Familial hemiplegic migraine type 1 (FMH-1) is a rare form of migraine with aura, which is characterized by transient hemiparesis, sensory loss and visual disturbances. This monogenic disease shares many common features with classic migraine, suggesting a similar molecular pathophysiology. Migraine is triggered by activation and sensitization of the trigeminovascular system, specifically the trigeminal nociceptive afferents innervating the meninges. Aura migraine is associated with cortical spreading depression (CSD), which is a short-lasting intense wave of neuronal and glial cell depolarization that slowly progresses over the cortex and is followed by long-lasting neuronal activity depression.

Missense mutations affecting conserved amino acids in the ion-conducting subunit of the P/Q-type Ca\(^{2+}\) channel (Ca\(_{2.1}\)\(\alpha_1\)) are responsible for FMH-1. These channels govern neurotransmitter release at synaptic terminals. FMH-1 is one of the most extensively studied channelopathies and many research groups are interested in how the symptoms of this disease are related to the molecular mechanisms of channel dysfunction and its misregulation. To date, 21 mutations in Ca\(_{2.1}\)\(\alpha_1\) have been associated with FMH-1. The mutation most frequently reported is a Methionine-to-Threonine substitution at position 666 (T666M), which has been found in 19 of 39 studied families.

FMH-1 mutations are thought to confer a gain-of-function phenotype on P/Q channels, because most of them induce a hyperpolarizing shift in channel activation. Moreover, at the single channel level, several FMH-1 mutations show increased open probability. However, there are some discrepancies in the results published to date.

The results obtained from FMH-1 mutations in model systems in which the channels are overexpressed, such as heterologous systems or knock out neurons, are still a matter of debate. Therefore, to validate the use of Ca\(_{2.1}\)\(\alpha_1\) neurons, Tao et al. expressed R192Q FMH-1 mutant channels and observed a significant increase in current density compared with control conditions. Interestingly, a similar increase has been found in the R192Q knock in mouse, suggesting that the changes in current amplitude induced by the FMH-1 mutations may not be dependent on the expression system.

In a recent paper published in the Journal of Neurophysiology, Tao and coworkers reported the effects of the T666M FMH-1 mutation expressed in trigeminal ganglion neurons of the Ca\(_{2.1}\)\(\alpha_1\) mouse. They showed that there was no difference in the cell surface expression level between WT and T666M channels. However, there was a significant decrease in the current density of T666M compared with WT channels at almost all voltages tested. In spite of possible space-clamp deficiencies as indicated by differences between the reversal potential for the currents in the current-voltage (IV) curves, there was an evident loss-of-function of T666M with respect to WT channels.
trigeminal neurons, the expression of low threshold (T-type) channels was modified. They concluded that the presence of T666M channels significantly increases T-type current density and modifies the voltage dependence of current activation to more hyperpolarized voltages.

In my opinion, the results in this paper may have an alternative interpretation. Neurons from the CaV2.1-/- mouse paper may have an alternative interpretation. Finally, CaV2.1-/- neurons expressing the latter, supporting this interpretation. A drastic reduction of T-type currents in the T666M channels significantly increases voltage dependence of current activation in T-type current amplitude may result in a loss-of-function phenotype, the increase in T-type current density. The mechanism whereby this occurs remains unknown and should be explored in more detail in order to determine the relationship between P/Q- and T-type channels in healthy subjects and subjects presenting FMH-1.

Acknowledgments
I am grateful to Dr. Gerald W. Zamponi and Dr. Ricardo Felix for all the comments, suggestions and corrections on the manuscript.

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