Rheumatoid Arthritis: A Comprehensive Study of its Causes, Progression, and Treatments

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Abstract:

The genes **HLA-DRB1**, **HLA-DR4, STAT4, TRAF1, and** pro-inflammatory protein **C5** all play a role in the genetic causes of Rheumatoid Arthritis (RA), and inheriting these genes can increase one's chances of being diagnosed with RA. The most common symptoms are joint pain, swelling, and tenderness and these symptoms present themselves in four stages. Everyone can be diagnosed with RA, but people from certain regions are more likely, which could be due to the history of the genes, environment, and living standards, as well as age and gender. There are treatments that are given to patients with RA; for those with less severe forms, medication and physical therapy are the best solutions, however, far more developed forms of RA may need surgery. Similar to RA, Lupus, another autoimmune disease that affects the kidneys, has a more widespread effect throughout the body.

Intro:

Arthritis is a very well-known disease; many have heard of it and maybe even have a family member or others suffering from it. The most commonly diagnosed form of arthritis is osteoarthritis, a disease in which the cartilage that caps the bones in the joints to cushion the joints starts to wear off. Alternatively, a specific autoimmune disease within arthritis is Rheumatoid arthritis (RA). An auto-immune disease is when the immune system mistakes healthy tissue as foreign and attacks them. In the case of RA, those who suffer from such a disease have an immune system that is unable to recognize the joints as healthy tissue, and it attacks the joints causing stiffness, pain, and inflammation. The immune system carries out its task to terminate the foreign tissue or substance to protect the body, unaware that the tissue or substance is healthy. This is very similar to an allergic reaction, but not the same process. The difference in allergic reactions is that the body mistakes an outside substance, such as a type of food, to be harmful. For example, someone who is allergic to peanuts is someone whose immune system does not recognize the peanuts and starts to attach to the body. The immune system produces antibodies to attach to the allergen, known as an antigen. Antibodies tag the antigens with a flag, allowing the lymphocytes to locate and remove the antigens from the body. In auto-immune disease, the tissue in the body is attacked. The destruction of the tissue in these diseases affects the body as a whole and sets off a chain reaction effect, slowly damaging all parts of the body.

Genetic Causes of RA and Heritability:

While **RA is not hereditary**, genetics can increase one's chances of developing this autoimmune disorder. Researchers have found several genetic markers that increase this risk. [1]These genes are associated with the immune system and increase the chances of developing chronic inflammation and RA in particular. As aforementioned, **rheumatoid arthritis may run in families**. If a person has a close family member, such as a sibling or parent with RA, they are three times more likely to develop RA than the general population. [2]

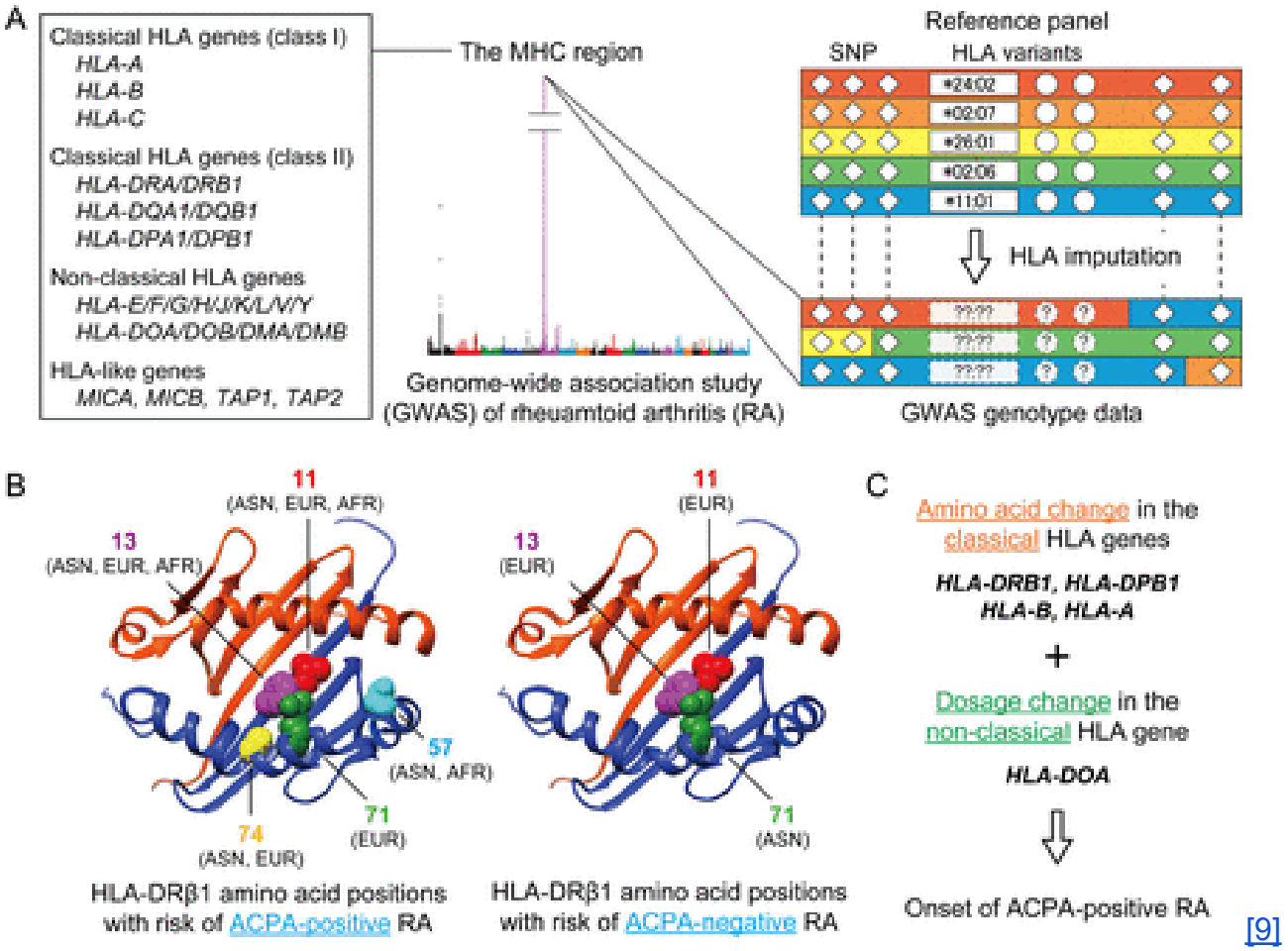
Since RA is an auto-immune disease, genetics play a role in disease development. Those with RA have a mutation or error in their genes that causes the body to program for an immune system to attack healthy tissue. Several factors within the genes can cause, determine, and diagnose the presence of RA.

The HLA (human leukocyte antigen) allele correlates with the greatest chance of developing RA and plays a huge part in the body's immune response. [3] The **HLA-DRB1 gene** is a gene that codes for proteins that are essential for the immune system, and the mutated form of this gene is the strongest known genetic risk factor for RA development [4]. In other words, having this gene mutation increases one's risk of having the disease. In addition to that gene, **HLA-DR4**—is another gene that is strongly associated with RA[5]. This gene is a marker that differentiates between two cells: its own, and a foreign cell. In cases where this gene is mutated, proteins and tissue in the body will start attacking itself, causing an autoimmune response in the body. If this gene marker is found in white blood cells, it can be an indicator of the presence of RA. [6] In fact, a person with the HLA genetic marker is five times more likely to develop rheumatoid arthritis than those who do not have this marker.

TRAF1, a gene that codes for the TRAF (tumor necrosis factor receptor-associated factor) protein, **and C5**, a pro-inflammatory protein, play a major role in causing chronic inflammation. The signaling adaptor, TRAF1, regulates inflammatory responses to pro-inflammatory cytokines. The C5 protein, also a signaling adaptor, signals inflammatory cells to come to a certain location within the body. C5 itself does not cause inflammation, but the gathering of inflammatory cells initiates the inflammation cascade. The increased inflammation will also lead to the worsening of symptoms for those with these mutated genes or proteins.

Another gene, **STAT4,** codes for a transcription factor that attaches to certain segments of DNA and controls the activity of the genes within that segment. [7]The main purpose of the STAT4 gene is to regulate and activate the immune system. When this gene is mutated, the immune system malfunctions and inflicts harm to the body, and could present in a form of an autoimmune disease.

Also, a specific antibody may form when RA is present in the body. In RA, **ACPA** (anti-citrullinated protein/peptide antibody) and **anti-CCP** (cyclic citrullinated peptide) antibody levels are highly elevated and are widely used for the diagnosis of RA. [8]



[9]

This diagram describes that RA has an ACPA-positive form and an ACPA-negative form. While ACPA levels are a tool used for diagnosis, patients without it can still be diagnosed with RA. Other factors play a role in RA that lead to a diagnosis, such as symptoms, family history, environment, etc.

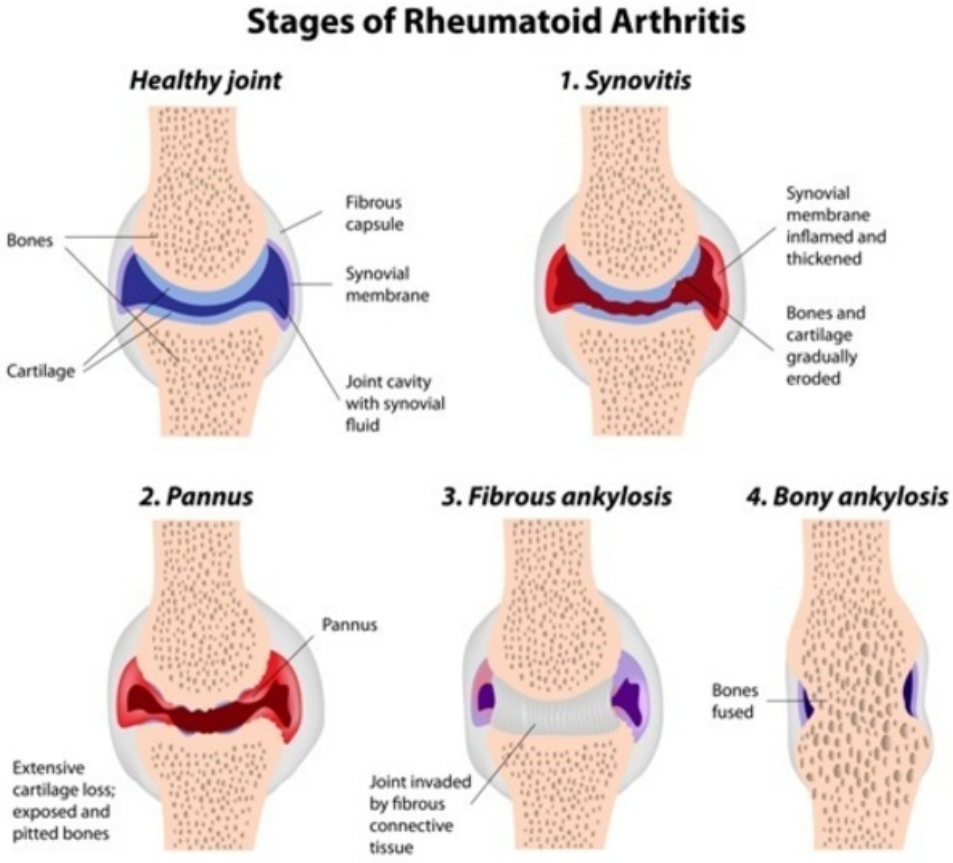
Symptoms and Presentation:

There are a variety of symptoms when it comes to RA. Some of the symptoms overlap with other diseases and some are very specific to rheumatoid arthritis. There are chances of feeling weakness, fatigue, and fever, which are the common symptoms of most diseases. However, looking specifically at RA, symptoms include pain or aching in more than one joint elicited by having a cold, stiffness in more than one joint, tenderness and swelling in more than one joint, and symptoms presenting in various locations of the body, such as in one's hands and one's knees. [10]

RA may also cause an increased risk of developing other diseases. People suffering from RA may be more likely to develop lung diseases. Since the autoimmune disease leads to an amplified immune response, it eventually leads to scarring of the lung tissue. [11] It is said that one in every 10 people suffering from RA is likely to develop interstitial lung diseases. This accounts for 10-12% of deaths of all RA-suffering patients. [12] Additionally, having RA can lead

to higher chances of contracting viral illnesses, such as COVID-19 and others. Their symptoms may be worse than those in a patient without RA. [13]

Looking at the stages, there are 4 stages of progression in RA:



[14]

Stage 1: Synovitis
This is the stage where the symptoms start to show. The joints start to become inflamed as well as stiff, which is accompanied by warmth and pain.[15] The synovium in the joints starts to attack itself[16] This stage can be reversible in RA if diagnosed early on. [17]

Stage 2: Pannus
This stage often is the starting point in RA and is not completely reversible. Some things can be done for treatment but there is no cure. [18] The synovium gets inflamed which forms a pannus. [19] This extra growth in one's joints increases the symptoms of stage one. [20]

Stage 3: fibrous Ankylosis
This stage is when one's range of motion is decreased due to fibrous connective tissue formation. The bones start to fuse causing stiffness within the joint [21]

Stage 4: Bony Ankylosis

This is the last stage. This is a union of bones of a joint. In other words, the joints have completely fused and no longer possess any sort of movement at all. There is complete immobility. [22]

Population Health:

Rheumatoid arthritis affects all ages, races, and social and ethnic groups, but there is a commonly seen pattern. At the regional level, age-standardized RA prevalence, where the disease is most common in terms of widespread regions, was highest in high-income **North America, Western Europe, and the Caribbean**, whereas Southeast Asia, Oceania, and Western Sub-Saharan Africa had the lowest age-standardized rates. [23] Non-Hispanic Blacks, Hispanics, and mixed groups with arthritis have been shown to have higher arthritic activity, work limitations, and more severe joint pain than non-Hispanic Whites with arthritis. [24] Previous studies have combined Asians and Pacific Islanders into one group. This data is seen as a whole and is an intentional community-based strategy to build a coalition with one another.

Environmental factors, livability, and assets come into play with these diseases as well. Since the distribution of RA is not random and certain areas and regions are more prone to having RA, genetics and living standards and other factors can either increase or decrease one's chances of developing RA. Those that have access to cleaner living environments, nutritious food, and good care, are overall less likely to have communicable diseases. This is because living in cleaner environments helps to prevent the spread of these diseases. [25]. There are chances that a lower standard of living can protect against some diseases, such as obesity, heart attack, and other illnesses, that are highly dependent on environmental factors. In fact, sources suggest that higher standards of living increase the chances of chronic diseases.[26] However, in the case of RA, regions with higher standards of living express a decreased prevalence of the disease. This is because those in these environments have jobs that are less prone to the development of RA, such as industrialized work. They also have better access to tools that help diagnose and manage RA symptoms.

There is also a difference in gender and the likelihood of getting the disease. About 75% of those affected with RA are women and women are two to three times more likely to develop rheumatoid arthritis than men. It is most likely to strike people 35-50, but it can occur in children, teenagers, and older adults.[27] Rheumatoid arthritis that begins in people under 16 years of age is similar, but not identical, to the disease in adults and is referred to as juvenile idiopathic arthritis (formerly juvenile rheumatoid arthritis). [28]

Treatments:

The main treatment goals with rheumatoid arthritis are to control inflammation and ease pain caused by RA. Keep in mind there is no cure for RA. However, some treatments and daily habits can be implemented into one's life to improve RA symptoms and side effects. Treatment usually includes **medications, occupational or physical therapy, and exercise**. [29]

Early treatment is key to good results. Keeping up with a regular annual check-up for RA will allow for an early diagnosis when the disease can be treated with ease. The best recommendation would be to keep moving the joints through regular therapy. Never overwork

the joint but work it enough with the guidance of a healthcare professional. [30] Physical therapy is key and must be completed with the medical assistance of a physical therapist when working on exercising the joints. Additionally, some may be prescribed **methotrexate,** which is an immunosuppressive drug commonly prescribed for the treatment of RA. [31]

Sometimes, if RA has extreme effects on the body that can not be fixed with just exercise or medication, it is best to look into surgery. However, proceeding with any treatment and even diagnosis should be done through a certified medical doctor. Looking things up and or giving a diagnosis through a non-professional environment can only further harm the health. The medications, treatments, and diagnosis need careful care and thorough medical examinations. Patient and family history, allergies, other health diseases, etc. all are considered in any treatment. These are some suggestions that can help manage symptoms, but any serious care or treatment should be given and looked at by a doctor.

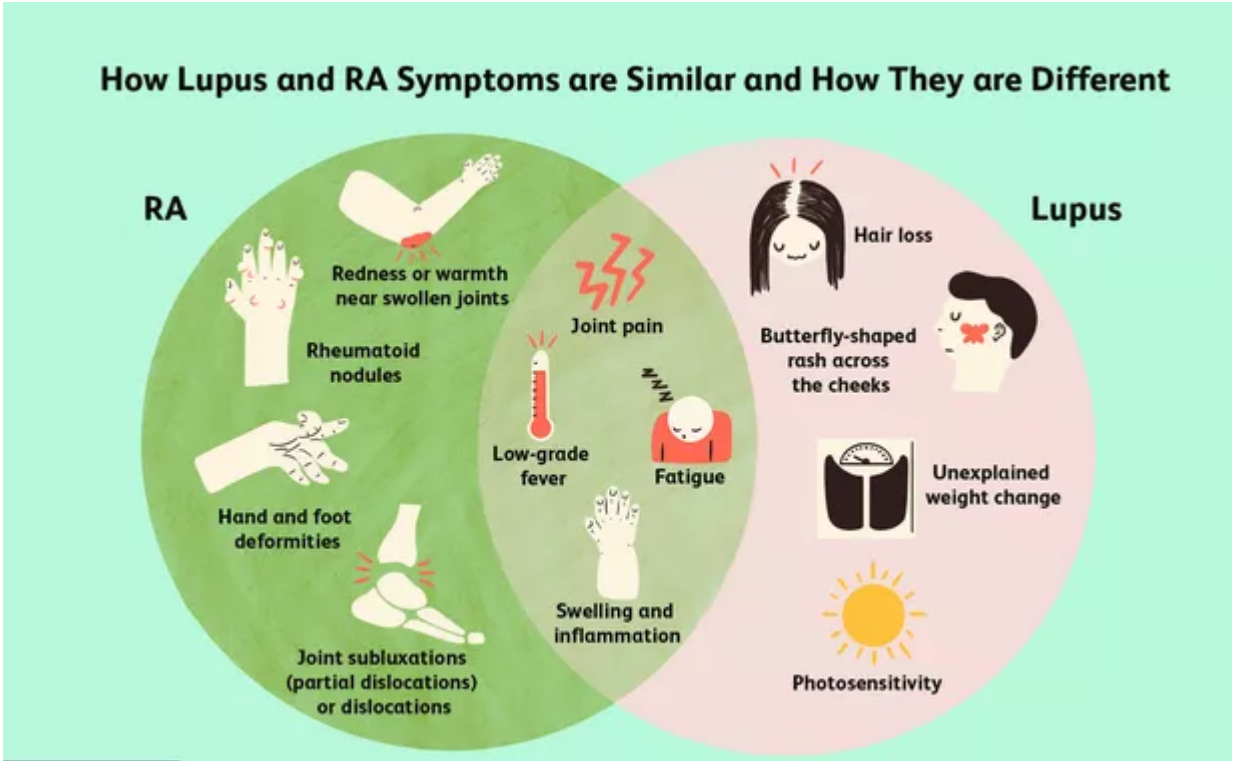
Comparison to Lupus:

Lupus is also an autoimmune disease that attacks healthy tissues. In a general overlook, RA is mainly limited to the joints, while Lupus affects more than just the joints. However, both diseases still have similar symptoms. The reason why the symptoms of Lupus are far more widespread throughout the body is that it is a kidney disease. Since the kidney plays a larger role in maintaining internal homeostasis, damage to the kidneys leads to a more widespread effect of symptoms [32]. In Lupus, the nephrons in the kidney start to attack themselves, also known as Lupus nephritis, and this causes a malfunction in the kidneys. According to some sources, when there is no filtration in the kidney, the waste starts to pile up within the body and is not excreted through urine. That can cause swelling in one's ankles, nausea, weakness, poor sleep, and shortness of breath. If the kidneys are not treated, they will eventually fail to work at all. This can be life-threatening and needs to be taken care of immediately. [33]

There is a similarity between Lupus and RA in terms of population health. Both Lupus and RA are more prominent in females than males. Data shows 9 out of 10 suffering from Lupus are women. Research is ongoing about why this is the case, but it could have something to do with the genetics or hormone differences between the two sexes. [34]

Although the age range for developing Lupus is about 15-44 years old, children, teens, and elders can still develop Lupus. The age range Lupus occurs in the most is the commonly defined ‘childbearing’ age range of a woman. Since it is more prevalent in women, this age range is also when women are at the highest risk of developing the disease. [35]

Just like with RA, Lupus favors certain regions of the world more than others. Lupus tends to affect **African Americans, Hispanics, and Asian Americans** more than others. In fact, Lupus is more prevalent among people of color rather than among Caucasians. However, anyone is capable of developing Lupus, but this just represents the highest density of Lupus prevalence. [36] Also, in the US, **Native Americans, Native Hawaiians, and Pacific Islanders** are more likely to develop Lupus. [37]



[38]

This is a Venn Diagram that gives a visual of the similarities and differences between Lupus in comparison to RA. This diagram gives insight into the symptoms that each presents with and where they tend to overlap.

Conclusion:

RA is an autoimmune disease that affects the joints of the body. There are genes that when mutated, lead to the development of RA. Inflammation of the joints leads to pain and distress throughout the body. Furthermore, RA can present through its 4 stages and require specific treatment at each stage. Additionally, there are a variety of treatments available for RA but there is no cure.

Select regions of the world have specific patterns of the prevalence of RA. These areas can reflect the environmental standards of living, indicating that genetics is not all when it comes to RA. To distinguish RA from Lupus, a similar autoimmune disease, Lupus is a renal disease that affects the whole body due to renal insufficiency. RA and Lupus show patterns of similarity in that women are more likely to develop those two diseases and they present with symptoms that can easily be mistaken for one another. On the whole, since RA is a common disease, the way RA develops, the signs, symptoms, prevalence, and treatments are all subjects of matter that society should be familiar with and take into consideration for the benefit of others and themselves.

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