Acute rheumatic fever (ARF) remains a major cause of heart disease and premature death in large parts of the world (Figure 1). ARF is a systemic inflammatory autoimmune disease that follows throat infection with Lancefield group A β-hemolytic streptococci (*Streptococcus pyogenes*). The pathogenesis of ARF is believed to involve the triad of a genetically susceptible individual, infection with a rheumatogenic strain of group A streptococcus, and an aberrant host immune response. There have been excellent recent reviews addressing group A streptococcal virulence and the immunopathogenesis of ARF.  

A key question that remains unanswered is why only a small fraction of those infected with rheumatogenic group A streptococci develop an abnormal immune response that leads to ARF.

An understanding of the mechanisms underlying host susceptibility can provide important insights into pathogenesis that in turn can inform new treatments. Extensive searches for susceptibility factors have been undertaken, including human leukocyte antigens, B-cell alloantigens, and cytokine genes. Although significant associations have been found between genetic factors and acute rheumatic fever, study results often conflict with each other. This review explores current understanding about host susceptibility to acute rheumatic fever and provides an overall perspective to the number of studies that have recently addressed this subject. *(Circulation. 2009; 119:742-753.)*  

**Key Words:** antigens ■ genetics ■ immunology ■ rheumatic heart disease ■ susceptibility
such hereditary taint. A more recent cohort study of children raised separately from their parents in an Israeli kibbutz showed that children whose parents had rheumatic heart disease (RHD) had a relative risk of 2.93 for the development of ARF compared with children whose parents did not have RHD.\(^{37}\) An inherited susceptibility to ARF and RHD is supported by twin studies that have found a significantly increased concordance in monozygotic twins compared with dizygotic twins\(^{38,39}\); however, the lower than expected concordance (3 of 16 pairs) in these studies indicates that it is not simple mendelian single-gene inheritance. The search for susceptibility genes has been vigorous.

**Human Leukocyte Antigens**

As critical components in antigen processing, the major histocompatibility complex human leukocyte antigen (HLA) molecules are attractive candidate antigens that might confer susceptibility to ARF. HLA class II molecules in particular are associated with other autoimmune diseases (for example, HLA-DR2 and systemic lupus erythematosus and HLA-DR3 and insulin-dependent diabetes mellitus).

In general, HLA class II molecules appear to have a closer association with increased risk of ARF or RHD than class I molecules, although no single HLA haplotype or combination exists that is consistently associated with susceptibility (Table 1). Similarly, intensive study of the DR locus in a Brazilian population showed an association with RHD but failed to find either a specific allele or unique nucleotide sequence that conferred susceptibility.\(^{48}\) The authors postulated that this might be due to either the cross-reacting peptide being indiscriminate or heterogeneity of the causative agent. Although most interest has been focused on association with increased risk, several HLA molecules have been found to be associated with decreased risk of ARF.\(^{40,45,46,48,52,53,58,61,63,64,67}\)

![Figure 1. Worldwide prevalence of RHD. Rates (in parentheses) are based on studies in school-age children unless indicated by an asterisk, in which case, they include adults.](http://circ.ahajournals.org/)

A wide variation exists in results of studies in different geographic regions and ethnic populations, as well as inconsistent findings between different studies in similar populations. Some of the differences may be attributable to the technique used for HLA typing. Earlier studies that used serological methods are subject to potential inaccuracies and are unable to distinguish between allelic subgroups; however, results from more recent molecular studies that have investigated allelic subgroups have also found differences between ethnic groups, both in alleles and in haplotypes\(^{50,59,61,63,64,66,67}\). Another potential source of variability between studies is the selection of control subjects. Where historical controls have been used, these may not be representative of the population from which the case subjects came. It is also possible that differences in clinical classification of ARF and RHD between studies are responsible for some of the different results. Some support can be seen for this in the finding that HLA associations are stronger in more clinically homogenous patients.\(^{47,57,63}\) Also, some studies have found HLA associations only with particular clinical features of ARF; for example, in 1 study, a significant association was found HLA associations only with particular clinical features of ARF; for example, in 1 study, a significant association was found between HLA-A10 and HLA-DR11 in patients with cardiac manifestations compared with ARF without cardiac features, the latter group having a higher frequency of HLA-C2.\(^{42}\) However, even with disease defined in exactly the same way, ethnic differences in HLA association are apparent,\(^{47}\) which supports a genuine ethnicity-specific genetic susceptibility. Overall, most studies support the notion of an HLA association with ARF/RHD.

The mechanism of HLA association is unknown. One theory is that similarity exists between antigens from rheumatogenic group A streptococcal strains and HLA molecules. If antigens from different strains of bacteria were structurally similar to different HLA molecules, this would result in an increased proportion of individuals of a specific HLA type with ARF during an outbreak or in a geographic population where a particular streptococcal strain dominates. To date, no study has investigated people from 1 ethnic group who have moved to a geographic area with a different predominant
Table 1. HLA Associations With ARF/RHD in Different Countries and Ethnic Populations

<table>
<thead>
<tr>
<th>HLA Antigen</th>
<th>Association</th>
<th>Lack of Association</th>
<th>Method</th>
<th>Disease</th>
<th>Country/Ethnicity</th>
<th>No. in Study</th>
<th>Year and Reference</th>
</tr>
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<tbody>
<tr>
<td>HLA class I</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>A33</td>
<td>↑</td>
<td>Rest of A, B</td>
<td>S</td>
<td>ARF/RHD</td>
<td>North India</td>
<td>134</td>
<td>1986 [40]</td>
</tr>
<tr>
<td>A19</td>
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<td>S</td>
<td>RHD</td>
<td>Kashmir</td>
<td>54</td>
<td>1997 [41]</td>
</tr>
<tr>
<td>A10</td>
<td>↑</td>
<td>Rest of A, rest of B, C, DR</td>
<td>S</td>
<td>ARF</td>
<td>Turkey</td>
<td>100</td>
<td>1993 [42]</td>
</tr>
<tr>
<td>B35</td>
<td>↑</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>B5</td>
<td>↓</td>
<td>Rest of B, A, C</td>
<td>S</td>
<td>RHD</td>
<td>Kashmir</td>
<td>50</td>
<td>1997 [43]</td>
</tr>
<tr>
<td>B35</td>
<td>↑</td>
<td>Rest of B, A, C</td>
<td>S</td>
<td>ARF</td>
<td>Martinique</td>
<td>88</td>
<td>1986 [44]</td>
</tr>
<tr>
<td>B14</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>B42</td>
<td>↓</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>B16</td>
<td>↑</td>
<td>Rest of B, A</td>
<td>S</td>
<td>RHD</td>
<td>Turkey</td>
<td>107</td>
<td>1993 [45]</td>
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<td>B51</td>
<td>↓</td>
<td>Rest of B, A</td>
<td>M</td>
<td>RHD</td>
<td>Turkey</td>
<td>85</td>
<td>2007 [46]</td>
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<tr>
<td>Cw*4</td>
<td>↓</td>
<td>Rest of C</td>
<td></td>
<td></td>
<td></td>
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<td>HLA class II DR</td>
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</tr>
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<td>DR2</td>
<td>↑</td>
<td>Rest of DR, A, B, C</td>
<td>S</td>
<td>ARF/RHD, especially with cardiac features</td>
<td>USA: black</td>
<td>48</td>
<td>1986 [47]</td>
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<tr>
<td>DR4</td>
<td>↑</td>
<td>Rest of DR</td>
<td>S</td>
<td>RHD</td>
<td>USA: white</td>
<td>24</td>
<td>1986 [48]</td>
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<tr>
<td>DR6</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DR1-9</td>
<td>↓</td>
<td>DR1-9</td>
<td>S</td>
<td>RHD</td>
<td>USA: white</td>
<td>57</td>
<td>1995 [49]</td>
</tr>
<tr>
<td>DR4</td>
<td>↑</td>
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</tr>
<tr>
<td>DR8*16</td>
<td>↑</td>
<td>Rest of DR81</td>
<td>M</td>
<td>ARF</td>
<td>USA: white</td>
<td>33</td>
<td>1998 [50]</td>
</tr>
<tr>
<td>DR1</td>
<td>↑</td>
<td>Rest of DR</td>
<td>S</td>
<td>ARF</td>
<td>Martinique</td>
<td>88</td>
<td>1986 [51]</td>
</tr>
<tr>
<td>DR1</td>
<td>↑</td>
<td>Rest of DR, A, B, DQ</td>
<td>S</td>
<td>Severe RHD</td>
<td>Black South Africans</td>
<td>103</td>
<td>1987 [52]</td>
</tr>
<tr>
<td>DR6</td>
<td>↑</td>
<td>Rest of DR</td>
<td>S</td>
<td>ARF/RHD</td>
<td>North India</td>
<td>134</td>
<td>1986 [53]</td>
</tr>
<tr>
<td>DR2</td>
<td>↓</td>
<td>Rest of DR</td>
<td>S</td>
<td>RHD</td>
<td>North India</td>
<td>52</td>
<td>1989 [54]</td>
</tr>
<tr>
<td>DR2</td>
<td>↓</td>
<td>Rest of DR, A, B, C</td>
<td>S</td>
<td>RHD</td>
<td>North India</td>
<td>165</td>
<td>1990 [55]</td>
</tr>
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<td>DR3</td>
<td>↑</td>
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</tr>
<tr>
<td>DR4</td>
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<td>Rest of DR, DQ</td>
<td>S</td>
<td>RHD</td>
<td>Kashmir</td>
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<td>↑</td>
<td>Rest of DR, DQ</td>
<td>S</td>
<td>RHD</td>
<td>Kashmir</td>
<td>50</td>
<td>1997 [57]</td>
</tr>
<tr>
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<td>↑</td>
<td>Rest of DR, A, B, C</td>
<td>S</td>
<td>ARF/RHD</td>
<td>Saudi Arabian Arabs</td>
<td>40</td>
<td>1987 [58]</td>
</tr>
<tr>
<td>DR7</td>
<td>↑</td>
<td>Rest of DR1 –10, DR52, A, B, DQ</td>
<td>S</td>
<td>ARF/RHD</td>
<td>Brazil: white/light mulatto</td>
<td>40</td>
<td>1991 [59]</td>
</tr>
<tr>
<td>DR7</td>
<td>↑</td>
<td>DR53</td>
<td>S</td>
<td>ARF/RHD</td>
<td>Brazil: white</td>
<td>35</td>
<td>2000 [60]</td>
</tr>
<tr>
<td>DR4</td>
<td>↑</td>
<td>Rest of DR, A, B</td>
<td>S</td>
<td>ARF, especially with cardiac features</td>
<td>Turkey</td>
<td>93</td>
<td>1992 [61]</td>
</tr>
<tr>
<td>DR3</td>
<td>↑</td>
<td>Rest of DR</td>
<td>S</td>
<td>RHD</td>
<td>Turkey</td>
<td>107</td>
<td>1993 [62]</td>
</tr>
<tr>
<td>DR7</td>
<td>↑</td>
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</tr>
<tr>
<td>DRB1*01</td>
<td>↓</td>
<td>Rest of DR</td>
<td>M</td>
<td>RHD</td>
<td>Turkey</td>
<td>85</td>
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</tr>
<tr>
<td>DRB1*04†</td>
<td>↓</td>
<td>Rest of DRB1</td>
<td>M</td>
<td>RHD</td>
<td>Turkey</td>
<td>55</td>
<td>2005 [64]</td>
</tr>
<tr>
<td>DRB1*13</td>
<td>↓</td>
<td>Rest of DRB1, A, B, C, DRB4 DQB1</td>
<td>M</td>
<td>RHD</td>
<td>Turkey</td>
<td>100</td>
<td>2006 [65]</td>
</tr>
<tr>
<td>DRB3</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DRB5</td>
<td>↓</td>
<td></td>
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<tr>
<td>DRB1*07</td>
<td>↑</td>
<td>Rest of DRB1*01-*18</td>
<td>M</td>
<td>RHD</td>
<td>Latvia</td>
<td>70</td>
<td>2003 [66]</td>
</tr>
<tr>
<td>DRB1*07‡</td>
<td>↓</td>
<td>DRB1: 5 alleles</td>
<td>M</td>
<td>RHD</td>
<td>Turkey</td>
<td>102</td>
<td>2006 [67]</td>
</tr>
<tr>
<td>DRB1*11</td>
<td>↓</td>
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</table>

(Continued)
streptococcal type. This theory is supported by a study in a population in which HLA-DR4 was associated with ARF.69 The investigators found that antistreptococcal serum caused significantly increased toxicity to B lymphocytes bearing HLA-DR4 compared with DR4-negative lymphocytes, and they suggested that a strong antigenic similarity existed between HLA-DR4 and the streptococcal antigen, which led to defective antigen presentation by the HLA molecule (Figure 2). This in turn could lead to aberrant cytokine production and ultimately antibody formation against proteins on valves, myocardium, brain, and joint tissue.71 However, this occurred in lymphocytes both from individuals with ARF/RHD and from control subjects, which left the progression to ARF in some individuals unexplained. This study has not been repeated with any other HLA types. An alternate theory is that structural similarity causes streptococcal antigens to mimic HLA molecules, which initiates an aberrant immune response.70

More recently, it has been suggested that after binding to the antigenic peptide, the particular HLA complexes may initiate inappropriate T-cell activation72 (Figure 2). In this model, the HLA complex on the surface of the antigen-presenting cell presents the streptococcal peptide to peripheral T cells that have escaped immune tolerance. These T cells recognize and are activated by the peptide, but then they cross-react with similar self-antigens that they are unable to identify as self, which initiates the autoimmune process. This concept of an autoimmune process that is initiated by HLA-specific antigen presentation is supported by a recent study that used T-cell lines from valves of patients with severe RHD.72 In that study, an immunodominant peptide of the streptococcal M5 protein bound to HLA-DR53 and was recognized by an infiltrating T-cell clone from an HLA-DR53–positive RHD patient, which suggests that the peptide is presented to T cells in the context of HLA-DR53 in this instance.

The fact that different ethnic groups with ARF/RHD may have different HLA associations suggests that cross-reactive peptides may bind to several different HLA alleles that have structural homology in the peptide-binding groove. Although not inconsistent with this model, most researchers, however, have concluded that the association between HLA and ARF/RHD is through linkage disequilibrium and that an ARF

Table 1. Continued

<table>
<thead>
<tr>
<th>HLA Antigen</th>
<th>Association</th>
<th>Lack of Association</th>
<th>Method</th>
<th>Disease</th>
<th>Country/Ethnicity</th>
<th>No. in Study</th>
<th>Year and Reference</th>
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<tr>
<td>DRB1*07</td>
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<td>DQA1, DOB1</td>
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<td>RHD</td>
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<tr>
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<td>Rest of DRB1</td>
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<td>88</td>
<td>199963</td>
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<td>DR16 (DRB1*1602)</td>
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<td>M</td>
<td>RHD</td>
<td>Mexico</td>
<td>98</td>
<td>200364</td>
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<tr>
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<td>↓</td>
<td>DRB1: 13 alleles</td>
<td>M</td>
<td>ARF</td>
<td>Italy</td>
<td>25</td>
<td>200465</td>
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<tr>
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<td>M</td>
<td>RHD</td>
<td>Japan</td>
<td>72</td>
<td>199666</td>
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<tr>
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<tr>
<td>DQA1*0101</td>
<td>↑</td>
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<td>M</td>
<td>ARF/RHD</td>
<td>South China</td>
<td>54</td>
<td>199767</td>
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</tr>
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<td>DQA1*0201</td>
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<td>Rest of DQA1, DOB1</td>
<td>M</td>
<td>RHD, especially with similar clinical features</td>
<td>Egypt</td>
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<td>M</td>
<td>ARF</td>
<td>Turkey</td>
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<td>RHD</td>
<td>Turkey</td>
<td>85</td>
<td>200766</td>
</tr>
</tbody>
</table>

S indicates serological; M, molecular.
†Only in combination with DQA1*03.
‡Association also found with recurrent streptococcal pharyngitis.
§Only in D8/17-positive patients.
susceptibility gene exists that is mapped within or near the HLA complex. This may explain ethnically defined differences. A cosegregation study of 22 families of different ethnic background with multiple individuals with RHD supported this hypothesis, concluding that the inheritance method was dominant with variable penetrance. This supports the original twin-study finding of lower than anticipated concordance in monozygotic twins.

**B-Cell Alloantigens**

The idea that genetic determinants within the host immune response may be relevant to susceptibility to ARF led Patarroyo et al to use B-cell antiserum to distinguish individuals with past ARF from control subjects. Using alloantisera, they identified a novel B-cell alloantigen, called 883, which was expressed on the B cells of 71% to 74% of rheumatic fever patients compared with only 17% of control subjects. Monoclonal antibodies were developed to the alloantigen by Zabriskie et al and subsequently to another B-cell surface antigen that more accurately identified ARF patients. A number of studies have investigated the association of this antigen, D8/17, and ARF (Table 2).

In some studies, results have been expressed as the percentage of B cells that stain positive for the D8/17 antigen. In others, a receiver operator curve or other method has been

![Figure 2. Possible mechanisms for HLA association with ARF. The left side of the figure (antibody theory) illustrates how antibodies may be central to the mechanism through which the HLA association is mediated, either through defective presentation by the HLA molecule because of antigenic similarity, or through streptococcal antigens mimicking the HLA molecule. This is proposed to lead to aberrant cytokine production, poor antigenic clearance, prolonged B cell stimulation and increased production of antibodies against the various tissues affected in ARF. The right side of the figure (antigen theory) illustrates how streptococcal antigens may be presented to T cells in the context of specific HLA molecules, which are cross reactive to epitopes on the tissues affected in ARF, initiating an aberrant T cell response. GpA indicates group A; TCR, T-cell receptor.]

<table>
<thead>
<tr>
<th>Country/Ethnicity</th>
<th>Proportion of Individuals Positive (%)</th>
<th>Proportion of B Cells Staining Positive for D8/17 (Mean %±1 SD)</th>
<th>Cutoff (% B Cells Stained)</th>
<th>Disease</th>
<th>No. of RHD Cases in Study</th>
<th>Year and Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States and Trinidad</td>
<td>98.8/14</td>
<td>33.5±8.5/13.7±5.8/7.5±4.3</td>
<td>11.8</td>
<td>RHD</td>
<td>84</td>
<td>1989</td>
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<td>North India</td>
<td>62.9/12.5</td>
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<td>40</td>
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<td>90</td>
<td>1992</td>
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<td>North India</td>
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<td>10</td>
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<td>63</td>
<td>1998</td>
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<td>14.4</td>
<td>ARF/RHD</td>
<td>39</td>
<td>1990</td>
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<td>Mexico</td>
<td>89.7/11.1</td>
<td>34.6±13.2/12.5±5.7/7.5±6.9</td>
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<td>RHD</td>
<td>10</td>
<td>1992</td>
</tr>
<tr>
<td>Brazil</td>
<td>90/0</td>
<td>38.8±17.8/16.2±9.4/4.6±2.8*</td>
<td></td>
<td>RHD/RHD</td>
<td>117</td>
<td>1991</td>
</tr>
<tr>
<td>Russia</td>
<td>88.9/10</td>
<td>24.8±0.4†/11.1±1.0†</td>
<td></td>
<td>ARF/RHD</td>
<td>40</td>
<td>1996</td>
</tr>
<tr>
<td>Israel</td>
<td>91/0</td>
<td>11.5±3.0/4.2±2.7</td>
<td>7.55</td>
<td>ARF</td>
<td>22</td>
<td>2002</td>
</tr>
<tr>
<td>Aboriginal Australian</td>
<td>94.7/4.4</td>
<td>39.3±11.8/22.5±5.2/11.6±7.3</td>
<td>22.1</td>
<td>ARF/RHD</td>
<td>41</td>
<td>2006</td>
</tr>
</tbody>
</table>

*Estimated SE.
†Insufficient data available to confirm SE.
used to find a cutoff that is subsequently used to classify individuals as either positive or negative. With both methods, a clear difference has been shown in the expression of this antigen between RHD and control patients (Figure 3). However, substantial differences exist between studies in the proportion of D8/17-positive B cells; for example, a study in Israel reported the same mean percentage of D8/17-positive B cells (11%) in the disease group as was documented in the control groups in studies in Russia and Australia. Whether this is a difference between study methodology or expression in different populations remains unresolved. Regardless, D8/17 antigen appears to be more robust than HLA typing as a marker for RHD in geographically and ethnically diverse populations.

D8/17 appears to be more than merely a marker of past or current disease. In first-degree relatives, the proportion of D8/17-positive cells or individuals classified as positive has been found to lie between the proportions measured in patients and control subjects with no family history of RHD (Table 2). Khanna et al showed that D8/17-positive phenotype is an inherited trait, possibly autosomal recessive with incomplete penetrance. An intriguing finding in a study of family members of individuals with RHD was that 1 unaffected sibling with a high level of positive B cells (30% positive, with 13% being the proportion of D8/17-positive B cells that discriminated between rheumatic and nonrheumatic individuals) developed ARF shortly afterward. This supports the hypothesis that it is a true marker of susceptibility, which makes it an attractive prospect for identifying potential recipients of a vaccine or early preventative antibiotics.

Expression of D8/17 in patients with acute disease was recently studied in Aboriginal Australians. A small number of individuals with ARF had a significantly higher proportion of D8/17-positive cells (83.7 ± 10.1%) than individuals with RHD (39.3 ± 11.8%), who in turn had a higher proportion than relatives (22.5 ± 5.2%), with healthy control subjects having the lowest proportion (11.6 ± 7.2%). The authors hypothesized that D8/17 was expressed in susceptible patients and that this was augmented by the process that leads to ARF.

Infectious stimuli such as pneumonia and gastroenteritis have not been associated with increased D8/17 expression, which suggests that D8/17 is not a nonspecific result of B-cell activation. Studies showing an increasing percentage of D8/17-positive B cells with age in both individuals with RHD and their relatives suggest that expression may be a result of cumulative exposure to group A streptococcal antigens. However, in the Aboriginal population in northern Australia, infection with group A streptococci is endemic, D8/17 expression was higher in relatives than in control subjects, which suggests that inheritance is a more important factor than exposure to streptococci. D8/17 expression appears to be specific to rheumatic fever, because no association is present with other diseases such as poststreptococcal glomerulonephritis, rheumatoid arthritis, or systemic lupus erythematosus. However, a recent finding that 19 patients with poststreptococcal reactive arthritis had higher D8/17 expression than control subjects puts this into question once again. It may suggest a shared genetic susceptibility with ARF, but it could also support the streptococcal exposure theory.

Most studies have reported D8/17-positive expression in >85% of individuals with previous ARF, but this is not universal. In 1 study, antibodies to D8/17 were only found to discriminate between ARF patients and control subjects when staining of total lymphocytes (B and T cells) was assessed, which led to the authors’ suggestion that the discriminatory nature of D8/17 found in previous studies is simply a measure of B-cell numbers. In studies in which it is not explicitly stated that only B cells were stained, this is a possibility; however, in studies in which it is clear in the methods that staining for D8/17 was only undertaken in B cells, the discriminatory nature of D8/17 is unambiguous. Inconsistencies in the results between D8/17 studies have also been ascribed to technical difficulties with the D8/17 antibody.

Differences between studies are more likely to be attributable to population differences in B-cell alloantigen expression. In several studies in northern India, the proportion of patients with RHD who were D8/17 positive was only 63% to 69%. Monoclonal antibodies (PG-12A, -13A, and -20A) were therefore developed against B-cell alloantigens in local patients with ARF/RHD. In combination, these antibodies identified >90% of north Indian patients with ARF/RHD and were better than antibodies to D8/17 at discriminating between RHD patients and control subjects. Like D8/17, these population-specific B-cell alloantigens are most highly expressed in ARF but remain positive in chronic RHD. This study also showed that the proportion of D8/17-positive cells in ARF diminished between the acute phase and 3-month follow-up. It is not known whether the best way to discriminate patients with ARF/RHD from control subjects in every population is to use D8/17 or other monoclonal antibodies directed against markers in the local population.
It is not clear whether or how the expression of these alloantigens on B cells relates to the host immune response to group A streptococci. Williams et al. showed that the monoclonal antibody binds to sites on the surface of reactive B cells very close to but distinct from sites that bind group A streptococcal membrane antigens. This suggests a close relationship between them, possibly involving recognition and binding. A study on the tissue distribution of D8/17 antigen showed strong expression in cardiac, skeletal, and smooth muscle in blood vessels, as well as various epithelial and hepatic tissues. In the same study, a monoclonal antibody to D8/17 bound to vimentin and myosin (cardiac proteins) and to recombinant streptococcal M protein. This suggests shared epitopes between the proteins, alluding to a potential role in pathogenesis. It is possible that D8/17 could be an anti-idiotype, mimicking the antigenic interaction with antibodies and T cells in ARF. The same group also showed that cells from the pathognomonic rheumatic fever Aschoff nodule expressed both HLA-DR and D8/17. However, no correlation has been found between the presence of D8/17 and clinical outcome, and any role it may have in pathogenesis remains uncertain.

### Immune Gene Polymorphisms

There have only been a limited number of studies investigating genetic susceptibility associated with other components of the immune response (Table 3). In most cases, these comprise single studies in 1 population. However, there have been several studies examining the role of polymorphisms in the promoter region of the tumor necrosis factor-α (TNF-α) gene. These have shown associations with RHD in Mexican patients, both in the allele (TNF-α-308A and -238G) and in the genotype. An association was also found with valve damage, but no relationship was found with the specific valve...
affected. A study in Turkey confirmed the TNF-α-308A polymorphism association in RHD and showed that these patients also had increased production of TNF-α compared with those with the TNF-α-308G allele. A recent study in Brazil confirmed that patients with ARF/RHD were more likely to have the TNF-α-308A polymorphism, but an Egyptian study found that this was only true in individuals homozygous for the TNF-α-308A allele; heterozygous A/G genotypes were significantly less common in patients with RHD. An association with the TNF-α-238 polymorphism was also found, but in this population, it was with the TNF-α-238A allele rather than the G allele found in Mexican patients. In addition, when patients were clinically stratified in the Egyptian study, the polymorphisms were found to be present in patients with RHD and valvular lesions but not in those with Sydenham’s chorea. One study in Turkish children showed no association between polymorphisms in the TNF-α gene and risk of ARF or disease progression. However, in general, there does appear to be a risk association with polymorphisms in the TNF-α promoter region. Although cytokines are thought to play a role in ARF, the TNF-α gene maps close to the major histocompatibility complex region, and as yet, it is unclear whether the association is related to the effects of TNF-α or linkage disequilibrium with HLA or other possible risk-associated genes. If it is a marker for development of particular clinical features, as has been suggested, there may be therapeutic implications.

Noncytokine components of the immune response have received less attention. One study found associations between immunoglobulin FcγRIIA gene polymorphisms and concomitant genotypes in susceptibility to ARF. A possible mechanism for the association is a genetically determined failure of removal of immune complexes. Circulating immune complexes previously have been found in the sera of RHD patients along with raised IgG. Conversely, no association was found between RHD and polymorphisms in the T-cell receptor α- and β-chains in a study in Caucasian and Maori populations. The discovery of Toll-like receptors (TLR), key components of the innate immune response to bacteria, has introduced new avenues for research in disease associations. The only TLR polymorphism to be studied in relation to ARF/RHD to date, TLR-2, showed a strong association with ARF in children.

Other Gene Associations

Familial Mediterranean fever is an inflammatory condition characterized by recurrent fever, abdominal pain, and arthritis that is caused by mutations in the MEFV gene that encodes pyrin. Polymorphisms in the MEFV gene are associated with a number of inflammatory conditions, including juvenile rheumatoid arthritis and psoriatic arthritis. Patients with familial Mediterranean fever have a higher prevalence of RHD than the general population, and polymorphisms in the MEFV gene are associated with ARF. However, a recent study found that the polymorphisms in the TNF-α promoter region that are associated with ARF are not associated with familial Mediterranean fever, which suggests the association is by an alternate mechanism. The most consistent feature in all of these diseases is arthritis, and in rheumatoid arthritis, MEFV mutations are associated with more severe joint symptoms. It has been suggested that MEFV polymorphisms cause impaired control of the type 1 helper T cell (Th1) immune response, which is consistent with the proposed pathogenesis of ARF.

Most studies have investigated gene associations with susceptibility to ARF rather than disease severity; however, polymorphisms of the ACE gene have recently been associated with chronic valvular fibrosis and calcification in RHD. These polymorphisms are strongly associated with valvular damage compared with individuals with previous ARF but normal valves.

Genetically Determined Host Responses in ARF

Despite the burgeoning number of studies, it remains uncertain whether the associations between ARF/RHD and HLA molecules, B-cell alloantigens, and immune and other gene polymorphisms have a role in pathogenesis or simply represent disease markers. Although the molecular pathogenesis and immunopathogenesis of ARF have been explored in extensive detail, there has been less work to date attempting to link the potential susceptibility factors described above with current knowledge about pathogenesis. Defining the role of susceptibility factors in pathogenesis will allow us to understand more than the mode of inheritance of ARF. Recent studies of the pathogenesis of other severe streptococcal diseases hint at how host genetic susceptibility might influence disease outcome. It is well described that the same invasive streptococcal strain can cause disease of varying severity in different individuals. Certain HLA types protect individuals against severe invasive disease caused by superantigens, whereas others confer susceptibility. Moreover, different combinations of HLA allelic variations presenting different superantigens result in different in vitro proliferative effects and production of cytokines. This has been further explored in a study that showed that binding of the superantigen streptococcal pyrogenic exotoxin B is dependent on an HLA-DQ α-chain polymorphism, which went on to show this affected T-cell proliferation and cytokine production. In a mouse model, genetic differences affected the deposition of anti-myosin autoantibodies and the subsequent development of myocarditis. Whether any of these mechanisms are involved in the pathogenesis of ARF is not known.

In a disease as complex as ARF, which involves different potential bacterial antigenic triggers, humoral and cellular arms of the immune response, and damage to multiple specific tissues, it is doubtful that a single gene holds the key to understanding the intricacies of its pathogenesis. This complexity is underlined by the fact that although strong associations exist between susceptibility and disease, genetically susceptible individuals (defined by a previous episode of ARF) do not invariably develop ARF after exposure to rheumatogenic strains of group A streptococci. The advent of microarray technology has provided an ideal tool for the investigation of complex diseases such as ARF/RHD through the global analysis of genes and gene expression. To date, there have been no studies analyzing the entire host genome...
in relation to susceptibility to ARF/RHD. There have, however, been 4 global gene expression studies that investigated the host response to group A streptococci; 2 of these studies analyzed gene expression in human cells after stimulation with the bacteria in vitro, and 2 investigated gene expression in vivo in mice. A comparison of gene expression responses in neutrophils after in vitro stimulation with various bacteria showed that group A streptococci induce a unique gene expression profile in addition to the changes induced by all bacteria. Phagocytosis of group A streptococci caused differential expression of 393 genes in neutrophils that differed significantly from those induced by other bacteria. These included altered expression of 71 genes involved in apoptosis and cell fate and 26 genes regulated by interferon-γ. The authors postulated that as a result of decreased neutrophil survival, this favors pathogen survival and consequently the likelihood of disease. Pharyngeal adherence by rheumatogenic group A streptococci is thought to be a necessary virulence mechanism in the pathogenesis of the disease Investigation of murine valvular disease in ARF, which implies their involvement in the host response to group A streptococci; 2 of these studies provided tantalizing clues to pathogenetic insight into the multiple genes and other susceptibility factors that are involved in the interplay between rheumatogenic bacteria and the host immune system that leads to the aberrant autoimmune response underlying the immunopathogenesis of ARF.

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Disclosures

None.

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Some of the People, Some of the Time: Susceptibility to Acute Rheumatic Fever
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