

A case report of HLA-Cw6 and phenotype discordances in monozygotic twins with psoriasis: The role of epigenetic mechanism

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Abstract Psoriasis is a systemic autoimmune disease influenced by genetic and environmental factors. The gene HLA-Cw6 is one of the most strongly associated proteins in psoriasis development. Recently, studies regarding monozygotic twins with psoriasis revealed that phenotype concordance among monozygotic twins was approximately 35-72%. We present a case of 15-year-old monozygotic twins female with psoriasis that exhibited difference in both onset and severity. HLA-Cw6 expression was negative in the twin that exhibited minimal cutaneous manifestation compared to the one with a more severe clinical presentation. We hypothesized that, epigenetic modification played an important role in phenotypic differences even though both patients theoretically have similar DNA sequences. This paper may merit further investigation regarding the nuanced interactions between genetics and the environment towards the clinical outcome of psoriasis patients.

Key words

Disease severity; Early onset; HLA-Cw6; Monozygotic twins; Psoriasis.

Introduction

Psoriasis is a systemic chronic inflammatory disease characterized with well-defined, scaly erythematous plaques.^{1,2} Its prevalence ranges from 0.09-11.4% worldwide.³ Psoriasis is strongly associated with the interaction between genetics and the environment. There are more than 80 genetic loci associated with psoriasis susceptibility. From twin studies, one of the most strongly associated alleles with psoriasis is HLA-Cw6, a major histocompatibility complex (MHC) class I variant.^{4,5} The expression of this protein is associated with early-onset psoriasis, guttate-type psoriasis, an increased disease severity, and higher Köbner phenomenon

incidence.⁵⁻⁷

Monozygotic twins when exhibit psoriasis have similarities in disease pattern, age of onset, distribution of lesions, severity, and clinical course of the disease.² However, the concordance of autoimmune diseases in monozygotic twins is well below 100%. In psoriasis, most studies reported concordance rates between 35-72% in monozygotic twins. These discordances are not clearly understood. However, it is hypothesized that epigenetic modification might play an important role in phenotype differences in the identical DNA sequence of twins.⁸ We report a case of a pair of monozygotic twins with psoriasis, with differences in HLA-Cw6 that demonstrated different onset and severity.

Epigenetic modification by DNA methylation, histone modification, and microRNA expression causes alteration of DNA expression level

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Figure 1 Erythematous plaques with thick silvery scales, hypopigmented macules on the anterior and posterior truncus, and bilateral extremities. In addition, the Autspitz sign and Köbner phenomenon were found.

without changing the DNA sequence. Environmental factors can influence the epigenetic program.⁹

Case report

A pair of 15-year-old monozygotic twin girls (Patients A and B) is diagnosed with psoriasis vulgaris confirmed through histopathological examination. Dermatological examination in Patient A revealed pruritic erythematous scaly plaques on the trunk and bilateral extremities, while in Patient B, there were hypopigmented and hyperpigmented plaques on the back and scalp. In Patient A, both Autspitz sign and Köbner phenomenon were positive, with a Psoriasis Area Severity Index (PASI Score) of 19.2 (**Figure 1**). However, patient B had a relatively limited cutaneous manifestation with a

PASI score of 1.2 (**Figure 2**). No abnormalities were found on the nails and joints of both patients. Further history taking revealed that patient B tend to be more physically active and easy to socialize in their daily life than Patient A. Furthermore, examination of the HLA-Cw6 levels of both patients carried out using GeneAmp® Polymerase Chain Reaction (PCR) System 9700 showed that the HLA-Cw6 expression was positive (330bp) in patient A, while in patient B, the HLA-Cw6 was negative (**Figure 3**). Both patients were treated with a combination of topical salicylic acid, liquor carbonis detergen (LCD), desoxymethasone, and an oral antihistamine. At one month follow-up, clinical improvement was observed in both patients, with a decrease of PASI score in Patient A to 2.3 and Patient B to 0.4.



Figure 2 Patient B showed thick white scales on the scalp and hyperpigmented macules with scales with hypopigmented macules obtained on the posterior truncus.

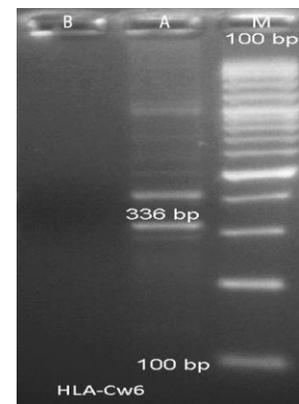


Figure 3 HLA-Cw6 PCR electrophoregram.

Discussion

The incidence of psoriasis is significantly higher in monozygotic (MZ) twins than in dizygotic (DZ) twins.⁵ Previous studies of psoriasis in twins showed a greater concordance rate in MZ twins (65-72%) compared to DZ twins (15-30%).¹⁰ This marked difference in psoriasis concordance rate suggests that psoriasis is influenced by genetic inheritance. Furthermore, psoriasis in MZ twins exhibited similar age of onset, lesion distribution, severity, and course of the disease.^{2,11} In this case however, examination of HLA-Cw6, one of the most strongly involved protein in psoriasis was only positive in one patient. HLA-Cw6 has effects on both innate and adaptive immune responses.^{12,13} In a study conducted on 201 psoriasis patients and 77 healthy controls in Sweden, it was found that 67% of psoriasis patients exhibited positive HLA-Cw6 allele, whereas in healthy controls, only 12% was positive. Theoretically, MZ twins should have 100% identical genes therefore the same genomic contribution to the disease. However, in reality the rate of psoriasis phenotype in MZ was only 35-72% (median 64%), suggesting that apart from genetic factors, variation in susceptibility to psoriasis is also influenced by environmental factors.¹⁴

Epigenetics summarizes all heritable changes in gene expression without alterations of the DNA sequence.¹⁵ Epigenetics may partially explain the cause of discordant disease presentations in MZ twins.⁸ Epigenetics includes DNA methylation, histone modification, or microRNA-mediated regulatory changes. Chromatin is a collection of DNA and DNA-linked proteins including histone and non-histone proteins. Epigenetics can alter gene expression without changing DNA sequences. These things ultimately lead to differences in gene expression, and these mechanisms may contribute to the incompatibility of monozygotic

twins in autoimmune diseases, including psoriasis.⁸ Methylation of DNA in CpG dinucleotides by the action of DNA methyltransferases (DNMT) is strongly associated with transcriptional repression.¹⁵ DNA methylation is involved in normal cellular control of expression, but aberrant hypermethylation can lead to pathological conditions like attenuation of the immune system and silencing of tumor-suppressor genes in carcinogenesis.¹⁶ MHC class 1 expression influences immune response. Epigenetics modification, especially DNA methylation, is inversely correlated to expressions of MHC class 1 mRNA level.¹⁷ Histone modifications control the accessibility of chromatin and transcriptional activities inside a cell. Modification of histone protein is done post-translationally with acetylation, methylation, ADP-ribosylation, ubiquitination, and phosphorylation which cause either transcriptional activation or repression based on the location and nature of the modification.^{15,18} Acetylation of histone, catalysed by histone acetyltransferase, can neutralize a positive charge of lysine and thus causes an impairment between the histone and DNA strand interaction.⁸ MicroRNA, an endogenous non-coding RNA, also plays a role in the post-translational regulator of gene expression. MicroRNA is encoded in our genome and transcribed by RNA polymerase II. MicroRNA can affect gene expression by inducing the degradation of targeted mRNA and modulating DNA methylation and histone modification.⁸

Epigenetics difference in monozygotic twin pairs was found by comparing total methylcytosine and histone acetylation levels from lymphocytes. The differences in methylcytosine and histone acetylation levels were higher in monozygotic twins with lesser time together which indirectly complied that different environmental factors can cause

different epigenetic pattern modifications.⁸ Twins with different environments might have different patterns of epigenetic alteration.⁸ As the twins aged, there were more differences between methylation and acetylation levels in 50-years old twins compared to 3-years old twins.¹⁹ Study from Burlando *et al.*²⁰ used homozygous twins with psoriasis and two HLA-Cw6 positives but had a different response to ustekinumab which a human monoclonal antibody to IL-12 and IL-23. It was known there were differences in body weight which might be a triggering factor to the attenuation of ustekinumab response.²⁰

Both patients are exposed to similar environmental conditions. Therefore, we hypothesized that aside from genetics, the role of lifestyle and dietary intake may play a role HLA-Cw6 expression. In our cases, patient B had higher exercise and fiber intake compared to patient A, which may explain the differences in phenotype. Similar to a study by Rezapour *et al.*,²¹ which reported that regular and continuous physical activity is one of the epigenetic-modifying factors through, alteration in histone and nucleus by increasing factor IIa and phosphorylation through CAMKII or AMPK.²¹

Conclusion

Psoriasis is an autoimmune disease that manifests as an erythematous plaques with thick scales in the skin. The presence of HLA-Cw6 has been shown to influence various aspects of psoriasis. Epigenetic alteration was assumed to have a role in phenotypic variations in twin patients with the identical DNA sequence.

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