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Review

Genetics of autoimmune myasthenia gravis: The multifaceted contribution of the HLA complex

Claire Vandiedonck, Matthieu Giraud, Henri-Jean Garchon*

Inserm U580, Université Paris Descartes, 161 rue de Sèvres, 75743 Paris Cedex 15, France

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Abstract

The HLA complex plays a prominent role in predisposition to many autoimmune diseases. Thus far, the highly polymorphic class I and class II loci have been considered as the prime candidates to explain this role. There is nonetheless growing evidence that other closely linked HLA loci are also involved in autoimmune susceptibility. Their search, however, has been hampered by the often strong linkage disequilibria, i.e. the non-random association of alleles at linked loci, across the HLA complex. Here, we discuss recent work from our laboratory on the dissection of this emblematic genetic region in a model autoimmune disease, acquired myasthenia gravis (MG).

Keywords: Myasthenia gravis; Genetics; HLA; Self-antigen; Autoantibody; Interaction

1. Autoimmune myasthenia gravis, a study model for antibody-mediated autoimmunity

Among the various autoimmune diseases currently subjected to genetic investigation, acquired generalized MG provides a remarkable model because the target of the autoimmune attack and the effector pathways are well identified [1–4]. This rare autoimmune disease (prevalence of 1×10^{-4} in Caucasians) is aimed at the neuromuscular junction and is clinically characterized by fatigability and weakness of striated muscles. It is potentially life threatening when respiratory muscles are affected. The symptoms are mediated by pathogenic autoantibodies directed against the nicotinic acetylcholine receptor (AChR), resulting in the postsynaptic blockade of the nerve transmission. These anti-AChR autoantibodies are absolutely specific of the disease and are detected in the majority (90%) of the patients [5].

Although patients share many characteristic clinical and biological features, MG is a heterogeneous disease [6]. The most remarkable factor of heterogeneity are anomalies of the thymus (in 50 to 70% of cases), the most frequent of which is thymus follicular hyperplasia (TFH) [7]. In these MG patients, the thymus does not undergo involution and is characterized by the presence of germinal centers. These germinal centers contain B cells producing autoantibodies. Patients with TFH are often grouped with those with an early onset of the disease and with a histologically normal thymus, defining the Early Onset Myasthenia Gravis (EOMG), as they share several features including the early age at onset (before 40 years), a marked sex bias (4:1 woman/man ratio), an absence of autoantibodies against titin and other striated muscles antigens [6,8]. Patients with TFH, however, show higher mean serum titers of anti-AChR autoantibodies than other, euthymic, EOMG patients [8].

Thus MG patients with TFH form a clinically homogeneous group that is better suited for a genetic analysis. Indeed, this form of MG has been reproducibly associated with particular alleles of HLA class I and class II loci [9,10]. Recently, using a family-based association design, we also established its genetic linkage to HLA, defining the MYAS1 locus [11].

* Corresponding author. Tel.: +33 1 4449 5367; fax: +33 1 4449 4100.
E-mail address: garchon@necker.fr (H.-J. Garchon).

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2. The HLA complex

The human leukocyte antigen (HLA) complex was discovered because of its central role in allograft rejection [12] and is now known to exert a major influence on most immune responses. Genome sequencing and interspecies comparative mapping have revealed that this large region of chromosome 6p21 extends over 7.8 Mbases and displays the highest density of genes of the human genome [13,14]. It is classically subdivided into three regions or classes (Fig. 1A). The class II region, on the centromeric side, and the class I region, on the telomeric side, are separated by class III loci and are flanked by the extended class I and class II regions. Genes of the class I, such as HLA-A and HLA-B, and those of the class II, such as DRB1, show several hundreds of alleles altogether and define the most polymorphic genetic system of the human species. They encode membrane-bound molecules of the immunoglobulin superfamily that present antigenic epitopes to lymphoid cells. Genes of the class III also encode proteins with essential immune functions, notably complement factors, heat shock proteins, tumor necrosis factor and lymphotoxins, receptors for natural killer cells, in addition to many newly discovered genes which are expressed in the immune system but whose function is not known yet.

A considerable number of studies have established an association of alleles of class I or class II HLA loci with inflammatory diseases and notably autoimmune diseases [15,16]. An exclusive role of these loci to explain HLA-linked predisposition to autoimmunity has nonetheless been questioned because extensive allelic associations occur across the HLA region [17]. Convincing evidence for additional loci contributing to disease susceptibility is now available [18–20] but to a large extent, these loci remain to be accurately mapped and identified.

3. The 8.1 ancestral HLA haplotype

The alleles involved in EOMG, including HLA-A1 and HLA-B8 for class I, and DRB1*03 (DR3) for class II, are tightly associated, together with those of many other linked loci, forming the most conserved HLA haplotype in Caucasians, also called the 8.1 ancestral haplotype (thus named by reference to the presence of the HLA-B8 allele) [17,21]. The 8.1 haplotype holds a special place in human immunogenetics also because it has been associated with a large number of autoimmune and immune-related diseases as well as with immune phenotypes such as cytokine production [22,23]. However, the 8.1 haplotype extends over 6 Mb, an unusually long distance, and thus strongly associates alleles of remote loci. Consequently, if a disease-predisposing allele is associated with the 8.1 haplotype, any marker with an 8.1-associated allele, even distantly situated relative to the actual disease locus, will be associated with the disease investigated, regardless of a causal relationship. This has certainly facilitated the discovery of HLA-disease associations. Conversely, the extension and the stability of the 8.1 haplotype become an obstacle at the stage of the fine mapping and the eventual identification of the disease loci.

Two previous studies, that had been conducted before the knowledge of the complete nucleotide sequence of HLA, indicated a stronger association of the disease locus with HLA-B than with DRB1 [24,25]. However, in both these studies, the relatively low density and informativity of the markers available at that time and the use of unphased genotypes prevented firm conclusions.

To overcome the difficulties arising from the strong LD on the 8.1 haplotype and to refine the location of the MYAS1 locus, we have conducted a family-based analysis of haplotype transmission [26]. In particular, we have

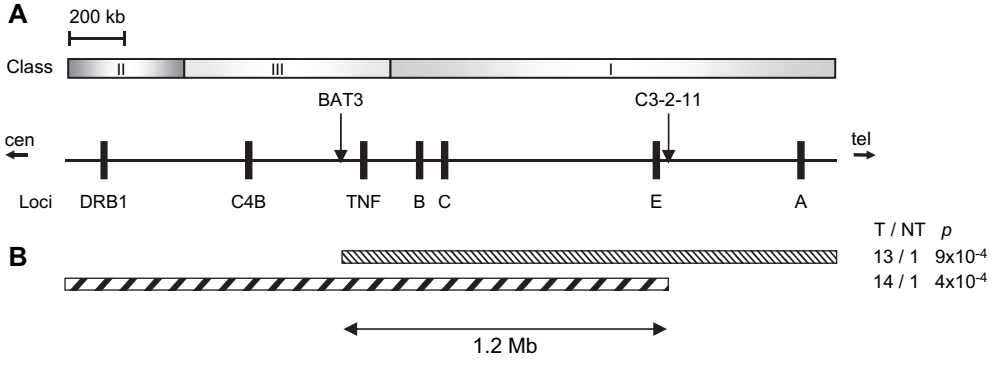

Fig. 1. Schematic map of the HLA complex and localization of the MYAS1 locus based on the transmission of recombinant 8.1 haplotypes. A. Map of the HLA region investigated in 73 families with an MG-affected offspring. The shaded bars at the top indicate the extent of the 3 main classes. Landmark genes and the two microsatellite markers that delimit the MYAS1 interval, BAT3 and C3.2.11, are shown. Altogether, 24 microsatellite markers spanning the region, in addition to DBR1, HLA-B and an SNP in the TNFα promoter, were genotyped. Cen: centromere; tel: telomere. B. Transmission of recombinant 8.1 HLA haplotypes in single-case families with an offspring affected with MG and thymus follicular hyperplasia. Characteristic alleles of the 8.1 ancestral haplotype were used to identify historically recombinant ones. These were grouped according to the position of the recombination breakpoint, either on the centromeric side with the breakpoint at BAT3 or distal to it (thin-hatched bar), or on the telomeric side at C3.2.11 or proximal to it (thick-hatched bar). Counts of transmitted and non-transmitted (T/NT) haplotypes and the *P* values are indicated on the right. The transmission/non-transmission ratio for all 8.1 haplotypes, whether full-length or recombinant, was 56/10 ($P = 6 \times 10^{-10}$). Details on haplotype reconstruction and findings were given in ref. [26].