Medical Xpress

Researchers pinpoint genes behind sex biases in autoimmune disorders, schizophrenia

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Some diseases exhibit a clear sex bias, occurring more often, hitting harder or eliciting different symptoms in men or women.

For instance, the autoimmune conditions lupus and Sjögren's syndrome affect nine times more women than men, while schizophrenia affects more men and tends to cause more severe symptoms in men than in women.

Likewise, early reports suggest that despite similar rates of infection, men are dying from COVID-19 more often than women, as happened during previous outbreaks of the related diseases SARS and MERS.

For decades, scientists have tried to pinpoint why some diseases have an unexpected sex bias. Behavior can play a role, but that explains only a piece of the puzzle. Hormones are commonly invoked, but how exactly they contribute to the disparity is unclear. As for genes, few, if any, answers have been found on the X and Y sex chromosomes for most diseases.

Now, work led by researchers in the Blavatnik Institute at Harvard Medical School and at the Broad Institute of MIT and Harvard provides a clear genetic explanation behind the sex bias observed in some of these diseases.

The team's findings, reported May 11 in *Nature*, suggest that greater abundance of an immune-related protein in men protects against lupus and Sjögren's but heightens vulnerability to schizophrenia.

The protein, called complement component 4 (C4) and produced by the

C4 gene, tags cellular debris for prompt removal by immune cells.

The team's key findings:

- Regardless of sex, natural variation in the number and type of C4 genes contained in people's DNA constitutes the largest common genetic risk factor for developing these three diseases. People with the most C4 genes were seven times less likely to develop systemic lupus erythematosus, an autoimmune condition that can range from mild to life-threatening, and 16 times less likely to develop primary Sjögren's syndrome, a systemic autoimmune syndrome characterized by dry eyes and dry mouth, than those with the fewest C4 genes. Conversely, those with the most C4 genes were 1.6 times more likely to develop the neuropsychiatric condition schizophrenia.
- Even in people with similar complement gene profiles, the genes produce more protein in men than in women, further skewing disease susceptibility and protection.

"Sex acts as a lens that magnifies the effects of genetic variation," said the study's first author, Nolan Kamitaki, research associate in genetics in the lab of Steven McCarroll at HMS and the Broad.

"We all know about illnesses that either women or men get a lot more, but we've had no idea why," said Steven McCarroll, the Dorothy and Milton Flier Professor of Biomedical Science and Genetics at HMS and director of genomic neurobiology at the Stanley Center for Psychiatric Research at the Broad. "This work is exciting because it gives us one of our first handles on the biology."

McCarroll is co-senior author of the study with Timothy Vyse of King's College London.

Although C4 variation appears to contribute powerfully to disease risk, it is only one among many genetic and environmental factors that influence disease development.

The study's results are informing the ongoing development of drugs that modulate the complement system, the authors said.

"For example, researchers will need to make sure that drugs that tone down the complement system do not unintentionally increase risk for autoimmune disease," said McCarroll. "Scientists will also need to consider the possibility that such drugs may be differentially helpful in male and female patients."

On a broader level, the work offers a more solid foundation for understanding sex variation in disease than has been available before.

"It's helpful to be able to think about sex-biased disease biology in terms of specific molecules, beyond vague references to 'hormones,'" McCarroll said. "We now realize that the complement system shapes vulnerability for a wide variety of illnesses."

Cell sweeper

In 2016, researchers led by Aswin Sekar, a former McCarroll lab member who is a co-author of the new study, made international headlines when they revealed that specific C4 gene variants underlie the largest common genetic risk factor for developing schizophrenia.

The new work suggests that C4 genes confer both an advantage and disadvantage to carriers, much as the gene variant that causes sickle cell disease also protects people against malaria.

"C4 gene variants come with this yin and yang of heightened and

reduced vulnerability in different organ systems," said McCarroll.

The findings, when combined with insights from earlier work, offer insights into what may be happening at the molecular level.

When cells are injured, whether from a sunburn or infection, they leak their contents into the surrounding tissue. Cells from the adaptive immune system, which specialize in recognizing unfamiliar molecules around distressed cells, spot debris from the cell nuclei. If these immune cells mistake the flotsam for an invading pathogen, they may instigate an attack against material that isn't foreign at all—the essence of autoimmunity.

Researchers believe that complement proteins help tag these leaked molecules as trash so they're quickly removed by other cells, before the adaptive immune system pays too much attention to them. In people with lower levels of complement proteins, however, the uncollected debris lingers longer, and adaptive immune cells may become confused into acting as if the debris is itself the cause of problem.

As part of the new study, Kamitaki and colleagues measured complement protein levels in the cerebrospinal fluid of 589 people and blood plasma of 1,844 people. They found that samples from women aged 20 through 50 had significantly fewer complement proteins—including not only C4 but also C3, which activates C4—than samples from men of the same age.

That's the same age range in which lupus, Sjögren's and schizophrenia vulnerabilities differ by sex, Kamitaki said.

The results align with previous observations by other groups that severe early-onset lupus is sometimes associated with a complete lack of complement proteins, that lupus flare-ups can be linked to drops in

complement protein levels and that a common gene variant associated with lupus affects the C3 receptor.

"There were all these medical hints," said McCarroll. "Human genetics helps put those hints together."

Two flavors

The bulk of the findings arose from analyses of whole genomes from 1,265 people along with single nucleotide polymorphism (SNP) data from 6,700 people with lupus and 11,500 controls.

C4 genes and proteins come in two types, C4A and C4B. The researchers found that having more copies of the C4A gene and higher levels of C4A proteins was associated with greater protection against lupus and Sjögren's, while C4B genes had a significant but more modest effect. On the other hand, C4A was linked with increased risk of schizophrenia, while C4B had no effect on that illness.

In men, common combinations of C4A and C4B produced a 14-fold range of risk for lupus and 31-fold range of risk for Sjögren's, compared to only 6-fold and 15-fold ranges in women, respectively.

The researchers didn't expect the genes' effects to be so strong.

"Large genetic effects tend to come from rare variants, while common gene variants generally have small effects," said McCarroll. "The C4 gene variants are common, yet they are very impactful in lupus and Sjögren's."

Still, complement genes don't tell the full story of lupus, Sjögren's or schizophrenia risk, none of which are caused entirely by genetics.

"The complement system contributes to the sex bias, but it's only one of probably many genetic and environmental contributors," said Kamitaki.

Answers from diversity

Complement genes and another family of immune-related genes, called human leukocyte antigen or HLA genes, are interspersed throughout the same complex stretch of the human genome. HLA variants have been shown to raise risk of developing other autoimmune diseases, including type 1 diabetes, celiac disease and rheumatoid arthritis, and researchers had long believed that something similar was happening with lupus and Sjögren's.

The culprit, however, remained stubbornly hard to pin down, because specific variants in HLA genes and C4 genes always seemed to appear together in the same people.

Kamitaki and colleagues overcame this hurdle by analyzing DNA from a cohort of several thousand African American research participants. The participants' DNA contained many more recombinations between complement and HLA genes, allowing the researchers to finally tease apart the genes' contributions.

"It became quite clear which gene was responsible," said McCarroll. "That was a real gift to science from African American research participants. The question had been unsolved for decades."

The discovery provides further proof that the field of genetics would benefit from diversifying the populations it studies, McCarroll said.

"It will really help for genetics to expand more strongly beyond European ancestries and learn from genetic variation and ancestries all over the world," he said.

C4 variation could contribute to sex-based vulnerabilities in other diseases not yet analyzed, the authors said. It's not yet clear whether C4 pertains to the sex bias seen in COVID-19.

"We don't know the mechanism yet for why men seem to get sicker from COVID-19," said McCarroll. "Complement molecules are potentially important in any immune or inflammatory condition, and in COVID-19, it seems the immune response can be part of a downward spiral in some patients. But we don't know the key details yet."

It also remains to be seen how the differing effects of complement genes apply to people with intersex traits, also known as disorders or differences of sex development, who don't always fit textbook genetic or biological definitions of male and female.

"That is important to understand," said McCarroll.

More information: Complement genes contribute sex-biased vulnerability in diverse disorders, *Nature* (2020). DOI: 10.1038/s41586-020-2277-x , www.nature.com/articles/s41586-020-2277-x

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