

The genetics of psoriasis, psoriatic arthritis and atopic dermatitis

Anne M. Bowcock^{1,*} and William O.C.M. Cookson²

¹Department of Genetics, Pediatrics and Medicine, Washington University School of Medicine, St Louis, MO 63110, USA and ²Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK

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Psoriasis and atopic dermatitis are chronic and relapsing inflammatory diseases of the skin associated with various immunologic abnormalities. Approximately 30% of psoriasis patients also have joint involvement, indicative of psoriatic arthritis. Genes and environment play a key role in the pathogenesis of these diseases. Genome-wide linkage scans have identified multiple loci linked to each disease and revealed overlap with psoriasis and atopic dermatitis susceptibility loci on chromosomes 1q21, 3q21, 17q25 and 20p12. The genes from these loci have not yet all been identified, or systematically tested for a role in psoriasis and atopic dermatitis; however, these locations suggest that some susceptibility factors lie within genes or gene families with common effects upon epithelial immunity. A strong HLA association is described for psoriasis, but not for atopic dermatitis. Knowledge of the genetic factors leading to these diseases will lead to an understanding of their variable age at onset, their waxing and waning and the variability of body surface environment. The effect of environmental triggers may also be understood once the altered pathways are elucidated. Genes implicated so far in atopic dermatitis are *SPINK5*, *FcεRI-β* and *PHF11*. Genes implicated in psoriasis so far are *HLA-C*, *SLC9A3R1*, *NAT9*, *RAPTOR* and *SLC12A8*. Genetic modifiers such as *CARD15* may predispose to psoriatic arthritis.

PSORIASIS

The term psoriasis is derived from the Greek (*psora*: scurf, itch, rash). The first clear description was by Willan in 1808 (1). The eponymic designation of this dermatologic condition was proposed by Russel in 1950 (2). Types of psoriasis include plaque, guttate, erythrodermic and pustular (3).

Psoriasis has a worldwide distribution with prevalence varying according to race and geographical location. It is commonest in Scandinavia and Northern Europe where it approaches 3%. In North America and the UK its prevalence is ~2%. In Japan, prevalence is ~0.2% of the population, and in Native American Indians it is rare (4). In the USA 3 million office visits for psoriasis are made each year, costing over \$3 billion. The concordance of psoriasis in monozygotic twins is 65–72%, versus 15–30% in dizygotic twins. Determination of concordance in older twin pairs from a national twin registry in Denmark revealed nearly 90–100% heritability (5). In an Australian study the monozygotic twin concordance rate is lower (35% for monozygotic twins and 12% for dizygotic twins), giving an estimated heritability of 80% (6).

Males and females are equally affected and 75% of patients develop the disease before the age of 40. First manifestations of

the disease are most common in the third decade. Two peaks of age of onset have been described: one at 20–30 years and a smaller peak at 50–60 years. This has given rise to the hypothesis that two forms of the disease exist (7). However, there are exceptions to this rule since some families with early-onset and severe disease appear to be segregating a highly penetrant autosomal dominant susceptibility gene that is distinct from *HLA* (8,9). Psoriasis can also occur with other inflammatory diseases such as (psoriatic) arthritis in 10–30% (recent NPF survey). Psoriasis also occurs in association with human immunodeficiency virus (HIV) infection (10). It is hypothesized that psoriasis is due to a combination of genetic predisposition and environmental assaults. These can include injury, infection, stress or certain medications. One intriguing characteristic of psoriasis is the ‘Koebner phenomenon’, first reported by Heinrich Koebner in 1872. It refers to the appearance of isomorphic pathological lesions following skin trauma patients with pre-existing cutaneous diseases and is most frequent in patients of psoriasis.

Understanding the pathogenesis of inflammatory diseases such as psoriasis has not been straightforward. An examination of transcripts and peptides with altered expression levels, including a global genome-wide expression study (11), has

*To whom correspondence should be addressed. Tel: +1 3147473261; Fax: +1 3147472489; Email: bowcock@genetics.wustl.edu

highlighted a large number of dysregulated genes and gene clusters, particularly those involved in epithelial proliferation and in the immune system. However, these studies have not provided sufficient insights to lead to an identification of the molecular defects underlying the disease.

The normal cycle of maturation of keratinocytes is 28–30 days. In psoriasis this is accelerated to 3–4 days. The immune system has been strongly implicated in the pathogenesis of psoriasis since it resembles a T cell-mediated autoimmune disease (12). During lesion formation, inflammation precedes epidermal hyperproliferation and increased numbers of T cells have been demonstrated in the uninvolved skin of psoriatics (13). T cells isolated from involved psoriatic skin may also enhance keratinocyte proliferation. Both CD4+ and CD8+ T cells in active skin lesions are strongly polarized as Th 1 cells (Th 1 and Tc1, respectively) and there is also a significant increase in circulating type 1 T cells in most patients. Psoriasis serves as the clearest (polar) example of a type 1-deviated skin disease, while atopic dermatitis is the clearest example of a skin disease with opposite (type 2) immune deviation. This is based on frequencies of IFN- γ -producing (type 1) T-cells versus IL-4 producing (type 2) T cells in the circulation.

Indirect evidence for the role of the immune system in psoriasis has come from clinical studies. Drugs that act by suppressing the activity of T cells such as cyclosporin, FK506, and the recently developed biologics are effective in treating psoriasis (14). Yet other evidence for a T cell basis for psoriasis susceptibility has come from bone marrow transplantations, where the psoriatic status of the donor has been transmitted to the recipient (15). Other evidence has come from animal models. For example, injection of activated blood-derived T lymphocytes into SCID mice with autologous human-grafted skin has resulted in psoriatic plaques and the presence of T cells with NK cell receptors (16) that accumulate immediately before the onset of acute lesions.

These type of observations reinforce the conjecture that psoriasis is an autoimmune disease with defects in self-tolerance, although a triggering antigen has not been identified.

ATOPIC DERMATITIS

Atopic dermatitis (AD, eczema) is typified by itchy, inflamed skin. The disease usually begins in infancy and early childhood, and infants with AD are prone to weeping inflammatory patches and crusted areas on the face, neck, extensor surfaces and groin. Children and young adults tend to have dermatitis of flexural skin, particularly in the antecubital and popliteal fossae.

AD is increasingly common in the developed world, affecting up to 15% of children in some countries (17). The cost of treating AD is substantial (18,19), and much of this cost is born by the families of patients with the disease (18). A significant proportion of children with the disease continue with problems into adult life.

The word 'atopy', meaning 'strange disease' (20) was coined to describe the familial syndrome of asthma and hay fever. AD subsequently came to be considered to be part of the same syndrome. The atopic state is recognized by skin prick tests to common allergens, by the presence of allergen-specific IgE in their serum, and by elevations of the total serum IgE (21).

Approximately 80% of cases of childhood eczema are atopic by these criteria (22,23). Atopic mechanisms consequently dominate current understanding of the pathogenesis of the disease. However, eczema in the 20% of children without atopic manifestations is clinically indistinguishable from disease in the 80% who are atopic (23,24), and it is not clear whether disease in non-atopics is the result of different processes.

Twin studies of eczema show concordance rates of 0.72–0.86 in monozygotic and 0.21–0.23 in dizygotic twin pairs (25,26). Physician-diagnosed asthma exhibits a similar pattern, with concordance of 0.65 in monozygotic twins and 0.25 in dizygotic twins (27). Total serum IgE levels show a heritability of ~50% (21,28). These studies indicate the presence of strong genetic factors underlying the development of atopy and atopic disease.

SHARED FEATURES OF AD AND PSORIASIS

Although AD is clinically and pathologically quite distinct from psoriasis, some features are shared by both diseases, including dry, scaly skin and disturbed epidermal differentiation (Fig. 1). Psoriasis is characterized by infiltration of inflammatory cells into the dermis and epidermis is accompanied by hyper-proliferation of keratinocytes. The latter is not seen in AD. However, a recent gene-expression study of 12 000 transcripts indicate that most of them were similarly expressed in both diseases (29). However, inflammatory cells invading the skin in psoriasis are TH1 cells (indicated by the overexpression of IFN- γ), macrophages, dendritic cells and neutrophils while infiltrating inflammatory cells in AD are TH2 cells, eosinophils and mast cells. These cells produce IL-4, IL5, IL-10 and IL-13. It is proposed that these may be attracted to the different chemokines in the skin of patients with each disease. For example, chemokines increased two-fold in AD versus psoriatic skin are CCL13/MCP-4, CCL-18/PARC and CCL-27/CTACK. It has also been proposed that keratinocytes of AD patients have high RANTES expression in lesions (30). Chemokines increased 2-fold in psoriatic versus AD skin are reported to be CCL-4/MIP-1 β , CCL20/MIP-3 α , CXCL-2/GRO- β , CXCL-8/IL8 and CXCR2/IL8R, as well as MCP-1 and IP-10 (29). Our recent gene expression profiling of psoriatic skin revealed the up-regulation of 19 chemokines in psoriatic skin (11) including most of those described above. Several of these are involved in the formation of secondary lymphoid tissue and we have proposed that the combination of many CCR7+ T cells, dendritic cells and regulating chemokines in psoriatic lesions, together with the detection of dendritic cell activation markers in uninvolved skin, could sustain chronic T cell activation and persistence within focal skin regions.

Increased keratinocyte proliferation in psoriasis may be reflected by the differential expression of genes of the epidermal differentiation complex (EDC) that are not seen in AD such as PRP2C, lipocalin, elafin and airway trypsin like protease (29). In AD, overexpression of Nel-1-like 2 protein, involved in the differentiation of growth factors of sensory nerves in the skin, has been interpreted to result in increased sensitivity and itching of AD skin (29). Tenascin C, an extracellular matrix protein and plasminogen activator inhibitor, is also observed. Within AD there are significantly lower

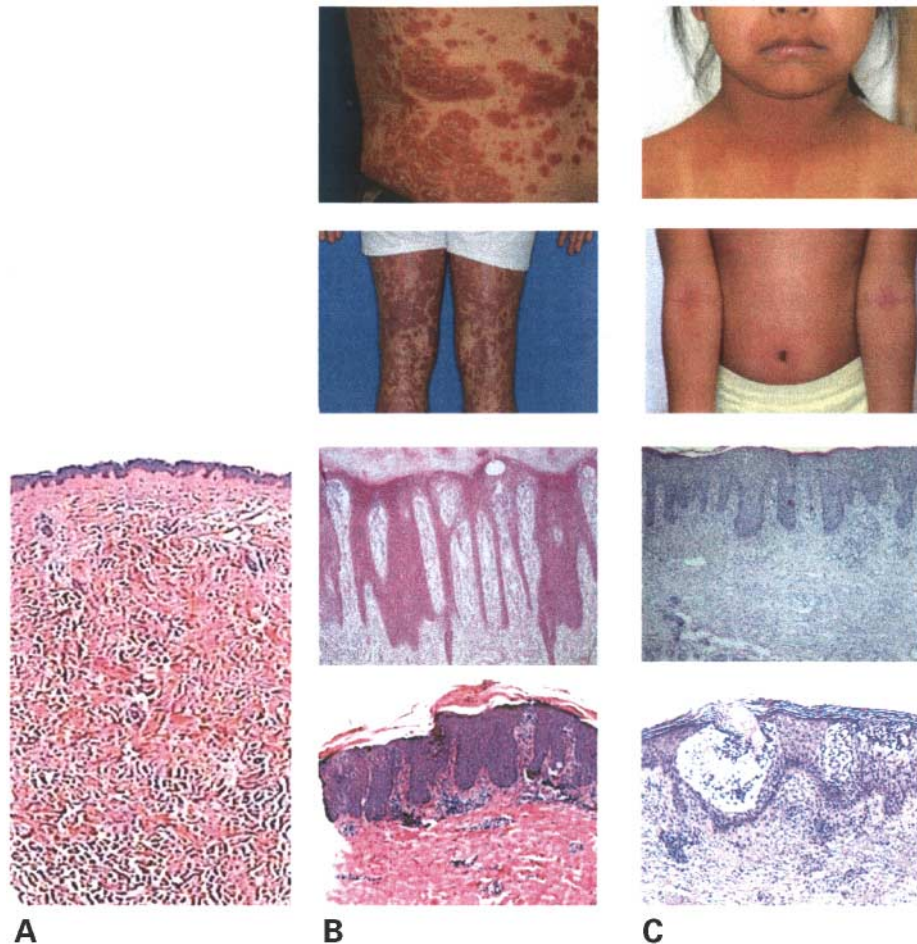


Figure 1. Upper: comparison of clinical features seen in psoriasis and atopic dermatitis. Lower: histopathology of skin (medium power view) from (A) healthy normal control, (B) individual with psoriasis (psoriasiform epidermal hyperplasia with thinning of the suprapapillary plate and the inflammation within the dermal papillae) and (C) an individual with atopic dermatitis (irregular acanthosis, focal spongiosis and mild inflammation within the dermis and epidermis).

levels of antimicrobial peptides such as beta-defensin, LL-37 and other innate immune effector molecules, and it has been proposed that this may explain the increase in the susceptibility of AD patients to recurrent skin infections (31).

GENETICS OF PSORIASIS

HLA association

In 1980 association of psoriasis with *HLA* class I alleles was demonstrated, with the most highly associated allele being *HLA-Cw6* (32). However, the identity of the *HLA* class I allele driving the association (*PSORS1*) is currently controversial. This is likely to be due to the extensive linkage disequilibrium that exists in patients within an interval of ~275 kb between *HLA-B* and a cluster of genes including *HCR* (alpha-helix coiled-coil rod homolog) and *CDSN* (corneodesmosin). Nair *et al.* (33) localized *PSORS1* to a 60 kb region telomeric to *HLA-C* (33). Others have proposed *CDSN* and *HCR* (34–36) lying in a non-overlapping region ~150 kb away from *HLA-C*. Association studies with a dense set of single-nucleotide

polymorphisms (SNPS) from throughout this region (37) refined *PSORS1* to a 10 kb interval very close to *HLA-C*.

Despite the association with *HLA*, however, not all affected members harbor *HLA-Cw6* (known as *HLA-Cw*0602* when identified with DNA typing). In independent sets of affected individuals/families this allele is only found in ~40–80% of cases. Moreover the penetrance of *HLA-Cw*0602* is ~10%, implicating environmental effects or additional genetic susceptibility factors.

Patients with psoriasis also have different clinical features depending on whether they are *HLA-Cw6* positive or negative. Besides having a lower age of onset, *HLA-Cw*0602* positive patients have more extensive plaques on their arms, legs and trunk, more severe disease, higher incidence of Koebner's phenomenon, reported more often that their psoriasis got worse during or after throat infections (see Environmental Triggers) and more often had a favorable response to sunlight. In contrast, dystrophic nail changes and psoriatic arthritis are more common in the *Cw6*-negative patients (38).

Linkage to *HLA* in large multiplex families has not been as convincing. The first demonstration of this was by Lin *et al.* (39). In large multiplex families when most affecteds harbor

*HLA-Cw*0602*, linkage to *HLA* is not always demonstrated (8). This is due to the existence of multiple *HLA* haplotypes segregating in single families. In the remaining families that do not show linkage to *HLA-Cw*0602* and where affecteds are not *HLA-Cw*0602*, linkage to other loci has been demonstrated (see below) in some cases.

Non-*HLA* loci

Localization of a second psoriasis susceptibility locus (*PSORS2*) to chromosome 17q25 was achieved following a genome-wide linkage scan on eight multiply affected families (8). In this study the family contributing the greatest evidence for linkage had 20 affected members, and the penetrance of the disease was very high (~80–90%). Several affected members also had psoriatic arthritis. This family alone provided a two-point LOD score of 5.33 ($\theta = 0.04$ with *D175784*).

In 1996 linkage of *PSORS3* to chromosome 4q35 was reported in a set of Irish families (40) where the maximum two-point LOD = 3.3. A recent genome-wide scan of families from the Chinese Han population revealed some evidence for linkage to a slightly proximal region (4q32) (41) (two-point LOD = 2.43). Additional scans have revealed evidence for linkage to 1q21 (*PSORS4*) in families from the Lazlo region of Italy (42), where a maximum two-point LOD score of 3.75 at $\theta = 0.05$ was obtained. Some evidence for linkage to 1q21 was also seen in a set of families from the USA (43). In each of the cases described above, psoriasis is inherited as an autosomal dominant trait with reduced penetrance, and the two-point LOD scores exceed the conventionally accepted threshold of 3.0. The remaining genome-wide scans provide suggestive evidence for linkage, and since the two-point LOD scores are not >3, results of non-parametric analyses are reported. These include linkage to 3q21 (*PSORS5*) in a set of families from the southwest of Sweden, where NPL = 2.77, $P = 0.003$ (44) and 19p13 in German families (45) (NPL = 3.50; $P = 0.0002$). A genome-wide scan of *PSORS1*-negative families from Sweden recently provided linkage to chromosome 18p (NPL = 3.58; $P = 0.0038$). This locus had been identified in two previous genome-wide scans of primarily nuclear families from the UK and Sweden (46,47), although it had failed to meet the accepted threshold for significance.

Genome-wide linkage scans in large sets of nuclear families and sibling pairs from the USA, the UK, Germany and Sweden have provided additional evidence for linkage to other loci that were initially identified as suggestive, and have also identified even more putative loci (46–49). Figure 2 summarizes the locations of confirmed and suggestive psoriasis and AD susceptibility loci.

The identification of multiple loci for psoriasis susceptibility indicates that psoriasis and psoriatic arthritis are genetically heterogeneous. It is also likely that epistasis exists between certain predisposing loci. In the Italian population some evidence for epistasis between *HLA* and chromosome 1q21 has been provided (50). Finally, it is possible that allele dosage plays a role in risk of developing psoriasis or severity. For example, homozygotes for *HLA-Cw*0602* from Iceland have a relative risk of developing psoriasis of 23.1 compared with heterozygotes who have a relative risk of 8.9. Moreover, the

mean age of onset of homozygotes is 15.0 versus 17.8 years for heterozygotes ($P = 0.04$) (51).

Psoriasis genes at 17q25

Further evidence for linkage of psoriasis to 17q24–q25 was provided by a number of other groups with psoriasis families from a variety of different Caucasian populations (USA, Sweden and Ireland) (48,52,53). Family-based association tests have led to the identification of two peaks harboring psoriasis susceptibility loci (54,55). One peak harbors *SLC9A3R1* and *NAT9* (55). A second peak harbors *RAPTOR* [p150 target of rapamycin (TOR)-scaffold protein containing WD-repeats] (55,56). After adjusting for multiple tests, these peaks remained significant, indicating that both are likely to be associated with disease.

SLC9A3R1 is a PDZ domain-containing phosphoprotein that associates with members of the ezrin–radixin–moesin family. It is implicated in diverse aspects of epithelial membrane biology and immune synapse formation in T cells. Expression of *SLC9A3R1* is highest in the uppermost stratum Malpighi of psoriatic and normal skin and in inactive versus active T cells (55).

There are five psoriasis-associated variants in the *SLC9A3R1/NAT9* region that drive the association at 17q25 (Fig. 3). One lies between the two genes and abolishes a putative site for the transcription factor RUNX1 (57). RUNX1 has a restricted pattern of expression, and is essential for hematopoietic cell development (58). It is also the target of mutations in sporadic and familial myeloid leukemias (59–61). It has long been suspected that the primary defect within psoriasis is an immune system defect and loss of a RUNX1 binding site suggests that the contribution of *SLC9A3R1* or *NAT9* may be due to dysregulation of these genes in cells of hematopoietic origin. However, *SLC9A3R1* is also expressed in polarized epithelial cells including the keratinocyte, and its dysregulation could be altering keratinocyte homeostasis in response to an immune signal.

DNA sequence variants associated with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) have recently been shown to lie within altered RUNX1 binding sites of the *PD-1* and *SLC22A4* genes, respectively (62,63). The involvement of RUNX1 in autoimmune disease may explain some of the variability in disease severity and organ involvement. For example each of the genes with altered RUNX1 sites harbors several potential binding sites and is possible that there is a threshold of RUNX1 binding that is required for gene activation or silencing.

Although there is a biologically plausible role for *SLC9A3R1* in psoriasis, since it is expressed in polarized epithelial cells, and is likely to be a negative regulator of the immune response, one cannot exclude *NAT9* as being involved in disease. *NAT9* is a novel *n*-acetyltransferase of the GNAT family. Glycosylation is known to play a role in MHC class I antigen presentation, T cell development and to affect the development of autoimmune disease (64,65). Experimental evidence in inflammatory diseases such as psoriasis also suggests that glycosylation might provide endothelial zip codes for organ-specific leukocyte traffic into inflammatory sites (66).

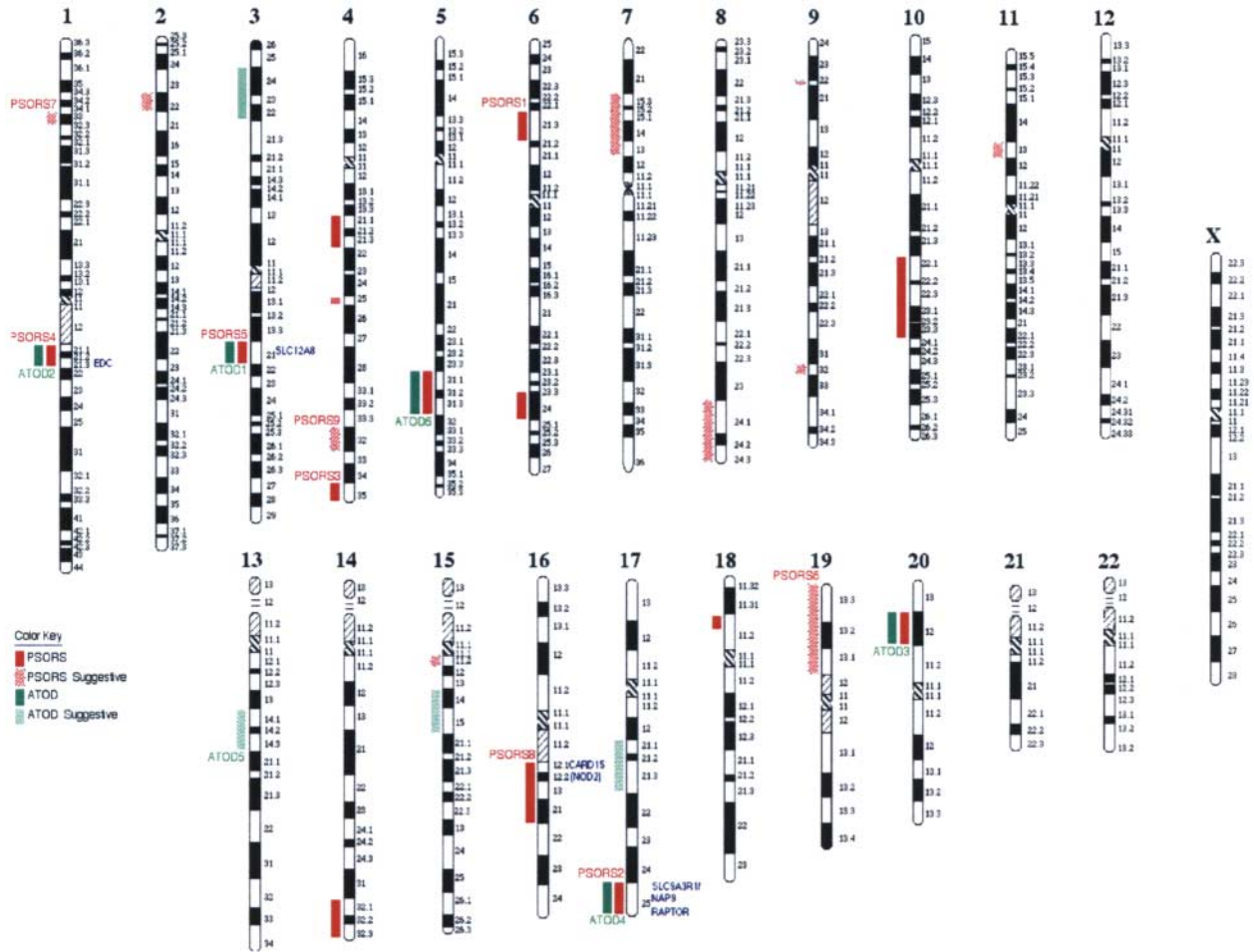


Figure 2. Localization of psoriasis (PSORS) and atopic dermatitis (ATOD) loci following genome-wide linkage scans. Loci which have been detected in only one linkage scan, and where the two-point LOD is <3, are considered suggestive. The locations of associated genes are also indicated.

GENETICS OF ATOPIC DERMATITIS

Two genome screens for childhood AD have been carried out (67,68). Both screens were of modest size and were of comparable power. Both used sophisticated statistics to generate empirical *P*-values to show that they had identified regions of real genetic linkage. The first screen, carried out in families of German and Scandinavian children with AD, found linkage to a region on chromosome 3q21 (68). The second screen, of British families recruited through children with AD attending a hospital of tertiary referral, found three regions of linkage to AD or to AD and asthma combined, on chromosomes 1q21, 17q25 and 20p (67).

The first study found also linkage of the total serum IgE to the 3q21 locus (68) and the second study found linkage of this trait to chromosomes 5q31 and 16qtel (67). In each case the evidence for linkage to the serum IgE was weaker than the evidence for linkage to AD.

A third genome screen has been reported, in which the subjects were Swedish adults with AD who were identified at hospital outpatient clinics (69). In general the results were less conclusive than the screens of children with AD. Suggestive

evidence was found for linkage of AD to chromosome 3p24–22. The authors also used a severity score of AD and found suggestive linkage to chromosomes 3q14, 13q14, 15q14–15 and 17q21. It is possible that the 3q14 locus and the 17q21 loci may correspond to the AD loci identified in children. Chromosome 13q14 has been previously linked to children with AD (70) and to atopy and asthma (71). The other loci may be considered to be novel.

Two observations can be made from the genome screens of children with AD. Firstly, despite the clinical overlap of atopic asthma and AD, the AD genome screens show strongest linkage to regions of the genome that are not associated with asthma susceptibility. Secondly, the AD genome screens show linkage to regions of the genome associated with psoriasis and other skin diseases.

ASTHMA

Eleven full genome screens have been reported for asthma and its associated phenotypes (72–82). These have consistently identified a limited number of regions containing genes influencing

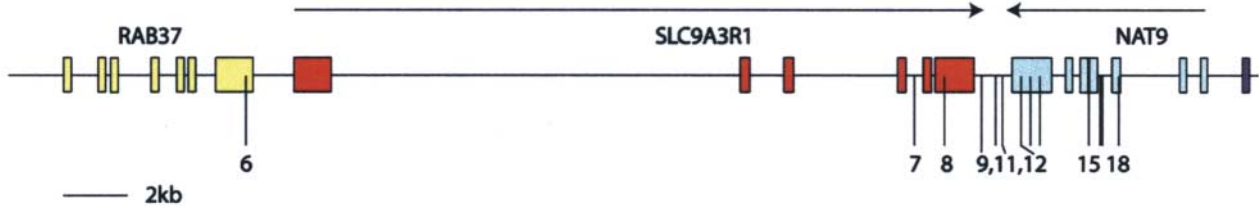


Figure 3. Localization of SNPs within proximal region of association with psoriasis on chromosome 17q25. The direction of transcription of *SLC9A3R1* and *NAT9* is indicated above the gene structure. Exons are shown as boxes. The associated region spans a 20 kb block between SNPs 7 and 21 (that lies within FLJ20255 and is not shown). The SNPs driving the association are 7, 9, 11, 12 and 15. All lie within non-coding DNA of *SLC9A3R1* or *NAT9*. The psoriasis-associated allele of SNP9 (allele A) abolishes a binding site for RUNX1 (G allele).

asthma, including chromosomes 2, 4, 5, 6, 7, 11, 12, 13 and 16 (74,83). Three genes underlying asthma have been recently identified by fine mapping and positional cloning in regions of genetic linkage. These include the membrane-anchored zinc-dependent metalloproteinase *ADAM33* from chromosome 20 (84), the putative modulator of transcription *PHF11* from chromosome 13q12 (85), and the prolyl peptidase *DPP10* from chromosome 2q14 (86).

ADAM33 and *DPP10* do not appear to have major roles in AD. However, chromosome 13q12 does show linkage to AD (87) and polymorphisms in *PHF11* are strongly associated with high IgE levels in families containing children with AD (85). The mode of action of *PHF11* is not yet known, but it encodes protein-binding zinc fingers that may modify both immunoglobulin production and clonal expansion of B-cells (85).

In general, however, the loci identified by asthma genome screens are not shared with the regions of linkage to AD, suggesting that AD and asthma are not simply part of the same spectrum of allergic disorders, but that they result at least in part from distinct mechanisms.

OVERLAP BETWEEN PSORIASIS AND AD LOCI

The putative chromosome 1q21, 17q25 and 20p loci identified in the UK genome screen for AD are closely coincident with regions known to contain psoriasis susceptibility genes (8,42,49) (Fig. 2). The conservative probability of this overlap occurring by chance is less than 3 in 100 000 (67). The German AD genome screen locus on chromosome 3q21 (68) also closely overlaps another psoriasis locus (52). The 17q25 locus also shows linkage to multiple sclerosis (88,89) and RA (90). This reinforces the conjecture that there is overlap between loci for different inflammatory diseases.

These findings suggest that the shared regions of linkage between AD and psoriasis contain polymorphic genes with general effects on dermal inflammation and immunity. These shared loci show a number of interesting features:

Epidermal differentiation cluster (chromosome 1q21)

The peak of linkage of eczema and psoriasis on chromosome 1q21 overlies the human epidermal differentiation complex (*EDC*) that spans a region of ~2 Mb (91). The genes of the *EDC* are expressed late during maturation of epidermal cells (92).

Several gene families are recognised within the complex: these code for small proline-rich proteins (*SPRRs*), *S100A*

calcium-binding proteins and late envelope proteins (*LEPs*) (93). The *SPRR* and *LEP* genes code for precursor proteins of the cornified cell envelope (CE). The expression of these genes is linked to keratinocyte terminal differentiation both *in vivo* and *in vitro* (93,94). In global expression studies of psoriasis, 203 genes represented in the U95A-3 arrays were identified in the 2 Mb EDC region and its 1 Mb flanking segments. Thirty transcripts were differentially expressed when normal and involved skin were compared. Many members of the *S100* protein family are overexpressed in psoriatic skin and none are down-regulated. These included *S100A1*, *S100A2*, *S100A7*, *S100A9*, *S100A10* and *S100A12*. Members of the small proline-rich protein family that are over-expressed include *SPRR3*, *SPRK*, *SPRR1B* and *SPRR2A* (11,95).

The known functions of some of the *EDC* gene products indicate that the skin is not functioning as a passive barrier. In particular the *S100* calcium binding proteins are often secreted and have a wide range of immunological actions (96). *S100A2* is chemotactic for eosinophils (97). *S100A7* (Psoriasin) is a potent and selective chemotactic inflammatory protein for CD4+ T lymphocytes and neutrophils (98). It is up-regulated in inflammatory skin disorders (99). *S100A8* and *S100A9* form a complex that displays cytostatic (100,101) and anti-microbial activities (102,103). The *S100A8/A9* complex also inhibits macrophage activation (104) and immunoglobulin synthesis by lymphocytes (105). *S100A8* as a homodimer is a potent chemotactic agent for leukocytes (106–108). *S100A12* has pro-inflammatory activity on endothelial cells and inflammatory cells (109).

Several other proteins from the *EDC* are involved in CE formation (110). *Involucrin*, *SPRR* and *LEPS* are characterized by common structural features such as a central region of short tandem peptide repeats. The multi-functional intermediate filament-associated proteins profilaggrin (*FLG*) and trichohyalin belong to a gene family with multiple tandem repeats of specific peptide motifs. They are thought to represent fused genes of CE precursor protein genes and genes of the *S100* family of small calcium binding proteins (111,112). The true functions of these genes remain obscure but, unlike the *S100* and *SPRR* genes, *FLG* is down-regulated in involved psoriatic skin (11,95).

Mutations in *loricrin* underlie the Mendelian skin disorder of Vohwinkel's syndrome (113), but mutations or variants in other genes of the *EDC* have not yet been recognized in common skin disease. The genes of this complex are nevertheless prime candidates for polymorphisms affecting eczema and psoriasis.

Association studies in Italian families further suggest that *PSORS4* lies within the *EDC*, within a 900 kb region between *DIS1664* and *DIS2715*. This harbors the *SPRR* and *S100* gene clusters. Association was seen with *DIS2346* ($P=0.004$), a marker lying close to loricrin and between these two clusters (114).

Chromosome 3q21

Linkage of chromosome 3q21 has been shown to AD (45,69), psoriasis (44) and asthma (82). Although a candidate for this linkage has not yet emerged, it is striking that three of these four genome screens were carried out in Scandinavians (44,69,82) and the fourth was carried out in a mixture of German and Swedish families (45). Allele frequencies for the HLA loci and the *CCR5* mutation (115) show distinct differences between European countries and it seems quite possible that a mutation or variant may be found in chromosome 3q21 that is at its highest frequency in Scandinavians.

An examination of 195 psoriasis families from Sweden, led to the identification of association with a five-marker haplotype spanning the 3' half of solute carrier family 12, member 8 (*SLC12A8*), a potassium/chloride transporter ($P=3.8 \times 10^{-5}$) (116). However, association of variants of this gene has not been detected in an independent cohort of northern European psoriasis families (unpublished results), suggesting that its involvement may be particular to the Swedish population. Nevertheless its involvement in psoriasis susceptibility is intriguing. This has become particularly evident with the observation that a second solute carrier at chromosome 5q31, *SLC22A4* (solute carrier family 22 member 4), an organic cation transporter, is associated with RA (63). *SLC22A4* is specific to hematological and immunological tissues, is induced by pro-inflammatory stimuli. It is highly expressed in the inflammatory joints of mice with collagen-induced arthritis. The defect associated with RA results in RUNX1 binding, and it is hypothesized that *SLC22A4* functions as a transporter in lymphoid organs or inflammatory milieu. Moreover, *SLC9A3R1*, from chromosome 17q25, is associated with psoriasis (55) and binds the solute carrier *SLC9A3* (solute carrier family 9, isoform 3 or NHE3), a sodium/hydrogen exchanger. In this case, loss of a RUNX1 site is associated with psoriasis susceptibility. Functional studies on these proteins may identify a common theme associated with alterations in cation transport in a variety of inflammatory diseases.

Chromosome 17q25

Psoriasis genes associated with this locus are described above. Given the overlap with chromosome 17q25 susceptibility loci for psoriasis and AD (67), the role of these genes in AD susceptibility is currently being investigated.

Chromosome 20p

Linkage to chromosome 20p has been reported to the distinctive phenotype of AD and asthma combined (67). Children with these two diseases together had a serum IgE concentration that was eight times higher than in children with asthma alone and five times higher than in children with AD

alone. These results suggest that the combination of AD and asthma may correspond to a genetic sub-type of both diseases. Genetic linkage of susceptibility to leprosy has been identified to the same genetic region (117), as has linkage to SLE (118).

SINGLE GENE DISORDERS AND ATOPY

Positional cloning of novel genes influencing complex diseases can be greatly facilitated by the study of Mendelian (single gene) disorders. Several Mendelian diseases show strong features of atopy.

Hyper-IgE

The hyper-IgE syndrome (HIES) is a rare primary immunodeficiency characterized by recurrent skin abscesses, pneumonia and highly elevated levels of serum IgE. It can be transmitted as an autosomal dominant trait with variable expressivity. Linkage analysis in extended families with multiple cases of HIES has identified genetic linkage to chromosome 4q12, near *D4S428* (119). It is of interest that linkage to the same region has been identified in two genome screens for asthma (72,79). The gene has not yet been identified.

Wiskott–Aldrich syndrome

Wiskott–Aldrich syndrome (WAS) is a rare X-linked disorder of T and B cell function which is typified by recurrent infections and thrombocytopenia. Many boys with the disease also develop a rash which is indistinguishable from AD. A study of the WAS gene region has been carried out in Swedish families with AD (120). One marker (*MAOB*) showed linkage to the severity score of atopic dermatitis ($P < 0.05$), but association to AD was not seen. These results should provoke further study of the gene in AD.

Familial eosinophilia

Familial eosinophilia (FE) is an autosomal dominant disorder characterized by peripheral hypereosinophilia of unidentifiable cause with or without other organ involvement (121). It has been localized on chromosome 5q34, near the *IL-4* cytokine cluster and *SPINK5*. Its gene has not yet been identified.

Netherton's

Netherton's disease is a rare recessive disorder characterized by generalized erythroderma, symptoms of atopic disease (hay fever, food allergy, urticaria and asthma) and very high levels of IgE (122). The gene for Netherton's disease has been identified (*SPINK5*) and encodes a 15-domain serine protease inhibitor called LEKTI which is expressed in epithelial and mucosal surfaces and in the thymus (123,124). Polymorphisms in this gene are associated with AD, asthma and elevated serum IgE levels (125).

Each of the LEKTI/SPINK5 protease inhibitory domains is slightly different from the others (124), perhaps suggesting a polyvalent action against multiple substrates. The protein is expressed in the outer epidermis, in sebaceous glands and

around the shafts of hair follicles (126), so that its actions seem directed towards the environment rather than internally.

In this context it is interesting that over 90% of patients with AD are colonized with *Staphylococcus aureus* (127), and that house dust mite allergens are proteases with activity against 19 epithelial surfaces.

STRATIFICATION

In a genome-wide scan of psoriatic arthritis, 39 Icelandic families provided a maximum two-point LOD score of 2.17 with chromosome 16q markers (128). When the analysis was conditioned on paternal transmission, an LOD score of 4.19 was obtained. This locus had previously been implicated from two genome-wide scans with nuclear families. It mapped 20 Mb from the *NOD2/CARD15* gene, a gene previously implicated in Blau syndrome, and Crohn's disease. Two groups had previously observed lack of association between Crohn's disease variants of *CARD15* and psoriasis in both US and Italian families (129,130). However, in a case-control study of psoriatic arthritis patients from Newfoundland, 28% of probands had at least one *CARD15* variant (*R702W*, *leu1007fsinsC* and *G908R*) compared with 12% of controls ($P=0.0005$) (131). It is hypothesized that *CARD15* is a psoriatic arthritis gene that is independent of *HLA-Cw*0602*. Hence, stratification of families may be important for unmasking some of the susceptibility loci of complex disease. There is also some evidence that a second potential psoriatic arthritis loci identified in Swedish families maps to chromosome 15 (*D15S817*) (NPL 2.96, $P=0.002$) (47).

Stratification, or gene-gene interactions may also be of importance to AD. However, in the absence of an effect to match *HLA-C* in psoriasis, sample sizes at present are too small to investigate such possibilities.

PARENTAL EFFECTS

The risk of transmission of atopic disease from an affected mother is approximately four times higher than from an affected father (132). Similar parent-of-origin effects have been noted in 20 psoriasis (133) and psoriatic arthritis, as noted above (128). However, in the two cases examined (*HLA* and 16q) the disease appeared to be more likely to be inherited through the father if he was affected.

The mechanisms for these parent of origin effects are unknown. Maternal effects may result from immune interactions between the fetus and the mother. These are recognized to take place through the placenta as well as through breast milk (134). Alternatively, the maternal effect may be the result of genomic imprinting (135,136).

Several known genes show parent-of-origin effects on allergic disease. These genes include the *FcεRI-β* locus on chromosome 11q (137,138) the *LEKTI/SPINK5* gene from chromosome 5q34 (67) and as yet undiscovered genes at loci on chromosomes 4 and 16 (72). Epigenetic markers of imprinting, such as the variable presence of methylation on CpG residues (136) now need to be combined with knowledge of parental disease status as well as parental genotype.

ENVIRONMENTAL TRIGGERS

As with many complex human diseases, both genetics and environment play a role in the development of psoriasis and AD. Environmental causes of psoriasis may include mechanical, ultraviolet and chemical injury, various infections, prescription drug use, psychological stress and smoking (3). The most compelling of these is infection with group A streptococci (139). Streptococcal throat infections frequently precede outbreaks of guttate psoriasis that can then lead to chronic plaque psoriasis. A recent study of 29 patients from the UK revealed that all patients with guttate psoriasis carried the *HLA-Cw*0602* allele. There are also claims that chronic plaque psoriasis may be made worse by infection (140).

A third of patients with AD suffer from frequent serious skin infections, and over 90% of eczema patients are colonized with *Staphylococcus aureus* (127). *S. aureus* and *Staphylococcal* enterotoxins have important roles in the exacerbation and prolongation of AD. *S. aureus* in eczema lesions are colonized on and in the horny layers of the eczematous skin, and *Staphylococcal* enterotoxins are distributed on the dermal-infiltrated cells, especially on eosinophils (141).

Nearly all strains of *S. aureus* from skin lesions of AD have been reported to produce proteolytic activity, with 60% producing activity comparable to that of the proteolytically hyperactive reference strain *S. aureus* V8 (142). This was in contrast to control strains isolated from the nose vestibules of 18 healthy carriers, in which proteolytic activity never exceeded 2.5% of the activity of the reference strain (142).

Toxins from bacteria including *S. aureus*, have been shown to function as superantigens. These antigens bypass the normal control of T-cell activation and activate all T-cell clones bearing certain types of variable chain on the T-cell receptor: this leads to vigorous T-cell activation and cytokine release. *S. aureus* from the skin of patients with eczema frequently produce superantigens, and application of a staphylococcal superantigen to human skin induces an eczematoid reaction (143).

Many children with AD have positive prick skin tests to common allergens. House dust mite (HDM) major allergens are also proteinases that exert profound effects on epithelial cells, including disruption of intercellular adhesion, increased paracellular permeability and initiation of cell death (144). *Fel d I*, the major cat allergen, degrades collagens and cleaves fibronectin (145) and the major grass allergen, *Phl p V*, is an RNAase (146).

Understanding of the genetic predisposition to AD should therefore also be informed by investigation of the roles of *S. aureus* and HDM proteinases in inducing an immune response in the skin of patients with the disease.

CONCLUSIONS

Genetic studies of both psoriasis and AD suggest that defects affecting cells of the skin need to be as seriously considered as defects in adaptive immunity. In evolutionary terms, epithelial surfaces had to cope with infections and other insults long before the appearance of the adaptive immune system. Keratinocytes are very active immunologically, and produce a wide range of cytokines (147). Although this activity has been assumed to be secondary to signalling from classical immune

cells (148), keratinocytes express functional receptors such as CD14 and TLR-4 (149) and are capable of inducing inflammatory responses without pre-induction by other cells.

The *EDC* has been implicated in AD and psoriasis. It transcribes within terminally differentiating keratinocytes and contains many genes that may modify immune processes in the epithelium. The observation that polymorphisms within the Netherton's Disease Gene *SPINK5* are associated with atopic dermatitis (125) suggests that protection of the skin against external proteases may also protect against allergic responses. It may be relevant that 1-proteinase inhibitor has been reported in a small trial to be effective in the treatment of AD (150).

The polymorphic nature of genes and gene families expressed in the skin suggest a polyvalent response to a number of different stimuli, including infections. In the case of psoriasis and psoriatic arthritis, genes of the immune system such as *CARD15*, as well as genes that play roles in the skin and synovium need to be considered. The fact that psoriasis is associated with *HLA* alleles, whereas AD is not, may be related to the hyperproliferation of keratinocytes, or with the presence of viral infections.

It is clear from the above that, while genes are important, how they influence the disease is complex and atopic dermatitis and psoriasis vulgaris may lie within a spectrum of genetic diseases of the skin immune system.

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