Immunoglobulin allotypes in caucasian and Chinese myasthenia gravis: differences from Japanese patients

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SUMMARY The G2m(n) allotype was significantly increased in Chinese female and high autoantibody cases, and in caucasians with pure ocular myasthenia, or undetectable autoantibody. In contrast to the strong Glm(x) association reported in Japanese, no overall Gm haplotype, or Am or Km allotype association was found in 90 (Taiwan) Chinese and 181 caucasian myasthenia gravis patients.

Myasthenia gravis is an autoimmune disease mediated by autoantibodies to the acetylcholine receptor (AChR) of skeletal muscle which ultimately cause clinical weakness. Two groups of genetic susceptibility factors have been identified. Firstly, in caucasians, there is a very strong association in non-thymoma cases of young onset (<40 years) with HLA–B8 and −DR3, plus a 3:1 female bias. In late onset cases HLA–B7 and −DR2 are increased and there is a slight excess of males.1 2 Secondly, in Japanese, HLA associations have not so far been striking, but there is a greatly increased frequency of the IgG allotype combination Gm 17: 1:2:21 (identical to Gm [zaxg]), particularly in thymoma cases but also in both young- and old-onset non-tumour cases.3 (Such combinations of allotypes are inherited en bloc, and will be referred to as haplotypes, even where the family studies necessary to confirm that formally have not been done). Such a Gm association has not been obvious in studies of caucasian myasthenics; neither Smith et al4 nor Gross-Wilde et al5 found overall associations with particular allotypes in their series, although associations were seen in some patient subgroups. The Ig heavy chain locus in man (chromosome 14) is shown in fig 1.

While the overall incidence and prevalence of myasthenia gravis do not vary greatly in different countries and races,6 there is a striking difference in age incidence and disease severity between western countries on the one hand, and Japan and China on the other.7 8 In the latter, children with onset before 10 years of age account for up to 25% of all myasthenics, whereas in occidentals they represent less than 5% and there is a compensatory excess of cases with onset between 10 and 40 years. We have recently shown that the great majority of these Chinese myasthenic children have detectable anti-AChR antibodies, and are thus truly autoimmune
Immunoglobulin allotypes in caucasians and Chinese myasthenia gravis

myasthenics. It is obviously important, therefore, to seek both environmental and immunogenetic factors that might explain these remarkable differences, and we now report a survey of Gm allotype frequencies in Chinese and caucasian cases of myasthenia gravis.

Patients and methods

The Chinese and caucasian patients in this study were drawn from two populations of 258 cases each randomly selected from the case records at myasthenic centres located respectively in Taipei and London. A comparison of the clinical features of these two populations has recently been reported. Sera were obtained from the 90 of 258 Chinese and the 181 of 258 caucasian patients who had received no treatment (other than anti-cholinesterase medication), whose clinical severity was representative of the primary patient populations.

Anti-AChR antibodies were measured in all cases (in London) using a standard radioimmunoprecipitation assay, the results are given in reference 8. All the sera were typed (in Amsterdam) for the following immunoglobulin allotypes: Gm (z, a, x, f), G2m(n), G3m (g1, g5, b0, b1, b3, b5, s, t, c3, c5), A2m (1, 2) and Km (1, 3), located on \( \gamma_1 \), \( \gamma_2 \), \( \gamma_3 \), a2 and \( \kappa \)-chains respectively. Typing was carried out with the conventional haemagglutination inhibition technique in microtitre plates with reagents described. A panel of 76 healthy donors from Taipei served as Chinese controls; the families of the Chinese myasthenic patients and controls mostly originated about 300 years ago from the Wuhan region of China, and Gm haplotype frequencies there are similar although G2m(n) is slightly commoner. Ig allotype frequencies of Dutch students were used as caucasian controls.

Results

The previously reported differences in age incidence between Chinese and caucasian myasthenia gravis cases and in the distribution of clinical severity grades were represented in the patients studied here, although caucasian children may be slightly over-represented. Ocular myasthenia was relatively three times commoner in the Chinese patients, whereas the more severe forms were infrequent (grade IIb 17%) or absent (grades III and IV; for explanation of grades, see table 2 legend). Anti-AChR antibody was detectable in 87% of patients in each group, but the mean titre was lower in the Chinese, consistent with the high frequency of ocular myasthenia gravis.

As already known, the predominant Gm haplotypes and their relative proportions also differ greatly in the two races (table 1). Their overall frequencies in myasthenia gravis were not significantly different from controls in either race, and nor were those of the Am and Km allotypes. However, an increase in the G2m(n) allotype was noted in all Chinese patients, being significant also in females and in cases with relatively high anti-AChR titres (table 2). In the caucasians, by contrast, the G2m(n) allotype was significantly increased in the "ocular" (grade I) patients, in those with undetectable anti-AChR, and in those with onset before the age of 10 years.

Discussion

It appears from previous work that disease associations may become quite strong when markers close to the immunoglobulin heavy chain variable region (V\( _H \)) are studied, even if they are weak or undetectable with IgG allotypes (Gm). Thus the lack of any clearcut overall increase in any Gm haplotype in the present study neither rules out the existence of such V\( _H \) genes, nor excludes variations in their frequencies between subgroups of myasthenics. Nevertheless, the contrast between our results and the strong Gm associations in the Japanese is striking, and suggests that the linkage disequilibrium between V\( _H \) and Gm genes may be very different in the Chinese, as indeed are the Gm haplotype frequencies in these two races. As the pattern of age incidence of myasthenia gravis is essentially similar in Japanese and Chinese, this difference in Gm associations argues strongly against predisposition by the Gm genes themselves: presumably other (possibly V\( _H \)) genes, or environmental factors, are involved.

The increases in Gm(n) are also interesting; they

Table 1  Gm "haplotype" frequencies in myasthenia gravis and control populations

<table>
<thead>
<tr>
<th>Number</th>
<th>Chinese myasthenia gravis</th>
<th>Chinese controls</th>
<th>Caucasian myasthenia gravis</th>
<th>Caucasian controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1m; G2m; G3m</td>
<td>90</td>
<td>76</td>
<td>181</td>
<td>792</td>
</tr>
<tr>
<td>za; z</td>
<td>g</td>
<td>0:23</td>
<td>0:26</td>
<td>0:19</td>
</tr>
<tr>
<td>zax; za</td>
<td>g</td>
<td>0:11</td>
<td>0:15</td>
<td>0:12</td>
</tr>
<tr>
<td>af; n; b</td>
<td>s</td>
<td>0:57</td>
<td>0:51</td>
<td>0:01</td>
</tr>
<tr>
<td>f; (n); b</td>
<td>s</td>
<td>0:02</td>
<td>0:04</td>
<td>0:02</td>
</tr>
<tr>
<td>zax; za</td>
<td>st</td>
<td>0:04</td>
<td>0:04</td>
<td>0</td>
</tr>
<tr>
<td>others</td>
<td>0:02</td>
<td>0:01</td>
<td>0:16</td>
<td>0:015</td>
</tr>
</tbody>
</table>

*G = gl, g5; b = b0, b1, b3, b5; st = b0, b3, b5, s, t; z = 17; a = 1; x = 2; f = 3; n = 23; g1 = 21; g5 = 28; b0 = 11; b1 = 5; b3 = 13; b5 = 10.
are inevitably hard to prove unequivocally as this allotype is normally so common in both races. However, their consistency in a series of related patient subgroups in the Chinese adds to our confidence. At first sight, it may seem puzzling that G2m(n) associates with a high anti-AChR titre in the Chinese and a low one in Caucasians. As already discussed, however, linkage relationships are not necessarily the same in different races; disease associations with HLA do not always follow the same patterns either (for example see reference 15). Thus, while G2m(n) clearly cannot itself be the predisposing factor, it might be in linkage disequilibrium with a “high responder” V gene(s) in one race and a “low responder” one in the other. This “high responsiveness” might, in reality, mean a V gene that encodes a combining site of highly pathogenic or very avid antibodies, or a particularly dominant clonotype. “Low responsiveness” might likewise mean a site that preferentially binds extra-ocular muscle AChR.

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