

Resource

## The genetics of rheumatoid arthritis

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### Introduction

Rheumatoid arthritis (RA) is considered to develop as a result of interactions between inherited (genetic) factors and environmental factors (things that we are exposed to in the environment such as cigarette smoking).

Recent technological advances have made it possible to examine, in detail, the genetic factors that

are associated with RA. To date, researchers have found over 100 genetic changes that occur more commonly in patients with RA. The advances in this field have required a considerable investment from patients, their families, physicians, researchers and their funding institutions.

Although there have been some exciting developments in the treatment of RA, it is clear that some of these medications work better in some patients than in others. It is hoped that, in the future, research into the genetics of RA might provide us with important information about the medications to which an individual is likely to respond.

The paragraphs below outline the progress that has been made so far into genetic research and RA and the potential benefits of this work in the longer term.

## Evidence for the role of genes in rheumatoid arthritis: family studies

Isolated reports of RA affecting several generations in families, which were all published in the early 20th century, prompted further studies in the 50s, 60s and 70s. These compared the number of cases of RA in relatives of patients with the disease with the number of cases in relatives of patients without the disease, or with the number of cases in the general population. These studies confirmed that relatives of individuals with RA had an increased risk of getting the disease themselves, compared to other relatives or the general population. The estimates of the degree of this risk varied quite widely between the studies, reflecting the different methods used. The most recent study assessing this issue, which was undertaken in Sweden, reported that first degree relatives of patients with RA (parent, sibling or child) were approximately three times more likely to develop RA when compared to first degree relatives of people from the general population.

## Twin studies

Studies on twins offered further evidence that genes contribute to the risk of RA. Identical twins (twins that share 100% of their genes) were more likely to both have RA than non-identical twins (twins that share 50% of their genes). In one study involving twins in the United Kingdom, both twins had RA in 15% of the sets of identical twins in the study, compared with 4% of non-identical twins.

## How much of the risk of developing rheumatoid arthritis is determined by genes?

Although the work outlined above clearly supports the role of genes in determining the risk of RA, it is also clear that they do not account for all of an individual's susceptibility to the disease. Many patients may not have a family history of disease, and in families with more than one individual affected, RA is not clearly transmitted from one generation to another. These observations suggest that genes, the environment and the interaction between the two, may determine who develops RA. The heritability of a disease is an estimate of the extent to which genes explain the risk of disease in a population and the 'disease heritability' for RA can be calculated using the data from twin studies. Heritability estimates for RA, in studies performed in Northern Europe, are between 53% and 68%, suggesting that genetic factors account for more than half of the disease susceptibility in these populations.

## Which genes are responsible for increasing the risk of rheumatoid arthritis?

Many genes are involved in making individuals more likely to develop RA. Each gene contributes a small amount to the overall risk of developing the disease. The genes involved appear to vary

between individuals and between populations in different parts of the world. To date, most work has been done by looking at the genetic markers associated with RA in people of European ancestry.

Finding genes that might increase the risk of developing RA, when they only have a small effect on that risk, is difficult, but much progress has been made. This has been made possible by two important developments. The first is the advances in technology, which have made it possible to test a large proportion of the genome (all of an individual's genetic material) relatively quickly and affordably in large numbers of individuals. The second is the large number of patient and healthy control samples that have been donated by patients and collected by researchers collaborating in different parts of the world.

The main method used to identify genes associated with the development of RA has been to look at differences in genetic markers between many thousands of people with and without RA. When there is a larger difference in the proportion of people with and without RA that have the genetic markers than you would expect to find, these markers are said to associate with RA. The largest genetic study in this area has identified 101 genetic areas that associate with RA.

Many of the genetic areas associated with RA are close to genes involved in the functioning of the body's immune system, which is responsible for driving inflammation in RA. They, therefore, highlight parts of the immune system that may benefit from targeted treatment in order to reduce the symptoms and signs of RA. Interestingly, many of the genetic areas associated with RA also associate with other autoimmune diseases such as systemic lupus erythematosus (SLE), coeliac disease and inflammatory bowel disease (IBD).

One of the main limitations of these studies is that they only find genetic markers that are associated with the development of RA and do not identify the precise genes that cause it. There are, however, two genes that are known to be involved with the development of RA:

1. The HLA-DRB1 gene: This gene is the strongest known genetic risk factor for RA development. There are many different variants of this gene, and several are associated with an increased risk of developing RA. There is also some evidence of an interaction between certain variants of the gene and environmental factors, as the risk of developing RA is particularly increased in individuals who smoke and who also have certain high-risk HLA-DRB1 variants.
2. The protein tyrosine phosphatase 22 gene (PTPN22): It is not yet clear exactly how this gene predisposes to autoimmune disease, but it is known to be associated with a stronger likelihood of developing RA.

It is possible to be confident that both these genes are involved because the genetic variants that associate with RA are located in the gene itself and alter their function. However, in many cases, the genetic variants associated with RA are in between genes. They act by controlling the amount of gene product, but a single genetic change can control more than one gene and/or can control genes some distance away. A lot of work is currently going on to confirm all the genes involved.

## Autoantibodies and genes?

Blood tests commonly performed on people with suspected RA include tests to check whether the person carries antibodies (proteins made by the body's immune system) associated with RA, called "rheumatoid factor" and "anti-cyclic citrullinated peptide" (anti-CCP). Studies indicate that the genetic

risk factors associated with RA differ between individuals with and without anti-CCP antibodies. In one recent study, approximately half of the genetic risk factors for RA had significantly stronger links to anti-CCP positive disease.

## How much of the genetic cause of RA have we identified?

Despite the success of studies in finding genetic markers associated with RA, approximately one-half of the genetic causes of RA remain unknown. There is therefore still a long way to go towards detailing the exact genetic causes of RA, although the constant improvements in the technology used to analyse genetic material offer much hope that, in the future, the “missing” genetic risk will be identified. It is likely that thousands of genes can contribute a very small increased risk and that patients will have different combinations to explain their genetic risk.

## Can genetic markers be used to predict who will respond to medications?

These are exciting times in the treatment of RA, with a number of different types of medications currently available to manage the condition. The recent explosion in the number of “biologic” and targeted therapies available to treat RA, all of which work through slightly different mechanisms, have made it important to develop ways to predict which individuals will benefit from which drug. This would allow us to tailor treatment to each person.

Several large studies have been carried out focussing on “anti-TNF” biologic drugs to find genetic markers that may predict whether these drugs are likely to work well in patients with RA. One study looked for genetic markers associated with a reduction in levels of disease activity in 2,706 RA patients receiving one of three anti-TNF medications (etanercept, infliximab or adalimumab). The researchers found that one marker was associated with a reduction in disease activity in individuals receiving etanercept. In another study, the HLA DRB1 gene variants that increase the risk of RA were also found to predict a better response to these treatments. Far more work is needed in this important area; however, before we can use genetic information to guide treatment decisions.

## Can genetic markers be used to predict how severe someone’s rheumatoid arthritis will be?

One way of looking at the severity of someone’s RA is to look at how much damage shows up on x-rays taken of their hands and feet. A recent study, using x-ray, in 325 Icelandic people with RA showed that a person’s genes are very important in determining how much damage they have, but studies looking into this issue are in their relative infancy. This is because, in order to look for genetic markers that predict this damage, you need to have genetic information on large groups of people and they would also need to have had regular x-rays performed over time. Although patient groups like this are relatively scarce, researchers have had some success in identifying genetic markers associated with damage shown on x-rays. As with genetic markers associated with treatment response, much more work is needed in this important area. ?

## Why is it important to identify the genes that are involved with RA?

There are a number of reasons why it is important to identify the individual genes involved in RA development, RA severity, and responses to RA treatments. These include:

1. Identifying new targets for treatment: through finding the genes that are involved in RA, researchers may be able to develop new drugs that target proteins produced by these genes; these may be very effective at treating RA.
2. Predicting who will develop RA: much research is underway to try to develop ways of combining genetic and environmental risk factors for developing RA, to estimate someone's lifetime risk of developing this disease. Information that can identify individuals at a very high risk of developing RA is important. It could enable researchers to look at ways to prevent the disease from occurring in people who have a significantly increased risk of developing it. Examples of how RA could be prevented include: (1) lifestyle changes such as stopping smoking (people who smoke are more likely to develop RA) but knowledge of genetic risk can result in a higher likelihood of changing behaviours such as smoking or (2) drug treatments (although further research would be needed in clinical trials to establish the best treatments).
3. Predicting how severe someone's RA is likely to be: as with genetic markers associated with the development of RA, any genetic markers that are found to be associated with severe RA could be used to predict someone's risk of developing severe RA when they first present with arthritis symptoms. This would allow the intensity of how people are treated to be tailored on an individual basis early on in their disease.
4. Predicting which treatment someone with RA will respond to: the wide variety of medications available to treat RA make it important to develop tools to identify which medication will work in which individuals. This will prevent unnecessarily treating someone with a medication that is unlikely to work for them. Our hope is that in the future, genes could be used in this manner.

## Summary

Although it has taken a considerable amount of effort to identify the genetic markers involved in RA development, RA severity, and responses to medications, the hard work has only just begun! Much more work is needed to understand the genes that are actually involved in these processes alongside how variations in these genes alter the immune system and the inflammatory process.

Updated: 24/09/2019

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