Mutation causes intense pain

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A mutation that enhances the function of a specific ion channel has been identified as the cause of a rare inherited pain disorder. The research, published by Cell Press in the June 10 issue of the journal *Neuron,* proposes a potential treatment for the disorder and may lead to a better understanding of chronic pain in humans.

There are multiple human neurological disorders that have been linked with mutations in ion channels. Ion channels are proteins that span the cell membrane and govern the movement of ions into or out of the cell. Ion channel function is critical for many different cell functions, and disruptions in specific channels have been linked with migraine, epilepsy, and multiple pathological pain disorders.

"Transient receptor potential (TRP) channels are ion channels that have been implicated in all aspects of sensation. However, despite mouse studies suggesting that a number of TRPs play an important role in pain pathways, no human heritable disorders of pain sensation have as yet been linked to mutations in TRP channels," explains study author, Dr. John N. Wood from the Wolfson Institute for Biomedical Research at University College London.

Dr. Wood, coauthor Dr. Andrés Ruiz-Linares, also of University College London, and their colleagues identified a mutation in a specific TRP gene called TRPA1 in individuals from a family in Columbia, South America, with a previously undescribed inherited pain syndrome called familial episodic pain syndrome (FEPS). FEPS is associated with episodes of debilitating upper body pain that are usually triggered by

fasting, physical stress, or fatigue.

"It was already established that TRPA1 is expressed in pain receptors in rodents and humans and that it plays an important role in response to environmental irritants in mouse models," says Dr. Ruiz-Linares. "We discovered a gain-of-function mutation associated with FEPS that could give rise to stereotyped episodes of severe pain affecting principally the upper body."

The researchers went on to show that the mutant channel exhibited altered biophysical properties, most notably an increased function and enhanced response to stimuli. Pharmacological compounds that are known to inhibit the normal channel were effective at inhibiting the mutant channel as well, suggesting that drugs that inhibit TRPA1 may prove to be a useful therapy for FEPS.

"Our findings provide the first evidence that variation in the TRPA1 gene can alter pain perception in humans," concludes Dr. Wood. "It will be of great interest to establish whether TRPA1 channel variants or misregulation contributes to the risk and severity of chronic pain in other patient populations."

More information: Kremeyer et al.: “Clinical Study: A Gain-of-Function Mutation in TRPA1 Causes Familial Episodic Pain Syndrome.” Publishing in Neuron 66, 671-680, June 10, 2010. DOI 10.1016/j.neuron.2010.04.030

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