**Gene Susceptibility in Rheumatoid Arthritis**

All living organisms are made of proteins. Proteins are synthesized by RNA some of which themselves are functional units on their own. The gene is the hereditary unit in an organism and it is made of stretches of DNA which code for the different proteins in an organism. Genes contain all the information on an organism’s cells and therefore characteristics. It is through genes that characteristics are carried from parents to the offspring hence it is the hereditary tool in organisms. A scientific definition of gene is a locatable region of a genomic sequence which can be inherited by an offspring and is associated with regulatory, transcribed and functional sequence regions. Human being has an approximated 20 000 genes.

Gregor Mendel discovered the science of gene when he observed that biological traits are inherited from parents by offsprings while he was studying pea crop. The genetic material in the gene is the DNA. Biological traits such as eye color, number of limbs, blood type and susceptibility to certain diseases are due to different genes. Deoxyribonucleic acid (DNA) consists of four nucleotides; adenine, cytosine, guanine and thymine. These are typically called bases[[1]](#footnote-1). The most common form of DNA in a cell is in a [double helix](http://en.wikipedia.org/wiki/Double_helix) structure, in which two individual DNA strands twist around each other in a right hand spiral while RNA exists as single strand.

          Substances called promoters and enhancers function to determine the portions of DNA that are transcribed into mRNA and finally translated into a protein in the organism. A promoter is a regulatory region in the gene. It provides the position that is recognized by the transcriptory machinery for a gene to be transcribed and expressed as trait in an organism. The set of rules by which a gene is translated into a functional protein is called the genetic code. The various nucleotides in the gene DNA must appear in a given order on both strands of the double helix structure of the gene for a given protein to be synthesized. The amino acid required for a given protein must be synthesized for the needed protein to be obtained. The protein must then fold into a three-dimensional form to carry out its function.

          Changes or mutations may occur in gene resulting in deformities in the progenies and diseases in both the parents and the offspring. Other types of mutations however do not cause diseases but rather predisposes the organism to the disease. The gene therefore has high chances of being attacked by the pathogens that cause the disease and the person is thus susceptible to developing the disease. Susceptibility of genes especially exposes one to diseases such as diabetes and rheumatoid arthritis. Recent findings have established a strong susceptibility to rheumatoid arthritis and autoimmunity in humans[[2]](#footnote-2). Autoimmunity is a case in which the body’s immune system attacks its own antigen. It fails to recognize its antigens. Rheumatoid arthritis is a systemic autoimmune disease, implying it affects a given organ system in the body and affects 1% of all adults in the world. Its symptoms include destruction of joints and affect more women than men. It is found to hereditary in about 60% of the cases, inferring that there is strong genetic component in its manifestation.

The gene associated with susceptibility to rheumatoid arthritis is a ‘missense’ SNPs (single-nucleotide polymorphism) in a gene encoding for protein tyrosine phosphorylase. This risk SNP is found in 28% of rheumatoid arthritis cases. A variant of this same SNP is found associated with type 1 diabetes which is also an autoimmune condition. This phosphatase seems to increase the reactivity of the immune system towards the body’s own antigens thus increasing the risk of autoimmune disorders[[3]](#footnote-3). Human leukocyte antigen (HLA) frequency is found to be high in rheumatoid arthritis patients in comparison to the levels in healthy individuals. Studies on linkages and association of HLA and DRB1 gene confirm that HLA is the major genetic susceptibility locus for rheumatoid arthritis[[4]](#footnote-4). Studies of this association give clue to the epidemiology, causes and risk factors of rheumatoid arthritis.

 The most recognized RA associations are with haplotypes of the HLA-DRB1 locus and variation in PTPN22, both of which have been widely replicated. The established loci for rheumatoid arthritis including HLA-DRB1 and PTPN22 do not fully account for the genetic component susceptibility to the disease. Rare variants also mediate gene susceptibility and a gene-based genome-wide method that scans the whole genome is applied to identify accumulations of rare variants associated with disease[[5]](#footnote-5). However, these two associations explain only half of the familial aggregation of the disease.

More recently, large-scale whole-genomic association (WGA) studies have suggested a number of novel RA susceptibility loci. These include distinctions close to IL2 receptors’ (IL2RA and IL2RB) beta and alpha chains, a single-nucleotide polymorphism (SNP)[[6]](#footnote-6). Despite the successes achieved in studies of gene susceptibility in rheumatoid arthritis, a large proportion of the genetic component of RA susceptibility remains unexplained[[7]](#footnote-7). Whole genome associations studies help detect the genetic effects of complex autoimmune diseases provided the functional variants are common.

The strongest signals of association are observed for genes in the MHC, where an accumulation of rare variants reduces risk of RA, presumably as a result of linkage disequilibrium with HLA-DRB1 haplotypes. Rare variants are represented in the other established rheumatoid arthritis loci (TRAF1-C5, IL2RA, and IL2RB), but results do not indicate any evidence of rare variant effects within these genes[[8]](#footnote-8). There are rare variant associations with rheumatoid arthritis within the MHC, independent of the effects of the HLA-DRB1 locus[[9]](#footnote-9). Furthermore, a number of novel putative RA susceptibility genes have been identified outside of the MHC with signals of association at least as strong as would be observed through application of traditional single-SNP methods.

It is interesting to note that for all of these genes, accumulations of rare variants are associated with decreased risk of RA, suggesting them to be protective. This could reflect the fact that we are able to identify more rare variants in the larger sample of controls than cases during studies, and hence that our analyses have greater power to detect protective associations. Stronger signals for association of gene with rheumatoid arthritis are observed with accumulation of rare variants in the MHC (major histocompatibility complex).the accumulation of rare variants at the MHC reduces risk of rheumatoid arthritis due to linkage equilibrium with HLA-DRB1 haplotypes. This portrays the positive effects of rare variations.

Conclusion

          The gene is the basic hereditary material in an organism and it determines the traits of that organism. The traits could be those visible as well as biochemical reactions that maintain life. Mutations in the genetic information could lead to deformities in the protein structure and function. Proteins, such as immunoglobulin which protects the body against infections if deformed, render the body susceptible to attack by autoimmune diseases like rheumatoid arthritis (RA). Association of the gene with human leukocyte antigen(HLA) renders it susceptible to rheumatoid arthritis. Rheumatoid susceptibility loci include variations close to the alpha and beta chains of the IL2 receptor (IL2RA and IL2RB).some associations between  rare gene variation and the MHC result in reduced risks of rheumatoid attack hence the associations also have positive effects.

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1. MacKay et al, p 149–153 [↑](#footnote-ref-1)
2. Rubinow, p 670. [↑](#footnote-ref-2)
3. Kurreeman et al, e278. [↑](#footnote-ref-3)
4. Darren et al, par6-14 [↑](#footnote-ref-4)
5. Jawaheer et al, p 910,14 [↑](#footnote-ref-5)
6. Morris et al, p131. [↑](#footnote-ref-6)
7. Haram et al, p 308 [↑](#footnote-ref-7)
8. #  Kurreeman et al, p*1789-1790*

 [↑](#footnote-ref-8)
9. Laëtitia et al, p1650. [↑](#footnote-ref-9)