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HLA and disease association

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Abstract The major histocompatibility complex (MHC) is a genetic system of over 70 known genes on the short arm of chromosome 6 and spans about 4 million base pairs of DNA. The high resolution typing of class I and class II MHC genes and the identification of other genes in the region have increased the definition of the genetic basis of immune responses and diseases of unknown etiology such as the autoimmune diseases. In this paper, I review the literature about HLA and migraine.

Key words HLA • Disease • Antigen • Migraine

Introduction

The human major histocompatibility complex (MHC) is also called the human leukocyte antigen (HLA) system. It was discovered by the observation that blood from multiparous women or from transfused persons contained antibodies which agglutinated leukocytes [1, 2]. The HLA complex of genes on the short arm of chromosome 6 (6p21.3) encodes proteins that are centrally involved in the actions of the human immune system. They play a fundamental role in donor-recipient matching in transplantations and can be associated with mostly autoimmune diseases [3].

Genetics

The MHC complex spans a region of about 4 million base pairs (equivalent to 0.1% of the human genome) and contains over 100 genes. The HLA genes are divided into classes I, II and III.

In the class I region, located telomerically, there are genes encoding the α chain of the classic class I antigens: HLA-A, -B and -C genes, and pseudogenes from HLA-E to HLA-L.

The centromeric class II genes, previously known as immune response genes, comprise those encoding HLA-DP, -DQ, -DR, -DM, and -DO molecules and a group of genes outside the MHC whose functions are related to antigen presentation: large multifunctional protease (LMP) and transporter associated with antigen processing (TAP) genes.

The HLA class III region contains many genes with varying functions. It lies between the class I and class II genes and includes 21α- and 21β-hydroxylase genes, genes for the complement proteins C4A, C4B, C2 and factor B, and also genes for tumor necrosis factor (TNF) and heat shock protein 70 (HSP70) [4, 5].

Crossing-over within the HLA region of chromosome 6 is relatively rare. We inherit *en bloc* one of maternal chromosomes 6 and one of paternal chromosomes 6. The HLA allele combination on chromosome 6 is called "haplotype".

Polymorphism

The HLA genes are the most polymorphic genes known. HLA-A has over 40 known alleles, and more are being discovered and sequenced all the time. The human HLA-B locus contains to date more than 250 discovered alleles. There are a number of genetic characteristics of HLA antigens: the polymorphism at the recognized HLA loci is extreme. As the role of HLA molecules is to present peptides from invasive organisms, it is likely that this extreme polymorphism has evolved as a mechanism for coping with all of the different peptides that are encountered.

However that is not all, as the polymorphism is population specific. The frequencies of HLA antigens in different populations are clearly different. For example, HLA-B8, which is present in 7% of Caucasoids, has a frequency of less than 2% in Asians, while in this population the frequency of DR9 is higher than in other populations. Thus, HLA antigens are of great significance in anthropological studies. Populations with similar HLA antigen frequencies are clearly derived from common stock. Conversely, from the point of view of transplantation it is difficult to match HLA types between populations.

One of the most conspicuous properties of HLA is that some alleles occur together more frequently than expected by chance. The non-random pairing of alleles is called linkage disequilibrium (LD). LD may extend over the whole HLA. For instance, the alleles A1, B8, TNFa2, DR3, DQ2, TAP2*0101 and DPB1*0101, which confer an increased risk for development of many autoimmune diseases, are known to often be inherited together in an "extended haplotype". The extended haplotypes may be evolutionary conserved and are often referred to as ancestral haplotypes [6]. It is difficult to determine which allele within an extended haplotype is the strongest associated with a disease.

Structure and function

Class I antigens are composed of two polypeptide chains: an α chain bound to the cellular membrane and a noncovalently associated β_2-microglobulin (β_2m). The alpha chain is a polymorphic 45 kilodalton (kDa) glycopeptide encoded by genes in the HLA region, while the β_2m is invariant and is encoded by a gene on chromosome 15, which plays an important role in the structural support of the heavy chain.

The HLA class I molecule is assembled inside the cell and ultimately sits on the cell surface with a section inserted into the lipid bilayer of the cell membrane and a short cytoplasmic tail.

The HLA class II molecule is a heterodimer composed of two transmembrane glycoproteins, alpha and beta chains, both polymorphic and encoded by MHC genes. Each class II antigen is the product of two different genes.

HLA class I antigens are expressed on the surface of most nucleated cells of the body. The tissue distribution of HLA class II antigens is confined to "immune competent" cells, including B lymphocytes, macrophages, endothelial cells and activated T lymphocytes, collectively called antigen presenting cells (APC). APC play a central role in specific immune responses against endogenous (viruses, parasites) as well as exogenous (bacteria) antigens.

The process of recognition of an antigen by T lymphocytes requires the association of the foreign antigen with MHC molecules in order to identify it as nonself and to initiate an immune response. The role of HLA class I molecules is to take the virally induced peptides to the surface of the cell and, by linking to the T cell receptor (TCR) of a cytotoxic $CD8^+$ T cell, form a trimolecular complex which triggers a cytotoxic immune response.

Exogenous antigens, internalized and degraded by APC into peptides, are associated with HLA class II molecules. Then, this complex is recognized by $CD4^+$ T cells to activate macrophages and B cells [4].

HLA typing is performed in different medical fields, for example matching in transplantation, disease association and forensic medicine.

Disease associations

The observation that some diseases are distinctly more common in individuals with a particular HLA allele or haplotype allowed studies on HLA and disease associations. There are several examples of these associations (Table 1). Some diseases, like insulin dependent diabetes mellitus (IDDM) or celiac disease, can be associated with more than one HLA allele. The strongest association is shown by ankylosing spondylitis: B27 antigens are present in nearly 90% of patients. Such diseases have unclear etiology, are generally matched with immunological changes, have familiar recurrence, and are supported by polygenic and environmental factors; their relation with HLA alleles identifies only one of the predisposing genetic factors [7, 8].

HLA-associated diseases can be divided according to their pathogenetic mechanisms into three groups (Table 2).

Table 1 HLA and disease associations

Disease	HLA antigens	Patients (%)	Controls (%)
Ankylosing spondylitis	B27	89	9
IDDM	DR3	52	22
	DR4	74	24
Rheumatoid arthritis	DR4	68	25
Celiac disease	DR3	79	22
	DR7	60	15
Multiple sclerosis	DR2	51	27
Narcolepsy	DQ6	> 95	33

IDDM, insulin dependent diabetes mellitus

Table 2 Some examples of HLA-associated diseases, divided according to their pathogenetic mechanism

Group	Disease
No autoimmune etiology	21-Hydroxylase deficiency Hemochromatosis
Autoimmune etiology	Ankylosing spondylitis Rheumatoid arthritis Celiac disease Insulin-dependent diabetes mellitus Multiple sclerosis
Unknown etiology	Narcolepsy

Studies of HLA and disease were begun when only the class I antigens were known. Thus, all the first associations discovered were with class I antigens. Subsequently, when the class II antigens were defined, many of these diseases were actually shown to have a stronger association with the class II antigens that are in linkage disequilibrium than with the previously associated class I antigens. The classic example is the assortment of diseases associated with the common northern European haplotype HLA-A1, Cw7, B8, DR3, DQ2. Diseases associated with this haplotype were first associated with HLA-B8 and later, more strongly with HLA-DR3 and DQ2.

Today, the majority of strong disease associations are with class II polymorphism; in this regard the strong association of ankylosing spondylitis and various other diseases with the class I antigens HLA-B27 stands out as being exceptional.

Relative risk is a measure of strength of association. Table 3 gives some examples of HLA-associated diseases, the relative risk being the chance of an individual with a particular allele to develop the disease compared with an individual lacking that allele.

Table 3 HLA and disease associations with their relative risks

Disease	HLA allele	Relative risk
IDDM	DR3	5
	DR4	6
	DR3/DR4	20
	DR2	0.25
Celiac disease	DR3	12
Narcolepsy	DQ6	24
Ankylosing spondylitis	B27	87

IDDM, insulin dependent diabetes mellitus

A question often asked of HLA and disease associations is whether the associated polymorphism is actually involved in the cause of disease or is just a marker for an undiscovered polymorphism in a linked gene. Until the mechanism causing the disease has been defined, this question cannot be answered. Thus, the ultimate goal of all studies on HLA-linked diseases is to determine the molecular and cellular basis for disease.

No situation has been identified where all individuals with a particular allele develop a disease, but some diseases have been identified in which most affected individuals have a particular HLA allele. Ankylosing spondylitis is strongly associated with HLA-B27, but the lifetime risk of a HLA-B27-positive individual developing it is only about 2%. This illustrates that in diseases with HLA associations, it is not the disease itself, but the predisposition to it that is inherited.

There are two general explanations for HLA and disease associations. First, there may be linkage disequilibrium between alleles at a particular disease-associated locus and the HLA allele associated with that disease. This is true for HLA-A3 and idiopathic hemochromatosis. Another possible explanation for these associations is that the HLA antigen itself plays a role in the disease, by one of the following models:

- Being a poor presenter of a certain viral or bacterial antigen
- Providing a binding site on the surface of the cell for a disease-provoking virus or bacterium
- Providing a transport piece for the virus which allows it to enter the cell
- Resembling the pathogenic molecule so that the immune system fails to recognize it as foreign and fails to mount an immune response against it.

Likely, all these mechanisms are involved, to a varying extent in different diseases. Whatever the explanation for the long list of HLA and disease associations, it is clear that the HLA system, collaborating with other non-linked genes,

has an influence on our response to environmental factors which provoke disease. In IDDM, more than 15 specific loci have been localized on different chromosomes, although the major genes are in the HLA region and are responsible only for 40% of the genetic predisposition.

The existence of HLA associations provides evidence, but not proof, that immune mechanisms are involved in the pathogenesis. In summary, a current view of HLA-associated disease is that the development of disease involves a genetic predisposition resulting from a combination of factors at HLA and other genes. Even among individuals who have a genetic predisposition, only a small minority becomes affected.

HLA alleles can also be negatively associated with disease, conferring protection. For example, class II allele DQB1*0602 confers almost complete protection from IDDM.

Decreased frequencies are much harder to detect than increased ones.

The HLA typing has diagnostic value only in doubtful cases of ankylosing spondylitis. In other HLA-associated diseases, HLA typing may identify individuals at risk of developing the same disease within a family before the clinical onset of disease.

HLA and migraine

Family and twin studies, derived from the observation of familial cases, provided conflicting results regarding the mode of inheritance [9,10]. In a large proband-oriented clinical study, first-degree family members of probands with migraine without aura had increased relative risk ratios, compared to the general population, for both migraine with aura ($\lambda = 1.4$) and migraine without aura ($\lambda = 1.9$). First-degree family members of probands with migraine with aura had a nearly four-fold increased risk ratio ($\lambda = 3.8$) for migraine with aura, but not for migraine without aura [11]. This suggests that genetic factors are involved in both types of migraine, but are strongest in migraine with aura.

The relative risk ratio for a sibling (λs), defined as the ratio of the prevalence of a disease in siblings of affected individuals divided by the prevalence of a disease in the population, can be calculated [12].

The first studies on HLA antigens in migraine were performed by Kudrow in 1978 [13] and O'Neill et al. in 1979 [14]. In a 1987 study of eight households, the distribution of migraine haplotypes shared by sib-pairs was greater than expected; it was hypothesized that migraine heredity was HLA linked [15]. To explain an association between HLA and non-immunologic disease (e.g. migraine), it has been hypothesized that HLA antigens interfere with the interaction between receptors and ligands on cell membranes [16].

Regarding the biological function of the HLA antigens, the observed decreased frequency of the DR2 antigen in migraine with aura patients suggests that the presence of DR2 means resistance to the disease. Because a relative risk lower than 1 is considered a sign of protection against disease, DR2 antigen or another gene of resistance in linkage disequilibrium with DR2 may be assumed to control the disease, the receptor expression at cellular level, or both [17].

The demonstration of a clear genomic difference between migraine with and without aura may provide an additional basis for the proposed difference within these two clinical entities [18], and it may represent another step in decifering the genetic basis of migraine [19]. To identify genes in the HLA region that are involved in migraine heredity, it will be useful to study polymorphisms of other genes located in the region.

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