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Human leukocyte antigens as psoriasis inheritance and susceptibility markers

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Summary

Psoriasis is a multifactorial and heterogenetically inherited disease. The role of hereditary transmission is supported by familial association, twin studies, and correlation with human leukocyte antigens (HLA). Numerous studies have proved that B13, B17, Cw6, and DR7 antigens are positively associated with psoriasis. Cw6 antigen has been repeatedly indicated to be the most significant marker for the risk prediction of the disease. On the basis of epidemiological studies and HLA analysis, a concept of two distinct disease patterns of psoriasis vulgaris was proposed. In type I psoriasis the disease has an early onset, strong correlation with Cw6, B13, B17, and DR7 antigens, and familial inheritance. Type II psoriasis has a late onset, weak correlation with HLA antigens, and sporadic familial occurrence. Both types seem to differ clinically. Moreover, some extended haplotypes were shown to be correlated with the disease, especially with the type I psoriasis. Although a psoriasis susceptibility gene(s) has not been yet identified, a number of candidate genes were studied, with evidence for a major locus located within the major histocompatibility complex (PSORS 1). Cw6 allele is the most extensively investigated candidate gene, but present evidence suggests that it is rather in strong linkage disequilibrium with the PSORS 1 gene than the susceptibility allele itself. This article reviews past and current data on the genetic background of psoriasis with special attention to its correlation with HLA antigens.

Key words: Cw6 • epidemiology • haplotypes • HLA • MHC • psoriasis

Abbreviations: Ala-73 – alanine at position 73, EH – extended haplotypes, HLA – human leukocyte antigen, LD – linkage disequilibrium, MHC – major histocompatibility complex, PV – psoriasis vulgaris, PSORS 1 – psoriasis susceptibility 1.

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INTRODUCTION

Psoriasis is a common, chronic, relapsing inflammatory skin disorder. Its prevalence varies with race, ethnic group, and geographic region. In Caucasians it affects approximately 2% of the population^{18, 26}. The disease is characterized by hyperproliferation of the epidermis, which manifests as rather monomorphic papular and scaling lesions in a symmetrical distribution. Psoriasis is a heterogeneous disease with a number of subgroups. Clinical features and severity of the disease vary among individuals. Most patients present mild to moderate forms of chronic plaque psoriasis (psoriasis vulgaris – PV) and guttate psoriasis. Rarely occurring forms include erythrodermic, palmo-plantar, pustular, and arthropathic psoriasis.

The pathogenesis of psoriasis still remains elusive. The disease is believed to have an autoimmune, T lymphocyte-mediated character. The cutaneous lesion is characterized by epidermal hyperproliferation, abnormal keratinocyte differentiation, and infiltration of T cells and other mononuclear cells^{20, 21}. A genetic background of the disease is unquestionable. The main line of evidence for a heritable nature of psoriasis was provided by epidemiological studies, first reported by Willan in 1801 and later supported by Lomholt⁴² in 1963, who investigated almost one-third of the entire population of the Faroe Islands and estimated the prevalence of the disease to be 2.8%. Moreover, it was also revealed that almost every patient with psoriasis had at least one affected relative⁴². These results were supported by extensive investigations by Burch and Rowell⁹ and by Farber and Nall¹⁸. The risk ratio of disease in siblings of affected subjects has been reported to be in the range of 4–6¹⁶. The hereditary transmission of psoriasis was supported by twin studies. In Farber's analysis of 219 twin pairs, the concordance rate of psoriasis in identical (monozygotic) twin pairs was 65% in comparison with 23% in dizygotic twins¹⁹. Further investigations supported the observation that the concordance rate in identical twins never reaches 100%, which indicates that, besides genotype, some triggering factors are necessary for the onset of the disease^{1, 6, 14}. Stress, skin injury, infections, and some drugs are the most important environmental factors influencing the onset and relapses of psoriasis. These environmental stimuli, acting with a predisposing gene (or genes), are essential for psoriasis onset. This fact supports the opinion that psoriasis follows a multifactoral mode of inheritance, with variation in familial distribution¹⁰.

HUMAN LEUKOCYTE ANTIGENS IN PV

A significant genetic component of psoriasis susceptibility was supported by the association of the dis-

ease with human leukocyte antigens (HLA), encoded by genes located within the major histocompatibility complex (MHC) on the short arm of chromosome 6. The HLA system encompasses class I antigens (HLA-A, -B, and -C), class II antigens (HLA-DP, -DQ, -DR) and class III determinants (tumor necrosis factor, heat shock proteins, components of complement). Class I antigens are expressed on the surface of nearly all cells, while class II antigens are present on B lymphocytes, macrophages, monocytes and, after induction by interferon γ , on T lymphocytes, keratinocytes, and endothelial cell surfaces.

Correlation of HLA antigens with psoriasis has attracted investigators' attention since the early 1970s. Russell et al.⁵⁵ and White et al.⁶⁹ were the first who independently observed statistically significant increases in the frequencies of B13 and B57 antigens in psoriatic patients compared with a control population. These pioneering studies were followed by further extensive investigations. The results consistently confirmed a strong association of B13 and B57 antigens with psoriasis in different ethnic populations^{2, 15, 24, 35, 38, 50, 52, 67}. In 1975, Svevgaard et al.⁶¹ pointed out a strong association between psoriasis and antigens encoded by the C locus. This observation was soon supported by other independent studies in ethnically and racially different regions. The studies reported the strongest correlation between the disease and Cw6 antigen^{15, 20, 32}. Only a few publications from Japan and China revealed an increased frequency of other C locus antigens, i.e. Cw2, Cw4, Cw7, and Cw11 in psoriatic populations^{3, 48, 51}. Numerous studies in ethnically and racially different regions reported unanimously the highest risk of developing psoriasis by individuals carrying Cw6 antigen, which was several times increased in comparison with Cw6-negative persons. The frequency of Cw6 antigen in psoriatic patients depends on geographic region (Table 1). In

Table 1. Cw6 frequency (%) in psoriatic patients in chosen populations

Country	Frequency	Reference
Greece	36.3	15
Denmark	87.0	61
Japan	8.2	49
Brazil	59.1	20
Finland	54.0	31
Poland	47.8	58
Sweden	54.0	17
India	30.0	53
Thailand	67.0	68
Croatia	59.3	36
Korea	76.0	37
Turkey	68.0	39
Taiwan	6.2	65
Iceland	64.2	22
China	32.4	12

Caucasian subjects it varies from 36.3% in a Greek population to 87% in a Danish one, compared with an approximately 20% frequency in a non-psoriatic population^{13, 62}. The lowest frequency of Cw6 antigen, 8.2%, was reported in Japanese subjects with psoriasis, which is explained by the lower frequency of Cw6 antigen in the whole oriental population compared with Caucasians^{11, 65}. The association between serotyped Cw6 and psoriasis was not confirmed in the early studies of Chinese patients, but consecutive investigations proved that Cw6 is a psoriasis risk factor in this population as well^{11, 12, 41}. This discrepancy may have been due to the lower sensitivity and specificity of previously applied serotyping in the determination of HLA-C compared with genomic techniques. In intensive studies of 604 individuals, Bunce assessed the validity of both methods and revealed that the frequencies of many HLA-C antigens had been underestimated by the complement-mediated cytotoxicity test. This could be explained by the low surface expression of HLA-C molecules and lack of reagents⁸. It is estimated that approximately 20–50% of the population carries serologically undetectable, undefined HLA-C alleles, so-called Cw “blank” alleles^{40, 47}.

The detection of class II antigens on B cells focused investigators' concern on their correlation with psoriasis. Although the first studies denied such an association, subsequent researches proved that the frequency of DR7 antigen is increased in psoriasis patients compared with controls^{5, 28, 46, 50, 52, 56, 60, 64, 66}. More sensitive detection of class II alleles with PCR methods compared with serologic techniques proved that, besides DRB1*0701 allele (a subtype of serologically detected DR7 antigen), DQA1*0201 and DQB1*0303 are associated with psoriasis^{31, 56, 68}. Moreover it was observed that DR7 is often combined with Cw6, which could suggest that at least two HLA-linked genes predisposing to psoriasis exist, one located close to the Cw6-encoding gene and the other located close to the DR7 gene¹⁷. This combination of alleles is attributable to the fact that genes encoding both Cw6 and DR7 are often inherited together (both alleles are inherited together). The phenomenon called linkage disequilibrium (LD) is defined as the tendency of specific combinations of alleles at two linked loci to occur together and is due to a low recombination fraction between them¹⁷. LD is also observed in Cw6, B13 and Cw6, B57 genetic transmission²⁶.

TYPE I AND TYPE II PSORIASIS

Epidemiological studies of psoriatic patients have shown that the disease is not uniform. In 1965, Burch and Rowell⁹ revealed that two peaks of psoriasis

onset exist: one in puberty and the other in the 4th and 5th decade of life. In contrast, Farber and Nall¹⁸, who analyzed a large population of 5600 patients with psoriasis, demonstrated only one peak age of onset in the second decade of life. The early observations of Burch and Rowell⁹ were supported by an extensive retrospective analysis of 2147 patients performed by German investigators, who revealed a bimodal distribution of age of onset of psoriasis^{13, 27}. They distinguished two groups of patients. The first included patients with early onset of the disease with the peak of onset at the age of 16 in females and 22 in males. The second group consisted of patients with late onset, determined to be 60 in females and 57 in males. Moreover, the authors observed that 40% of the patients with early onset have at least one first-degree relative affected by psoriasis. In the late-onset group only 2% of the patients indicated relatives having symptoms of the disease. Comparison of HLA antigen frequencies in both groups revealed statistically significant differences. The most striking observation was the increased frequency of Cw6 in patients with the early-onset disease. B13 and B57 antigens were also more frequent in the early-onset subjects, which could be explained only partially by the LD phenomenon. In early-onset psoriasis the combination of Cw6 and B57 or Cw6 and B13 is increased 30 and 20 times, respectively, while in controls there is only a 6-fold increase in these antigen combinations²⁷. These observations led to a definition of two distinct disease subtypes (Table 2). In type I, with early onset, Cw6 antigen is much more frequent, with a high prevalence of psoriasis among first-degree relatives. In type II, with late onset, the frequency of Cw6 is similar to that observed in the healthy population. Moreover, a sporadic incidence of psoriasis in family pedigrees is observed²⁷. The significant correlation of the early-onset type psoriasis with Cw6 antigen was confirmed subsequently by numerous studies on different ethnic populations. In most studies the frequency of Cw6 antigen in early-onset psoriasis exceeds 60% vs. approximately 20% in control groups^{7, 17, 27, 36, 57, 58}. A significant correlation of Cw6 antigen and the early onset of psoriasis was also reported in a Polish population^{43, 58, 59}.

Independent studies have also pointed out a psoriasis-specific nucleotide sequence of the C alleles^{3, 30}.

Table 2. Types of psoriasis vulgaris according to Henseler and Christophers²⁷

Type	I	II
Age of onset	early	late
Cw6 expression	73.8%	31.8%
Familial occurrence	40.0%	2.0%

An elevated frequency of alanine at position 73 (Ala-73) of the HLA-C molecule was observed in psoriatic patients, which could suggest that this sequence is related to a high risk of psoriasis development. The hypothesis of a significant role of Ala-73 in psoriasis susceptibility was later verified in consecutive studies which revealed that Ala-73 is present in many other HLA-C alleles^{45, 54}. Subsequent studies have failed to reveal any differences in Ala-73 frequency between psoriatics and controls. The significant increase in Ala-73 frequency was observed only in male type I psoriasis⁴⁵.

HLA RISK HAPLOTYPES IN PSORIASIS

While the data on single HLA antigen frequencies in psoriasis have been widely and well documented for over three decades, analysis of psoriatic haplotypes has been carried out in recent years. Studies of different populations have revealed that distinct extended haplotypes (EH) involved in psoriasis pathogenesis (Table 3). EH are defined as a combination of several distinct alleles inherited as a full complex and unchanged throughout evolution²⁶. An increased frequency of an extended haplotype EH57.1 (Cw6-B-57-DRB1*0701-DQA1*0201-DQB1*0303) was observed in type I psoriasis. The risk of developing psoriasis was calculated to be 26 times higher for EH57.1 haplotype compared with controls⁵⁷. Schmitt-Egenolf's study indicated that HLA-Cw6 and HLA-B57 are the alleles that show the most significant association. The author concluded that the susceptibility gene lies towards the class I side of the EH57.1 haplotype⁵⁶. In a study of ethnic Thai psoriatics, two haplotypes were associated with psoriasis: EH57.1 (HLA-A1-B57-DRB1*0701-DQA1*0201-DQB1*0303) and H46.1 (HLA-B46-DRB1*0901-DQA1*0301-DQB1*0303). The first haplotype was correlated with type I psoriasis, while the second with both types of the disease. As these two haplotypes carry DQB1*0303 (encoding DQ9 molecule), it is suggested to be one of the important alleles associated with psoriasis susceptibility⁶⁸. This observation was partially in agreement with earlier studies by Jenisch et

al., who revealed that the DQB1*0303 allele indeed increases susceptibility to type I psoriasis, but only in the presence of Cw6^{33, 34}.

CW6 ALLELE CORRELATION WITH THE CLINICAL PICTURE OF PV

The important role of the Cw6 molecule in psoriasis susceptibility prompted investigators to analyze the correlation between Cw6 antigen expression and clinical features of the disease. The results were disputable. Ikäheimo et al.³¹ failed to show any correlation between Cw6 and clinical disease expression. In contrast, Henseler and Christophers²⁷ showed that patients with type I of psoriasis (Cw6-positive) are more likely to have widespread and recurrent disease. This observation was confirmed in a study from a cohort in northern Poland which revealed that Cw6 is positively associated with more severe forms of psoriasis⁵⁹. A recent investigation of an Icelandic population of 369 patients with PV also revealed that Cw6-positive and Cw6-negative differ significantly when distinct disease features are analyzed²³. The most striking observation was that the guttate-type onset of psoriasis, induced by group A β hemolytic streptococcal infections of the upper respiratory tract, was predominantly observed in Cw6-positive patients. The authors suggested that Cw6 molecule could be directly involved in psoriasis pathogenesis through molecular mimicry or presentation of endogenous or exogenous epitopes to T lymphocytes. The results are in concordance with an earlier study which reported a high incidence of Cw6 allele in individuals with guttate psoriasis⁴⁴. Moreover, in a study of a large population of 1006 psoriatics it was shown that the phenotype of psoriasis is not influenced by Cw*0602 homozygosity²².

Over the last several years a number of linkage studies have been performed to identify psoriasis genetic susceptibility loci. Particular attention has been paid to genetic research of the MHC region. Genome scan studies have generated evidence for a major locus within the MHC complex (psoriasis susceptibility 1 – PSORS 1). It has been estimated that a susceptibility gene (or genes) at this locus accounts for 30–50% of the genetic contribution to psoriasis⁶³. HLA-C is a known candidate gene. The two others extensively investigated are the corneodesmosin and the α -helix coiled-coil rod homologue genes. Researchers are collecting evidence that the association of HLA molecules with psoriasis might be indirect and that HLA-Cw6 is not a susceptibility allele itself, but a marker, being in strong LD with the PSORS 1 gene⁴. What is more, independent genome-wide scans have indicated involvement of a large number of chromosomal

Table 3. Extended haplotypes in psoriasis

Extended haplotypes	Reference
A1, A2, B39, Bw46, Cw6, Cw7, Cw11	49
A1, B37, Cw*0602, DRB1*10, DQA1*01, DQA1*01, DQB1*05	37
Cw6-B57-DRB1*0701/02-DQA1*0201-DQB1*0303	57
A1, A2, B13, B17, Cw6, DR7, DQA1*0201	29
A1-B57-DRB1*0701-DQA1*0201-DQB1*0303	68
A2-B46-DRB1*0901-DQA1*0301-DQB1*0303	

Modified from Henseler²⁵.

regions, suggesting that psoriasis is a polygenic disease and that multiple genes are likely to be involved in its pathogenesis. Further work is being conducted to elucidate the exact location of psoriasis susceptibility genes, and it is likely that candidate genes will be identified soon.

CONCLUSION

Currently there is a consensus that psoriasis is a multifactorial disease with a complex genetic basis. The mul-

tifactoral character of psoriasis results from the observation that environmental or endogenous factors trigger the disease in genetically susceptible individuals. The heterogeneity of psoriasis is evident by the variety of genetically linked markers of psoriasis. Among the most important are MHC class I antigens. Of these, Cw6 confers the largest and most consistently demonstrated risk factor, especially for early-onset psoriasis. Today it is also clear that a major candidate gene (or genes) for psoriasis is located within the MHC complex and that is linked with the HLA-Cw6 locus.

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