PAIN

New familial pain syndrome caused by *TRPA1* mutation

The discovery of a new heritable pain syndrome in a Colombian family, as reported in *Neuron*, could provide key insights into the roles of the transient receptor potential (TRP) cation channels in pain disorders. Previous studies in animal models have strongly implicated the TRP channels in pain generation, but FEPS (familial episodic pain syndrome) is the first human pain-related channelopathy to be linked to the *TRP* gene superfamily.

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According to James Cox, one of the lead authors, "a large family was ascertained [by Francisco Lopera and colleagues] with a previously undescribed pain syndrome characterized by episodes of debilitating upper body pain, triggered by fasting and physical stress." The team, led by John Wood and Andrés Ruiz-Linares at University College London, UK, performed a whole genome linkage scan, which identified a candidate locus for FEPS on chromosome 8q12–8q13. Sequencing of this region uncovered a missense mutation in the *TRPA1* gene.

"TRPA1 was already known to be an important sensor of chemical irritants and cold," says Cox. The FEPS-associated mutation, which causes asparagine to be replaced by serine at amino acid residue 855 in the transmembrane segment of TRPA1, is a gain-of-function mutation with an autosomal dominant pattern of inheritance. The researchers suggest that the mutation might increase the activity of TRPA1 in response to endogenous pain mediators, and that the localized nature of the pain could be related to the pattern of expression of the channel and/or its ligands. Future research will focus on identification of the activator that triggers the pain episodes.

The discovery of the *TRPA1* mutation as the underlying cause of FEPS could also guide the development of therapies for this debilitating condition. *In vitro* studies have shown that the mutant channel can be inhibited by specific TRPA1 antagonists, which could be explored as potential therapeutic agents.

"This is the first demonstration of a Mendelian pain phenotype caused by a mutation in *TRPA1*," says Ruiz-Llinares. "This observation corresponds to a type of natural genetic experiment for probing the physiology of pain." The team intends to investigate the possible roles of common *TRPA1* polymorphisms in pain perception, both in the general population and in patients with other pain conditions. "We also plan to expand our human gene-finding efforts and use next-generation sequencing in our cohort of families with other Mendelian pain disorders to try to identify further major players involved in human pain perception," says Cox.

Heather Wood

Original article Kremeyer, B. *et al.* A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome. *Neuron* **66**, 671–680 (2010)