

ABSTRACT

Myasthenia gravis (MG) is an autoimmune disorder in which patients experience weakness of the skeletal or ocular-bulbar muscles. In most patients, anti-AChR antibodies affect the signal across the neuromuscular junction necessary for muscular contraction. It is a complex disorder, wherein multiple genes plus environmental factors are likely necessary for disease manifestation.

IgA deficiency (IgAD) is defined as serum IgA levels less than 0.07 g/l with normal levels of IgG and IgM. Due to the role of IgA in mucosal barriers, some patients experience recurrent infections, although many individuals are asymptomatic. Both MG and IgAD patients experience concomitant autoimmunity more often than in the background population, and IgAD may be caused by autoimmune mechanisms.

Investigations into genetic associations with MG have targeted genes implicated previously in autoimmune disorders. The *PTPN22* rs2476601 polymorphism was genotyped in 409 MG patients and 1557 controls, and was associated with the entire cohort ($p=2.7 \times 10^{-4}$, OR=1.52), as well as with hyperplasia ($p=1.4 \times 10^{-4}$, OR=1.87), anti-AChR positivity ($p=4.9 \times 10^{-4}$, OR=1.52), and patients exhibiting both ($p=6.6 \times 10^{-5}$, OR=1.96). Furthermore, after antigen activation, a significant increase in IL-2 producing cells ($p=0.002$) and IgG secreting cells ($p=0.004$) in patients carrying the T allele was observed, indicating that the allele may be a gain-of-function variant in MG.

Genotyping of 446 MG patients and 1866 controls for the *CIITA* rs3087456 was conducted without a statistically significant difference observed between MG patients and controls for either allele frequencies ($p=0.092$) or genotypes ($p=0.251$). The control material differed significantly from the original study reporting association of the SNP with several disorders (0.266 and 0.216, respectively, $p < 10^{-5}$). A lack of association in replication cohorts (4 of 26 reported association) may indicate that the SNP does not predispose to autoimmunity. The *CD45* SNP rs17612648 was genotyped in 446 MG patients and 2303 matched controls, with no association with MG ($p=0.199$). A lack of replication in subsequent studies (4 of 24 reported association), as well as the identification of a homozygous blood donor without obvious disease, indicates that this SNP's role in autoimmunity may have to be reconsidered.

The HLA A1, B8, DR3, DQ2 (8.1) haplotype has been associated with several autoimmune disorders, and homozygosity for this haplotype has been reported to impart high risk for IgAD development (RR=77.8). Using 117 identified homozygous individuals, 2 were found to be IgAD (1.7%), indicating that the RR for IgAD for such carriers is estimated to be 11.89. Despite overlapping 8.1 association in IgAD and MG, IgAD is not elevated in MG patients ($p=0.14$), although concomitant autoimmunity is higher than expected in MG (15.9%). The overlapping effects of the haplotype may be due to an independent association of B8 in MG. Examining overlapping genes in autoimmunity has thus proved to be a valuable method of identifying patterns of predisposition.

Using the summary associations to determine complex disease predisposition has proven to be difficult. A method was created to use complex disease MZ and DZ twins concordance to estimate the frequency of the predisposition (1:5240 in MG) and number of overlapping genetic regions contributing to disease (2-4 in MG). This information has made it possible to formulate a model of complex disease which is flexible to the number of underlying genetic subgroups of disease, and future genetic information can be used to predict the probability of disease development.