โรคยูเวียอักเสบที่สัมพันธ์กับ Human leukocyte antigen ในประชากรไทย: ทบทวนโดยย่อ

Human leukocyte antigen-associated uveitis in Thai population: Brief review

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Abstract

Human Leukocyte Antigen (HLA) has been associated with several immune-mediated diseases, malignancies and infectious diseases. Due to the HLA complexity and polymorphisms, several types of HLA have been used as the molecular markers in diagnosis. Among different ethnic groups, HLA is genetically diverse resulting in the differences of disease susceptibility. The study of HLA in Thai population will help an understanding of diseases pathogenesis and the genetic linkage leading to the development of genetic markers that are specific to Thai population. Vogt-Koyanagi-Harada (VKH) syndrome, HLA-B27-associated acute anterior uveitis (AAU) and Behçet's disease (BD) were found to be the major causes of non-infectious and autoimmune-related uveitis in Thai patients. Several etiologic studies in Western, European and other Asian populations reported the strong association between HLA-DR4 and VKH, HLA-B27 and AAU as well as HLA-B51 and BD. However, few in HLA-B27 and none in HLA-B51 and HLA-DR4 related uveitis study have been reported in Thailand. This briefly review discusses the association of HLA and non-infectious uveitis among populations and future research aspects for Thai populations.
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Keywords: Human leukocyte antigen, HLA, uveitis, disease association

บทคัดย่อ

Human leukocyte antigen (HLA) เป็นแอนติเจนในคนที่พบว่ามีความสัมพันธ์กับโรคที่เกี่ยวข้องกับระบบภูมิคุ้มกัน โรคมะเร็ง และโรคติดเชื้อหลายโรค เนื่องจากระบบ HLA เป็นระบบที่มีความซับซ้อนและมีความหลากหลายมาก HLA หลายชนิดจึงมีประโยชน์ในการใช้เป็นเครื่องหมายโมเลกุลในการวินิจฉัยโรค ในประชากรที่มีเชื้อชาติแตกต่างกัน HLA มีความหลากหลายมากในระดับพันธุกรรม จึงเป็นผลให้ความไวต่อการเกิดโรคในแต่ละบุคคลแตกต่างกันไปด้วย การศึกษาชนิดของ HLA ในประชากรไทยจะช่วยให้เกิดความเข้าใจในพยาธิกำเนิดของโรคและความเชื่อมโยงทางพันธุกรรม เพื่อค้นหาเครื่องหมายทางพันธุกรรมที่จำเพาะกับประชากรไทยต่อไปในอนาคต สำหรับโรคยูเวียอักเสบที่มีสาเหตุจากการไม่ติดเชื้อและโรคภูมิต้านตนเองในผู้ป่วยชาวไทยมีสาเหตุหลักมาจากโรค Vogt-Koyanagi-Harada (VKH) syndrome, HLA-B27-associated acute anterior uveitis (AAU) และ Behçet's disease (BD) จากการศึกษาเพื่อหาสาเหตุของโรคในประชากรของประเทศแถบตะวันตก ยุโรป และเอเชียอื่นๆ พบว่า HLA-DR4, HLA-B27 และ HLA-B51 มีความสัมพันธ์กับ VKH syndrome, AAU และ BD ตามลำดับ อย่างไรก็ตาม ในประเทศไทยยังมีการศึกษาถึงความสัมพันธ์ของ HLA และโรคทั้งสามนี้น้อยมาก ในบทความนี้กล่าวถึงความสัมพันธ์ระหว่าง HLA และโรคยูเวียอักเสบที่ไม่มีสาเหตุมาจากการติดเชื้อที่ศึกษาในประชากรเชื้อชาติต่างๆ และหามุมมองสำหรับงานวิจัยในอนาคตสำหรับประชากรไทย

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คำหัส : Human leukocyte antigen, HLA, โรคยูเวียอักเสบ ความสัมพันธ์กับโรค

Introduction

Over the past forty years, several human leukocyte antigens (HLA) have been identified as HLA-associated diseases involving in disease susceptibility and being the diagnostic markers. These associations found in immune-mediated diseases, malignancies and infectious diseases. The most well-known and classic HLA antigen is HLA-B27 associated with ankylosing spondylitis.[1] The advance technologies in genetics and molecular biology together with the successful of the human genome project lead to the understanding of HLA polymorphisms and found several HLA alleles associated with a number of human diseases. For example, HLA-DQA1*0501/DQB1*0201 encoded HLA-DQ2 antigen and HLA-DQA1*03/DQB1*0302 encoded HLA-DQ8 antigen are strongly associated with coeliac disease,[2] HLA-DRB1 alleles associated 30-50% with rheumatoid arthritis,[3] HLA-DPA1 and HLA-DPB1 alleles associated with chronic hepatitis B virus infection,[4] HLA-DRB1*1602-DQA1*0102-DQB1*0502 associated with Graves'disease[5] and HLA DQB1*0602 associated with narcolepsy, a lifelong sleep disorder.[6-8] The studies of HLA disease association vary widely among different ethnic group; however, it is still unclear regarding to the actual mechanisms of HLA in the disease development and still requires the larger case-control studies in diverse populations.[9] The person who carries particular HLA antigen or allele associated to one disease may not suffer with the disease; nevertheless, the patients who suffer with their disease usually have such specific HLA antigen or allele. Therefore, identification of specific HLA alleles and antigens associated diseases is beneficial for understanding the disease immunopathogenesis supporting the proposed theory of HLA markers for disease diagnosis.

Since there are several emblematic HLA-ssociated diseases reported with a particular HLA haplotype and/or alleles, we will focus on HLA associated with only one disease, uveitis, a major cause of visual impairment and blindness accounting for 45 million people worldwide in which one third are Asian. In Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand, almost 500 patients each year suffer from uveitis. 60% of patients were non-infection and/or autoimmune-related diseases and about 19% of patients were undetermined etiology.[10] This review aims to discuss the association between HLA-related genetic linkage and these three causes of uveitis, non-infection, autoimmune diseases and unidentified cause.

Pathogenesis and causes of uveitis

Uveitis is the major cause of blindness. The inflammation can occur at uvea, including iris, ciliary body, choroid, vitreous, optic nerve and/or retina. It can be divided into 4 classes based on anatomical classification including anterior, intermediate, posterior and panuveitis. Anterior uveitis (Figure 1) occurs in anterior chamber resulting in iritis, iridocyclitis or anterior cyclitis. Intermediate uveitis occurs in vitreous and/or par plana leading to pars planitis, posterior cyclitis or hyalitis. Posterior uveitis occurs in retina or choroid, whilst, panuveitis occurs in all site.

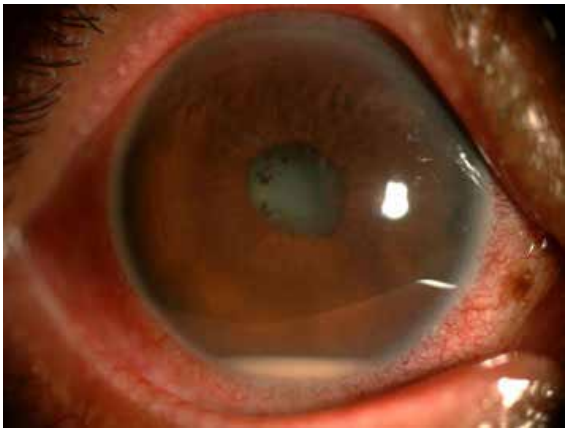

Figure 1. *Anterior photography of acute-anterior uveitis presented with ciliary injection, anterior chamber cells, hypopyon and posterior synechia*

To identify the cause of uveitis, medical history, ophthalmic and physical examination together with laboratory tests are needed for the accurate treatment. Misdiagnosis might lead to the harmful treatment resulting in worse disease development. The causes of uveitis can be infection, autoimmune-related diseases, eyes trauma, malignancy and unidentified factors. The major causes of non-infectious uveitis in Thailand was reported in Pathanapitoon *et al*. (2008) including HLA-B27-associated acute anterior uveitis (AAU)(7%), Behçet's disease (5.8%) and Vogt-Koyanagi-Harada (VKH) syndrome (16%) which differ from the West and other Asian populations.[10] Non-infectious uveitis is a matter of interesting with HLA association including HLA-DR4 can be associated with Vogt-Koyanagi-Harada (VKH) syndrome (Figure 2), HLA-B27-associated with acute anterior uveitis (AAU) and HLA-B51-associated with Behçet's disease.

The genetic risk has been concerned since the period of nineteen centuries when the massive migration of Chinese into Thailand was noticed.[11] Intermarriage of different ethnic groups between Asian-Asian and Asian-Western or European has been widespread which affects the transfer of genetic information among populations. New genetic marker for certain disease susceptibility is a matter of concern and can vary among ethnic groups due to the population movement.

Association between HLA and non-infectious uveitis and its study in Thailand

HLA-B27, HLA-B51 and HLA-DR4 can be found in Thai population with the frequency of 4.4%, 2.5% and 4.6% (DRB1*0405), respectively.[11] However, the gene frequency of first two HLA in Northern Thais is higher (6% and 4.9%, respectively),[12] whilst, those of HLA-DRB1*0405 is lower with the frequency of 3.3%.[11]

HLA-B27-associated acute anterior uveitis (AAU)

The first study of HLA-B27-associated AAU in Northern Thailand was described in 2006.[13] About 43% of patients with AAU presented HLA-B27-positive similar to the findings in the West. This HLA allele showed a strong association with AAU and tended to have more disease recurrences. The prevalence of HLA-B27-associated AAU differ among the ethnic groups such as 97.5% in Chinese,[14] 77.7% in French study,[15] 50% in British study,[16] 40% in Turkish[17] and 15.9% in Switzerland.[18] Differences in the severity of uveitis and the prevalence of HLA-B27-associated AAU might be influenced by the genetic factors.

Fifteen percent of HLA-B27-associated AAU Thai patients had ankylosing spondylitis (AS).[13] Previous studies in Korean and Turkish demonstrated that HLA-B27-associated AAU had more developed hypopyon, fibrin in anterior chamber and more association with spondyloarthropathy than HLA-B27-negative AAU.[17,19] Almost half of AAU Thai patients were HLA-B27-negative and the cause remains unknown.[13]

HLA-B27 subtypes or other HLA alleles might be related to these patients and should be further investigated.

Approximately 62 subtypes of HLA-B27 with different protein translation were identified, but not all subtypes are disease-related.[20] The most widely distributed disease-associated subtypes worldwide is HLA-B*2705, whilst, HLA-B*2702 and HLA-B*2704 are common in Mediterranean Caucasian populations and Asian populations, respectively.[20] HLA-B*2704 showed strong association with AS in Chinese,[21,22] Japanese,[23] Taiwan[24] and Thai.[25]

HLA-B51-associated Behçet's disease

Behçet's disease (BD) is a systemic vasculitis resulting in oral ulcers, genital ulcers, skin, ocular lesions and gastrointestinal and neurological systems involvement. It occurs predominantly in Asian, Middle Eastern and Mediterranean populations with 10 times higher in prevalence than in European and Amerindian populations.[26] Uveitis is the most common ocular complication of BD. The most common type of involvement in patients with Behçet's uveitis (BU) is posterior or panuveitis (Figure 2 and 3). In Thai patients, BD is one of the major causes of retinal vasculitis[27] (Figure 3). The cause of BD is unknown but genetic factor might play a role in the pathogenesis.[26]

Figure 2. *Anterior segment photography demonstrated acute anterior uveitis with hypopyon in Behçet's uveitis*

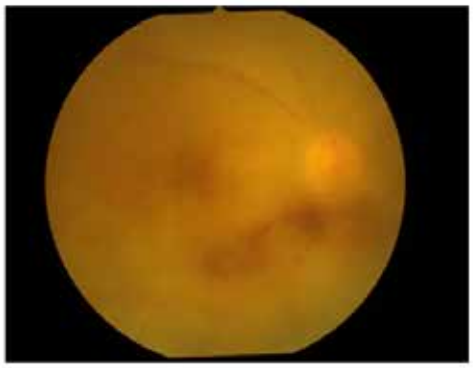

Figure 3. *Fundus photography of right eye shows retinal vasculitis in Behçet's uveitis*

HLA-B5 is a strong genetic involvement with BD which specifically links to the predominant sub-allele HLA-B51.[28] Since BD is commonly found in Asians including Chinese, Korean and Japanese,[29-31] HLA-B5/B51 might be also the risk factor for BD or BU in Thais. Until now, there was no report regarding to the prevalence of HLA-B5/B51 in Thai patients with BU.

Although Amerindian peoples have high prevalence of HLA-B51, no cases of BD have been reported.[26] Therefore, the presence of HLA-B51 in the western population does not correlate to BD susceptibility and might be specific only to Asian populations.

HLA-DR4-associated Vogt-Koyanagi-Harada (VKH) syndrome

Vogt-Koyanagi-Harada (VKH) disease is a multi-systemic autoimmune disorder with granulomatous panuveitis, serious retinal detachment (Figure 4), skin, auditory and central nervous system involvement. VKH syndrome commonly occurs in various ethnic groups worldwide including Asian, Middle Eastern, Hispanic and Native American population but rarely in Caucasian. In Thailand, women patients were found dominantly with 48% of retinal detachment.[32-34] Previous genetic studies revealed that several HLA have been linked with VKH syndrome including HLA-DR4, HLA-DR53 and HLA-DQ4 with strongest associated risk for HLA-DRB1*0405 and DRB1*0410 haplotype.[35,36]

The strong association between HLA alleles and VKH syndrome is different among races. However, there was no report about HLA-linked VKH syndrome in Thailand. For Asian populations, only the studies in Japanese, Chinese and Vietnamese have been published. HLA-DR4, HLA-DR53 and HLA-DQ4 are strongly associated with VKH syndrome in Japanese,[37] whilst, HLA-DR4, HLA-DR53 and HLA-DQ7 are found in Chinese patients.[38] Likewise, HLA-DR4 presents 75% frequency with DRB1*0405 allele expression in Vietnamese patients.[39] All these reports suggest that HLA-DR locus could be the primary susceptibility genes for VKH pathogenesis.

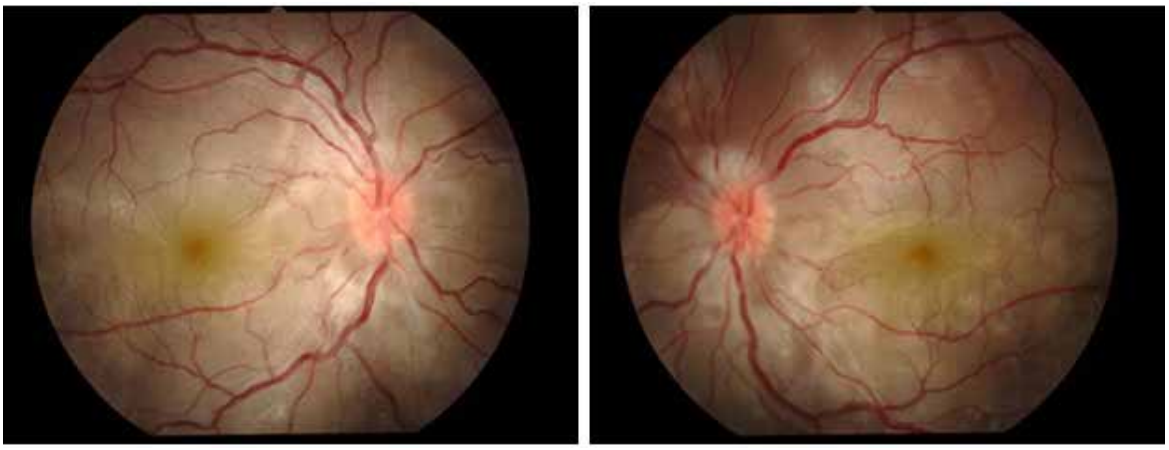

Figure 4 *Fundus photography shows bilateral serous retinal detachment in Vogt-Koyanagi-Harada disease*

Other susceptibility genes with uveitis symptoms

Several other genes including other HLA class I, class II and genes outside HLA locus might be also associated with uveitis. Other HLA class I genes are HLA-A2 and HLA-B58. HLA-A2 was found in Japanese psoriatic arthritis patients with uveitis but its strong correlation remains uncertain.[40] In inflammatory bowel disease (IBD)-associated uveitis, HLA-B58 was reported to be the susceptibility gene.[41] The roles of these two HLA genes in disease pathogenesis are still to be clarified.

Other HLA class II genes might also affect uveitis. HLA-DRB1*08 was reported to be associated with acute anterior uveitis (AAU) in Japanese, Norwegian and Mexican Mestizo patients with AS.[42-44] But the specific role of HLA-DRB1*08 in AAU remain unclear. In Caucasian studies, HLA-DRB1 *0801/DQA1*0401/DQB1*0402 was associated with AAU.45 Another allele, HLA-DRB1*0802 was revealed in Mestizo pars planitis patients.[46] Besides HLA-B58, HLA-DRB1*0103 might be also related to IBD-associated uveitis. However, this HLA subtype has not been found to be associated with other uveitis entity.[41]

For other genes located within HLA locus, MHC class I polypeptide-related sequence A (MICA) located near HLA-B locus was strongly associated with BD. A study of triplet repeat (GCT/AGC) in the transmembrane region of MICA gene demonstrated that MICA*A6 allele showed the strong association in Korean patients,[47] while, MICA009 was reported in Japanese patients[30] (Mizuki et al., 1999). Another gene cluster implicated AAU is low-molecular weight polypeptide 2 (LMP2 or PSMB9) with LMP7, TAP1 and TAP2 reported in SNP studies which not all provided the positive results. Therefore, the mechanism of these genes remains to be clarified.[48]

From genome-wide association studies (GWAS) and SNP studies, several uveitis-susceptible genes were reported outside the HLA locus. Multiple RNA transcripts, multiple protein genes and autoantibodies have been revealed the potential of uveitis susceptibility and might be the novel target for pharmaceutical drugs. The examples of significant genes linked to AAU and non-infectious uveitis include Killer Immunoglobulin Receptor (KIR) genes, genes of

cytokines such as IL-1 cluster, IL-10, TNF, TNFR1 and IL23R, ANTXR2, CARD9, ERAP1, TRADD, STAT3, two intergenic regions on chromosome 2p15 and 21q22 and a region on chromosome 9p.[48,49] However, very few genetic studies in this field have been performed in Thailand.

Conclusion

This review briefly explains the previous studies related to the association of HLA, other genes and the actual causes of uveitis among populations. Non-infectious, autoimmune related uveitis and undetermined patients are of interesting to investigate whether genetic factors are linked or not. Although several etiologic reports presented the strong association between HLA-DR4 and Vogt-Koyanagi-Harada (VKH) syndrome, HLA-B27 and acute anterior uveitis (AAU) as well as HLA-B51 and Behçet's disease (BD) in Western, European and Asian populations, few have been reported in Thailand. Therefore, the study of more HLA alleles and other genes related to uveitis together with gene frequency in uveitis Thai patients is very interesting for further investigation. This will benefit the physicians for disease prognosis and diagnosis in the earlier stage of disease to provide the effective treatments and can be used as a genetic marker for uveitis susceptibility in Thai population.

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