Rheumatoid arthritis is a condition that causes chronic inflammatory arthritis. It has been linked to multiple etiologies; the cause is thought to be a combination of the environment, infection, hormones and a genetic component. The precise contribution of genetics to the development and course of rheumatoid arthritis is currently under investigation, and numerous gene candidates have been identified. The HLA-DR gene has been widely studied and numerous alleles have been identified that correlate to the development of rheumatoid arthritis. The role of genetics in rheumatoid arthritis is explored in this article.

**Background**

Rheumatoid arthritis (RA) is a chronic autoimmune disorder which causes inflammatory arthritis and occurs in approximately 1% of the population.\(^1\) It frequently presents as peripheral polyarticular arthritis, is symmetrical, and often progresses with joint damage and loss of function. There may be periods of remission, although variations on this pattern occur. In addition, the extra-articular manifestations vary greatly among patients. Without treatment, it leads to significant deformities as cartilage and bone are destroyed, so called erosive disease.

The precise cause is unknown, but genetic predisposition, the environment, infections, and hormones (potential precipitators) are thought to all play a role. The genetic component has been the subject of much research in recent decades, as RA has been found to cluster in families and occurs more frequently in families with other autoimmune disorders. The heritability of RA is estimated to be approximately 60%, with a 12-15% concordance rate among twins.\(^2\)

Several key genes have been targeted as they are implicated in the development of RA and the course of the disease. The group of human leukocyte antigen (HLA) genes on chromosome 6 has been at the forefront of genetic research in RA. Certain alleles have been associated with an increased risk of developing the disease and predicting its severity, and others are involved in protection from RA. The HLA gene products are involved in immune function, particularly coding for antigens expressed on the surface of white blood cells. Many genes aside from the HLA group have been linked to RA.

**Current Research**

The HLA region in the human genome is one of the most heterogeneous and is frequently targeted for studies involving disease susceptibility. For RA, the HLA-DR family has been studied extensively. Several theories exist for how the HLA molecule could influence the immune system. HLA molecules bind peptides and present them to receptors on the CD4+ T lymphocytes, so the epitope associated with RA could determine which peptides bind successfully, the affinity with which they bind, the epitope itself could be antigenic, or the epitope could influence which T lymphocytes survive in the thymus (i.e. giving a propensity for autoreactive lymphocytes to survive).\(^1\) In the majority of genetically-linked cases of RA, a shared epitope at amino acid positions 67-74 of HLA-DRB1 (the beta 1 subunit of the HLA-DR molecule) has been found. HLA-DR4, one of the most well studied, seems to be associated with both higher risk of disease and worse prognosis, particularly certain haplotypes within HLA-DR4 such as 0401.\(^3\)
Interestingly, some HLA-DR alleles are associated with protection from RA, even counteracting the increased susceptibility when the sister allele was associated with an increased RA risk.4

These protective HLA-DR alleles have a different conserved sequence than the so-called shared epitope associated with an increased risk. A well known example is HLA-DRB1 with the conserved epitope DERAA at positions 70-74 of the amino acid sequence. This allele was not only correlated with a lesser risk of developing RA, but was also linked to a less severe form in people with RA.5

The presence of the HLA alleles with the shared epitope has also been shown to have a high concurrence with the presence of anti-cyclic citrullinated peptides antibodies (anti-CCP), which are used in diagnosing RA. One theory is that the citrullinated peptide binds the HLA shared epitope resulting in activation of T lymphocytes. This may in turn lead to increased autoantibody production that results in the formation of anti-CCP antibodies.6 Anti-CCP is a stronger predictor of radiographic damage in early inflammatory arthritis than Rheumatoid Factor (RF) and is especially useful as a marker in those with negative RF who have RA. However, anti-CCP is not sufficiently sensitive to identify all those who will have radiological damage in early inflammatory arthritis.

Some important discoveries related to the HLA susceptibility region include7:

- Having two copies of a susceptibility allele makes a person even more likely to develop RA compared to having only one copy
- Having one or two copies of a susceptibility allele makes a person more likely to have severe disease
- The combination of alleles present alters the relative risk (i.e DR4/DR1 vs. DR4/X)
- Presence of the allele may also influence if a person will have extra-articular manifestations
- The timeline of progression of RA is influenced by the alleles present

The HLA-DR genes cannot be the only genetic contribution though, as not all RA patients have the implicated alleles and there is still a wide clinical heterogeneity amongst those that do. It has been estimated through sibship studies that HLA linked genes contribute about 30-40% of the genetic component in RA.8 Numerous other genes have been identified, and the more popular ones are summarized in Table 1.

The products of these genes are proteins or molecules that are involved in the immune response; as an intracellular signalling molecule, in the formation of antibodies, or in carrier molecules. A physiologic mechanism through which they contribute to the development of RA has been postulated for each one. Currently, screening of whole genomes of families where RA is prevalent is being undertaken to possibly discover other genes and better characterize the genes that have been discovered.

<p>| Table 1. Summary of genes that confer susceptibility to rheumatoid arthritis |</p>
<table>
<thead>
<tr>
<th>Gene</th>
<th>Product</th>
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<tbody>
<tr>
<td>HLA-DR9</td>
<td>Encodes cell surface antigens that present proteins to the T lymphocytes</td>
</tr>
<tr>
<td>STAT410</td>
<td>Encodes a transcription factor for signals from certain cytokines</td>
</tr>
<tr>
<td>PAD114</td>
<td>Encodes an enzyme that catalyzes peptidyl arginine to peptidyl citrulline</td>
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<tr>
<td>N22/PTPN2211</td>
<td>Encodes intracellular tyrosine phosphatase in T and B cells</td>
</tr>
<tr>
<td>SLC22A412</td>
<td>Encodes for an organic cation transporter</td>
</tr>
<tr>
<td>FCRL313</td>
<td>Encodes a B-lymphocyte specific membrane molecule</td>
</tr>
<tr>
<td>CTLA4/CD1521</td>
<td>Encodes a protein produced by activated T cells</td>
</tr>
</tbody>
</table>
The presence and implications of these genes vary widely by ethnic population with respect to rheumatoid arthritis. The prevalence of RA itself differs by ethnic group, for example Native Americans have been reported to have a prevalence as high as 2% whereas Asian populations as low as 0.3%.\textsuperscript{14} In addition, the polymorphisms of the human genome sequence in the alleles that are related to RA vary by ethnic populations, with higher concordance amongst more closely related populations.\textsuperscript{15}

Relevance

The key question regarding this research is whether it is limited to being an expensive research tool or if it will become relevant to patients and physicians. Given that many of these alleles are common in the general population, gene screening will not be useful as a screening tool to discover asymptomatic patients that will develop RA. However, since HLA alleles remain constant over a lifetime, typing may be useful as a predictor of the course of disease in patients already diagnosed with RA, it can be used to decide which patients will have more severe disease and who will progress quickly so that aggressive therapy can be initiated. Whether this will change outcomes needs to be studied. For now, its value seems limited to research where family members at risk for RA are being prospectively studied, particularly those who have already developed anti-CCP or RF.

Conclusions

It cannot yet be said what interaction and combination of alleles is necessary for the development of RA and for the specific phenotypes that are expressed. RF testing is done to determine who with early inflammatory arthritis will develop erosions, but combining RF and HLA may increase the sensitivity and specificity so that early aggressive treatment can be implemented. Since anti-CCP antibodies may have higher specificity for the development of RA, the combination of these two components could possibly increase the ability to predict the development and course of progression of the disease.

References