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Scientists discover gene linked to a common form of migraine

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An international study led by scientists at Université de Montréal and University of Oxford, has identified a gene associated with common migraines. Their findings show that a mutation in the KCNK18 gene inhibits the function of a protein called TRESK. TRESK normally plays a key role in nerve cell communication. Published today in *Nature Medicine,* this study may have implications for people who suffer from recurrent headaches, which include more than six million Canadians.

Previously, genes for migraine have been found only in a rare form involving headaches combined with limb weakness limited to one side of the body. "We focused on the more common types of migraine, without this muscle weakness, in our study, and looked at genes controlling brain excitability," says lead author Ron Lafreniere, Associate Director of the Centre of Excellence in Neuromics of the Université de Montréal (CENUM).

The researchers compared the DNA from migraine sufferers to that of non-sufferers. "We found a mutation in the KCNK18 gene that interrupts TRESK function in one large family suffering from migraine with aura," say Lafreniere. "When we tested everyone in the family, all those who suffered from migraine also had the mutation."

Aura migraines are those that are preceded or accompanied by sensory warning symptoms or signs (auras), such as flashes of light, blind spots or tingling in an arm or leg. The ensuing headache can be associated with sensitivity to lights, sounds, and smells, as well as nausea and occasional

vomiting.

Mutation results in incomplete TRESK protein

The mutation causes production of an incomplete form of TRESK which disrupt the normal functioning of this protein. The end result is an alteration in the electrical activity (excitability) of cells. "We now have direct evidence that migraine is a nerve excitability problem and have highlighted a key causal pathway in migraine' says the joint lead author, Dr Zameel Cader from the MRC Functional Genomics Unit at Oxford.

TRESK present in migraine-relevant areas

Cell culture and in vitro experiments revealed that TRESK is present in certain neurons of the brain. "We showed that TRESK is in specific neuronal structures (trigeminal ganglia and dorsal root ganglia) that have been linked to migraine and pain pathways," says Lafreniere.

"This is a highly significant finding because activation of trigeminal ganglion neurons is central to migraine development and increased activation of these neurons could very plausibly increase the risk for developing a migraine attack," explains senior author Guy Rouleau, a Université de Montréal professor and Director of the Sainte-Justine University Hospital Research Center. "While TRESK mutations are present only in a small number of migraine sufferers, because we believe that TRESK helps control the excitability of nerve cells, our results suggest that increasing TRESK activity pharmacologically may help reduce the frequency or severity of migraine episodes, irrespective of their origin."

More information: www.nature.com/nm/index.html

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