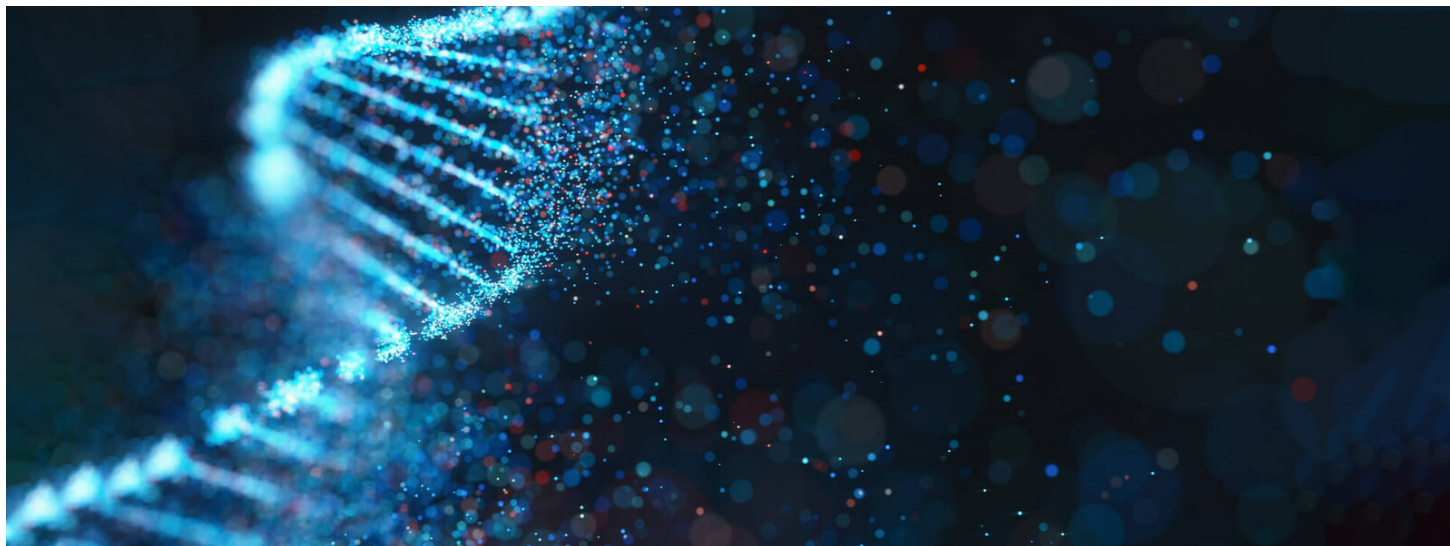


Is Rheumatoid Arthritis Genetic or Hereditary?

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More than 1 million people in the United States live with rheumatoid arthritis.¹ Rheumatoid arthritis, or RA, is a chronic autoimmune disorder that affects the joints—mostly in the wrists and hands, spine, knees, ankles, and feet.² In RA, the immune system attacks the healthy tissues surrounding the joints, causing inflammation that can lead to pain, swelling, stiffness, and, over time, limited mobility and loss of joint function. If left undiagnosed or untreated, RA can be quite debilitating for some patients.³

To what extent is RA hereditary? While all the factors that cause RA are not entirely understood, the disease tends to cluster in families, and is driven in part by genetics.

But one thing is certain: the more experts understand RA and the genetic markers associated with the condition, the more likely that patients can be diagnosed earlier and receive more effective, tailored treatment options.¹

Genetics and RA⁴

"The bulk of genetic heritability is carried in the Human Leukocyte Antigen (HLA, also called the major histocompatibility complex, MHC) genes," says Xinli Hu, MD, PhD, a senior computational geneticist in Systems Immunology at Pfizer. These HLA genes encode for proteins that normally help the immune system distinguish 'self' from pathogenic cellular materials (such as proteins found in viruses and bacteria). Outside of the HLA genes, the majority of involved genes also function within the immune system."

Many autoimmune diseases, like RA, have a genetic basis, meaning, people with certain genetic markers have a slightly higher chance of developing the disease. Studying genetic markers that are associated with RA can help shed light on the condition.

Researchers have identified four main genetic markers that are linked to RA:

HLA-DR4—This is the gene that is most associated with RA. People who have this gene are more likely to develop RA than those who do not and symptoms may be worse.^{5,7}

STAT4—This particular gene regulates and activates the immune system.⁶ **TRAF1 and C5**—These genes play a major role in causing chronic inflammation. **PTPN22**—This gene influences the progression and expression of RA, however, the reasons why are still to be determined.⁷

According to Hu, there are more than 100 regions across the genome discovered to be associated with the risk of developing RA across multiple ethnicities. Yet it's important to note that not everyone with these genes will develop RA, and not everyone with RA has these genes. More research is needed to understand how it develops in some people, but not others.

Hereditry and RA

If a relative (parent, sibling, etc.) has RA, it increases one's risk of getting the disease, 0.8% compared to 0.5% for those who have no family history.⁸ Another study, conducted on identical twins, found that if one twin has RA, there is a 12-15% chance the other one will also have it.⁸

"RA, like many autoimmune diseases, is quite heritable and unfortunately tends to cluster in families," says Hu. "Many genetic studies have gone into identifying genes that predispose individuals to the risk of RA."

In short, family history plays a role in developing RA, however environmental factors such as age, gender, and smoking factor in as well.

Environmental and behavioral risk factors

Evidence suggests that environmental factors play as much a role in RA as our genes and family history do. Researchers are finding that an RA diagnosis is a combination of genetics, family history, and environmental triggers.⁸ For example, a person may have the genetic markers for RA, but they haven't been "switched on," so to speak, until something triggers it.

Several environmental risk factors may trigger RA, including:

Age—Risk for RA has been shown to increase with age. The condition is highest among adults in their 60s and older.^{2,3} But, Hu explains that it's a bit more nuanced than that. "RA that occurs (with age of onset) after age 60 tends to be clinically and demographically quite different, and is known as elderly-onset RA or late-onset RA. In any case, it may not be as linear as we think, though there is definitely a peak of onset concentrated in the 30-50 range (it's within this group that female: male ratio is much higher)."

Gender—RA affects more women than men, 2-3 times as much.^{2,3,9}

Smoking—Multiple studies show that smoking significantly increases the risk of RA, especially for those with the genetic marker, HLA-DR4.^{2,3}

Obesity—People who are obese are also at an increased risk of RA and the increased weight can make the disease worse.^{2,3}

Treatment Advances & Research

While there is no cure for RA, there are several treatment options that can help slow the progression of the disease—another reason why early diagnosis is so critical. Rheumatologists may suggest medications that slow the disease and prevent joint deformity. In addition to medication, they may also recommend physical and occupational therapy and/or surgery (joint replacement surgery). Lifestyle modifications like regular exercise, stress management, and weight loss can also help reduce RA symptoms and help with pain management.^{2,3}

"There are two broad types of research aimed at understanding the link between genetics and RA," says Hu. "One is identifying genetic variations across the genome that are associated with the risk of disease, and the other is investigating the biological

consequences of such genetic changes in cells, tissues, and organisms."

Clinical trials offer some hope as well. These trials are actively working to understand RA better and to develop newer, more advanced treatment options. By analyzing RA's genetic markers, researchers will be better able to tailor drugs and medications for patients.

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