Model of a migraine indicates increased neuronal excitability as a possible cause

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Familial hemiplegic migraine is a rare and severe subtype of migraine with aura, an unusual sensory experience preceding the migraine attack. Researchers from the San Raffaele Scientific Institute in Milan, and CNR Institute of Neuroscience in Pisa, Italy, have developed a mouse model of Familial Hemiplegic Migraine type 2 (FHM2) and used it to investigate the migraine's cause. The study will be published on June 23rd in the open-access journal *PLoS Genetics*.

The researchers developed a knock-in animal model for FHM2 by inserting the W887R mutation of the ATP1A2 gene into the mouse genome. Mutations of this gene have previously been identified in patients as leading to a mutation of the α2 Na,K-ATPase protein with loss of function. As migraine is a complex phenotype, the research focused on a specific endophenotype that is functionally linked to migraine: cortical spreading depression (CSD). CSD is a wave of neuronal and glial depolarisation that progresses slowly across the cortex and frequently causes migraine aura.

The in vivo analysis of the FHM2 mouse model indicated an increased CSD susceptibility. This increase is a consequence of the accelerated degradation of the mutant protein by means of the cellular proteasome system, resulting in a decreased amount of functional α2 Na,K-ATPase protein. Since several lines of evidence involve a specific role of the α2 Na,K pump in active reuptake of glutamate from the synaptic cleft operated by glial cells, the authors hypothesize that CSD facilitation in the FHM2 mouse model is sustained by inefficient glutamate clearance

by astrocytes and consequent increased cortical excitatory neurotransmission. The authors therefore propose that episodic disruptions of the excitation-inhibition balance underlie the vulnerability to "spontaneous" CSD ignition in both the rare form of FHM and, probably, at least a fraction of common migraine cases.

More information: Leo L, Gherardini L, Barone V, De Fusco M, Pietrobon D, et al. (2011) Increased Susceptibility to Cortical Spreading Depression in the Mouse Model of Familial Hemiplegic Migraine Type 2. PLoS Genet 7(6): e1002129. doi:10.1371/journal.pgen.1002129