Genetics may be responsible for one-third of complex regional pain syndrome cases

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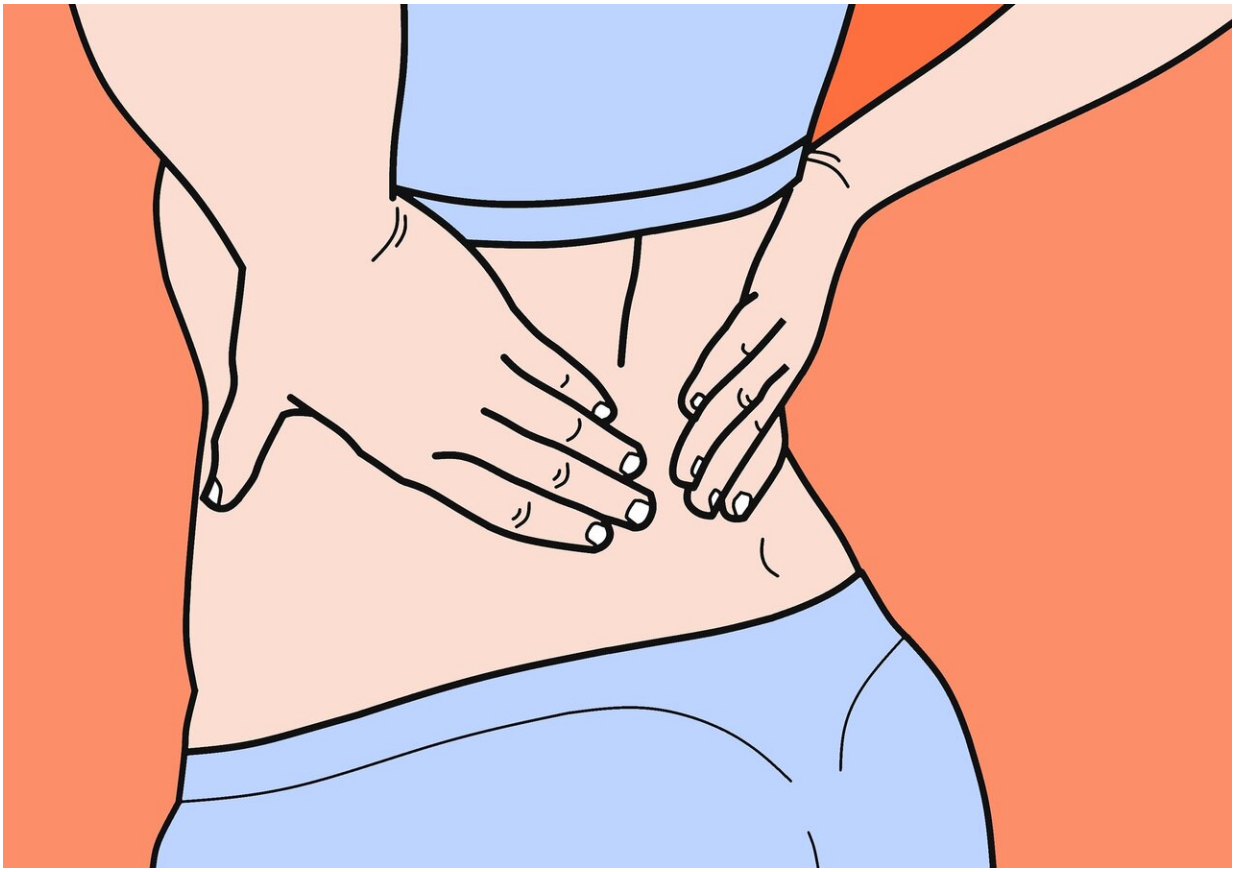

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Genetic susceptibility may be responsible for around 1 in 3 cases of complex regional pain syndrome (CRPS), a poorly understood condition

causing persistent severe and disabling pain, finds research published online in the *Journal of Medical Genetics*.

But the condition is less common in men, even though they are more likely to have the four genetic variations implicated in heightened risk, suggesting that there may be sex specific causes, say the researchers.

Most cases of CRPS are usually triggered by an injury, with the skin of the affected body part hypersensitive to the slightest touch or temperature change. CRPS is difficult to treat, and while it often improves with time, some people experience intense pain for many years.

But why some people develop CRPS yet others don't after the same injury, isn't clear. A heritable component to CRPS has been suggested, sparking the theory that some people might be genetically predisposed to the condition.

To explore this further, the researchers looked for variations in genes, formally known as single nucleotide polymorphisms, or SNPs for short, in DNA samples from 34 people diagnosed with CRPS (discovery group).

These were then searched for in 39 people with chronic back pain (comparison group), and then in another 50 people with CRPS (confirmatory group). The average age was mid 40s to mid 50s across all three groups, but ranged from 20 to 86.

A single SNP in each of four genes (ANO10, P2RX7, PRKAG1 and SLC12A9) was more common in those with CRPS in both the discovery and confirmatory groups than it was in the back pain group.

In all, 25 out of 84 (30%) patients who had had CRPS for more than a

year expressed these variations in at least 1 of the 4 genes. None of these variations was evident in those with back pain.

CRPS is more common in men than it is in women, by a ratio of 3–4:1. But more men than women expressed these genetic variations: 8 out of 14 (57%) vs. 17 out of 70 (24%) women, although this discrepancy would need to be confirmed in a larger group, say the researchers.

"This raises the possibility of different mechanisms of disease in males and females in [CRPS] and that therapeutic responses may also be influenced by sex," they write.

"We acknowledge that our genetic results may be only part of the [CRPS] story; autoimmune disease is more common in women than men, and recent studies strongly suggest it could be causative in some cases of [CRPS]," they add.

There may be plausible biological explanations for their findings, they suggest, as ANO10, P2RX7and SLC12A9 are expressed in immune cells in the peripheral nervous system, both of which are involved in the types of symptoms seen in people with CRPS.

And all four genes are normally expressed in macrophages—a type of white blood cell involved in the immune response—in healthy people, they note.

This is an observational study, and as such, no definitive conclusions can be drawn about cause and effect. The researchers also acknowledge that the sample sizes were relatively small, which may well have precluded other SNPs from being detected. And the participants were mostly white.

But they conclude, "Our data support an underlying genetic

predisposition to [chronic regional pain syndrome] in up to a third of cases, with this effect being most prominent in males….Further study of these genes and SNPs may catalyze the generation of personalized precision diagnosis and treatments for [the condition]."

More information: Evidence of a genetic background predisposing to complex regional pain syndrome type 1, *Journal of Medical Genetics* (2023). DOI: 10.1136/jmg-2023-109236

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