morohashi M, Yamagishi T, Hasegawa Y. Comparative study of staphylococci from the skin of atopic dermatitis patients and from healthy subjects. *Int J Dermatol* 1999;38:265-9.
65. Travers JB, Norris DA, Leung DY. The keratinocyte as a target for staphylococcal bacterial toxins. *J Investig Dermatol Symp Proc* 2001;6:225-30.
66. Ricci G, Patrizi A, Neri I, Bendandi B, Masi M. Frequency and clinical role of *Staphylococcus aureus* overinfection in atopic dermatitis in children. *Pediatr Dermatol* 2003;20:389-92.
67. Sugimoto K, Ishikawa N, Terano T, Kitukawa Y, Kubosawa H, Ito S, et al. The importance of bacterial superantigens produced by *Staphylococcus aureus* in the treatment of atopic dermatitis using povidone-iodine. *Dermatology* 2006;212(suppl 1):26-34.
68. Warner JA, McGirt LY, Beck LA. Biomarkers of Th2 polarity are predictive of staphylococcal colonization in subjects with atopic dermatitis. *Br J Dermatol* 2009;160:183-5.
69. Niessen CM. Tight junctions/adherens junctions: basic structure and function. *J Invest Dermatol* 2007;127:2525-32.
70. Aijaz S, D'Atri F, Citi S, Balda MS, Matter K. Binding of GEF-H1 to the tight junction-associated adaptor cingulin results in inhibition of Rho signaling and G1/S phase transition. *Dev Cell* 2005;8:777-86.
71. Sawada N, Murata M, Kikuchi K, Osanai M, Tobioka H, Kojima T, et al. Tight junctions and human diseases. *Med Electron Microsc* 2003;36:147-56.
72. Hoffman S, Stemmler S. On the role of the epidermal differentiation complex in ichthyosis vulgaris, atopic dermatitis and psoriasis. *Br J Dermatol* 2007;157:441-9.
73. O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. *J Allergy Clin Immunol* 2008;122:689-93.
74. McKinley-Grant LJ, Idler WW, Bernstein IA, Parry DA, Cannizzaro L, Croce CM, et al. Characterization of a cDNA clone encoding human filaggrin and localization of the gene to chromosome region 1q21. *Proc Natl Acad Sci U S A* 1989;86:4848-52.
75. Gan SQ, McBride OW, Idler WW, Markova N, Steinert PM. Organization, structure, and polymorphisms of the human profilaggrin gene. *Biochemistry* 1990;29:9432-40.
76. Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006;38:337-42.
77. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.
78. Sandilands A, Terron-Kwiatkowski A, Hull PR, O'Regan GM, Clayton TH, Watson RM, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007;39:650-4.
79. Rodriguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol* 2009;123:1361-70, e7.
80. Palmer CN, Ismail T, Lee SP, Terron-Kwiatkowski A, Zhao Y, Liao H, et al. Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 2007;120:64-8.
81. Novak N, Baurecht H, Schafer T, Rodriguez E, Wagenpfeil S, Klopp N, et al. Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. *J Invest Dermatol* 2008;128:1430-5.
82. Ekelund E, Lieden A, Link J, Lee SP, D'Amato M, Palmer CN, et al. Loss-of-function variants of the filaggrin gene are associated with atopic eczema and associated phenotypes in Swedish families. *Acta Derm Venereol* 2008;88:15-9.
83. Basu K, Palmer CN, Lipworth BJ, Irwin McLean WH, Terron-Kwiatkowski A, Zhao Y, et al. Filaggrin null mutations are associated with increased asthma exacerbations in children and young adults. *Allergy* 2008;63:1211-7.
84. Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrey M, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol* 2008;121:872-7, e9.
85. Weidinger S, O'Sullivan M, Illig T, Baurecht H, Depner M, Rodriguez E, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 2008;121:1203-9, e1.
86. de Jongh CM, Khrenova L, Verberk MM, Calkoen F, van Dijk FJ, Voss H, et al. Loss-of-function polymorphisms in the filaggrin gene are associated with an increased susceptibility to chronic irritant contact dermatitis: a case-control study. *Br J Dermatol* 2008;159:621-7.
87. Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet* 2005;6:95-108.
88. Esparza-Gordillo J, Weidinger S, Folster-Holst R, Bauerfeind A, Ruschendorf F, Patone G, et al. A common variant on chromosome 11q13 is associated with atopic dermatitis. *Nat Genet* 2009;41:596-601.
89. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008;40:955-62.
90. Sugiura H, Ebise H, Tazawa T, Tanaka K, Sugiura Y, Uehara M, et al. 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* 2005;152:146-9.
91. Lu ZR, Park D, Lee KA, Ryu JW, Bhak J, Shi L, et al. Profiling the dysregulated genes of keratinocytes in atopic dermatitis patients: cDNA microarray and interatomic analyses. *J Dermatol Sci* 2009;54:126-9.
92. Toulza E, Mattiuzzo NR, Galliano MF, Jonca N, Dossat C, Jacob D, et al. Large-scale identification of human genes implicated in epidermal barrier function. *Genome Biol* 2007;8:R107.
93. Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* 1953;171:737-8.
94. Morgan JK. Sensitization and eczema. *Occup Med (London)* 1953;3:274-82.
95. Gereda JE, Leung DY, Thatayatikom A, Streib JE, Price MR, Klinnert MD, et al. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. *Lancet* 2000;355:1680-3.
96. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869-77.
97. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259-60.
98. Sherriff A, Golding J. Hygiene levels in a contemporary population cohort are associated with wheezing and atopic eczema in preschool infants. *Arch Dis Child* 2002;87:26-9.
99. Bisgaard H, Simpson A, Palmer CN, Bonnelykke K, McLean I, Mukhopadhyay S, et al. Gene-environment interaction in the onset of eczema in infancy: filaggrin loss-of-function mutations enhanced by neonatal cat exposure. *PLoS Med* 2008;5:e131.
100. Anderson HR. The epidemiological and allergic features of asthma in the New Guinea Highlands. *Clin Allergy* 1974;4:171-83.
101. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. Replication validity of genetic association studies. *Nat Genet* 2001;29:306-9.
102. Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K. A comprehensive review of genetic association studies. *Genet Med* 2002;4:45-61.
103. Colhoun HM, McKeigue PM, Davey Smith G. Problems of reporting genetic associations with complex outcomes. *Lancet* 2003;361:865-72.
104. Janupally SR, Feldman SR, Gupta AK, Fleischer ABJ. In the United States, blacks and Asian/Pacific Islanders are more likely than whites to seek medical care for atopic dermatitis. *Arch Dermatol* 2002;138:634-7.
105. Nomura T, Sandilands A, Akiyama M, Liao H, Evans AT, Sakai K, et al. Unique mutations in the filaggrin gene in Japanese patients with ichthyosis vulgaris and atopic dermatitis. *J Allergy Clin Immunol* 2007;119:434-40.
106. Giardina E, Paolillo N, Sinibaldi C, Novelli G. R501X and 2282del4 filaggrin mutations do not confer susceptibility to psoriasis and atopic dermatitis in Italian patients. *Dermatology* 2008;216:83-4.

REFERENCES

- E1. Matsusue A, Kiyohara C, Tanaka K, Sasaki S, Miyake Y. ADAM33 genetic polymorphisms and risk of atopic dermatitis among Japanese children. *Clin Biochem* 2009;42:477-83.
- E2. Ma L, Gao XH, Zhao LP, Di ZH, McHepange UO, Zhang L, et al. Brain-derived neurotrophic factor gene polymorphisms and serum levels in Chinese atopic dermatitis patients. *J Eur Acad Dermatol Venereol* 2009;23:1277-81.
- E3. Hoffjan S, Parwez Q, Petrasch-Parwez E, Stemmler S. Variation in the BDNF and NGFB genes in German atopic dermatitis patients. *Mol Cell Probes* 2009;23:35-8.
- E4. Gray A, Stewart H, Pravica V, Fryer AA, Lenney W, Hutchinson IV, et al. Polymorphisms of the Bcl-2 family member bfl-1 in children with atopic dermatitis. *Pediatr Allergy Immunol* 2006;17:578-82.
- E5. Purwar R, Langer K, Werfel T. Polymorphisms within the C3 gene are associated with specific IgE levels to common allergens and super-antigens among atopic dermatitis patients. *Exp Dermatol* 2009;18:30-4.
- E6. Macaluso F, Nothnagel M, Parwez Q, Petrasch-Parwez E, Bechara FG, Epplen JT, et al. Polymorphisms in NACHT-LRR (NLR) genes in atopic dermatitis. *Exp Dermatol* 2007;16:692-8.
- E7. Kabesch M, Peters W, Carr D, Leupold W, Weiland SK, von Mutius E. Association between polymorphisms in caspase recruitment domain containing protein 15 and allergy in two German populations. *J Allergy Clin Immunol* 2003;111:813-7.
- E8. Tsunemi Y, Sekiya T, Saeki H, Hirai K, Ohta K, Nakamura K, et al. Lack of association of CCR4 single nucleotide polymorphism with atopic dermatitis in Japanese patients. *Acta Derm Venereol* 2004;84:187-90.
- E9. Gern JE, Reardon CL, Hoffjan S, Nicolae D, Li Z, Roberg KA, et al. Effects of dog ownership and genotype on immune development and atopy in infancy. *J Allergy Clin Immunol* 2004;113:307-14.
- E10. Lange J, Heinzmann A, Zehle C, Kopp M. CT genotype of promotor polymorphism C159T in the CD14 gene is associated with lower prevalence of atopic dermatitis and lower IL-13 production. *Pediatr Allergy Immunol* 2005;16:456-7.
- E11. Sengler C, Haider A, Sommerfeld C, Lau S, Baldini M, Martinez F, et al. Evaluation of the CD14 C-159 T polymorphism in the German Multicenter Allergy Study cohort. *Clin Exp Allergy* 2003;33:166-9.
- E12. Liang XH, Cheung W, Heng CK, Liu JJ, Li CW, Lim B, et al. CD14 promoter polymorphisms have no functional significance and are not associated with atopic phenotypes. *Pharmacogenet Genomics* 2006;16:229-36.
- E13. Zhang HL, Ni LY, Bao QY, Chen ZM, Li CC. [Association of CD14 gene polymorphism with atopic diseases in Chinese Han ethnic group children]. *Zhonghua Er Ke Za Zhi* 2007;45:105-8.
- E14. Mao XQ, Shirakawa T, Yoshikawa T, Yoshikawa K, Kawai M, Sasaki S, et al. Association between genetic variants of mast-cell chymase and eczema. *Lancet* 1996;348:581-3.
- E15. Mao XQ, Shirakawa T, Enomoto T, Shimazu S, Dake Y, Kitano H, et al. Association between variants of mast cell chymase gene and serum IgE levels in eczema. *Hum Hered* 1998;48:38-41.
- E16. Kawashima T, Noguchi E, Arinami T, Kobayashi K, Otsuka F, Hamaguchi H. 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* 1998;48:271-4.
- E17. Tanaka K, Sugiura H, Uehara M, Sato H, Hashimoto-Tamaoki T, Furuyama J. Association between mast cell chymase genotype and atopic eczema: comparison between patients with atopic eczema alone and those with atopic eczema and atopic respiratory disease. *Clin Exp Allergy* 1999;29:800-3.
- E18. Weidinger S, Rummeler L, Klopp N, Wagenpfeil S, Baurecht HJ, Fischer G, et al. Association study of mast cell chymase polymorphisms with atopy. *Allergy* 2005;60:1256-61.
- E19. Pascale E, Tarani L, Meglio P, Businco L, Battiloro E, Cimino-Reale G, et al. Absence of association between a variant of the mast cell chymase gene and atopic dermatitis in an Italian population. *Hum Hered* 2001;51:177-9.
- E20. Soderhall C, Marenholz I, Kerscher T, Ruschendorf F, Esparza-Gordillo J, Worm M, et al. Variants in a novel epidermal collagen gene (COL29A1) are associated with atopic dermatitis. *PLoS Biol* 2007;5:e242.
- E21. Rafatpanah H, Bennett E, Pravica V, McCoy MJ, David TJ, Hutchinson IV, et al. Association between novel GM-CSF gene polymorphisms and the frequency and severity of atopic dermatitis. *J Allergy Clin Immunol* 2003;112:593-8.
- E22. Saeki H, Tsunemi Y, Asano N, Nakamura K, Sekiya T, Hirai K, et al. Analysis of GM-CSF gene polymorphisms (3606T/C and 3928C/T) in Japanese patients with atopic dermatitis. *Clin Exp Dermatol* 2006;31:278-80.
- E23. Vasilopoulos Y, Cork MJ, Teare D, Marinou I, Ward SJ, Duff GW, et al. A non-synonymous substitution of cystatin A, a cysteine protease inhibitor of house dust mite protease, leads to decreased mRNA stability and shows a significant association with atopic dermatitis. *Allergy* 2007;62:514-9.
- E24. Jones G, Wu S, Jang N, Fulcher D, Hogan P, Stewart G. Polymorphisms within the CTLA4 gene are associated with infant atopic dermatitis. *Br J Dermatol* 2006;154:467-71.
- E25. Arriba-Mendez S, Sanz C, Isidoro-Garcia M, Davild I, Laffond E, Horeno E, et al. 927T>C polymorphism of the cysteinyl-leukotriene type-1 receptor (CYSLTR1) gene in children with asthma and atopic dermatitis. *Pediatr Allergy Immunol* 2006;17:323-8.
- E26. Kim E, Lee JE, Namkung JH, Kim PS, Kim S, Shin ES, et al. Single nucleotide polymorphisms and the haplotype in the DEFB1 gene are associated with atopic dermatitis in a Korean population. *J Dermatol Sci* 2009;54:25-30.
- E27. Prado-Montes de Oca E, Garcia-Vargas A, Lozano-Inocencio R, Gallegos-Arreola MP, Sandoval-Ramirez L, Davalos-Rodriguez NO, et al. Association of beta-defensin 1 single nucleotide polymorphisms with atopic dermatitis. *Int Arch Allergy Immunol* 2007;142:211-8.
- E28. Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Fujita H, et al. 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* 2002;29:222-8.
- E29. Rigoli L, Caminiti L, Di Bella C, Procopio V, Cuppari C, Vita D, et al. Investigation of the eotaxin gene -426C→T, -384A→G and 67G→A single-nucleotide polymorphisms and atopic dermatitis in Italian children using family-based association methods. *Clin Exp Dermatol* 2008;33:316-21.
- E30. Cox HE, Moffatt MF, Faux JA, Walley AJ, Coleman R, Trembath RC, et al. Association of atopic dermatitis to the beta subunit of the high affinity immunoglobulin E receptor. *Br J Dermatol* 1998;138:182-7.
- E31. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.
- E32. Ruether A, Stoll M, Schwarz T, Schreiber S, Folster-Holst R. Filaggrin loss-of-function variant contributes to atopic dermatitis risk in the population of Northern Germany. *Br J Dermatol* 2006;155:1093-4.
- E33. Marenholz I, Nickel R, Ruschendorf F, Schulz F, Esparza-Gordillo J, Kerscher T, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006;118:866-71.
- E34. Barker JN, Palmer CN, Zhao Y, Liao H, Hull PR, Lee SP, et al. Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J Invest Dermatol* 2007;127:564-7.
- E35. Rogers AJ, Celedon JC, Lasky-Su JA, Weiss ST, Raby BA. Filaggrin mutations confer susceptibility to atopic dermatitis but not to asthma. *J Allergy Clin Immunol* 2007;120:1332-7.
- E36. Hubiche T, Ged C, Benard A, Leaute-Labreze C, McElreavey K, de Verneuil H, et al. Analysis of SPINK 5, KLK 7 and FLG genotypes in a French atopic dermatitis cohort. *Acta Derm Venereol* 2007;87:499-505.
- E37. Morar N, Cookson WO, Harper JI, Moffatt MF. Filaggrin mutations in children with severe atopic dermatitis. *J Invest Dermatol* 2007;127:1667-72.
- E38. Brown SJ, Sandilands A, Zhao Y, Liao H, Relton CL, Meggitt SJ, et al. Prevalent and low-frequency null mutations in the filaggrin gene are associated with early-onset and persistent atopic eczema. *J Invest Dermatol* 2008;128:1591-4.
- E39. Ekelund E, Lieden A, Link J, Lee SP, D'Amato M, Palmer CN, et al. Loss-of-function variants of the filaggrin gene are associated with atopic eczema and associated phenotypes in Swedish families. *Acta Derm Venereol* 2008;88:15-9.
- E40. Giardina E, Paolillo N, Sinibaldi C, Novelli G. R501X and 2282del4 filaggrin mutations do not confer susceptibility to psoriasis and atopic dermatitis in Italian patients. *Dermatology* 2008;216:83-4.
- E41. Betz RC, Pforr J, Flaquer A, Redler S, Hanneken S, Eigelshoven S, et al. Loss-of-function mutations in the filaggrin gene and alopecia areata: strong risk factor for a severe course of disease in patients comorbid for atopic disease. *J Invest Dermatol* 2007;127:2539-43.
- E42. Weidinger S, Illig T, Baurecht H, Irvine AD, Rodriguez E, Diaz-Lacava A, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* 2006;118:214-9.
- E43. Bisgaard H, Simpson A, Palmer CN, Bonnelykke K, McLean I, Mukhopadhyay S, et al. Gene-environment interaction in the onset of eczema in infancy: filaggrin loss-of-function mutations enhanced by neonatal cat exposure. *PLoS Med* 2008;5:e131.
- E44. Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrey M, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol* 2008;121:872-7, e9.
- E45. Sandilands A, Terron-Kwiatkowski A, Hull PR, O'Regan GM, Clayton TH, Watson RM, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007;39:650-4.

- E46. Weidinger S, O'Sullivan M, Illig T, Baurecht H, Depner M, Rodriguez E, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 2008;121:1203-9, e1.
- E47. Bisgaard H, Halkjaer LB, Hinge R, Giwercman C, Palmer C, Silveira L, et al. Risk analysis of early childhood eczema. *J Allergy Clin Immunol* 2009;123:1355-60, e5.
- E48. Nomura T, Akiyama M, Sandilands A, Nemoto-Hasebe I, Sakai K, Nagasaki A, et al. Prevalent and rare mutations in the gene encoding filaggrin in Japanese patients with ichthyosis vulgaris and atopic dermatitis. *J Invest Dermatol* 2009;129:1302-5.
- E49. Enomoto H, Hirata K, Otsuka K, Kawai T, Takahashi T, Hirota T, et al. Filaggrin null mutations are associated with atopic dermatitis and elevated levels of IgE in the Japanese population: a family and case-control study. *J Hum Genet* 2008;53:615-21.
- E50. Nomura T, Akiyama M, Sandilands A, Nemoto-Hasebe I, Sakai K, Nagasaki A, et al. Specific filaggrin mutations cause ichthyosis vulgaris and are significantly associated with atopic dermatitis in Japan. *J Invest Dermatol* 2008;128:1436-41.
- E51. Arshad SH, Karmaus W, Kurukulaaratchy R, Sadeghnejad A, Huebner M, Ewart S. Polymorphisms in the interleukin 13 and GATA binding protein 3 genes and the development of eczema during childhood. *Br J Dermatol* 2008;158:1315-22.
- E52. Soderhall C, Marenholz I, Nickel R, Gruber C, Kehrt R, Rohde K, et al. Lack of association of the G protein-coupled receptor for asthma susceptibility gene with atopic dermatitis. *J Allergy Clin Immunol* 2005;116:220-1.
- E53. Safronova OG, Vavilin VA, Lyapunova AA, Makarova SI, Lyakhovich VV, Kaznacheeva LF, et al. Relationship between glutathione S-transferase P1 polymorphism and bronchial asthma and atopic dermatitis. *Bull Exp Biol Med* 2003;136:73-5.
- E54. Vavilin VA, Safronova OG, Lyapunova AA, Lyakhovich VV, Kaznacheeva LF, Manankin NA, et al. Interaction of GSTM1, GSTT1, and GSTP1 genotypes in determination of predisposition to atopic dermatitis. *Bull Exp Biol Med* 2003;136:388-91.
- E55. Kennedy MJ, Loehle JA, Griffin AR, Doll MA, Kearns GL, Sullivan JE, et al. Association of the histamine N-methyltransferase C314T (Thr105Ile) polymorphism with atopic dermatitis in Caucasian children. *Pharmacotherapy* 2008;28:1495-501.
- E56. Chang YT, Lee WR, Yu CW, Liu HN, Lin MW, Huang CH, et al. No association of cytokine gene polymorphisms in Chinese patients with atopic dermatitis. *Clin Exp Dermatol* 2006;31:419-23.
- E57. Reich K, Westphal G, Konig IR, Mossner R, Schupp P, Gutesell C, et al. Cytokine gene polymorphisms in atopic dermatitis. *Br J Dermatol* 2003;148:1237-41.
- E58. Kawashima T, Noguchi E, Arinami T, Yamakawa-Kobayashi K, Nakagawa H, Otsuka F, et al. Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. *J Med Genet* 1998;35:502-4.
- E59. Elliott K, Fitzpatrick E, Hill D, Brown J, Adams S, Chee P, et al. The -590C/T and -34C/T interleukin-4 promoter polymorphisms are not associated with atopic eczema in childhood. *J Allergy Clin Immunol* 2001;108:285-7.
- E60. Tanaka K, Sugiura H, Uehara M, Hashimoto Y, Donnelly C, Montgomery DS. 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* 2001;31:1522-7.
- E61. Novak N, Kruse S, Kraft S, Geiger E, Klucken H, Fimmers R, et al. 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* 2002;119:870-5.
- E62. Soderhall C, Bradley M, Kockum I, Luthman H, Wahlgren CF, Nordenskjold M. Analysis of association and linkage for the interleukin-4 and interleukin-4 receptor b alpha regions in Swedish atopic dermatitis families. *Clin Exp Allergy* 2002;32:1199-202.
- E63. He JQ, Chan-Yeung M, Becker AB, Dimich-Ward H, Ferguson AC, Manfreda J, et al. Genetic variants of the IL13 and IL4 genes and atopic diseases in at-risk children. *Genes Immun* 2003;4:385-9.
- E64. Hosomi N, Fukai K, Oiso N, Kato A, Ishii M, Kunitomo H, et al. Polymorphisms in the promoter of the interleukin-4 receptor alpha chain gene are associated with atopic dermatitis in Japan. *J Invest Dermatol* 2004;122:843-5.
- E65. Yamamoto N, Sugiura H, Tanaka K, Uehara M. Heterogeneity of interleukin 5 genetic background in atopic dermatitis patients: significant difference between those with blood eosinophilia and normal eosinophil levels. *J Dermatol Sci* 2003;33:121-6.
- E66. Oiso N, Fukai K, Ishii M. Interleukin 4 receptor alpha chain polymorphism Gln551Arg is associated with adult atopic dermatitis in Japan. *Br J Dermatol* 2000;142:1003-6.
- E67. Callard RE, Hamvas R, Chatterton C, Blanco C, Pembrey M, Jones R, et al. An interaction between the IL-4Ralpha gene and infection is associated with atopic eczema in young children. *Clin Exp Allergy* 2002;32:990-3.
- E68. Namkung JH, Lee JE, Kim E, Cho HJ, Kim S, Shin ES, et al. IL-5 and IL-5 receptor alpha polymorphisms are associated with atopic dermatitis in Koreans. *Allergy* 2007;62:934-42.
- E69. Arkwright PD, Chase JM, Babbage S, Pravica V, David TJ, Hutchinson IV. Atopic dermatitis is associated with a low-producer transforming growth factor beta(1) cytokine genotype. *J Allergy Clin Immunol* 2001;108:281-4.
- E70. Sohn MH, Song JS, Kim KW, Kim ES, Kim KE, Lee JM. Association of interleukin-10 gene promoter polymorphism in children with atopic dermatitis. *J Pediatr* 2007;150:106-8.
- E71. Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Fujita H, et al. Interleukin-12 p40 gene (IL12B) 3'-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris. *J Dermatol Sci* 2002;30:161-6.
- E72. Takahashi N, Akahoshi M, Matsuda A, Ebe K, Inomata N, Obara K, et al. Association of the IL12RB1 promoter polymorphisms with increased risk of atopic dermatitis and other allergic phenotypes. *Hum Mol Genet* 2005;14:3149-59.
- E73. Hummelshoj T, Bodtger U, Datta P, Malling HJ, Oturai A, Poulsen LK, et al. Association between an interleukin-13 promoter polymorphism and atopy. *Eur J Immunogenet* 2003;30:355-9.
- E74. Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Kakinuma T, et al. Interleukin-13 gene polymorphism G4257A is associated with atopic dermatitis in Japanese patients. *J Dermatol Sci* 2002;30:100-7.
- E75. Liu X, Nickel R, Beyer K, Wahn U, Ehrlich E, Freidhoff LR, et al. 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* 2000;106:167-70.
- E76. Shibata S, Saeki H, Tsunemi Y, Kato T, Nakamura K, Kakinuma T, et al. IL-17F single nucleotide polymorphism is not associated with psoriasis vulgaris or atopic dermatitis in the Japanese population. *J Dermatol Sci* 2009;53:163-5.
- E77. Novak N, Kruse S, Potreck J, Maintz L, Jenneck C, Weidinger S, et al. Single nucleotide polymorphisms of the IL18 gene are associated with atopic eczema. *J Allergy Clin Immunol* 2005;115:828-33.
- E78. Kim E, Lee JE, Namkung JH, Park JH, Kim S, Shin ES, et al. Association of the single-nucleotide polymorphism and haplotype of the interleukin 18 gene with atopic dermatitis in Koreans. *Clin Exp Allergy* 2007;37:865-71.
- E79. Kato T, Tsunemi Y, Saeki H, Shibata S, Sekiya T, Nakamura K, et al. Interleukin-18 gene polymorphism -137 G/C is associated with susceptibility to psoriasis vulgaris but not with atopic dermatitis in Japanese patients. *J Dermatol Sci* 2009;53:162-3.
- E80. Beygo J, Parwez Q, Petrasch-Parwez E, Epplen JT, Hoffjan S. No evidence of an association between polymorphisms in the IRAK-M gene and atopic dermatitis in a German cohort. *Mol Cell Probes* 2009;23:16-9.
- E81. Nishio Y, Noguchi E, Ito S, Ichikawa E, Umebayashi Y, Otsuka F, et al. Mutation and association analysis of the interferon regulatory factor 2 gene (IRF2) with atopic dermatitis. *J Hum Genet* 2001;46:664-7.
- E82. Lee HJ, Ha SJ, Han H, Kim JW. Distribution of HLA-A, B alleles and polymorphisms of TAP and LMP genes in Korean patients with atopic dermatitis. *Clin Exp Allergy* 2001;31:1867-74.
- E83. Kozma GT, Falus A, Bojszko A, Krikovszky D, Szabo T, Nagy A, et al. Lack of association between atopic eczema/dermatitis syndrome and polymorphisms in the promoter region of RANTES and regulatory region of MCP-1. *Allergy* 2002;57:160-3.
- E84. Xin X, Nakamura K, Liu H, Nakayama EE, Goto M, Nagai Y, et al. Novel polymorphisms in human macrophage inflammatory protein-1 alpha (MIP-1alpha) gene. *Genes Immun* 2001;2:156-8.
- E85. Makarova SI, Dodunova EM, Ivanova GG, Vavilin VA, Kaznacheeva LF, Lyakhovich VV. Polymorphism of arylamine-N-acetyltransferase 2 gene is associated with the risk of atopic dermatitis. *Bull Exp Biol Med* 2005;139:662-4.
- E86. Brocvielle H, Muret P, Goydadin AC, Boone P, Broly F, Kantelip JP, et al. N-acetyltransferase 2 acetylation polymorphism: prevalence of slow acetylators does not differ between atopic dermatitis patients and healthy subjects. *Skin Pharmacol Appl Skin Physiol* 2003;16:386-92.
- E87. Weidinger S, Klopp N, Rummeler L, Wagenpfeil S, Novak N, Baurecht HJ, et al. Association of NOD1 polymorphisms with atopic eczema and related phenotypes. *J Allergy Clin Immunol* 2005;116:177-84.
- E88. Ekelund E, Bradley M, Weidinger S, Jovanovic DL, Johansson C, Lindgren CM, et al. Lack of association between neuropeptide S receptor 1 gene (NPSR1) and eczema in five European populations. *Acta Derm Venereol* 2009;89:115-21.

- E89. Greisenegger EK, Zimprich A, Zimprich F, Stingl G, Kopp T. Analysis of the prodynorphin promoter polymorphism in atopic dermatitis and disease-related pruritus. *Clin Exp Dermatol* 2009;34:728-30.
- E90. Jang N, Stewart G, Jones G. Polymorphisms within the PHF11 gene at chromosome 13q14 are associated with childhood atopic dermatitis. *Genes Immun* 2005;6:262-4.
- E91. Nickel R, Casolaro V, Wahn U, Beyer K, Barnes KC, Plunkett B, et al. Atopic dermatitis is associated with a functional mutation in the promoter of the CC chemokine RANTES. *J Immunol* 2000;164:1612-6.
- E92. Bai B, Tanaka K, Tazawa T, Yamamoto N, Sugiura H. Association between RANTES promoter polymorphism -401A enhanced RANTES production in atopic dermatitis patients. *J Dermatol Sci* 2005;39:189-91.
- E93. Tanaka K, Roberts MH, Yamamoto N, Sugiura H, Uehara M, Hopkin JM. Up-regulating promoter polymorphisms of RANTES relate to atopic dermatitis. *Int J Immunogenet* 2006;33:423-8.
- E94. Vasilopoulos Y, Cork MJ, Murphy R, Williams HC, Robinson DA, Duff GW, et al. Genetic association between an AACC insertion in the 3'UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis. *J Invest Dermatol* 2004;123:62-6.
- E95. Kim HT, Lee JY, Han BG, Kimm K, Oh B, Shin HD, et al. Association analysis of sphingomyelinase 2 polymorphisms for the extrinsic type of atopic dermatitis in Koreans. *J Dermatol Sci* 2007;46:143-6.
- E96. Ekelund E, Saaf A, Tengvall-Linder M, Melen E, Link J, Barker J, et al. Elevated expression and genetic association links the SOCS3 gene to atopic dermatitis. *Am J Hum Genet* 2006;78:1060-5.
- E97. Jongepier H, Koppelman GH, Nolte IM, Bruinenberg M, Bleecker ER, Meyers DA, et al. Polymorphisms in SPINK5 are not associated with asthma in a Dutch population. *J Allergy Clin Immunol* 2005;115:486-92.
- E98. Liu Q, Xia Y, Zhang W, Li J, Wang P, Li H, et al. A functional polymorphism in the SPINK5 gene is associated with asthma in a Chinese Han Population. *BMC Med Genet* 2009;10:59.
- E99. Nishio Y, Noguchi E, Shibasaki M, Kamioka M, Ichikawa E, Ichikawa K, et al. Association between polymorphisms in the SPINK5 gene and atopic dermatitis in the Japanese. *Genes Immun* 2003;4:515-7.
- E100. Walley AJ, Chavanas S, Moffatt MF, Esnouf RM, Ubhi B, Lawrence R, et al. Gene polymorphism in Netherton and common atopic disease. *Nat Genet* 2001;29:175-8.
- E101. Kato A, Fukai K, Oiso N, Hosomi M, Murakami T, Ishii M. Association of SPINK5 gene polymorphisms with atopic dermatitis in the Japanese population. *Br J Dermatol* 2003;48:665-9.
- E102. Kabesch M, Carr D, Weiland SK, von Mutius E. Association between polymorphisms in serine protease inhibitor, Kazal type 5 and asthma phenotypes in a large German population sample. *Clin Exp Allergy* 2004;34:340-5.
- E103. Kusunoki T, Okafuji I, Yoshioka T, Saito M, Nishikomori R, Heike T, et al. SPINK5 polymorphism is associated with disease severity and food allergy in children with atopic dermatitis. *J Allergy Clin Immunol* 2005;115:636-8.
- E104. Shimizu M, Matsuda A, Yanagisawa K, Hirota T, Akahoshi M, Inomata N, et al. Functional SNPs in the distal promoter of the ST2 gene are associated with atopic dermatitis. *Hum Mol Genet* 2005;14:2919-27.
- E105. Tsunemi Y, Komine M, Sekiya T, Saeki H, Nakamura K, Hirai K, et al. The -431C>T polymorphism of thymus and activation-regulated chemokine increases the promoter activity but is not associated with susceptibility to atopic dermatitis in Japanese patients. *Exp Dermatol* 2004;13:715-9.
- E106. Sekiya T, Tsunemi Y, Miyamasu M, Ohta K, Morita A, Saeki H, et al. Variations in the human Th2-specific chemokine TARC gene. *Immunogenetics* 2003;54:742-5.
- E107. Chae SC, Song JH, Lee YC, Kim JW, Chung HT. The association of the exon 4 variations of Tim-1 gene with allergic diseases in a Korean population. *Biochem Biophys Res Commun* 2003;312:346-50.
- E108. Page NS, Jones G, Stewart GJ. Genetic association studies between the T cell immunoglobulin mucin (TIM) gene locus and childhood atopic dermatitis. *Int Arch Allergy Immunol* 2006;141:331-6.
- E109. Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, Klotz M, Werfel T, Herz U, et al. The toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol* 2004;113:565-7.
- E110. Hoffjan S, Stemmler S, Parwez Q, Petrasch-Parwez E, Arinir U, Rohde G, et al. Evaluation of the toll-like receptor 6 Ser249Pro polymorphism in patients with asthma, atopic dermatitis and chronic obstructive pulmonary disease. *BMC Med Genet* 2005;6:34.
- E111. Novak N, Yu CF, Bussmann C, Maintz L, Peng WM, Hart J, et al. Putative association of a TLR9 promoter polymorphism with atopic eczema. *Allergy* 2007;62:766-72.
- E112. Schimming TT, Parwez Q, Petrasch-Parwez E, Nothnagel M, Epplen JT, Hoffjan S. Association of toll-interacting protein gene polymorphisms with atopic dermatitis. *BMC Dermatol* 2007;7:3.
- E113. Zablotna M, Sobjanek M, Glen J, Niedoszytko M, Wilkowska A, Roszkiewicz J, et al. Association between the -1154 G/A promoter polymorphism of the vascular endothelial growth factor gene and atopic dermatitis. *J Eur Acad Dermatol Venereol* 2009 [Epub ahead of print].

TABLE E1. Genes associated with atopic dermatitis in at least one study

Gene (alias)	Chromosomal location	Variant	Association	Population	No. of subjects*	Reference no.
<i>ADAM33</i>	20p13	rs2853209	Yes	Japanese	140/258	E1
		rs2787094	No	—	—	
		rs2280091	No	—	—	
		rs2280090	No	—	—	
		rs628977	No	—	—	
		rs597980	No	—	—	
<i>BDNF</i>	11p13	rs528557	No	—	—	E2
		C270T	Yes	Chinese	160/169	
		G196A	No	—	—	
<i>BFL1</i> (<i>BCL2A1</i>)	15q24.3	Val66Met	No	German	361/325	E3
		G-1182C haplotype	Yes	British	105/110	E4
<i>C3</i>	19p13.3-p13.2	A141G	Yes	—	—	E5
		rs10410674	No	German	96/49	
		rs366510	No	—	—	
		rs10402876	No	—	—	
		rs423490	No	—	—	
<i>CARD12</i>	2p22-p21	Promoter	Yes	German	392/297	E6
<i>CARD15</i>		G2722C	Yes	German	1,872†	E7
<i>CCR4</i>	3p24	R792 W	No	German	392/297	E6
		C1014 T	No	Japanese	198/183	E8
<i>CD14</i>	5q31.1	C-159T/C-260T (rs2569190)	Yes	European American	285†	E9
		—	Yes	German	10:20	E10
		—	No	German	872	E11
		—	No	Chinese	171/160	E12
		—	No	Chinese	113/67	E13
<i>CMA1</i> (<i>MCC</i>)		BstXI	Yes	Japanese	100/100	E14
		—	Yes	Japanese	145/706	E15
		—	No	Japanese	100/101	E16
		—	Yes	Japanese	169†	E17
		rs1800875	Yes	German	242/1633	E18
		rs1956923	No	—	—	
		rs5244	No	—	—	
		rs5246	No	—	—	
		rs5247	No	—	—	
		rs5248	No	—	—	
		rs5250	No	—	—	
		BstXI	No	Italian	70/100	E19
<i>COL29A1</i>	3q21	A36637742	Yes	German	199 + 292 families	E20
<i>CSF2</i> (<i>GMCSF</i>)	5q31.1	A-677C	Yes	British	113/114	E21
		T-1916C	Yes	—	—	
		T3606C	No	Japanese	181/100	E22
		C3928T	No	—	—	
<i>CSTA</i>	3q21	C344T	Yes	British	100/203	E23
<i>CTLA4</i>	2q33	49 exon 1/CT60 haplotype	Yes	Australian	112 families	E24
<i>CYSLTR1</i>	Xq13-q21	T927C	Yes	Spanish	41/79	E25
<i>DEFA4</i>	8p23.1	G-6298C (rs2951853)	No	Korean	631/458	E26
		T-5144G (rs3888293)	No	—	—	
		G-4477C (rs2615772)	No	—	—	
		T-2576C (rs3780078)	No	—	—	
		G-1780A (rs2741676)	No	—	—	
		T-668C (rs2741678)	No	—	—	
		T-446A (rs2741679)	No	—	—	
		G85G (rs2738100)	No	—	—	
<i>DEFA5</i>	8p23.1	G2277A (rs2702863)	No	—	—	E26
		G-2819A (rs10093453)	No	Korean	631/458	
		G-1027C (rs6988319)	No	—	—	
		G-427A (rs4395911)	No	—	—	
		T69T (rs2272719)	No	—	—	

(Continued)

TABLE E1. (Continued)

Gene (alias)	Chromosomal location	Variant	Association	Population	No. of subjects*	Reference no.
DEFA6	8p23.1	G3357A (rs4392921)	No	—	—	
		G-4844A (rs2741683)	No	Korean	631/458	E26
		G-3145A (rs3918350)	No	—	—	
		C-79A (rs11784359)	No	—	—	
		IVS1-268 G/C (rs2738119)	No	—	—	
		G957A (rs28738121)	No	—	—	
DEFB1	8p23.1	T1953 G (rs4994852)	No	—	—	
		G2844A (rs4294209)	No	—	—	
		C668 G	Yes	Mexican	59/151	E27
		A692 G	Yes	—	—	
		G1654A	Yes	—	—	
		A1836 G	No	—	—	
		T-2266C (rs5743399)	Yes	Korean	631/458	E26
		T-1241G (rs5743409)	Yes	—	—	
		T-390A (rs2738182)	No	—	—	
		C-44G (rs1800972)	No	—	—	
EOTAXIN (CCL11)	17q21.1-q21.2	IVS1+2262T/C (rs2980923)	No	—	—	
		IVS1-3050T/A (rs2977776)	No	—	—	
		C-426 T	No	Japanese	140/140	E28
		—	Yes	Italian	130 families	E29
		—	No	Japanese	140/140	E28
		A-384 G	No	Japanese	140/140	E28
		—	No	Italian	130 families	E29
		—	No	Japanese	140/140	E28
		G67A	No	Japanese	140/140	E28
		—	No	Italian	130 families	E29
FCER1B		RsaIvex2*2	Yes	British	60 families + 88 families	E30
		RsaIvex7*1	Yes	—	—	
FLG	1q21.3	R501X	Yes	Irish, Scottish, Danish	52/189, 1,612,† 372†	E31
		—	Yes	German	272/276	E32
		—	Yes	German	490 families + 1,314 children*	E33
		—	Yes	United Kingdom	163?1,463	E34
		—	Yes	European American	646 probands (460 families)	E35
		—	Yes	French	99/102	E36
		—	Yes	United Kingdom	426 families	E37
		—	Yes	United Kingdom	186?1,035	E38
		—	Yes	Swedish	406 families	E39
		—	No	Italian	178?210	E40
		2242del4	Yes	Irish, Scottish, Danish	52:189, 1,612,† 372†	E31
		—	Yes	German	272/276	E32
		—	Yes	German	490 families + 1,314 children†	E33
		—	Yes	United Kingdom	163/1,463	E34
		—	Yes	European American	646 probands (460 families)	E35
		—	Yes	French	99/102	E36
		—	Yes	United Kingdom	426 families	E37
		—	Yes	United Kingdom	186/1,035	E38
		—	Yes	Swedish	406 families	E39
		—	No	Italian	178/210	E40
		R501X, 2242del4	Yes	German	145/430	E41
		—	Yes	German	490 families + 1,314 children†	E33
		—	Yes	German	476 families	E42
		—	Yes	United Kingdom	426 families	E37

(Continued)

TABLE E1. (Continued)

Gene (alias)	Chromosomal location	Variant	Association	Population	No. of subjects*	Reference no.
		—	Yes	Danish, United Kingdom	379,† 503†	E43
		—	Yes	United Kingdom	7,000*	E44
		R501X, 2282del4, R2447X, S3247X, 3702delG, and 3673delC	Yes	Irish	188/548	E45
		—	Yes	United Kingdom	186/1,035	E38
		R501X, 2282del4, R2447X, S3247X	Yes	German	3,099	E46
		—	Yes	Danish	356†	E47
		R501X, 3321delA, S1695X, Q1701X, S2554X, S2889X, S3296X	Yes	Japanese	118/134	E48
		R2447X	Yes	United Kingdom	186/1,035	E38
		S3247X	No	United Kingdom	186/1,035	E38
		3702delG	No	United Kingdom	186/1,035	E38
		2673delC	No	United Kingdom	186/1,035	E38
		S2554X	Yes	Japanese	105 families, 376/923	E49
		S2554X, S2889X, S3296X, and 3321delA	Yes	Japanese	125/133	E50
GATA3	10p15	rs2275806	Yes	British	1,456†	E51
		rs444762	Yes	—	—	
GPRA (NPSR1)	7p15-p14	rs323922	No	German	283 multiplex and 222 simplex families	E52
GSTP1	11q13	Ile105Val	Yes	Russian	258/96	E53
		—	Yes	Russian	126/99	E54
GSTT1	22q11.2	haplotypes	Yes	Russian	126/99	E54
HNMT	2q22	Thr105Ile	Yes	European American	127/122	E55
IFNG	12q14	STR at first intron	No	Chinese	94/186	E56
IL1B	2q14	T3953C	No	British	113/114	E21
		T-511C	No	German	94/212	E57
		T3953C	No	—	—	
IL1RN (IL1RA)	2q14.1	intron 2	No	German	94/212	E57
IL4	5q31.1	C-589T (C-590 T)	Yes	Japanese	88 families	E58
		—	No	Australian	76 families, 25 trios	E59
		—	No	Japanese	302/122	E60
		—	Yes	German	90	E61
		—	Yes	Swedish	406 families	E62
		—	Haplotype (with IL13)	European American (Canadian)	368 children	E63
		—	No	Chinese	94/186	E56
		C-34T	No	Australian	76 families, 25 trios	E59
		C-3112 T	Yes	Japanese	202/150	E64
		T-1803C	Yes	Japanese	—	E64
		C-327A	Yes	Japanese	—	E64
		A-326C	Yes	Japanese	—	E64
		G-186A	Yes	Japanese	—	E64
		A-184 G	No	Japanese	—	E64
		T33C	No	Chinese	94/186	E56
IL4RA	5p13	C-703 T	Yes	Japanese	451/116	E65
		Ile50Val	No	Japanese	27/29	E66
		—	No	Japanese	302/122	E60
		—	No	German	90	E61
		A184G	No	Japanese	202/150	E64
		G186A	Yes	Japanese	—	E64
		A326C	Yes	Japanese	—	E64
		C327A	Yes	Japanese	—	E64
		Glu375Ala	No	Japanese	27/29	E66
		—	No	Japanese	302/122	E60
		—	No	German	90	E61
		E375A	No	Chinese	94/186	E56
		L389L	No	Chinese	94/186	E56
		Cys406Arg	No	Japanese	27/29	E66

(Continued)

TABLE E1. (Continued)

Gene (alias)	Chromosomal location	Variant	Association	Population	No. of subjects*	Reference no.
		—	No	German	90	E61
		C406R	No	Chinese	94/186	E56
		S478P	No	German	90	E61
		S503P	No	Chinese	94/186	E56
		Glu 551Arg	Yes	Japanese	27/29	E66
		—	No	Japanese	302/122	E60
		—	Yes	British	1,051 children	E67
		—	No	German	90	E61
		Q576R	No	Chinese	94/186	E56
		S761P	No	German	90	E61
		T1803C	Yes	Japanese	202/150	E64
		C3112 T	Yes	Japanese	202/150	E64
		C3223 T	Yes	German	90	E61
<i>IL5</i>	5q31.1	−4597T/A (rs2522411)	Yes	Korean	646/474	E68
		3237A/C (rs2706400)	No	—	—	
<i>IL5R</i>	3p26-p24	−8380C/A (rs17026903)	No	Korean	646/474	E68
		−5568G/C (rs3806681)	No	—	—	
		−3783C/A (rs35428885)	No	—	—	
		IVS4−866T/A (rs17881144)	No	—	—	
		IVS6 + 109 G/C (rs6771148)	No	—	—	
		IVS6 + 1204 T/C (rs9831572)	No	—	—	
		I129 V (rs2290610)	No	—	—	
		IVS10 + 3687T/A (rs334809)	No	—	—	
		IVS10 + 4276 G/A (rs3804797)	No	—	—	
		IVS10−186 T/C (rs17882210)	No	—	—	
		IVS12−1835 G/C (rs340808)	No	—	—	
		4535 G/A (rs340830)	No	—	—	
<i>IL6 (IFNB2)</i>	7p21	C-174G	No	German	94/212	E57
<i>IL8</i>	4q12-q13	−352A/T (rs4073)	No	Korean	646/474	E68
<i>IL8RA</i> (<i>CXCR1</i>)	2q35	3047C/T (rs1008563)	No	Korean	646/474	E68
<i>IL8RB</i> (<i>CXCR2</i>)	2q35	L262L (rs2230054)	No	Korean	646/474	E68
		−1945T/C (rs6723449)	No	—	—	
<i>IL10</i>	1q31-q32	A-1082 G	No	British	68/50	E69
			No	German	94/212	E57
			No	Korean	276/140	E70
			No	Chinese	94/186	E56
		T-819C	Yes	Korean	276/140	E70
			No	Chinese	94/186	E56
		A-592C	Yes	Korean	276/140	E70
			No	Chinese	94/186	E56
<i>IL12B</i>	5q31.1-q33.1	A1188C	Yes	Japanese	164/100	E71
		G4237A	No	Chinese	94/186	E56
		A4496 G	No	—	—	
		G4510A	No	—	—	
<i>IL12RB1</i>	19p31.1	A-111 T	Yes	Japanese	382/658	E72
		C-2T	Yes			
<i>IL13</i>	5q31	C-1112T	Yes	European American (Canadian)	368 children	E63
			No	Chinese	94/186	E56
		C-1055T (C-1024T)	Yes	Dutch	238/104	E73
		Arg130Gln	Yes	European American (Canadian)	368 children	E63
		A704C	No	Japanese	185/102	E74
		—	No	Japanese	185/102	E74
		C1103T	No	Japanese	185/102	E74
		—	No	Japanese	185/102	E74
		G4257A	Yes	Japanese	185/102	E74
		—	Yes	German	187/98	E75

(Continued)

TABLE E1. (Continued)

Gene (alias)	Chromosomal location	Variant	Association	Population	No. of subjects*	Reference no.
		—	Yes	Japanese	185/102	E74
		G4464A	No	Chinese	94/186	E56
		rs1800925	No	British	1,456†	E51
		rs2066960	No	British	1,456†	E51
		rs1295686	No	British	1,456†	E51
		rs20541	No	British	1,456†	E51
		rs1295685	No	British	1,456†	E51
		T7488C	No	Japanese	160/103	E76
<i>IL13RA</i>	X	R110Q	No	German	90	E61
<i>IL18 (IGIF)</i>	11q22.2-q22.3	T113G	Yes	German	225/175	E77
		C127T	Yes	German	225/175	E77
		G137C	Yes	German	225/175	E77
		C133G	Yes	German	225/175	E77
		rs795437	Yes	Korean	646/474	E78
		G-137C	No	Japanese	160/104	E79
<i>IRAKM</i> (<i>IRAK3</i>)	12q14.3	rs2870784	No	German	361/325	E80
		rs1177578	No	—	—	
		rs2141709	No	—	—	
		rs11465955	No	—	—	
		rs1624395	No	—	—	
		rs1370128	No	—	—	
<i>IRF2</i>	4q35.1	C-829T (C-830 T)	No	Japanese	49 families	E81
		C-684T	No	—	—	
		G-467A	Yes	—	—	
		G921A	Haplotype	—	—	
		3' UTR 1739(ATCCC)6-8	Yes	—	—	
<i>KLK7</i>	19q13.33	4 bp INS	No	French	99/102	E36
<i>LMP2</i> (<i>PSMB9</i>)	6p21.3	LMP2*R	No	Korean	53/184	E82
		LMP2*H	No	—	—	
<i>LMP7</i> (<i>PSMB8</i>)	6p21.3	LMP7*A	No	Korean	53/184	E82
		LMP7*B	No	—	—	
		LMP7*C	No	—	—	
		LMP7*D	No	—	—	
<i>MCPI (CCL2)</i>	17q11.2-q12	A-2518G	No	Hungarian	128/303	E83
<i>MHC2TA</i>	16p13	unknown	No	German	392/297	E6
<i>MIP1A (CCL3)</i>	17q12	C954T	No	Japanese	39/65	E84
		A1245G	No	—	—	
		C1728G	No	—	—	
		A1771G	No	—	—	
<i>NALP1</i> (<i>NLRP1</i>)	17p13	Promoter	No	German	392/297	E6
<i>NALP3</i> (<i>NLRP3</i>)	1q44	Unknown	No	German	392/297	E6
<i>NALP12</i>		NALP12_In9 T allele	No	German	392/297	E6
<i>NAT2</i>	8p23.1-p21.3	C481T	Yes	Russian	87/101	E85
		G590A	Yes	—	—	
		C481T	No	French	20/20	E86
		G590A	No	—	—	
		G857A	No	—	—	
<i>NGFB</i>	1p13.1	Promoter (rs11102930)	No	German	361/325	E3
		rs7530686	No	—	—	
		rs7555016	No	—	—	
		rs6678788	No	—	—	
		rs910330	No	—	—	
		Ala35Val	No	—	—	
<i>NOD1</i> (<i>CARD4</i>)	7p15-p14	Haplotype	Yes	German	1,417 adults, 454 AD, 189 trios	E87
		Haplotype	Yes	German	392/297	E6

(Continued)

TABLE E1. (Continued)

Gene (alias)	Chromosomal location	Variant	Association	Population	No. of subjects*	Reference no.
<i>NPSR1</i> (<i>GPRA</i>)	7p15-p14	rs323917	No	European (N=5)	1,848/4,427	E88
		rs323922	No	—	—	
		rs324377	No	—	—	
		SNP546333	No	—	—	
		rs324384	No	—	—	
		rs324396	No	—	—	
<i>PDYN</i> <i>PHF11</i>	20pter-p12.2 13q14.1	rs74037	No	—	—	
		Promoter	No	Austrian	211/197	E89
		rs2031532	No	Australian	111 families	E90
		rs2247119	Yes	—	—	
<i>RANTES</i> (<i>CCL5</i>)	17q11.2-q12	rs2274276	No	—	—	
		rs1046295	Yes	—	—	
		G-401A	Yes	German	188/98	E91
		—	Yes	Japanese	62/14	E92
		G-403A	No	Hungarian	128/303	E83
		—	Yes	Japanese	389/177	E93
<i>SCCE</i> (<i>KLK7</i>)	19q13.33	C-28 G	No	Hungarian	128/303	E83
		—	Yes	Japanese	389/177	E93
		3' UTR 4 bp (AACC) insertion	Yes	British	103/261	E94
		—	Yes	—	—	
<i>SETDB2</i>	13q14.1	rs2077848	No	Australian	111 families	E90
		rs2057413	No	—	—	
		rs4941643	No	—	—	
<i>SMPD2</i>	6q21	Haplotype	Yes	Korean	284/248	E95
<i>SOCS3</i>	17q25.3	Haplotype	Yes	Swedish, United Kingdom	406 families, 187/230	E96
<i>SPINK5</i> (<i>LEKTI</i>)	5q32	A-785 G	No	Dutch	200 families, 252 trios	E97
		G-206A	Yes	Chinese	669/711	E98
		Asp106Asn	No	Japanese	41 families	E99
		Glu420Lys	Yes	British	148 families + 73 families	E100
		Asn368Ser	No	British	148 families + 73 families	E100
		—	Yes	Japanese	124/110	E101
		—	No	Dutch	200 families, 252 trios	E97
		—	Yes	Japanese	41 families	E99
		Asp386Asn	No	British	148 families + 73 families	E100
		—	No	Japanese	124/110	E101
		—	No	Japanese	41 families	E99
		His396His	Yes	Japanese	124/110	E101
		Glu420Lys	Yes	Japanese	124/110	E101
		—	No	German	1161 children	E102
		—	Yes	Japanese	118	E103
		—	Yes	Japanese	41 families	E99
		Lys420Glu	No	Dutch	200 families, 252 trios	E97
		Glu420Lys	No	Chinese	669/711	E98
		E420K	No	French	99/102	E36
		Glu825Asp	No	Japanese	41 families	E99
		A1103G	No	Chinese	669/711	E98
		G1156A	No	Chinese	669/711	E98
		G2475 T	No	Chinese	669/711	E98
		IVS12-26C → T	Yes	Japanese	124/110	E101
		IVS12-10A → G	Yes	Japanese	124/110	E101
		IVS13-50G → A	Yes	Japanese	124/110	E101
		IVS14+19G → A	Yes	Japanese	124/110	E101
<i>ST2</i>	11p14.3-p12	A-27639G	No	Japanese	452/636	E104

(Continued)

TABLE E1. (Continued)

Gene (alias)	Chromosomal location	Variant	Association	Population	No. of subjects*	Reference no.
		G-26999G	Yes	—	—	
		C744A	No	—	—	
		C2992T	No	—	—	
		G5283A	No	—	—	
		C5860A	No	—	—	
		C11147 T	No	—	—	
STAT6	12q13	STR at exon 1	No	Chinese	94/186	E56
TAP1	6p21.3	TAP1*A	No	Korean	53/184	E82
		TAP1*B	No	—	—	
		TAP1*C	No	—	—	
TAP2	6p21.3	TAP2*A	Haplotype	Korean	53/184	E82
		TAP2*B	No	—	—	
		TAP2*C	Yes	—	—	
		TAP2*D	No	—	—	
		TAP2*E	No	—	—	
		TAP2*G	No	—	—	
TARC (CCL17)	16q13	C-431T	No	Japanese	193/158	E105
		C2134T	No	Japanese	148/158	E106
		G2037A	No	—	—	
TGFB1	19q13.1	G915C	Yes	British	68/50	E69
		T869C	No	—	—	
TIM1	12q12-q13	5383_5397del	Yes	Korean	112/201	E107
		5509_5511delCAA	No	—	—	
		—1454	No	Australian/Asian	93 families + 123 mixed families	E108
			No	—	—	
		rs6420075	No	—	—	
		157insMTTVP(rs1809941)	No	—	—	
		157insMTTTVP	Yes	—	—	
		rs1553316	—	—	—	
TIM3 (HAVCR2)	5q33.2	rs4704853	No	Australian/Asian	93 families + 123 mixed families	E108
		rs1036200	No	—	—	
		L140R(rs1036199)	No	—	—	
		rs4704846	No	—	—	
TIM4 (TIMD4)	5q33.3	rs1363232	Haplotype	Australian/Asian	93 families + 123 mixed families	E108
		rs4704727	—	—	—	
		rs7717984	—	—	—	
		rs7700944	—	—	—	
		rs1345616	—	—	—	
		rs77332745	—	—	—	
		rs10070224	—	—	—	
TLR2	4q32	R753Q	Yes	German	78/39	E109
TLR6	4p14	Ser249Pro	No	German	295/212	E110
TLR9	3p21.3	C-1486T (rs187084)	No	German	483 trios; 274/252	E111
		C-1237T (rs5743836)	Yes	—	—	
		G1174A (rs352139)	No	—	—	
		G2848A (rs352140)	No	—	—	
TOLLIP	11p15.5	C-526G	Yes	German	317/224	E112
		Intron1a	No	—	—	
		Intron1b	No	—	—	
		Pro139Pro	No	—	—	
		Ala222Ser	No	—	—	
		3'UTR	No	—	—	
TNFA	6p21.3	G-238A	No	German	94/212	E57
		—	No	Chinese	94/186	E56
		G-308A	No	German	94/212	E57
		—	No	Chinese	94/186	E56
		—	No	British	113/114	E21

(Continued)

TABLE E1. (Continued)

Gene (alias)	Chromosomal location	Variant	Association	Population	No. of subjects*	Reference no.
VEGF	6p12	C-857 T	No	Chinese	94/186	E56
		C-863A	No	Chinese	94/186	E56
		T-1031C	No	Chinese	94/186	E56
		G-1154A	Yes	Polish	100/154	E113

ADAM33, A disintegrin and metalloproteinase domain 33; *BDNF*, brain-derived neurotrophic factor; *BFL1*, BCL2-related protein A1; *C3*, complement component 3; *CARD12*, caspase recruitment domain-containing protein 12; *CARD15*, caspase recruitment domain-containing protein 15; *CCR4*, chemokine, CC motif receptor 4; *CD14*, monocyte differentiation antigen CD14; *CMA1*, chymase 1; *COL29A1*, collagen, type XXIX, α -1; *CSF2*, colony-stimulating factor 2; *CSTA*, cystatin A; *CTLA4*, cytotoxic T lymphocyte-associated 4; *CYSLTR1*, cysteinyl leukotriene receptor 1; *DEFA4*, defensin α 4; *DEFA5*, defensin α 5; *DEFA6*, defensin α 6; *DEFB1*, defensin β 1; *EOTAXIN*, chemokine, CC motif, ligand 11; *FCER1B*, Fc fragment of IgE, high affinity I, receptor for, β subunit; *FLG*, filaggrin; *GATA3*, GATA-binding protein 3; *GPRA*, neuropeptide S receptor 1; *GSTP1*, Glutathione S-transferase, PI; *GSTT1*, glutathione S-transferase, θ -1; *HNMT*, histamine N-methyltransferase; *IFNG*, Interferon γ ; *IL1B*, IL-1 β ; *IL1RN*, IL-1 receptor antagonist; *IL4*, IL-4; *IL4RA*, IL-4 receptor; *IL5*, IL-5; *IL5R*, IL-5 receptor α ; *IL6*, IL-6; *IL8*, IL-8; *IL8RA*, IL-8 receptor α ; *IL8RB*, IL-8 receptor β ; *IL10*, IL-10; *IL12B*, IL-12 β ; *IL12RB1*, IL-12 receptor β 1; *IL13*, IL-13; *IL13RA*, IL-13 receptor α 1; *IL18*, IL-18; *IRAKM*, IL-1 receptor-associated kinase 3; *IRF2*, IFN regulatory factor 2; *KLK7*, kallikrein-related peptidase 7; *LMP2*, large multifunctional protease 2; *LMP7*, large multifunctional protease 7; *MCPI*, monocyte chemotactic protein 1; *MHC2TA*, MHC class II transactivator; *MIPIA*, macrophage inflammatory protein 1- α ; *NALP1*, Nacht domain-, leucine-rich repeat-, and PVD-containing protein 1; *NALP3*, Nacht domain-, leucine-rich repeat-, and pyd-containing protein 3; *NALP12*, Nacht domain-, leucine-rich repeat-, and pyd-containing protein 12; *NAT2*, arylamine-N-acetyltransferase 2; *NGFB*, nerve growth factor β ; *NPSR1*, neuropeptide S receptor 1 gene; *PDYN*, prodynorphin; *PHF11*, PHD finger protein 11; *RANTES*, regulated on activation, normally T-expressed, and presumably secreted; *SCCE*, stratum corneum chymotryptic enzyme; *SETDB2*, SET domain protein, bifurcated, 2; *SMPD2*, sphingomyelinase 2; *SOC3*, suppressor of cytokine signaling 3; *SPINK5*, Kazal-type serine protease inhibitor 5; *ST2*, suppressor of tumorigenicity 2; *STAT6*, signal transducer and activator of transcription 6; *TAP1*, transporter, ATP-binding cassette, major histocompatibility complex, 1; *TAP2*, transporter, ATP-binding cassette, MHC, 2; *TARC*, thymus and activation-regulated chemokine; *TGFB1*, TGF- β 1; *TIM1*, timeless, *Drosophila*, homolog of; *TIM3*, T-cell immunoglobulin and mucin domains-containing protein 3; *TIM4*, T-cell immunoglobulin and mucin domains-containing protein 4; *TNFA*, TNF- α ; *TOLLIP*, Toll-interacting protein; *UTR*, untranslated region; *VEGF*, vascular endothelial growth factor.

*Refers to the number of subjects in the reported study. Numbers separated by / indicate case/control subject.

†Cohort.

—Information was not available in the reference. Families are indicated as such.