What Causes Migraines? According to Research, It’s All in the Genetics

by JAIME SANDERS

Are Migraines Genetic?

A migraine is often seen running in families from clinical practice and is confirmed in formal scientific studies.

Take me for example. Migraines go back at least three generations on my mother’s side of the family. My grandfather, mother, aunt, cousins and myself all have or had a migraine.

A migraine is a complex genetic disorder where genes, environment, stress and hormonal changes interact together.

These types of disorders are hard to understand because of how complex they are.

What makes it hard is many genes are combining in different ways in different people. Picking out the genes responsible for a migraine then becomes like picking out a needle in a haystack.

Familial Hemiplegic Migraine (FHM)

By looking at the DNA of large families where a migraine is passed down every generation, it is possible to find these genes.

One example of this is with familial hemiplegic migraine. Four genes have been identified with familial hemiplegic migraine:

- CACNA1A
- ATP1A2
- SCN1A
- PRRT2

These four genes have been found to cause a familial hemiplegic migraine.

Researchers believe that mutations in the first three genes can upset the balance of ions in neurons and disrupt the regular release and uptake of certain neurotransmitters in the brain.

Mutations in the PRRT2 genes, although the mechanism is unknown, is also speculated to disrupt normal control of neurotransmitter release. The changes in signaling between neurons because of these mutations lead people with familial hemiplegic migraine to develop severe headaches.

ATPase Na+/K+ Transporting Subunit Alpha 2 (ATP1A2) Gene

The ATP1A2 gene provides instructions for making one part (the alpha-2 subunit) of a protein known as a Na+/K+ ATPase.

This protein uses energy from a molecule called adenosine triphosphate (ATP) to transport charged atoms (ions) into and out of cells. Specifically, it pumps sodium ions (Na+) out of cells and potassium ions (K+) into cells.

Calcium Voltage-Gated Channel Alpha Subunit 1 (CACNA1A) Gene

The CACNA1A gene provides instructions for making one part (the alpha-1 subunit) of a calcium channel called CaV2.1. This subunit forms the hole (pore) through which calcium ions can flow.

CaV2.1 channels play an essential role in communication between nerve cells (neurons) in the brain.

These channels help control the release of neurotransmitters, which are chemicals that relay signals from one neuron to another. Researchers believe that CaV2.1 channels are also involved in the survival of neurons and the ability of these cells to change and adapt over time.

Sodium Voltage-Gated Channel Alpha Subunit 1 (SCN1A) Gene

The SCN1A gene provides instructions for making one part (the alpha subunit) of a sodium channel called NaV1.1. These channels are found in the brain and muscles, where they control the flow of sodium ions into cells.

In the brain, NaV1.1 channels are involved in transmitting signals from one neuron to another.

Communication between neurons depends on chemicals called neurotransmitters, which are released from one neuron and taken up by neighboring neurons. The flow of sodium ions through NaV1.1 channels helps determine when neurotransmitters will be released.

Proline Rich Transmembrane Protein 2 (PRRT2) Gene

The PRRT2 gene provides instructions for making the proline-rich transmembrane protein 2. The function of this protein is unknown, although it is thought to be involved in signaling in the brain.

Studies show that it interacts with another protein called SNAP25, which participates in signaling between neurons in the brain. SNAP25 helps control the release of neurotransmitters, which are chemicals that relay signals from one neuron to another.

Next page: Other genes that may influence migraines and actionable steps to take to diagnosis and identify gene mutations.

The Role of the MTHFR Gene in a Migraine

Another gene that may influence a migraine is methylenetetrahydrofolate reductase or MTHFR. A mutation of the gene, C677T, has garnered much attention from scientists. According to an Italian 2007 study, the gene mutation was more likely to appear in people who had a migraine with aura.

What does having the gene mutation mean?

In a 2012 study, migraine patients with the MTHFR gene mutation were found to have higher levels of homocysteine, an amino acid, in their blood. Having elevated levels of this amino acid makes breaking down methionine, another amino acid, impossible. It can also lead to heart attacks, migraine, and stroke. It produces neurotoxic effects and hyperexcitability in the brain’s neurons.

Taking oral or injection B-12 supplements and methylated Folate can help manage homocysteine levels which

can also contribute to managing triggers, symptoms, and migraine attacks.

I have this gene mutation and must take oral B-12 and folic acid daily to control my elevated homocysteine level. Starting these treatments, in addition to my prevention medication, has helped to lower the frequency of migraine attacks.

Genetics and Functional Neuroimaging

A 2012 study found that “genetic studies are increasingly focusing on occasional migraine and the utilization of unbiased searches of the human genome to identify novel variants associated with disease susceptibility.

"At the same time, neuroimaging studies have provided novel insights into the altered neuronal and network dynamics of the migrainous brain. These two parallel approaches provide complementary insights into the complexity and heterogeneity of a migraine.”

Ion Channel Genes and Migraine

A migraine is a disorder of the nervous system and not a blood vessel disorder or inflammation problem as previously thought. It is found that people living with migraines have an increased responsiveness of the nervous system to stimulation, even between migraine attacks.

Ion channels determine nerve excitability; therefore, their genes could explain why the nervous systems of people with a migraine are more excitable.

Genome-Wide Association Studies (GWAS)

A genome-wide association study is an examination of a genome-wide set of genetic variants in different individuals to see if any variant is associated with a trait.

Unbiased genome-wide association studies have been performed on large groups of cases and controls, which have identified at least twelve loci associated with migraine susceptibility; mostly migraine without aura (MWoA). In population versus clinic-based samples, different loci have been identified suggesting a possible association between genetic susceptibility and disease severity.

The loci identified from genome-wide association studies have diverse functions in synaptic regulation, glutamate signaling, neuropathic pain transmission, and some whose pathophysiological significance is yet to be understood.

Further studies of migraine genetics hold great promise for a greater depth of understanding of migraine neurobiology and in the identification of novel targets for therapeutic intervention.

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Steps to Take to Diagnose and Identify Gene Mutations

The first step is to examine your family history. It is important to consider any occurrences of a migraine on either side of your family, as well as any history of:

- Stroke
- Myocardial infarction
- Venous thrombosis
- Congenital heart defects
- Inflammatory bowel disease (IBS)
- Crohn’s disease
- Parkinson’s disease
- Epilepsy
- Bipolar disorder
- Depression
- Alzheimer’s disease
- Anxiety

Secondly, ask your neurologist to run a blood test to check for MTHFR, ATP1A2, CACNA1A, SCN1A, PRRT2 gene mutations.

Third, pursue effective treatments when applicable to help manage your migraine, triggers, and symptoms.