Published in final edited form as:

Ocul Immunol Inflamm. 2011 April ; 19(2): 108–114. doi:10.3109/09273948.2011.559302.

An update on the genetics of HLA-B27 associated acute anterior uveitis

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Abstract

The discovery of the association of HLA B27 with spondyloarthropathy led to more questions than answers about the role of this gene in disease susceptibility. The realization that HLA B27 was not responsible for all of the genetic effect helped to lay a foundation for further investigation into the genetics of uveitis. Over several decades, genetic findings have provided clues to advance the understanding of mechanisms of uveitis and to catalyze new research on diagnostics, animal models and therapies. From the early candidate gene studies on immune mediators to the recent genome-wide investigations, much has been discovered. However, these discoveries have come with the caveat that a genetic finding does not automatically reveal the disease-relevant functional effect of the associated variant.

Introduction

The major histocompatibility complex (MHC) type I allele, HLA B27 was first recognized as a risk factor for acute anterior uveitis (AAU) in 1973,¹ shortly after HLA B27 had been discovered as a risk factor for ankylosing spondylitis (AS) and reactive arthritis.^{2–6} In the initial report, 50% of subjects in a British study with anterior uveitis were found to be HLA B27 positive.¹ The predominant clinical phenotype associated with HLA B27 is a sudden onset, unilateral, anterior uveitis that tends to be recurrent with these recurrences sometimes affecting the contralateral eye. If one narrows the spectrum of anterior uveitis to this phenotype, many more than 50% of such individuals will be HLA B27 positive. In Europe and North America, anterior uveitis is roughly four times as common as intermediate or posterior uveitis.⁷ Thus uveitis associated with HLA B27 is the most common form of uveitis on these continents.

Although estimates vary, the majority of individuals with HLA B27-associated uveitis have an associated spondyloarthropathy.^{8–10} The prototypical disease is ankylosing spondylitis, a disease which includes bilateral inflammation of the sacroiliac joints and variable inflammation elsewhere in the axial skeleton or in peripheral joints. Subclinical bowel involvement and cardiac disease are additional frequent findings in patients with ankylosing spondylitis. The joint disease is most commonly recognized in males, although women with AS are being increasingly diagnosed. Other forms of spondyloarthropathy include reactive arthritis (formerly called Reiter's syndrome), arthritis associated with inflammatory bowel disease, psoriatic arthritis, undifferentiated spondyloarthropathy, or juvenile forms of these diseases. HLA B27 does not affect the likelihood of developing peripheral arthritis in association with either psoriatic arthritis or inflammatory bowel disease (IBD). HLA B27 only affects the risk of developing spinal disease in patients with either psoriasis or IBD. While roughly 40 to 50% of patients with either psoriasis or Crohn's disease and sacroiliitis are HLA B27 positive, approximately 90% of patients with ankylosing spondylitis are HLA B27 positive. The classification criteria to recognize ankylosing spondylitis have recently been revised.¹¹

Although HLA B27 greatly increases the likelihood that an individual will develop spondyloarthritis and/or uveitis, it is also clear that the majority of individuals who are HLA B27 positive never develop either spinal inflammation or anterior uveitis. Accordingly there must be other genetic or environmental factors that contribute to the development of these diseases. Environmental factors include bacteria such as *Salmonella* and *Shigella* which are known to trigger reactive arthritis. Based on observations in rats which are transgenic to express both HLA B27 and human beta two microglobulin, normal bowel flora must also contribute to risk.¹² Genetic factors in addition to HLA B27 are being rapidly described for diseases that include ankylosing spondylitis, psoriasis, and Crohn's disease. These studies have revealed common genetic factors that help explain the clinical overlap among these entities. But the studies also identify genetic factors which appear to be specific for distinct clinical entities. Such genetic factors could account for observations such as a frequent family history for IBD among patients with anterior uveitis or a tendency for family members to "breed true" for reactive arthritis in some cases or AS in others. This review addresses the genetic factors, including genes other than HLA B27, which might predispose to developing uveitis.

HLA B27

HLA B27 is distributed throughout the world with the prevalence of spondyloarthritis correlating with the frequency of HLA B27 in the population.¹³ For example, HLA B27 is rare in Africa and spondyloarthritis is rare on that continent. HLA B27 is extremely common in the Haida Pacific Northwest Indian tribe and AS is correspondingly common. HLA B27 was initially typed using serological methods. More recent typing methods have appreciated that serology does not distinguish many subsets of HLA B27 that can be defined by DNA sequencing. This molecular typing allows the recognition of more than 60 subtypes of HLA B27.¹³ The most common subtype is designated HLA B2705. All common subtypes are associated with predisposition to AS with the exceptions of B2706 which is common in Sardinia and B2709.¹⁴

The evidence for a gene dosage effect has been somewhat controversial. Several studies have not found an increased risk associated with HLA B27 homozygosity, but a well designed Finnish study found that HLA B27 homozygotes were slightly more common among patients with AS than one would expect from chance alone.¹⁵ Surprisingly, those patients who were homozygous for HLA B27 tended to have disease that was more mild than those patients who had only a single copy of the allele. A few studies have compared patients with HLA B27 negative acute anterior uveitis with HLA B27 positive acute anterior uveitis.^{16–18} Patients with acute anterior uveitis who are HLA B27 positive are more likely to develop hypopyon, have fibrin in the anterior chamber, and on average have more cells in the anterior chamber. The HLA B27 positive patients tend to be male, tend to have more recurrences, more posterior synechiae, and of course more association with spondyloarthritis. The general prognosis is similarly good for both HLA B27 positive and B27 negative patients. Similar studies have been done to compare patients with AS who are B27 positive or negative.

Other classical HLA genes

HLA B27 is the only class I MHC gene with an association to AAU, and this finding has been reproduced in many populations. Within the spectrum of spondyloarthritis-related uveitis, one study does report a possible role for HLA A2 in uveitis susceptibility among Japanese psoriatic arthritis patients.¹⁹ However, HLA A2 has also been shown to be associated with psoriatic arthritis itself in the Japanese patient population. Thus, it is difficult to determine whether HLA A2 is a uveitis susceptibility gene or not, especially considering

the rarity of uveitis among Japanese patients with psoriasis. Another class I MHC gene, HLA B58, has been reported with IBD-associated uveitis (in comparison to IBD patients without uveitis).²⁰ For both of these class I MHC gene findings for spondyloarthropathy-related uveitis, associations with additional cohorts are needed to fully understand the role of these other class I MHC genes.

In addition to class I MHC molecules, class II genes might influence AAU. One such possible gene is HLA DRB1*08. The class II HLA DR8 serotype was found to be associated with the presence of AAU in a cohort of Japanese subjects with AS.²¹ Another group examined Norwegian AS patients and found an association between HLA DRB1*08 and early onset of AS²². However, a specific role for HLA DRB1*08 in AAU was not described in the Norwegian cohort. Additional studies to explore the role of HLA DRB1*08 provided some evidence for association with AS disease in Mexican Mestizo²³ and among HLA B27-negative AS cases²⁴, while, no support for an association with AAU was observed in these studies. However, using molecular typing methods, the HLA haplotype DRB1*0801/DQA1*0401/DQB1*0402 was found to be associated with a Caucasian AAU cohort.²⁵ Interestingly, AAU is not the only uveitis phenotype for which some evidence of DRB1*08 association has been reported. A cohort of Mestizo pars planitis patients revealed an association with DRB1*0802.²⁶ Furthermore, a recent study examining HLA in patients with bilateral anterior uveitis manifestations similar to those seen in tubulointerstitial nephritis and uveitis (TINU) syndrome, but who have not developed renal inflammation, detected an association of uveitis with DRB1*08.²⁷

One other HLA class II gene, DRB1*0103, has been implicated in spondyloarthropathy-related, IBD-associated uveitis (the same UK cohort mentioned above reporting an HLA B58 association).²⁰ While there are several studies implicating DR1 in other uveitis phenotypes (for example, Behçet's disease, TINU, and VKH), the more common subtypes of DRB1*0101 and DRB1*0102 are responsible for these associations.^{28–34} The particular IBD-associated uveitis subtype (DRB1*0103) has not been found to be associated with other uveitic diseases.

Candidate genes located within the MHC locus

The majority of genetic studies on AAU susceptibility have been designed as candidate gene studies, whereby the gene of interest was chosen based on biological plausibility or known association with another related disease phenotype. Some of these genes also reside in the MHC gene region on chromosome 6, but are not classical HLA molecules. One such gene, MHC class I polypeptide-related sequence A (MICA), resides near the HLA B genetic locus and was strongly implicated in Behçet's disease. We now understand that MICA is in strong linkage disequilibrium with HLA B51, the major genetic factor in that disease.^{35, 36} Interestingly, there are two studies which demonstrated an AAU association with the A4 allele (a triple repeat polymorphism located in the transmembrane domain of the protein) of MICA: one was conducted with a Japanese AAU cohort and the other utilized data from Caucasian AAU patients.^{37, 38} The A4 allele is not the same polymorphism implicated in Behçet's disease. Furthermore, to complicate matters, MICA is also in linkage with HLA B27 and its role in AS is secondary to HLA B27.³⁹ Nevertheless, it was shown in that not all of the observed association with MICA A4 in the AAU studies was due to linkage with HLA B27 since the finding was also noted in HLA B27 negative patients.³⁷ MICA expression is upregulated under cellular stress and is found on many tumors. It is known to bind the C-type lectin family member, NKG2D, a natural killer (NK) cell receptor important in tumor surveillance, but which may also have a role in immunosuppression⁴⁰. Its specific role in uveitis is not understood.

Another gene found at the MHC locus which has been implicated in AAU is low-molecular weight polypeptide 2 (LMP2, official gene symbol PSMB9). LMP2, along with LMP7, TAP1 and TAP2 are found in a gene cluster within the MHC class II region on the chromosome. Several studies published in the 1990s demonstrated an association with AAU in AS cohorts, although not all studies were positive.^{22, 41–46} These investigations focused on a SNP (rs17587) encoding the Arg60His amino acid substitution in LMP2. Although the LMP2 protein is an integral component of the immunoproteasome machinery in cells, it is unclear if this mutation alters processing of peptides for antigenic presentation. Furthermore, polymorphisms of other proteasome components, namely TAP1 and TAP2, have been examined in a Japanese cohort, but without any demonstration of association with AAU.⁴⁷ Thus, the molecular mechanism of a possible role for genetic alteration of proteasome function in AAU remains to be determined.

TNF α is a pivotal cytokine in immune responses and thus has been extensively studied in inflammatory diseases. It is also located within the MHC locus. Several common polymorphisms in the TNF promoter region have been implicated in disease susceptibility. The uveitic disease most investigated for TNF variants is Behçet's disease. Although several studies have demonstrated an association, several studies have not produced a positive result in Behçet's cohorts and a recent meta-analysis validated association with three promoter region SNPs.⁴⁸ Furthermore, there does appear to be a role for TNF in the genetic predisposition to AAU, as evidenced by at least in two Caucasian cohorts.^{49, 50} Moreover, a study of chronic or recurrent anterior uveitis patients demonstrated a statistical difference in the TNF –308 polymorphism (rs1800629) when comparing HLA B27 positive versus HLA B27 negative subjects.⁵¹ Given the wide use of biologic TNF inhibitors in various uveitis patients and the possibility of these therapies exacerbating inflammation in specific situations, the role of TNF in genetic predisposition and the molecular mechanisms involved in disease pathogenesis is of considerable interest.

Susceptibility genes encoded outside the MHC locus

Killer Immunoglobulin Receptor (KIR) genes are located on chromosome 19q, in a region known as the leukocyte receptor cluster. Nomenclature of these genes is based on their protein structure, and the repertoire of these genes between individuals varies in the type and number present. KIRs are expressed on NK cells and some T cell subsets and they bind to HLA class I proteins. The resultant cell-cell interactions mediated by various KIR-HLA combinations may be either inhibitory or activating for the KIR-expressing cell. Specific KIR genes have been found to be involved in disease susceptibility of several infectious and inflammatory diseases.⁵² Regarding uveitic diseases, KIR associations have been reported for birdshot chorioretinopathy, VKH, Behçet's (although with mixed results), and AAU.^{53–59} The AAU study found evidence for KIR-HLA combinations which could favor weaker inhibition.⁵⁴ Moreover, several studies have reported association with KIR genes in AS cohorts, albeit with inconsistent findings.^{60–68}

In addition to TNF, other cytokines are viable candidate genes in any inflammatory disease and it is not surprising to find associations with susceptibility. There are numerous studies examining polymorphisms of major inflammatory cytokines in various diseases, but a paucity of reports which focus on AAU. Atan, et al. surveyed several cytokines in noninfectious uveitis subjects and noted significant associations with IL-10 and TNF haplotype tagging SNPs.⁶⁹ However, this cohort was devoid of AAU cases. IL-10 variants have also been implicated in Behçet's disease, VKH, sympathetic ophthalmia and idiopathic forms of uveitis, but not in all cohorts studied.^{69–74} With respect to AS susceptibility, several cytokines have been implicated in various studies, including genes of the IL-1 cluster, TNFR1, and IL23R.^{75, 76}

The discovery that IL23R plays a role in ankylosing spondylitis susceptibility strongly implicates the Th17 cellular responses in disease pathogenesis. This genetic finding was discovered with genome-wide association studies (GWAS) and has been investigated further in several cohorts.^{77–79} IL23R was first implicated in IBD and is now also known to contribute to psoriasis and psoriatic arthritis.^{80–83} With regard to uveitis, an association with several IL23R SNPs has been demonstrated, a finding which was not diminished when the cohort was stratified to examine only those AAU subjects with no known axial spondylitis symptoms.⁸⁴ More recently, both the IL-10 and IL23R genes have been implicated in Behçet's disease as well.^{85–87}

Early GWAS studies on AS were performed using microsatellite markers and demonstrated disease association with several loci outside the MHC.^{88–90} Recently, GWAS studies using SNP markers and large cohorts of AS subjects have been completed.^{77, 78} In addition to IL23R and TNFR1, studies have identified or confirmed associations with several genes, including ANTXR2, CARD9, ERAP1, IL1R2, KIR genes, TNFSF15, TRADD, STAT3 and two intergenic regions on chromosome 2p15 and 21q22.^{75, 91} These findings have generated new insights into the pathogenesis of AS. For most of these genes, it is still an unanswered question as to whether they also contribute to uveitis susceptibility in the context of HLA B27-associated disease. The first GWAS study of AAU was able to demonstrate the feasibility of detecting AS-specific, AAU-specific and overlapping genetic associations.⁹² This study (performed with microsatellite markers) identified a region on chromosome 9p with significant linkage to AAU, but without a strong signal for AS. A more recent GWAS for AAU performed with SNPs has been reported and among the findings is a new uveitis gene, cub and sushi multiple domain 2 (CSMD2).⁹³ This gene has not been extensively studied and its role in uveitis is unknown. It is a very large protein, with a large extracellular domain, a single transmembrane domain and a short cytoplasmic tail. Expression is reported to be primarily on neuronal tissues, such as brain (and of interest to the anterior eye, ciliary ganglia). Confirmatory studies will be needed to validate this finding.

Perspectives

GWAS in ankylosing spondylitis and other complex, immune mediated diseases have been both revealing and simultaneously disappointing. Those who celebrate the success of the GWAS approach often cite macular degeneration where the implication of complement regulation has unquestionably stimulated interest in complement within the eye and has led to innovative clinical trials based on efforts to inhibit complement activation within the eye. GWAS have certainly helped establish the concept of common genes predisposing to immune dysregulation and unique genes helping to distinguish syndromes such as psoriasis versus Crohn's disease. Critics of the GWAS approach point to the expense and labor involved. These critics note the vast majority of implicated genes contribute only minimally to the odds ratio for developing a disease. For example, ERAP1 polymorphisms increase the relative risk for developing AS only slightly and much, much less than the effect of HLA B27. Finally, GWAS have often only confirmed what had been suspected through other modalities. Complement deposition had been implicated in macular degeneration before GWAS were undertaken.

Implicating a gene by either a GWAS or by testing a specific target does not indicate a functional change. For example, findings that polymorphisms in the IL-23 receptor are associated with susceptibility to AS, Behçet's disease, or acute anterior uveitis does not reveal the functional consequence of the polymorphism. The IL-23 receptor is expressed on lymphocytes that synthesize the cytokine, IL-17 (Th17 cells) and this subset of helper T cells is implicated in diseases that include uveitis and Behçet's. So there is a presumption that the polymorphism results in an increased functional effect, but the direct proof for this

is minimal. Furthermore, different polymorphisms can be implicated for different disease or between different populations. A monoclonal antibody that inhibits IL-23 is now approved in the United States to treat psoriasis, although the clinical testing of this antibody began well before results were available from a GWAS or other genetic study to implicate IL-23.

In addition to the high throughput approach of a GWAS, the measurement of multiple RNA transcripts, multiple proteins, or multiple autoantibodies is another discovery approach that offers the potential to reveal unexpected disease pathways or novel pharmacologic targets. The ability to correlate an observation from a GWAS with a “downstream” read out such as a change in an mRNA level has been to date the exception rather than the rule. A recent success in this regard might be CARD9. This is an intracellular protein strongly implicated in the response to fungal infections. Dectin-1 is a receptor that recognizes fungal cell wall and signals through CARD9. Genetic abnormalities in CARD9 can result in chronic fungal infection.⁹⁴ CARD9 polymorphisms are linked to susceptibility to AS. A recent preliminary report shows that mice with a T cell abnormality that predisposes to inflammatory arthritis develop an AS like disease with spine, tendon, bowel, and uveal involvement after injection of fungal cell wall.⁹⁵ We lack data to show that anti-fungal therapy and/or inhibition of CARD9 would affect the course of AS.

The traditional approach of a grant review panel is to demand research that tests a hypothesis. The typical GWAS does not test a hypothesis. Rather, the hope is that the GWAS will generate discoveries to lead to new insights into disease pathogenesis. The example of complement and macular degeneration as cited above is arguably the greatest such success. Gene expression studies in systemic lupus erythematosus focused attention on alpha interferon as pathogenic factor and this in turn has stimulated clinical trials to treat SLE by inhibiting alpha interferon. The cynics counter that identification of a gene that increases the odds ratio to develop a disease by a factor of 1.2 to 1.5 is not likely to succeed as a target for pharmacotherapy. All research approaches have specific strengths and limitations, but the advances in molecular techniques will undoubtedly provide large stores of new data to ponder and debate.

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