

## CACNA1A: The Exciting Headache Gene

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### Summary

**Migraine is a chronic, debilitating condition that affects scores of individuals each day. Remarkably, a new study has demonstrated that mutations in the neuronal calcium channel Cav2.1 are the molecular basis for migraine headaches**

### Introduction

Migraine headache is a common, chronic, debilitating pain that affects roughly 6-8% of men and 15-18% of women in the U.S. and Europe (WHO, 2004). In the U.S., the annual cost of migraine treatment ranges from 13-17 billion dollars (Goldberg, 2005; Blumenfeld, 2005). Often it causes deficits in cognition, function, and sleep. Until recently, no research had defined the molecular basis for such a widespread illness. However, a remarkable study conducted by Maagdenberg and colleagues (2004) suggested that mutations in a gene encoding neuronal calcium channels were the molecular basis for migraine.

The different types of migraine headaches are distinguished by their symptoms. The known genetic form of migraine is called Familial Hemiplegic Migraine (FHM). It is characterized by an aura beginning 10-30 minutes before head pain. The aura can consist of hallucinations, visual impairments, hearing malfunctions, etc. Cortical spreading depression (CSD), consisting of sharp increases in neuron excitability followed by a depression in activity, has been known to be a precursor to aura (Hadjikhani et al., 2001; Gursoy-Ozdemir et al., 2004).

At the molecular level, many types of transmembrane protein channels allow various ionic species to travel into and out of the cell. Specifically, upon depolarization of the cell, calcium channels release a large influx of calcium ions into the cell which bind and release neurotransmitter vesicles. Calcium ion channels regulate this crucial event in synaptic transmission and are composed of numerous proteins (subunits) that work together to form a single entity.

FHM results from mutations within the *Cacna1a* gene and is autosomal dominant. This gene encodes the alpha subunit of a specific calcium channel Cav2.1. It has been suggested that mutations in this gene cause FHM to occur, making it a prime target for research (Tottene et al., 2002; Jun and Piedras-Renteria, 1999).

Prior to the research done by Maagdenberg and colleagues (2004), there was a significant contradiction in regards to mutated Cav2.1 activity. Several previous studies have been conducted on Cav2.1 channels with mutations in the *Cacna1a* gene. One study used cells that were heterozygous for the mutant Cav2.1 channel alpha subunit (Maagdenberg et al., 2004). Their data showed individual channels conducted increased amounts of calcium ions from the

outside to the inside of the cell. Another group studied Cav2.1 at the whole cell level instead of individual channels and found that the Cav2.1 channels had a decrease in conductivity at the whole cell level (Tottene et al., 2002).

These two contradictory findings highlight the previous gaps in knowledge. It was unknown whether a mutation in the *Cacna1a* gene leads to a gain of function or a loss of function in the Cav2.1 channels, and if this mutation triggers CSD and aura. To fill these gaps, three experiments were performed using a mouse homozygous for the mutated form of *Cacna1a*.

Maagdenberg and colleagues (2004) expressed the mutated channel in cerebellar granule cells and found that they opened and conducted more calcium ions into the cell at a lower voltage. The implications of these results are significant because an increase in calcium would cause an increase in neurotransmitter release and potentially hyper-excitability of the neuron.

The next step in this study made use of the neuromuscular junction, located at the synapse between motor neuron and skeletal muscle. The concentration of extracellular calcium ions was varied to observe whether the channels would release higher levels of neurotransmitter at low extra-cellular calcium concentration. It was found that low extra-cellular calcium lead to an elevated release of neurotransmitter in *Cacna1a* knockin mice.

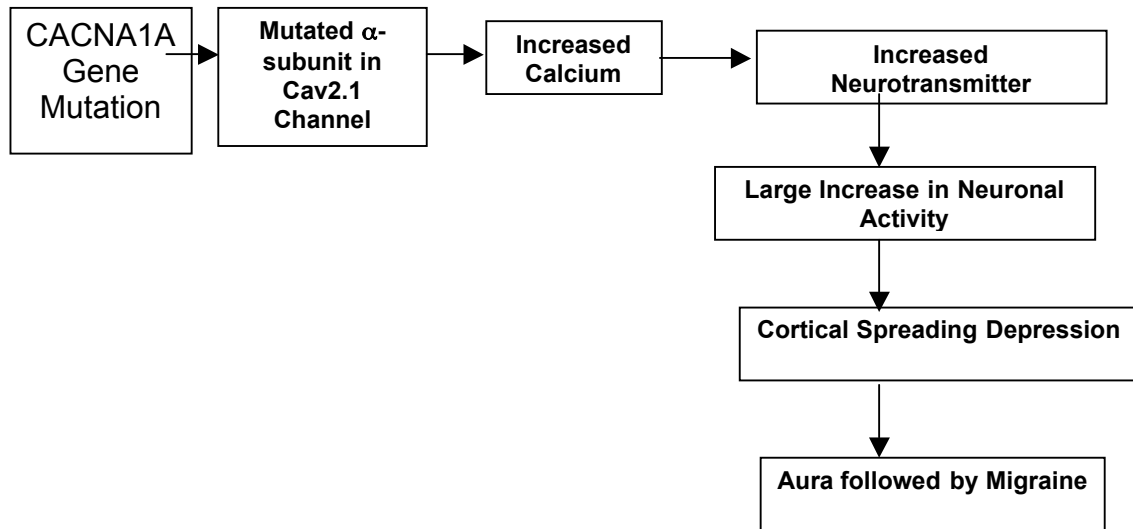
This finding suggested that the mutated Cav2.1 channels allow for an increased calcium influx and that they cause more neurotransmitter release. An increase in neurotransmitter release causes transient neuronal hyper-excitability and shows that there is increased calcium influx and more release of neurotransmitter in the migraine brain. The only connection that has not been made is that of increased neuronal excitability to CSD and aura.

Maagdenberg and colleagues (2004) performed three experiments to link the mutation in *Cacna1a* gene to CSD and aura. The first was a measure of the CSD activation threshold, which is the amount of neuronal activity that must be reached in order to trigger CSD. They found the CSD threshold to be lower in mutants, meaning that CSD could be triggered more easily in mutants than in the wild-type.

Next, they tested for a change in the rate of CSD propagation and duration. The knockins were found to have CSD propagation at a much higher speed compared to the wild type. This, along with the finding that the CSD activation threshold was lower in the knockins, revealed a clear link between the mutated alpha-subunit and the precursor to aura, CSD. When the duration of CSD was analyzed, they found the mutants to have increased CSD duration compared to the wild-type.

The impacts of these findings are quite significant to this field of study, because Maagdenberg and colleagues (2004) found mutated Cav2.1 channels to open at lower voltages, allowing for an increase in calcium ion conductivity that triggers an increase in neurotransmitter release. Furthermore, this lowers the activation threshold, rate of propagation, and duration of CSD. These experiments lay a simple map that begins with a mutation in the alpha-subunit of the calcium channel Cav2.1 and ends in migraine (Figure 1).

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**Figure 1: Pathway showing the steps leading to migraine.**  
(Maagdenberg et al., 2004)

As a result of these findings, migraine research can move toward developing better treatment methods that affect or block one point in the pathway further detailed by Maagdenberg and colleagues (2004). For those suffering from FHM, a viral vector could be used to replace the defective gene and alleviate chronic migraine pain. Another possibility is development of a drug that decreases Cav2.1 channel activity and prevents CSD from developing and leading to aura and migraine (Maagdenberg et al., 2004).

Though many different sub-types of migraines exist, it is hopeful that these findings will stimulate further research in the field and lead to breakthrough treatments for this debilitating condition that affects so many.

*Note: Eukaryon is published by students at Lake Forest College, who are solely responsible for its content. The views expressed in Eukaryon do not necessarily reflect those of the College.*

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