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Review

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

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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].

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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

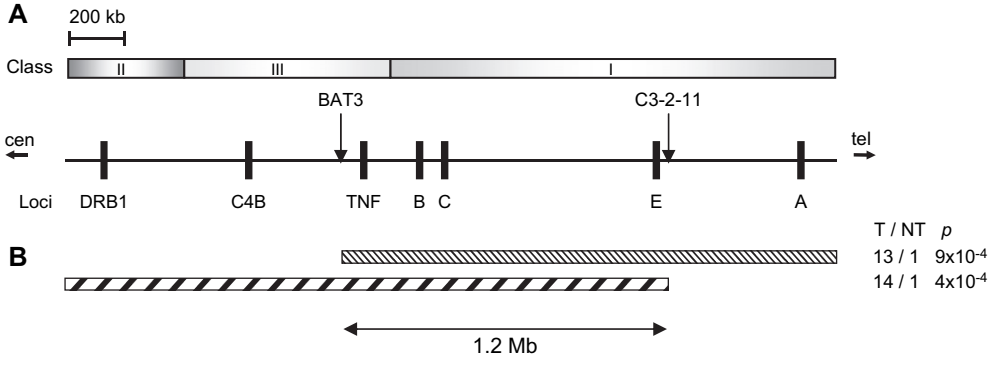

Fig. 1. Schematic map of the HLA complex and localization of the MYAS1 locus based on the transmission of recombinant 8.1 haplotypes. A. Map of the HLA region investigated in 73 families with an MG-affected offspring. The shaded bars at the top indicate the extent of the 3 main classes. Landmark genes 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].

reconstructed the haplotypes and assessed the transmission of historically recombinant ones. This approach was pioneered by R. Dawkins et coworkers [24] who established the interest of characterizing recombinant haplotypes for association mapping. The method has seen its power considerably increased by the recent availability of a large collection of polymorphic microsatellite markers allowing an efficient coverage of the HLA region, as recently illustrated by studies of psoriasis [27], systemic lupus erythematosus [28], rheumatoid arthritis [29], multiple sclerosis [20] or type 1 diabetes [30,31]. In this context, a family-based analysis currently provides most efficient means for reconstructing haplotypes, identifying recombinant haplotypes and estimating their association with the disease, using the transmission-disequilibrium test.

4. Fine mapping of the MYAS1 locus to the HLA central region

Fig. 1 summarizes the findings of our family-based study [26]. Overall, the 8.1 haplotype was strongly associated, as indicated by a highly significant overtransmission to the affected offspring (transmission/non-transmission ratio: 56/10, $P = 6 \times 10^{-10}$). The majority of the patients (46/73, 63%) harbored one or two copies of the 8.1 haplotype. Counts of transmitted haplotypes that were historically recombinant revealed that the MYAS1 locus mapped in a 1.2 Mbases segment in the HLA central region. This interval is currently bounded by two anonymous microsatellite markers, BAT3 on the centromeric side and C3-2-11 on the telomeric side (Fig. 1B). It encompasses the distal part of the class III region and the proximal class I region. Very interestingly, it overlaps with the region recently highlighted in patients with rheumatoid arthritis [29,32,33] that is also associated with the 8.1 haplotype. This might explain the frequent association of rheumatoid arthritis in MG patients [34]. This region notably contains the cluster of the TNF/Lymphotoxin genes. These are major candidates given their role in the formation of germinal centers [35,36]. Other potential candidates include the IkB-L gene which has been recently associated with susceptibility to rheumatoid arthritis [33].

Class I loci, including HLA-B and -C, and class I-like genes such as MICA and MICB, were also included in the susceptibility interval. However, markers in this region were much less strongly associated with MG than those of the central region. In particular, the microsatellite at the MICA locus, a triplet repeat coding for a poly-glutamine in the transmembrane segment of the protein that was previously associated with type I diabetes [37], was not associated in our study. Therefore, although their implication in MG susceptibility cannot be formally ruled out, class I genes do not appear presently as the best candidates in MG susceptibility as they do in other class I-associated diseases, such as ankylosing spondylitis, psoriasis and Behçet's disease.

Interestingly, the MYAS1 interval excludes the cluster of complement factor genes. The gene that encodes the C4A component in this cluster is known to harbor a null allele associated with the 8.1 haplotype [17]. In the murine model of autoimmune MG, germline-inactivation of complement genes, including C3, C4 and C5, results in a protection against induction of MG [38,39]. Therefore, an exclusion of the C4A locus from the MYAS1 interval is consistent with the observation of the experimental model. Allelic variation in complement factor genes could nonetheless modify the phenotype (autoantibody expression, severity) of MG patients, independently of a primary role in MG pathogenesis.

Importantly, the class II alleles on the 8.1 haplotype were definitively excluded from the MYAS1 interval while they are associated with a predisposition to type I diabetes, celiac disease and systemic lupus erythematosus. It should be stressed that we have previously shown that a different class II gene allele, DQA1*0101, that is not associated with the 8.1 haplotype, was associated with MG and interacted with a polymorphism of CHRNA1, one of the AChR-encoding genes [40,41]. Therefore, class II loci do contribute to MG predisposition as they do in many autoimmune diseases [42]. Their lack of association with the 8.1 haplotype in MG, however, should facilitate the mapping of the additional non-class II HLA-linked loci in contrast to type I diabetes and celiac disease. In this regard, MG provides a most useful model.

5. A partially dominant genetic model for MYAS1

We also performed a population study, i.e. comparing unrelated patients and population-matched controls, and we tested different models of association of MG, using a core haplotype corresponding to the newly circumscribed region [26]. We obtained very strong evidence for an additive model (Fig. 2). The

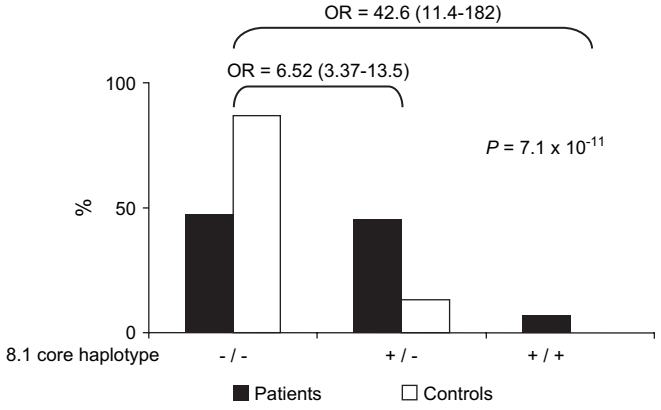

Fig. 2. Case-control comparison of the frequency of the core 8.1 haplotype in 130 patients with MG and thymus follicular hyperplasia (closed bars) and 105 unrelated Caucasian controls (open bars). Three microsatellite markers in the central HLA region, including 9N-I, 82-2 and C1-2-5, showing the strongest association, were used to tag the 8.1 haplotype. The number of patients and controls carrying 0 (−/−), 1 (−/+) or 2 (+/+) copies of the core haplotype were compared using an additive model, with the Cochran-Armitage trend test. The odds ratio (OR) for one or two copies of the core 8.1 haplotype and the 95% confidence interval are given at the top. Altogether, the frequency of the core 8.1 haplotype was 60% in the patients and 5% in the controls.

odds ratios, 6.5 for a single dose of the 8.1 haplotype and 42 for a double dose, were higher than those measured in most previous studies, demonstrating the importance of appropriate modeling and marker selection.

The frequency (~5%) of the disease-associated core haplotype in our control group was similar to that reported in different Caucasian populations [43–46]. The actual frequency of the disease allele at the MYAS1 locus is likely to be even lower if the causative polymorphism has appeared after the constitution of the 8.1 ancestral haplotype. Therefore, the disease-causing variant might be a rare polymorphism. This has important implications for designing future studies aimed at identifying the MYAS1 locus.

6. Two antagonizing HLA loci modulate serum autoantibody expression

Early studies had suggested an HLA-dependent control of anti-AChR autoantibody serum titers in non-thymoma MG patients [6,47]. We found that, in the group of MG patients with TFH, several alleles of the 8.1 haplotype, essentially at loci in the central region and the proximal class I region, were individually associated with increased titers of autoantibodies [26]. However, unexpectedly, patients harboring the full 8.1 haplotype did not differ from those who did not carry the 8.1 haplotype. This discrepancy between the single-locus and the haplotypic analyses could be resolved by postulating the existence of two antagonizing loci with opposing effects on autoantibody titers. A conditional analysis provided the statistical support for this hypothesis [48], indicating the presence of a quantitative trait locus (QTL) increasing anti-AChR autoantibody titers by 7 to 8-fold, mapping in an interval that overlaps with that of MYAS1, and a cis-suppressor locus, located towards the class II region or in the proximal class III region and showing complete suppression of the effect of the QTL (Fig. 3).

Whether this QTL is identical to MYAS1 or is a different locus requires additional investigation. It is also not known whether both these loci that modulate serum levels of anti-AChR autoantibodies, also influence expression of other autoantibodies or even humoral responses at large. In this regard, they might be related to the locus altering antibody response to hepatitis B vaccine or IgA serum levels in patients with IgA deficiency and more recently to the locus altering allergen-specific IgE responses [49–51].

An understanding of the mechanisms of production and regulation of autoantibodies will be also most useful if not essential to assess the other factors necessary for disease expression, such as the complement pathway or other components of the AChR complex [52].

7. Conclusions and perspectives

The HLA complex is presently the only genomic region that has been reproducibly linked to several autoimmune diseases and, compared to other loci, it often shows the largest effect on disease predisposition. Still, the molecular basis of its contribution is far from being fully understood. This region, however, is also at the foremost place of the Genome program, providing a wealth of knowledge invaluable for mapping disease genes. Autoimmune MG offers a stimulating model to exploit this information and to investigate the complex but also very significant and reasonably large influences of HLA loci in an autoimmune disease. Three loci associated with the 8.1 haplotype may be now listed in addition to the class II genes, which are dissociated from the 8.1 haplotype. Two of these loci, one associated with the presence of thymic germinal centers, MYAS1, and the other positively modulating anti-AChR autoantibody serum titers, are located in the central region of HLA. The third locus, that downregulates autoantibody expression, can be mapped towards the proximal HLA region. These pleiotropic effects of the 8.1 haplotype are not unexpected given its involvement in multiple autoimmune diseases and immune phenotypes [22]. They are also consistent with recent findings in the model of the non-obese diabetic mouse where the fine genetic analysis of the H2 complex using congenic strains, formally demonstrates the presence of several closely linked loci influencing susceptibility to type I diabetes and autoimmune thyroiditis [53]. Future studies, combining high-density genotyping, expression analysis of candidate genes and the use of intermediate phenotypes such as cytokine production, should shed new light on the loci accounting for the central role of the major histocompatibility complex in MG and in other autoimmune traits.

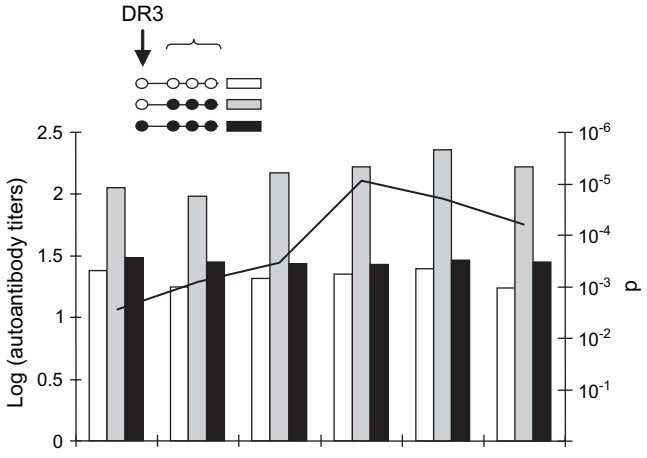

Fig. 3. Conditional analysis of serum anti-AChR autoantibody expression at the HLA complex in MG patients with thymus follicular hyperplasia. The HLA complex was scanned with a three-locus window (inset: bracket), conditioned or not on the DRB1*03 (DR3) allele. Autoantibody titers associated with haplotypes harboring the 8.1-associated alleles but missing the DR3 allele (gray bars) were significantly increased when compared to those associated with full-length DR3+ 8.1 haplotypes (closed bars) or with haplotypes not harboring these alleles (open bars). The joining line indicates the *P* values at each window for the effect of the ancestrally recombinant haplotype compared to the other haplotypes. The data shown concern the 8 markers in the HLA central and proximal class I region that were significantly associated with autoantibody titers in a single-locus analysis, including 82.3, TNFd, TNFb, C1.2.C, MIB, HLA-B8, C1.4.4 and C2.4.5 (see ref. [26] for details). The data analysis was conducted with the QTPhase software (ref. [48]). Inset: closed circles indicate an 8.1-associated allele and open circles represent all other alleles.

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