

## **Ca<sub>v</sub>2.1 channel mutations causing familial hemiplegic migraine type 1 increase the susceptibility for cortical spreading depolarizations and seizures and worsen outcome after experimental traumatic brain injury**

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### **Familial Hemiplegic Migraine Type 1: scientists study a story of two outcomes**

Driven by curiosity, Dr. Arn MJM van den Maagdenberg, a neurogeneticist and neurobiologist at Leiden University Medical Center in the Netherlands teamed up with Drs. Nicole A Terpolilli and Nikolaus Plesnila, neuroscientists at Munich University Hospital in Germany, to better understand the varied clinical outcomes observed in patients with *CACNA1A* mutations. They recently published their work in the prestigious scientific journal *eLife*. Dr. van den Maagdenberg started by developing two *CACNA1A* gain-of-function mouse models of Familial Hemiplegic Migraine type 1 (FHM1). One knock-in mouse strain carried the S218L missense variant that has been clinically associated with hemiplegic migraine, cerebellar ataxia, epilepsy, and poor outcomes following minor head trauma. The second mouse line carries the R192Q FHM1 gain-of-function missense mutation and has been associated with a milder phenotype of hemiplegic migraine without risk of additional clinical symptoms. Interestingly, the variants are located only a few amino acids away from each other in the  $\alpha 1$  subunit protein and lead to increased calcium influx, but the 218L mutation results in significantly more calcium influx in neurons and a much more severe functional outcome.

**Why do some mutations have more favorable outcomes than others? Typically, mutation-dependent comparisons of *CACNA1A* gene function focus on channel function. What other mechanisms may be contributing?**

The collaborators designed a study to investigate possible mechanisms responsible for varied outcomes in response to head trauma (or brain injury). Due to their history working with clinicians in the familial hemiplegic migraine field, the investigators were aware of *CACNA1A* patient cases that result in dramatically different outcomes following mild head injuries. Drs. Terpolilli and Plesnila utilized a technique called controlled cortical impact (CCI) to simulate a head injury and measured a number of important endpoints that relate to susceptibility of subsequent migraine, seizure, and tissue damage. The CCI procedure allowed the investigators to finely control the size of the contusion, the region of impact, the velocity of impact, and the duration the impact. CCI was performed on homozygous, heterozygous, and wildtype littermates and investigators measured cortical spreading depolarizations (CSDs), lesion volume, brain edema formation, and functional outcome.

CSDs are the electrographic correlate of the migraine aura. It is a pathologic disruption of cortical and glial activity resulting from a spreading loss of ion homeostasis (or balance). It is still unclear how the wave of altered electrical activity is triggered and propagated throughout by calcium influx into a network of neurons in the cortex. Other ions like extracellular potassium and neurotransmitter glutamate also contribute to the CSD. Discovered by Leao in 1944, this phenomenon has been studied extensively in both animal models and humans to better understand the mechanisms of migraine.

The results demonstrated that homozygous mutant mice with the more severe S218L mutation showed 20 times more CSDs, long-lasting generalized seizures, more brain edema formation, larger lesion volumes, and worse functional outcome after CCI relative to S218L heterozygous mice, homozygous mice expressing the milder R192Q mutation, and wildtype mice. These results suggest that increased susceptibility of FHM1 mutant mice to CCI-induced CSDs may underly the worse outcomes observed in human S218L mutation carriers after head trauma.