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Editorial

Role of HLA-DRB1*04 in Malay patients with Vogt-Koyanagi-Harada syndrome

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In this issue of the Malaysian Journal of Ophthalmology, Alvernia *et al.* report the results of their study into the association between HLA-DRB1*04 and Vogt-Koyanagi-Harada (VKH) syndrome in patients of Malay descent. VKH is a useful condition on which to focus this type of study as, unlike many types of uveitis, it has validated international diagnostic criteria.[1,2] VKH is also among the most common causes of uveitis in Asia, where it accounts for almost one-third of all causes of panuveitis.

The combination of a genetic predisposition, including HLA haplotype as well as other genetic polymorphisms, and environmental factors is generally held responsible for the breakdown of tolerance and the development of autoimmunity in many disease entities. However, with the exception of acute anterior uveitis and HLA-B27, there is a disappointing lack of correlation between clinical phenotype, disease outcome, and HLA haplotype in uveitis. This lack of clarity also applies to VKH: there are distinct HLA associations across different ethnic populations, as has been shown in Hispanic and Japanese VKH patients with their HLA-DRB1*01 and *0405 associations; similarly, whilst VKH shares almost identical phenotypical and histopathological findings with sympathetic ophthalmia, and both share an association with HLA-DR1*0405 subtypes, they have completely different precipitating disease triggers.

Unsurprisingly, the exact aetiology of VKH remains unknown. Several immunological and histopathological studies suggest a T-cell mediated process directed against different antigens associated with melanocytes, including tyrosine or tyrosine-related proteins, in the presence of the DRB1*0405 peptide-binding motif.3 A systematic review and meta-analysis by Shi *et al.* showed an association with VKH disease and various HLA-DRB1*04 subtypes among different races, but other HLA associations, such as -DR53 or -DQ, have also been described, making it difficult to establish risk correlations. This suggests that specific HLA associations are not sufficient to explain the complex pathogenesis of VKH and that other genetic variations may also play a role. In support of this, upregulated Th17 responses and increased IL-17 production from T-cells have been associated with VKH disease in the Chine Han population, particularly in patients homozygous for the IL-17F-

rs763780 allele T.[4] Similarly, two separate studies have suggested the involvement of killer cell immunoglobulin-like receptors cluster (KIR), with an increased frequency of activating receptor KIR2DS3 in Saudi Arabian patients and the KIR gene cluster 3DS1-2DL5-2DS1-2DS5 in Japanese VKH patients. (Interestingly, there was a predominance of KIR2DL/2DL3+HLA-C1 in the Saudi Arabian control group of this study, suggesting a possible preventive role for this variant.)[5,6]

The importance of defining these associations between HLA and clinical entities lies in the potential to provide new insights into the pathogenesis of the disease, and to be able to identify those populations at risk of developing the disease or of having worse clinical outcomes. Identification of alternate targets, such as KIR genes that encode inhibitory and activating receptors on natural killer cells, and therefore may affect susceptibility or even influence disease severity, thus provides an exciting avenue for research. It is in this context that the current study provides useful and interesting information that should assist in the search for the pathogenesis of this and similar autoimmune uveitides.

References

1. Read RW, Holland GN, Rao NA, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. Am J Ophthalmol. 2001;131(5):647-52.
2. Yang P, Zhong Y, Du L, et al. Development and evaluation of diagnostic criteria for Vogt-Koyanagi-Harada disease. JAMA Ophthalmol. 2018;136(9):1025-31.
3. Kobayashi H, Kokubo T, Takahashi M, et al. Tyrosinase epitope recognized by an HLA-DR-restricted T-cell line from a Vogt-Koyanagi-Harada disease patient. Immunogenetics. 1998;47(5):398-403.
4. Shu Q, Yang P, Hou S, et al. Interleukin-17 gene polymorphism is associated with Vogt-Koyanagi-Harada syndrome but not with Behcet's disease in a Chinese Han population. Hum Immunol. 2010;71(10):988-91.
5. Levinson RD, Okada AA, Ashouri E, Keino H, Rajalingam R. Killer cell immunoglobulin-like receptor gene-cluster 3DS1-2DL5-2DS1-2DS5 predisposes susceptibility to Vogt-Koyanagi-Harada syndrome in Japanese individuals. Hum Immunol. 2010;71(2):192-4.
6. Sheereen A, Gaafar A, Iqneibi A, et al. A study of KIR genes and HLA-C in Vogt-Koyanagi-Harada disease in Saudi Arabia. Mol Vis. 2011;17:3523-8.