Genetic Aspects of Susceptibility to Multiple Myeloma

By Heinz Ludwig and Wolfgang Mayr

An up-dated survey of the information pertaining to the role of genetic factors in susceptibility to multiple myeloma is attempted. Our own results include the HLA-A, B, and C types in 88 patients, the G1m and Km allotypes in 86 patients, and the frequencies of ABO blood groups in 126 patients with multiple myeloma. The allotype G1m(x) was significantly (p < 0.05) more frequent in the patient group. Since the results in the literature on a possible HLA association have been inconsistent, all relevant available data were combined for an assessment of 379 patients versus 5041 controls. In this comparatively large patient group, the previously reported increase of HLA-4c (HLA-B5 + B18 + Bw35) complex could be confirmed and identified as a weak (RR = 1.7) but significant (p < 0.05) association of susceptibility to multiple myeloma with HLA-B5. Evaluation of G1m allotypes in the combined sample of 258 patients and 4550 controls and Km in 179 and 2457, respectively yielded no significant differences.

Several observations suggest that susceptibility or resistance to malignant plasma cell dyscrasias might involve genetic factors. Multiple myeloma incidence rates vary among different ethnic groups, with rates reported for blacks being nearly twice as high as for whites,1 while among Japanese, Chinese, and South Koreans, particularly low incidences were observed.2 In most countries there is a prevalence of male over female patients.3

The gathering of familial data constitutes another approach to a genetically determined predisposition. A review of multiple myeloma literature covers 75 cases from 35 families,7 and 8 instances of familial occurrence were observed in a single center.8 Pedigrees of families with exceptionally high incidences of monoclonal gammopathy have been published,16 and benign monoclonal gammopathy can frequently be observed in blood relatives of patients with immunoproliferative neoplasias or autoimmune diseases.7

For murine plasmocytoma, which is accessible to experimental investigation, precise data on strain differences are available. Induction of transplantable plasma cell tumors by intraperitoneal stimulation is largely confined to two inbred strains of mice, namely, to BALB/c and NZB, with success rates of 70% and 77%, respectively.8,9 One resistance gene and one or two susceptibility genes have been postulated, the latter tentatively localized on chromosome IX.10

In human multiple myeloma, the topic to which we confine this article, chromosome aberrations have been observed,11 but so far, no typical pattern has conclusively evolved. At present, two gene complexes are known to be relevant to immune regulation and therefore can serve as genetic markers when no other clues to hereditary mechanisms are available. The first is localized within the major histocompatibility complex (MHC), a biologically very important and well defined gene complex. Association between certain HLA types and susceptibility was reported for various diseases, such as ankylosing spondylitis, with a striking prevalence (85%–97%) of HLA-B27.12 Among the first studies on HLA-associated disease susceptibility was the discovery of a weak association of Hodgkin’s disease with HLA-A1.13 Humoral immune and autoimmune responses were found to correlate with certain HLA antigens,14,15 and a linkage disequilibrium between HLA genes and hypothetical immune response genes, which might even be identical with HLA-D or HLA-DR genes, has been postulated.16

Another gene complex apparently involved in immune regulation is linked to the Gm complex, which codes for allotypes of the IgG heavy chain. Increased frequencies of certain Gm allotypes were reported for myasthenia gravis17 and other autoimmune diseases,18 and Gm- and Km-associated differences in immune responses to natural immunogens were found.19 Km allotypes are located on the kappa light chain only, and the possible mode of immune response association has not yet been specified.

In other malignancies the frequencies of ABO blood groups are known to deviate from those of the reference population.20 For multiple myeloma, in one investigation21 no differences were found between patients and controls. Another report22 claims blood-group-associated differences, but their magnitude does not exceed the limit for probable random variations. In one study a significant association was found between blood group A and benign monoclonal gammopathy.23

In this article we report the results of typing patients with multiple myeloma for gene products of the HLA-A, B, and C loci, G1m and Km allotypes, and the ABO blood groups. The data from nine published investiga-
tions for HLA-A and B antigens\textsuperscript{21,24-31} were combined with our own results, and weighed relative risks were calculated for the comparatively large population. For lack of detailed information, the results of an additional publication\textsuperscript{12} could not be included and we were unable to obtain a Russian paper\textsuperscript{33} that is quoted in a review of the pertinent literature.\textsuperscript{14} No attempt was made to test for association with the HLA-D/DR loci because of the susceptibility to spurious positive results of the combination—small size of the test sample and multiple comparisons, conditions inherent to the point in question. Our patient group appeared too small and no other published data were available for combination. For immunoglobulin allotypes, our own results were combined with the data of three published investigations.\textsuperscript{21,35,36} One survey on serum group factors in paraproteinemia\textsuperscript{37} could not be included, because the authors made no distinction between plasma cell malignancies and benign monoclonal gammopathies.

**MATERIALS AND METHODS**

The diagnosis of multiple myeloma was established according to standard criteria requiring the presence of at least two of the following characteristics: (1) serum or urinary M-component, (2) bone marrow plasma cell infiltration >15%, and (3) osteolytic bone lesions. One-hundred and twenty-six Caucasoid patients living in the area of Vienna, Austria (67 IgG, 17 IgA, 24 light chain, 2 IgD, and 16 with undetermined paraprotein type) were tested for ABO blood groups; for 84 patients (50 IgG, 14 IgA, 13 light chain, 2 IgD, and 5 with undetermined paraprotein), the GIm and Km allotypes were determined, and in 68 patients (43 IgG, 12 IgA, 12 light chain, and 1 IgD) HLA antigens were identified. Healthy blood donors served as controls.

For HLA typing, 14 antigens of the HLA-A locus (A1, A2, A3, Aw23, Aw24, A25, A26, A11, A28, A29, Aw30, Aw31, Aw32, and Aw33), 18 antigens of the HLA-B locus (B5, B7, B8, B12, B13, B14, B15, B17, B18, B27, B37, B40, Bw16, Bw22, Bw35, Bw41, Bw49, and Bw50), and 5 antigens of the HLA-C locus (Cw1, Cw2, Cw3, Cw4, and Cw5) were tested using the NIH standard lymphocytotoxicity test. The standard hemagglutination inhibition technique\textsuperscript{48} was used to detect GIm (a, x, f) and Km (I) antigens. ABO blood groups were determined by routine techniques.

**Statistical Evaluation**

Frequencies were compared using the $x^2$ test for values $>5$; for smaller numbers, Fisher's exact test for $2 \times 2$ tables was applied. The limit of significance was corrected according to the method of Bonferroni, e.g., for the total of 37 HLA antigens tested on a single patient group, the limit of significance (5%) was raised to $x^2 = 10.228$ or lowered to $p = 0.0014$ for Fisher's exact test. Data from 9 published studies were combined with our own results to allow an estimation of relative risks based on 379 patients and 504 controls. Using the methods recommended by Woolf\textsuperscript{99} and the appropriate corrections for small samples suggested by Haldane,\textsuperscript{100} the relative risk was calculated separately for each antigen and for each investigation. For each HLA antigen, the weighed relative risk and its 95% fiducial limits were determined. Chi-square analysis refers to deviation of loge relative risk from 0; the limits of significance were adjusted according to Bonferroni statistics. The combined population was tested for heterogeneity, and significance at the 5% limit was determined without correction for 9 degrees of freedom.

**RESULTS**

The results of typing for gene products of the HLA-A, B, and C locus are listed in Tables 1, 2, and 3, respectively. Although the relative risks ranged from 0.27 through 2.19, the comparison of patients to controls did not yield a significant difference for any antigen.

Table 4 presents the combined data from the literature for HLA-B14. We selected a rather extreme example to illustrate that differences among the various investigations ranging from a relative risk of 0.41 through 6.24 combine to a relative risk of close to 1 and

<table>
<thead>
<tr>
<th>HLA</th>
<th>Positive (n = 68)</th>
<th>Controls (n = 3,000)</th>
<th>Controls (n = 3,000)</th>
<th>RR</th>
<th>$x^2$</th>
<th>10.228*</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>19</td>
<td>27.9</td>
<td>820</td>
<td>27.3</td>
<td>1.05</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>30</td>
<td>44.1</td>
<td>1,455</td>
<td>48.5</td>
<td>0.84</td>
<td>0.507</td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>24</td>
<td>35.3</td>
<td>795</td>
<td>26.6</td>
<td>1.53</td>
<td>2.581</td>
<td></td>
</tr>
<tr>
<td>Aw23</td>
<td>5</td>
<td>7.9</td>
<td>181</td>
<td>6.0</td>
<td>1.12</td>
<td>0.609</td>
<td></td>
</tr>
<tr>
<td>Aw24</td>
<td>9</td>
<td>13.2</td>
<td>570</td>
<td>19.0</td>
<td>0.68</td>
<td>1.422</td>
<td></td>
</tr>
<tr>
<td>A25</td>
<td>6</td>
<td>8.8</td>
<td>159</td>
<td>5.3</td>
<td>1.85</td>
<td>1.547</td>
<td></td>
</tr>
<tr>
<td>A26</td>
<td>5</td>
<td>7.4</td>
<td>277</td>
<td>9.2</td>
<td>0.85</td>
<td>0.302</td>
<td></td>
</tr>
<tr>
<td>A11</td>
<td>10</td>
<td>14.7</td>
<td>288</td>
<td>9.6</td>
<td>1.69</td>
<td>1.984</td>
<td></td>
</tr>
<tr>
<td>A28</td>
<td>6</td>
<td>8.8</td>
<td>242</td>
<td>8.1</td>
<td>1.18</td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>A29</td>
<td>2</td>
<td>2.9</td>
<td>135</td>
<td>4.5</td>
<td>0.80</td>
<td>0.407</td>
<td></td>
</tr>
<tr>
<td>Aw30</td>
<td>1</td>
<td>1.5</td>
<td>154</td>
<td>5.1</td>
<td>0.41</td>
<td>0.133</td>
<td></td>
</tr>
<tr>
<td>Aw31</td>
<td>5</td>
<td>7.3</td>
<td>139</td>
<td>4.6</td>
<td>1.78</td>
<td>1.087</td>
<td></td>
</tr>
<tr>
<td>Aw32</td>
<td>6</td>
<td>8.8</td>
<td>215</td>
<td>7.2</td>
<td>1.34</td>
<td>0.272</td>
<td></td>
</tr>
<tr>
<td>Aw33</td>
<td>2</td>
<td>2.9</td>
<td>91</td>
<td>3.0</td>
<td>1.20</td>
<td>0.660</td>
<td></td>
</tr>
</tbody>
</table>

*Limit of significance (5%).
Table 2. Comparisons of Patients to Controls for Gene Products of the HLA-C Locus. No Difference Was Statistically Significant

<table>
<thead>
<tr>
<th>HLA</th>
<th>Patients (n = 68)</th>
<th>Controls (n = 3,000)</th>
<th>RR</th>
<th>$\chi^2$</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>B5</td>
<td>11 16.2</td>
<td>488 16.5</td>
<td>1.01</td>
<td>10.228*</td>
<td>0.005</td>
</tr>
<tr>
<td>B7</td>
<td>19 27.9</td>
<td>682 22.7</td>
<td>1.34</td>
<td>1.046</td>
<td></td>
</tr>
<tr>
<td>B8</td>
<td>11 16.2</td>
<td>543 18.1</td>
<td>0.90</td>
<td>0.171</td>
<td></td>
</tr>
<tr>
<td>B12</td>
<td>8 11.8</td>
<td>677 22.6</td>
<td>0.48</td>
<td>4.470</td>
<td></td>
</tr>
<tr>
<td>B13</td>
<td>4  5.9</td>
<td>240  8.0</td>
<td>0.80</td>
<td>0.814</td>
<td></td>
</tr>
<tr>
<td>B14</td>
<td>2  2.9</td>
<td>163   5.4</td>
<td>0.65</td>
<td>0.286</td>
<td></td>
</tr>
<tr>
<td>B15</td>
<td>12 17.6</td>
<td>355 11.8</td>
<td>1.65</td>
<td>2.180</td>
<td></td>
</tr>
<tr>
<td>B17</td>
<td>4  5.9</td>
<td>269   9.0</td>
<td>0.71</td>
<td>0.260</td>
<td></td>
</tr>
<tr>
<td>B18</td>
<td>11 16.2</td>
<td>330 11.0</td>
<td>1.62</td>
<td>1.751</td>
<td></td>
</tr>
<tr>
<td>B27</td>
<td>9  13.2</td>
<td>242   8.1</td>
<td>1.82</td>
<td>2.300</td>
<td></td>
</tr>
<tr>
<td>B37</td>
<td>3   4.4</td>
<td>71    2.4</td>
<td>2.19</td>
<td>0.917</td>
<td></td>
</tr>
<tr>
<td>B40</td>
<td>10 14.7</td>
<td>345  11.5</td>
<td>1.38</td>
<td>0.646</td>
<td></td>
</tr>
<tr>
<td>Bw16</td>
<td>12 17.6</td>
<td>279   9.3</td>
<td>2.15</td>
<td>5.531</td>
<td></td>
</tr>
<tr>
<td>Bw22</td>
<td>3   4.4</td>
<td>146   4.9</td>
<td>1.04</td>
<td>0.577</td>
<td></td>
</tr>
<tr>
<td>Bw35</td>
<td>11 16.2</td>
<td>580   19.3</td>
<td>0.83</td>
<td>0.427</td>
<td></td>
</tr>
<tr>
<td>Bw41</td>
<td>0   0.0</td>
<td>80    2.7</td>
<td>0.27</td>
<td>0.183</td>
<td></td>
</tr>
<tr>
<td>Bw49</td>
<td>1   1.5</td>
<td>86    2.9</td>
<td>0.75</td>
<td>0.413</td>
<td></td>
</tr>
<tr>
<td>Bw50</td>
<td>1   1.5</td>
<td>94    3.1</td>
<td>0.68</td>
<td>0.376</td>
<td></td>
</tr>
</tbody>
</table>

*Limit of significance (5%).

Table 3. Comparisons of Patients to Controls for Gene Products of the HLA-C Locus. No Difference Was Statistically Significant

<table>
<thead>
<tr>
<th>HLA</th>
<th>Patients (n = 68)</th>
<th>Controls (n = 3,000)</th>
<th>RR</th>
<th>$\chi^2$</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cw1</td>
<td>5   7.4</td>
<td>224    7.5</td>
<td>1.07</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Cw2</td>
<td>10  14.7</td>
<td>327    10.9</td>
<td>1.47</td>
<td>0.957</td>
<td></td>
</tr>
<tr>
<td>Cw3</td>
<td>18  26.5</td>
<td>654    21.5</td>
<td>1.31</td>
<td>0.845</td>
<td></td>
</tr>
<tr>
<td>Cw4</td>
<td>14  20.6</td>
<td>711    23.7</td>
<td>0.86</td>
<td>0.367</td>
<td></td>
</tr>
<tr>
<td>Cw5</td>
<td>6   8.8</td>
<td>344    11.5</td>
<td>0.80</td>
<td>0.479</td>
<td></td>
</tr>
</tbody>
</table>

*Limit of significance (5%).

a very low $\chi^2$ value. The exact figures are given in Table 5. There was no significant heterogeneity among the various populations, and the wide fluctuation of the results has to be considered random.

In Table 5, the results from the combined data are listed for HLA-A and HLA-B antigens. By stringent methods for multiple comparisons relating to the same samples, only one of the relative risks deviates significantly ($p < 0.05$) from 1, namely HLA-B5 with a weighted relative risk of 1.69 and the 95% fiducial limits 1.25–2.29. Significant ($p < 0.05$) heterogeneity of the combined data was only observed in the HLA-B18 antigen.

Table 6 shows the comparisons between patients and controls for the observed frequencies of the allotypes. For Glm(x) the relative risk amounts to 2.09 and the

Table 4. Example of Data From the Literature Combined With Our Own Results. The Relative Risks Vary Randomly Over a Wide Range

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients Compared</th>
<th>B14 Positive</th>
<th>Controls Compared</th>
<th>B14 Positive</th>
<th>RR</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>68</td>
<td>2</td>
<td>3,000</td>
<td>163</td>
<td>0.65</td>
<td>0.514</td>
</tr>
<tr>
<td>Mason and Cullen</td>
<td>63</td>
<td>4</td>
<td>83</td>
<td>7</td>
<td>0.77</td>
<td>0.190</td>
</tr>
<tr>
<td>Cassuto et al.</td>
<td>60</td>
<td>3</td>
<td>172</td>
<td>22</td>
<td>0.41</td>
<td>2.544</td>
</tr>
<tr>
<td>Bertrams et al.</td>
<td>40</td>
<td>3</td>
<td>160</td>
<td>14</td>
<td>0.94</td>
<td>0.010</td>
</tr>
<tr>
<td>Saleün et al.</td>
<td>33</td>
<td>4</td>
<td>200</td>
<td>18</td>
<td>1.50</td>
<td>0.573</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>32</td>
<td>2</td>
<td>131</td>
<td>10</td>
<td>0.95</td>
<td>0.006</td>
</tr>
<tr>
<td>Festen et al.</td>
<td>30</td>
<td>1</td>
<td>533</td>
<td>31</td>
<td>0.81</td>
<td>0.077</td>
</tr>
<tr>
<td>Van Camp et al.</td>
<td>23</td>
<td>2</td>
<td>285</td>
<td>20</td>
<td>1.51</td>
<td>0.390</td>
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<tr>
<td>Marras and Magri</td>
<td>16</td>
<td>0</td>
<td>77</td>
<td>2</td>
<td>0.92</td>
<td>0.005</td>
</tr>
<tr>
<td>Jeannet and Magnin</td>
<td>14</td>
<td>2</td>
<td>305</td>
<td>9</td>
<td>6.24</td>
<td>6.530</td>
</tr>
<tr>
<td>Total</td>
<td>379</td>
<td>23</td>
<td>4,946</td>
<td></td>
<td></td>
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</table>
Table 5. Results of the Combined Data for Gene Products of the HLA-A and the HLA-B Loci. The Increased RR Associated With HLA-B5 is Statistically Significant ($p < 0.05$)

<table>
<thead>
<tr>
<th>HLA</th>
<th>Patients Compared</th>
<th>Controls Compared</th>
<th>$\chi^2$</th>
<th>HLA</th>
<th>Patients Compared</th>
<th>Controls Compared</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>379</td>
<td>5,041</td>
<td>1.04</td>
<td>0.081</td>
<td>86</td>
<td>379</td>
<td>5,041</td>
</tr>
<tr>
<td>A2</td>
<td>379</td>
<td>5,041</td>
<td>1.12</td>
<td>0.972</td>
<td>87</td>
<td>379</td>
<td>5,041</td>
</tr>
<tr>
<td>A3</td>
<td>379</td>
<td>5,041</td>
<td>0.89</td>
<td>0.850</td>
<td>88</td>
<td>379</td>
<td>5,041</td>
</tr>
<tr>
<td>A9</td>
<td>379</td>
<td>5,041</td>
<td>1.26</td>
<td>3.311</td>
<td>B12</td>
<td>379</td>
<td>5,041</td>
</tr>
<tr>
<td>A10</td>
<td>379</td>
<td>5,041</td>
<td>1.07</td>
<td>1.151</td>
<td>B13</td>
<td>379</td>
<td>5,041</td>
</tr>
<tr>
<td>A11</td>
<td>379</td>
<td>5,041</td>
<td>1.11</td>
<td>0.369</td>
<td>B14</td>
<td>379</td>
<td>5,041</td>
</tr>
<tr>
<td>A28</td>
<td>347</td>
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<td>3.812</td>
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<td>A29</td>
<td>287</td>
<td>4,245</td>
<td>1.31</td>
<td>1.600</td>
<td>B17</td>
<td>379</td>
<td>5,041</td>
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<tr>
<td>Aw30 + Aw31</td>
<td>303</td>
<td>4,481</td>
<td>1.12</td>
<td>0.285</td>
<td>B18</td>
<td>316</td>
<td>4,958</td>
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<tr>
<td>Aw32</td>
<td>214</td>
<td>4,039</td>
<td>1.04</td>
<td>0.021</td>
<td>B27</td>
<td>379</td>
<td>5,041</td>
</tr>
<tr>
<td>Aw33</td>
<td>128</td>
<td>3,172</td>
<td>0.76</td>
<td>0.266</td>
<td>B37</td>
<td>161</td>
<td>3,372</td>
</tr>
<tr>
<td>B40</td>
<td>379</td>
<td>5,041</td>
<td>1.11</td>
<td>0.373</td>
<td>Bw16</td>
<td>262</td>
<td>4,398</td>
</tr>
<tr>
<td>Bw22</td>
<td>379</td>
<td>5,041</td>
<td>0.98</td>
<td>0.014</td>
<td>Bw23</td>
<td>379</td>
<td>5,041</td>
</tr>
<tr>
<td>Bw41</td>
<td>128</td>
<td>3,172</td>
<td>0.32</td>
<td>2.298</td>
<td>Bw27</td>
<td>214</td>
<td>4,039</td>
</tr>
</tbody>
</table>

*Limit of significance (5%).

difference between both groups is statistically significant ($p < 0.05$). There was no significant difference of Km(1) allotypes between the groups for subsamples of light chain myeloma ($n = 12$) and patients with paraproteins of the kappa light chain class ($n = 42$, data not shown).

In Table 7, the combined results regarding immunoglobulin allotypes are presented. Calculations based on 258 patients and 4550 controls do not support our own observation of an elevated Glm(x) frequency in multiple myeloma. There were no significant differences between patients and controls and no significant heterogeneity among the various patient and control samples.

The distribution of ABO blood group frequencies in the patient and in the control group are shown in Table 8. No significant difference could be detected either in our own samples or in the combined data from another investigation and our results (data not shown).

**DIFFUSION**

In a rare human disease such as multiple myeloma, the demonstration of a genetically determined susceptibility is very difficult. Epidemiologic data should be taken as indication rather than proof, because multiple environmental differences exist among different ethnic groups and direct comparison of incidence patterns presupposes identical population characteristics. Collection of accumulated familial instances seems to be the method of choice, but for multiple myeloma there are several drawbacks to the method. Unequivocal interpretation of pedigrees has to await another one or two generations, because facilities for exact diagnosis have been available only comparatively recently and epidemiologic data suggest that the disease is still underdiagnosed in the eldest age group of patients.

The probability of random coincidence in siblings is very small and penetrance would have to be high, if sibpairs could be expected regularly in the usual small patient groups. The reported familial data can be taken as strong indication, but their quantitative interpretation is difficult. Large and renowned treatment centers serve not only the local community, but also attract patients from other parts of the country. Their patient sample can neither be considered representa-
tive for the local population nor is the reference population clearly defined. Furthermore, the high manifestation age for multiple myeloma aggravates the problem of excluding a predisposition in siblings who do not live long enough to reach old age.

A promising method seems to be the search for a genetic marker for susceptibility to multiple myeloma, a condition characterized by the unlimited growth of a single malignantly transformed plasma cell clone, i.e., an immunoproliferative disease. Since the human MHC is associated with a variety of immunologic disorders, it is an obvious choice for the start of an investigation. Reports in the literature pointed to constituents of the 4c (HLA-B5 + B18 + Bw35) complex, but random error probability is high: when a series of characteristics is tested on the same sample and only in one publication, the significance of differences did not vanish with the proper corrections. Since there is no a priori basis to assume linkage disequilibrium with a component of the 4c complex to be more likely than an association with any other allele of the three major histocompatibility loci, we decided to test the whole series of HLA-A, B, and C antigens. Comparisons between the frequencies observed in patients and those of the control group yielded no significant differences, but when the data of all available studies related to the topic (that to our knowledge have been published up to date) were combined in order to allow the evaluation of a comparatively large patient group, an increased frequency of HLA-B5 proved to be significant. None of the other suspected associations could be confirmed.

The other marker apparently involved in immune regulation—the gene complex coding for immunoglobulin allotypes—was tested on 84 white patients with multiple myeloma. A significant increase of Glm(x) was found that could not be confirmed in the larger sample of combined data. For the Km allotypes, no difference was found between patients and controls. Evaluation of the Km(1) type of patients with light chain myeloma and of a subsample of paraprotein restricted to the kappa light chain class did not change the results. Nevertheless, we suggest the testing for Km allotypes in multiple myeloma only under conditions that exclude unspecific binding of antiserum to irrelevant determinants of free light chains.

The previous reports of an HLA-associated higher relative risk in multiple myeloma could be confirmed and identified as a weak association with HLA-B5. Though the relative risk of 1.7 for B5-positive individuals at this stage cannot be exploited clinically, this finding and epidemiologic data suggest genetic factors influencing the susceptibility to multiple myeloma.

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Genetic aspects of susceptibility to multiple myeloma

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