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The role of HLA-Cw6 in psoriasis and psoriatic arthritis

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Psoriasis (Ps) is an inflammatory disease of complex etiology. The development and course of psoriasis are influenced by genetic, environmental and immunological factors [1, 2]. Psoriasis is a disease with a multi-gene model of inheritance, which means that its manifestation is caused by the interaction of many genes and environmental factors. The environmental factors associated with the development of Ps include infections, medications, alcohol and stress [3, 4].

The direct mechanism for the development of Ps is still not fully understood. The importance of a genetic predisposition is supported by the familial occurrence of the disease. Population-based studies show that psoriasis is more common among first- and second-degree relatives compared to the general population [4, 5]. Monozygotic twins also have a 2–3 times higher risk of Ps compared to dizygotic twins [6]. The inheritance type of psoriasis is complex. Several areas associated with psoriasis susceptibility termed PSORS (psoriasis susceptibility) have been located in the genome. The following gene variants and their locations on chromosomes are associated with psoriasis development: PSORS1 (6p21), PSORS2 (17q24-q25), PSORS3 (4q34), PSORS4 (1q21), PSORS5 (3q2), PSORS6 (19p13), PSORS7 (1p32), PSORS8 (16q), PSORS9 (4q31-q34), PSORS10 (18p11. 23), PSORS11 (5q31.1-q33.1), PSORS12 (20q13), PSORS13 (6q21), PSORS14 (2q14.1) and PSORS15 (2q36.1) [7].

However, it is still unclear which genes play the crucial role in Ps. Genetic diversity may result in a different clinical picture in patients. The most important correlation with Ps susceptibility has been found with PSORS1 [4]. PSORS1 is located within the major histocompatibility complex (MHC). The association of psoriasis vulgaris with human leukocyte antigens (HLA) has been described for a long time. Based on current data, within PSORS1, HLA-Cw6 is the allele most likely to be associated with psoriasis susceptibility. The role of HLA-Cw6 in the pathogenesis of Ps is not fully understood, but its involvement in innate and acquired immunity mechanisms is indicated. No disease-specific mutations have been identified to date. The role of alleles at this locus is not fully known, although the possibility of specific differences in HLA-C expression and regulation by cytokines involved in the inflammatory process in Ps has been suggested. Thus, it may be a link between the genetics of psoriasis and the immunological basis of the disease. HLA-C is an interesting candidate gene as it may participate in the immune response at the level of both CD8+ antigen presentation to T lymphocytes and NK cell regulation.

In the innate response, HLA-Cw6 can bind to KIR2DL1. Killer-cell immunoglobulin-like receptors (KIR) are receptors from the so-called immunoglobulin-like molecule family. They are found on the surface of NK cells. HLA molecules are ligands for KIR. KIR2DL and KIR3DL inhibit cell activation, while KIR2DS and KIR3DS activate the NK cell [5, 8]. The role of CD8 is to bind MHC class I molecules, which, on the one hand, stabilizes the contact between the cytotoxic T lymphocyte and the target cell and, on the other, promotes lymphocyte activation by enhancing signaling pathways running from the TCR receptor. Thus, in the adaptive response, HLA-Cw6 is involved in the presentation of specific autoantigens causing clonal expansion of CD8+ T cells in psoriatic lesions. Interaction between LL-37 and HLA-Cw6 is found in Ps [4, 5, 9, 10]. This confirms the clinical association of guttate psoriasis and streptococcal pharyngitis [11]. It also appears to have a higher prevalence of the HLA-Cw6 allele

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in HIV-infected patients with psoriasis (80%) compared to its presence in HIV patients without Ps (24.5%) [12].

The prevalence of the HLA-Cw6 allele in the general population varies from 14.1% to 59.1%. In the Ps population, the percentage of patients with the presence of HLA-Cw6 varies from 10.5% to 77.2% [5]. The presence of HLA-Cw6 in patients with Ps is more frequently found in Caucasian patients than in the Asian population [4, 5]. The differences in the presence of HLA-Cw6 observed in the studies may be attributed to small sample size and ethnic diversity.

The presence of the HLA-Cw6 antigen has been shown to be strongly associated with type I of psoriasis. In type I, skin lesions appear before 40 years of age, with a peak incidence at 18–22 years of age. Diffuse skin lesions and a family history of the disease are also more common. In contrast to type I, psoriasis type II occurs after the age of 40. In this type, medications and other chronic diseases appear to play a greater role as triggers [3, 13]. In patients with HLA-Cw6 antigen, the triggering factors are often streptococcal pharyngitis and/or tonsillitis and stress. These patients are more likely to be obese.

Phenotypically, HLA-Cw6 has also been shown to be associated with guttate psoriasis [3, 5, 14]. In the clinical picture of guttate psoriasis, skin lesions occur on the limbs and trunk and the Koebner phenomenon is observed. HLA-Cw6 was found in 73% of the Finnish population with guttate psoriasis, 100% of the British population with guttate type and 86% of the Irish population with this type of psoriasis [3, 15–17].

In the Polish population, the presence of the HLA-Cw6 allele was found in 70% (49/70) of patients with guttate psoriasis. An association with streptococcal infection was observed in 48.5% (34/70) studied patients. In the group with an association with streptococcal infection, the HLA-Cw6 allele was detected in 79% of psoriasis patients. In healthy volunteers, the presence of HLA-Cw6 was found in 30% [11].

In patients with guttate psoriasis, a higher prevalence of HLA-Cw6 was also observed in the Asian population [4, 5]. Studies have shown a beneficial effect of tonsillectomy on the course of the disease in patients with homozygous HLA-Cw6 [18].

Studies have shown that HLA-Cw6 negative patients have more frequent nail lesions and psoriatic arthritis (PsA). A trend towards more frequent scalp involvement was also found in these patients. This is important as these areas are predictive of a higher incidence of PsA [5, 19]. In HLA-Cw6-positive patients, who developed PsA, most often the skin lesions preceded the onset of joint lesions for many years and their development was at a young age. It was also reported that HLA-Cw6-positive patients with PsA had a positive family history, early onset and severe psoriasis.

The association of HLA-Cw6 with the clinical picture of PsA requires verification. In HLA-Cw6 positive patients, enthesitis, polyarthritis or oligoarthritis has been described. In HLA-Cw6-negative patients dactylitis, axial disease or sacroiliitis has been noted. Data on the course of PsA are also inconclusive, but HLA-Cw6-positive patients may have a milder disease course [5, 20, 21].

HLA-Cw6-positive women experienced significantly more frequent remissions during pregnancy [22]. There are also emerging data indicating a relationship between the development of Ps in HLA-Cw6-positive individuals and environmental factors. An association has been found between smoking and obesity in HLA-Cw6-positive patients [5]. The risk of Ps in HLA-Cw6-positive patients who are overweight is 35 times higher than in HLA-Cw6-negative patients with a normal body weight [23]. The association between HLA-Cw6 and obesity may be due to overexpression of circulating pro-inflammatory cytokines in these patients, which increases the risk of Ps. Stressful life events have also been shown to increase this risk by almost 20-fold. Data also suggest that HLA-Cw6-positive patients may have a higher prevalence of cardiovascular disease [5, 24]. However, these observations need to be confirmed in studies on large groups of patients.

Studies have also been conducted to assess the response to therapy in HLA-Cw6-positive patients. The data are inconclusive, but in some of them the association with a better response to therapy was confirmed [25]. A better response to methotrexate and ustekinumab was associated with HLA-Cw6 [26, 27]. In contrast, there was no effect on response to adalimumab, etanercept or infliximab therapy [28]. Also, the response to secukinumab is not related to the presence of HLA-Cw6 [29]. However, it was reported that patients with the presence of the allele had less frequent failures after non-biologic systemic therapies [5].

In light of the data presented, the role of HLA-Cw6 as a predictor of clinical response to most therapies still remains unknown and requires further investigation.

Conclusions

Studies to date show that HLA-Cw6 positivity is associated with early onset of psoriasis and severe course of the disease. Nevertheless, further research is needed to fully clarify its role in psoriasis. The data also suggest that HLA-Cw6 is not a significant genetic marker for the development of psoriatic arthritis.

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