Genetic Background of Psoriasis

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Abstract

Psoriasis is a chronic inflammatory dermatosis that contributes to approximately 1-5% of all skin disorders in Saudi Arabia. The genetic basis of psoriasis is supported by family based investigations; population based epidemiological studies, association studies with human leucocyte antigens (HLAs), genome-wide linkage scans, and candidate gene studies within and outside the major histocompatibility complex. Psoriasis represents a complex disease at the cellular, genomic and genetic levels, with infiltration of many types of leukocytes into the skin, altered growth and differentiation of skin-resident cells, and altered expression of more than 1,300 genes in psoriatic lesions. It is also apparent that there is considerable overlap between the molecular pathways that are involved in psoriasis and those that lead to other inflammatory or autoimmune diseases in humans. In this Review article, we describe the immune-genetic basis of psoriasis, the molecular pathways of pathogenic inflammation and the potential role of the genes that confer increased susceptibility to psoriasis.

Key words: Psoriasis, Genetics, Autoimmune, HLA

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Introduction

Psoriasis is a chronic inflammatory dermatosis characterized by thickened, scaly plaques. The most common form, psoriasis vulgaris, affects 2–3% of the Caucasian population, most frequently beginning in young adults and persisting throughout life.[1] It affects 2% of the UK population.[2] In Saudi Arabia, it contributes to approximately 5.3% of all skin disorders in the eastern part compared to 1.1% of the southern part of the kingdom.[3] There was a male preponderance with sex ratio of 1.4:1. The mean age of onset in males was 26.9 years while in females it was 22.3 years. Fifty-three percent of psoriatic cases developed before the age of 30 years. Family history of psoriasis was recorded in 8.4% of the cases. Plaque psoriasis was the most common clinical type (87.1%), followed by erythrodermic (4.2%), pustular (3%), guttate (1.9%), flexural (2.3%) and follicular type (0.4%).[4]

The disease is thought to manifest as a consequence of an inappropriate immune response against currently unknown causal agents, of self (e.g. Autoantigen) or non-self (e.g. bacteria) origin, whereupon leucocyte recruitment and activation at the site of the developing cutaneous lesion perpetuates the disease.[5]

Moreover, many of the genes that are associated with increased susceptibility to psoriasis are being identified. This knowledge, together with evidence from both animal models and clinical studies, has improved our understanding of the pathological pathways of psoriasis, making it one of the best understood chronic inflammatory disorders in humans.[6]

Establishing a Genetic Component

Cumulative evidence implicates a substantive role for genetic factors in respect to disease susceptibility and expression. The genetic basis of psoriasis is supported by family based investigations; population based epidemiological studies, association studies with human leucocyte antigens (HLAs), genome-wide linkage scans, and candidate gene studies within and outside the major histocompatibility complex (MHC) region.[7]

Twin Studies

There is a three fold increased risk of psoriasis in monozygotic twins compared to fraternal twins. However, as the concordance for psoriasis is never 100% among monozygotic twins, and can be as low as 35%, the data suggest that environmental factors also play an important role.[8]

Population Based Studies

Three major population based epidemiological studies, from the Faroe-Islands and Sweden, and one clinic-based study from Germany have revealed a substantially higher incidence of psoriasis in relatives compared with the general population. From these studies, a multilocus model for psoriasis is predicted. The heritability (the proportion of variability of a trait attributed to a genetic factor) for psoriasis has been estimated to be between 60% and 90%.[8, 9]

Inheritance and Risk Pattern

Elucidating the mode of inheritance of psoriasis has been plagued with all the problems associated with a common and complex disease. Sometimes sporadic cases can be mistaken for familial segregations because the disease is so common. Other factors that confound linkage analyses are incomplete penetrance of the trait in susceptible individuals and variations in phenotypic expression that may depend on age, gender, modifier genes and environmental trigger factors. The existence of genetic heterogeneity is likely, again decreasing the ability to detect linkage by combining scores from different families. However, it is not currently clear what proportion of cases are due to such predisposing alleles, and what proportion of cases are polygenic.[10, 11]

It is now universally acknowledged that psoriasis is consistent with a multifactorial pattern of inheritance.[10] However, there are scattered reports where an autosomal dominant and autosomal recessive pattern of inheritance for psoriasis has been proposed. For instance, transmission through many generations of a large kindred supports dominant inheritance,[11]; yet others suggested a recessive mode of inheritance was compatible with recurrence risks among first

degree relatives.[12,13] Swanbeck et al presented empirical data that may be of relevance for genetic counseling. After assessing over 3000 families in which one or both parents had psoriasis, the calculated lifetime risk of getting psoriasis if no parent, one parent , or both parents have psoriasis was found to be 0.04, 0.28, and 0.65, respectively. If there was already one affected child in the family, the corresponding risks were 0.24, 0.51, and 0.83, respectively.[12, 13]

Candidate Genes

To map genes successfully in complex multi-factorial diseases like psoriasis, a combination of several approaches may be required and include: (i) linkage analysis; (ii) allele sharing methods; (iii) association studies; and (iv) animal models.[14] All approaches are now being tried by a variety of groups.

The psoriasis susceptibility loci that have been mapped using linkage methods include: PSORS1 on 6p21.3, PSORS2 on 17q, PSORS3 on 4q, PSORS4 on 1cenq21, PSORS5 on 3q21, PSORS6 on 19p, PSORS7 on 1p, and PSORS9 on 4q31.[15] Additional putative psoriasis candidate loci have been reported on 16q and 20p.[16, 17] The loci on 6p and17q have been replicated with independent linkage studies. The replication for some other loci has proved to be quite difficult.[18]

Chromosome 6p Location

Association of psoriasis with alleles in the MHC region has been recognized for over three decades and presently there are a plethora of association studies with HLA alleles. The International Psoriasis Genetics Consortium analyzed 53 polymorphic micro-satellites spanning 14 psoriasis candidate regions and found maximum linkage for markers within the MHC.[18] This study once again highlights the importance of this region in the pathogenesis of psoriasis. For instance class I antigens HLA-B13, HLA-B17 and its split HLA-B57, and HLA-Cw6 have consistently shown a positive association with psoriasis, across various population studies. The presence of HLA-Cw*0602 is associated with more severe and early onset psoriasis and was found in 100% of patients with guttate psoriasis.[19, 20]

Furthermore, significant evidence was obtained for association with HLA-C described by Trembath *et al*. The most common HLA alleles observed were: A*0101, Cw* 0602 and B*5701, with the association with Cw6 being the strongest, followed by B57, A1, B47 and B13. Inspection of individual families where all affected members were Cw6 revealed that this was frequently due to the Cw6 allele present on more than one haplotype in a family.[18]

The nature of the contribution of the HLA region to disease is still unexplained. Elder *et al*. describe refinement of the susceptibility region to a 400 kb interval between HLA-B and C.[14] The availability of the genomic sequence of this region will help in gene discovery. The identification of the gene(s) in the HLA region predisposing to psoriasis will not only identify an important gene for psoriasis susceptibility, but should provide important information regarding the development of autoimmunity.[22]

Chromosome 17q25 Location

A genome-wide scan with polymorphic micro-satellites revealed linkage of psoriasis susceptibility to a locus at 17q25 that has autosomal dominant pattern of inheritance.[23] This locus was designated *PSORS2*. Several other groups independently have confirmed linkage to 17q.[24] However, as with any complex disease, not all groups have detected linkage to this region. Trembath *et al*., failed to find any evidence for linkage to *D17S784* at 17q25. [18]

Chromosome 4q Location

Matthews *et al*. reported linkage to *D4S1535* on chromosome 4q that is designated *PSORS3*. Evidence for genetic heterogeneity was also seen. Although this locus could not be confirmed in other studies.[25]

CX3CL1 and CX3CR1

CX3CL1 (formerly known as fractalkine) and its receptor, CX3CR1 represent plausible pathogenic genes in psoriasis.[24] Both genes map to genomic regions that have been linked

previously to psoriasis, play a role in leucocyte extravasation and modulate the actions of immuno-competent cells in infectious and inflammatory disease expressed in a number of organs, including skin, tonsil, brain and kidney.[26,27] CX3CL1 can exist in two forms: membrane-anchored or a shed 95-kDa soluble glycoprotein. The soluble form is chemotactic to natural killer (NK) cells, T cells and monocytes, whereas the membrane-anchored form promotes strong intercellular adhesion of leucocytes via CX3CR1.[28,29] CX3CL1-induced distribution of CX3CR1-positive inflammatory leucocytes has been implicated in the development of a number of diseases which have shared characteristics with psoriasis, including rheumatoid arthritis and cardiovascular disease (CVD).[28,30] Expression of CX3CL1 and CX3CR1 is elevated in plaques of psoriasis when compared with normal skin.[24,29] This observation implicates a role for CX3CL1/CX3CR1 in the extravasation of leucocytes that occurs both during the development and maintenance of a plaque of psoriasis.

Plant et al 2006 hypothesized that genetic variations in CX3CL1 and/or CX3CR1 might influence susceptibility to psoriasis development. They studied allele, genotype and haplotype frequencies within the CX3CL1 and CX3CR1 genes in a large cohort of psoriasis patients and control subjects; suggested a possible role for CX3CL1-CX3CR1 system in the pathogenesis of psoriasis and identified single nucleotide polymorphisms (SNPs) within CX3CR1 that are associated with the disease.[32]

Single Nucleotide Polymorphisms (SNPs)

With the advent of single nucleotide polymorphism technology and high throughput genotyping, the potential for association and linkage disequilibrium methods has expanded greatly. The linkage and association methods should not be thought of as being mutually exclusive strategies but rather complementary, as association studies are often being attempted in genome regions that have been localized by previous linkage studies. The best example is the association with cytokine genes polymorphisms.[33]

Other Possible Disease Loci

Across the remainder of the genome, the strongest evidence of allele sharing was obtained on 16q and 10q22-q23.[13]

In addition, Trembath *et al*. identified regions on chromosome2 (*D2S134*), 8 (*D8S284*) and 20 (*D20S186*).[18]

The *EXT1* locus on chromosome 8 lies within 10 cM of the locus described by Trembath *et al.* Researchers described a small family in which psoriasis and multiple exostoses co-segregated for three generations. It will be interesting to see if affected members in this family harbor alterations in the *EXT1* gene.[34]

On the other hand, Nair *et al*. identified linkages to 16q (*D16S3110*, LOD = 2.92) and 20p (*D20S851*, LOD = 1.55.[17] The locus at 16q maps close to a Crohn's disease susceptibility locus[35] which is likely to be significant since the occurrence of psoriasis is significantly increased in some families with Crohn's disease.[36] Both psoriasis and Crohn's disease are characterized by inflammation of stratified epithelium.[37]

Other potential susceptibility regions included loci at 1q21 near the Duffy blood group (*D1S1679*), 2p (*D2S177*), 4q13–21(*D4S400*) and 14q31 (*D14S617*). Interestingly the 2p21–22region is homologous to the region on mouse chromosome 17 that harbors the flaky skin mutation. The locus on chromosome 1 maps close to the epidermal differentiation complex (EDC), a group of genes that collectively are super-regulated in psoriatic skin and linkage to this region is also seen in some Italian families.[38]

Animal Models

Several naturally occurring diseases in animals such as lichenoid-psoriasiform dermatitis in Springer spaniels, psoriasiform dermatoses in non-human primates and pityriasis rosea in pigs have been proposed as models for human psoriasis. Mouse models include *cpd* (chronic proliferative dermatitis), *me* (moth eaten), *mev* (viable moth eaten), *ic* (ichthyosis), *ab* (asebia) and *hr* (hairless) and *fsn* (flaky skin). Transgenic

and knockout gene technologies have yielded several animal models as the transgenic mice (TgIL-1.1 and TgIL-1.2) which over-express IL-1 alpha in basal keratinocytes [39], mice expressing alpha 5 or beta 1 alone or alpha 2 beta 1 or alpha 5 beta 1 heterodimers of integrin [40] and rats expressing B27 and human beta 2-microglobulin genes [41]. Models employing the SCID/SCID mice for skin grafting or immunocyte injection studies have also been reported.[42]

Genotype Phenotype Correlation

Although clinical features and severity vary between individuals and with time, psoriasis is characterized by four abnormalities[43]: (i) Vascular changes where the capillary blood vessels become dilated and tortuous. This results in redness or erythema, one hallmark of psoriasis. (ii) Inflammation, where polymorphonuclear leukocytes from the dermal vessels enter the epidermis. Lesions are also rich in activated CD4+ and CD8+ T cells that release pro-inflammatory cytokines. (iii) Hyper-proliferation of the keratinocytic layer (acanthosis). (IV) Altered epidermal differentiation where keratinocytes retain their nuclei in the cornified layer (parakeratosis) and the granular layer is lost. These changes in the epidermis result in scaling, another hallmark of psoriasis.[44]

While collecting multiple affected and nuclear families with psoriasis, dermatologists have observed a variety of different phenotypes in some family members. These include psoriatic arthritis, sebopsoriasis, seborrheic dermatitis, eczema and a variety of other dermatoses. Once predisposing genes are identified, it will be interesting to correlate the existence of these other phenotypes with predisposing alleles. It would appear from these preliminary observations that phenotypic expressivity is more a factor of environmental effects or modifier genes. For example, in a large family showing linkage to 17q25, members are affected with a range of phenotypes from mild to severe psoriasis, with concomitant psoriatic arthritis.

Psoriatic arthritis has been found in five of 25 families from the National Psoriasis Tissue Bank. Interestingly, none of the members of the HLA-Cw6 families has been diagnosed with psoriatic arthritis. Whether this correlation reflects a true effect of the chromosome 6 phenotype, or would disappear if larger numbers of families were tested, remains to be determined. Within both HLA-Cw6 families and others, there were affected members with hand and foot psoriasis, suggesting that the development of this clinical type of psoriasis is more dependent on other genes and environmental effects than on particular predisposing alleles.[45]

Henseler and Christophers in 1985 noted that type I psoriasis defined by the onset of psoriasis before age 40 years, had a stronger genetic basis as a greater proportion of patients had a family history of psoriasis, stronger HLA associations (HLA-Cw6, HLA-DR7, HLA-B13, and HLA-Bw57) and more severe psoriasis.[46]

On the other hand, patients with type II psoriasis were characterized by a later age of onset (after 40 years) and were found to have lower familial tendency. The risk ratio for first degree relatives for type I psoriasis was 10, compared with 1 or 2 for those with type II psoriasis. As identifying a subset of psoriasis decreases the heterogeneity of this complex disorder, most genetic studies now focus exclusively on probands with type 1 psoriasis.[1]

Conclusion

Psoriasis belongs to the class of complex autoimmune genetic diseases that include diabetes, rheumatoid arthritis, multiple sclerosis and Crohn's disease. The proportion of genetic as opposed to environmental contributions in these diseases is not clear. Positional cloning of suggested susceptibility genes will help in understanding the genetic causes for psoriasis and determine the proportion of cases that are due to single, dominantly or recessively acting genes, versus those that are due to polygenic effects. Potentially susceptibility genomic loci include 17q25, 4q, 6p (HLA), 16q and 20p that warrant further attention. Animal models such as the flaky skin mouse and transgenic animals can also aid to our understanding of the underlying mechanism of the disease. Studying association to cytokine gene polymorphisms is also of benefit for the evolution of new modalities of therapy using immune modulators.

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