Endometriosis: gene identified which could be potential treatment target – new study

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Up to 10% of women experience endometriosis worldwide. The condition is chronic, extremely painful, and can result in infertility. Endometriosis happens when tissue similar to the lining of the womb

(the endometrium) grows outside of the womb, in the abdominal cavity and sometimes on the ovaries and the fallopian tubes. These tissues respond to the hormonal signals of the menstrual cycle just like the endometrium does, which can cause severe pelvic or period pain.

How and why endometriosis develops is unknown—and currently there's no cure. While treatments such as painkillers, surgery and even hormonal contraceptives are available, they don't always work, and many women find them to be insufficient.

But our recent collaborative study might have brought us one step closer towards finding a potential new target for treatment. We have discovered that DNA variations in the gene that produces the protein neuropeptide S receptor 1 (NPSR1) occur more often in women with endometriosis than in women who don't have the condition. NPSR1 plays a role in the transmission of nerve signals and in inflammation.

Our team at Oxford University has been working for decades to understand what genes cause endometriosis. We initially began conducting our research after observing that the condition can run in families—and that up to 50% of endometriosis risk in women is due to genetics. But finding the genes that cause the condition wasn't a straightforward task. Endometriosis is complex and influenced by many factors—including a person's genetic make-up, the environment, and the way these two factors interact.

To see what was different in the genetic make-up of endometriosis patients, we analysed the genome—the complete set of genes any person carries—of women with endometriosis and a family history of the condition, and those without a known family history. We then compared their DNA to women without endometriosis. In total, we analysed the genomes from 32 families with at least three women who had endometriosis and 105 women without endometriosis. We also consulted

another genetic dataset of more than 3,000 endometriosis cases and 2,300 controls.

The familial analysis at first narrowed the cause down to an area on chromosome seven, which contains around 100 genes. Only after further and more detailed DNA sequencing did we find that it was the NPSR1 gene that carried significantly more harmful variants in women with endometriosis than other genes within the chromosome seven area. Women without endometriosis tended to have the normal NPSR1 gene more often.

To further confirm these findings, our collaborators at the University of Wisconsin-Madison and Baylor College of Medicine then checked DNA variations in a colony of rhesus macaques. These monkeys have periods like humans do—and also get endometriosis. Sure enough, we found that changes within the same region on the macaque equivalent of human chromosome seven occurred more often in monkeys with endometriosis.

After confirming this link, the next step of our research was to test whether shutting down the activity of NPSR1 had any effect on inflammation associated with endometriosis. To do this, we first conducted experiments using cells, then mice. Our team and our collaborators at German pharma group Bayer found that if we shut down the activity of NPSR1 in immune cells, they became less responsive and produced less of a protein that normally drives inflammation. The mice in turn showed diminished inflammation and were in less pain than without the treatment.

However, the drug we used in these experiments is what's known as a "tool compound"—meaning it's only approved for use in cell and animal experiments, but is not able to be used on humans. The next step of research will be finding a drug that can be used in humans to similarly shut down NPSR1 activity, and see whether doing so also reduces

symptoms of endometriosis.

Understanding NPSR1

There's still a whole lot we don't know, though. For example, how exactly is NPSR1 connected to endometriosis—and what does it do (or not do) that leads to inflammation and pain? It will also be important to uncover how DNA variants of NPSR1 affect the protein's function, and in which tissues.

Interestingly, NPSR1 also has a role in inflammation that occurs with other health conditions, including asthma and inflammatory bowel disease. It's also found in certain regions of the brain, where it has effects on anxiety and behaviour. This could mean that NPSR1 could play a role in the perception of pain, and in the anxiety that goes along with endometriosis.

Chronic suffering and exposure to pain also changes the brain's architecture—meaning the wiring of the brain cells and nerves respond differently and change over time. It might also be possible that the connection of NPSR1 to endometriosis happens not just in inflammation and abdominal pain, but also in the brain itself. This is another aspect of NSPR1 that will need to be explored.

Regardless, our research has shown that shutting down this receptor eases pain and inflammation in mouse models of inflammation and endometriosis. This opens up the future possibility for developing drugs against NPSR1 that would ease symptoms of endometriosis without shutting down the menstrual cycle, and potentially alleviate pain for millions of women.

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