# Genetics of Migraine

*Thesis*

**Submitted for Partial Fulfillment of Master Degree in Neuropsychiatry**

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## Abstract

Migraine is one of the most common neurovascular disorders, characterized by recurrent attacks of disabling headache that lasts from a few hours to a few days. Usually, migraine patients are perfectly well in between attacks**.**

Migraine affects about 15% of people in developed countries and three times more common in women than in men**.**

The pathophysiology of migraine involves both neural and vascular mechanisms, but it's not completely known why and how migraine attacks are initiated.

Genetic factors play an important role in physiological processes by lowering threshold for migraine attacks. Genetic research in the field of migraine has mainly focused on identification of genes involved in familial hemiplegic migraine, a rare monogenic subtype of migraine with aura. Familial hemiplegic migraine is considered a valid model to study molecular mechanisms involved in the common forms of migraine**.**

Recently it has been found that calcitonin gene related peptides (CGRPs) play a role in the pathogenesis of the pain associated with migraine. CGRP receptor antagonists are being investigated both in vitro and clinical studies for the treatment of migraine**.**

Conventional treatment focuses on three areas: trigger avoidance, symptomatic control and prophylactic pharmacological drugs. Patients who experience migraines often find that the recommended migraine treatments are not 100% effective at preventing migraines, and sometimes not be effective at all. Pharmocological treatment is considered effective if they reduce the frequency or severity of migraine attacks by 50%**.**

**Keywords** : migraine, genetics, evilexy , strock

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*Reham Yousif Eiz El-Deen*

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# List of Abbreviations

| | | |
|---|---|---|
| ACA | : | Anterior cerebral arteries |
| ACE-DD | : | Angiotensin converting enzyme deletion polymorphism |
| AGS | : | Aicardi-Goutie res syndrome |
| ATPIA2 | : | The α2-subunit of voltage gated sodium-potassium pumps |
| BRV | : | Benign recurrent vertigo |
| CACNAIA | : | The pore-forming α1-subunit of voltage-gated neuron (P/Q type) calcium channels |
| CADASIL | : | Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencphalopathy |
| CDH | : | Chronic daily headache |
| CGRPs | : | Calcitonin gene related peptides |
| CHORD | : | Canadian headache outpatient registry and database |
| CI | : | Confidence interval |
| CSD | : | Cortical spreading depression |
| CWM | : | Canadian women and migraine |
| DZ | : | Dizygotic twins |
| EA1 | : | Episodic ataxia type 1 |
| EA2 | : | Episodic ataxia type 2 |
| ESR | : | Estrogens receptor |
| FCL | : | Familial chilblain lupus |
| GEFSs | : | Generalized epilepsy with febrile seizures |
| ICHDs | : | International classification of headache disorders |
| IHS | : | International headache society classification |
| MA | : | Migraine with aura |
| MAV | : | Migranous vertigo |
| MO | : | Migraine without aura |
| MOH | : | Medication overuse headache |
| MTHFR | : | Methylenetetrahydrofolate reductase |
| MZ | : | Monozygotic twins |

# List of Abbreviations (Cont.)

| | | |
|---|---|---|
| NO | : | Nitric oxide |
| NsAIDs | : | Non steroidal anti-inflammatory drugs |
| OA | : | Ophthalmic artery |
| OMIM | : | Online Mendelian Inheritance in Men Database |
| OR | : | Odds ratio |
| PGR | : | Progesterone receptor |
| RVCL | : | Retinal vasculopathy with cerebral leukodystrophy |
| SCNIA | : | The pore-forming α1-subunit of voltage gated $Na_v$ 1.1 sodium channel |
| SHM | : | Sporadic hemiplegic migraine |
| SME1 | : | Severe myclonic epilepsy of infancy |
| SNP | : | Single nucleotide polymorphism |
| SUNCT | : | Short lasting unilateral neurolgiform headache attacks with conjunctival injection and treating |
| TGVS | : | Trigeminovascular system |
| TNC | : | Trigeminal nucleus caudalis |
| TREX1 | : | A new migraine – associated gene |
| WMLs | : | White matter lesions |
| PAMP1 | : | The modifying protein necessary to bind CRP to its receptor. |

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# Introduction

Migraine is one of the most common neurovascular disorders, characterized by recurrent attacks of disabling headache that lasts from a few hours to a few days. Usually, migraine patients are perfectly well in between attacks ***(Norberg, 2006).***

Migraine is identified by the world health organization as among the 20 leading causes of world wide disability on individuals and on society. The most recent 10 years of studies show extremely variable migraine prevalence in the general population ranging from 5% to 19%. However, those studies, whether from high or low prevalence countries, all provide consistent evidence that migraine is far more common in women than men. One year prevalence rate in females ranging from 6.9-25% are also greater than those of males at 2.3- 13%, while lifetime prevalence is approximately 7 -33% in women and 2.6- 14.8% in men ***(Wang et al., 2008).***

Migraine affects about 15% of people in developed countries and three times more common in women than in men ***(Wessman et al., 2007).***

Migraine is classified according to the international headache society into various types: Migraine without aura, Migraine with aura, Childhood periodic syndromes that are commonly precursors of migraine (Cyclic vomiting, abdominal migraine, benign paroxysmal vertigo of childhood). It includes also retinal migraine and complications of migraine (chronic migraine, status migrainosus, persistent aura without infarction, migrainous infarction, migraine- triggered seizure). In addition to probable migraine (probable migraine without aura, probable migraine with aura, probable chronic migraine) ***(Evans and Randolph, 2005)***

The pathophysiology of migraine involves both neural and vascular mechanisms, but it's not completely known why and how migraine attacks are initiated. Activation of the sensory trigeminovascular system is thought to be responsible for the pain of migraine, whereas cortical spreading depression (CSD) seems to underlie the visual aura symptoms. CSD is characterized by a wave of intense neuronal activity that slowly spreads across the brain cortex and this followed by along-lasting neuronal inhibition ***(Pietrobon and Stressing, 2003)***.

Animal models of migraine pathogenesis have suggested that CSD triggers activation of the nociceptive trigeminovascular system, which leads to release of various factors, such as the calcitonin gene- related peptide (CGRP), substance P, neurokinin A, and nitric oxide (No). These molecules subsequently cause vasodilatation and neurogenic inflammation of the pain- sensitive meningeal blood vessels, these generating a headache. Furthermore, the depolarization phase of CSD has been associated with an increase in cerebral blood flow ***(Norberg, 2006).***

Genetic factors play an important role in physiological processes by lowering threshold for migraine attacks. Genetic research in the field of migraine has mainly focused on identification of genes involved in familial hemiplegic migraine, a rare monogenic subtype of migraine with aura. Familial hemiplegic migraine is considered a valid model to study molecular mechanisms involved in the common forms of migraine ***(Ferrari and Goadsby, 2006).***

Three genes for familial hemiplegic migraine have been identified: CACNA1A ($FHM_1$) encoding the pore-forming α1-subunit of voltage-gated neurons (P/Q type) calcium channels ***(Ophoff et al., 1996)***, ATP1A2 ($FHM_2$) encoding the α2-subunit of glial cell sodium-potassium pumps ***(De Fuscs et al., 2003)*** and SCN1A ($FHM_3$) encoding the pore forming α1-

Subunit of voltage-gated $Na_v1.1$ sodium channels ***(Dichgans et al., 2005).*** With the identification of these genes, the concept that FHM and like common types of migraine, are ionopathies, that is, disorders of disturbed ion transport has increasing acceptance ***(Ferrari and Goadsby, 2006).***

Mutations of FHM1, affect the function of $Ca_v2.1$ calcium channels ***(Pietrobon and Striessnig, 2003),*** FHM2 mutations in the ATP1A2 gene affect the $Na^+$ $K^+$ pumps that are primarily expressed in glial cells ***(De fuscs et al., 2003),*** FHM3 mutations in the SCN1A gene cause a more rapid recovery from fast inactivation of negative sodium channels after depolarization ***(Dichgans et al., 2005).***

Based on cellular studies, it can be hypothesized that increased susceptibility to FHM and common forms of migraine may arise from disturbed ionic balance and concomitantly increased release of neurotransmitter glutamate ***(Moskowitz et al., 2004).***

There are some mutant mouse models that may be useful for investigation of the mechanisms of migraine. The main advantage of knock- in mouse models carrying human mutations is that they express the mutant gene in its most natural environment, the FHM1, R192Q mutation, previously identified in patients with pure FHM introduced into the endogenous CACNA1A mouse gene ***(Van den Maagdinberg et al., 2004).*** Electrophysiological measurements of cerebellar granule cells isolated from R192Q FHM1 mice show increased neuronal calcium current, also on a whole cell level ***(Kaja et al., 2005).***

Knock- in FHM2 and FHM3 mouse models are not yet available, but will be of great interest to knock-out mice that

completely lack the Na+, K+ pumps that have been generated, but appear to be less homozygous animals die at birth due to respiratory problems ***(Ferrai and Goadsby, 2006).***

The observation that in these mice- whole brain γ-aminobutyric acid and glutamate levels are increased under scores, the in vivo importance of the FHM2 gene in the regulation of neurotransmitter homeostasis ***(Rob et al., 2007).***

Positive diagnosis of migraine requires a good history of the disorder including family history, accompanying symptoms and triggers ***(Randolph and Evans, 2005).***

Identification of susceptibility genes for a disease can be done in two main ways. Commonly, a genome-wide scan of the entire genome is performed in related individuals and then a chromosol disease region is located through linkage analysis. Alternatively, if the pathophysiology of the disease is fairly well understood, genes can be selected and tested for association with disease phenotype based on their function. This is usually performed by a case- control association study ***(Norberg, 2006).***

Conventional treatment focuses on three areas: trigger avoidance, symptomatic control and prophylactic pharmacological drugs. Patients who experience migraines often find that the recommended migraine treatments are not 100% effective at preventing migraines, and sometimes not be effective at all. Pharmocological treatment is considered effective if they reduce the frequency or severity of migraine attacks by 50% ***(Kaniecki and Lucas, 2004).***

Recently it has been found that calcitonin gene related peptides (CGRPs) play a role in the pathogenesis of the pain associated with migraine. CGRP receptor antagonists are being investigated both in vitro and clinical studies for the treatment of migraine ***(Tepper and Stillman, 2008).***

# Aim of the work

To highlight the recent updates of the genetics of migraine and stress their implications in the management of migraine.

# Pathophysiology and types of migraine

## *Anatomical consideration*

### *Vascular supply of the brain*

The brain is perfused by the carotid and vertebral arteries, which begin as extracranial arteries leading from the aorta or other great vessels and course through the neck and base of the skull to reach the intracranial cavity. The carotid and its branches are reffered to as the anterior circulation and the vertebrobasilar as the posterior circulation. The internal carotid arteries enter the cranium through the carotid canal. The four main segments of the internal carotid artery are

cervical, petrous, cavernous and supraclinoid. The internal carotid artery ends by dividing into the middle and anterior cerebral arteries (ACA), after giving ophthalmic (OA), superior hypophyscal posterior communicating, and anterior choroidal arteries (as shown in figure 1). The vertebral artery usually arise from the subclavian artery. The basilar artery originates as the merger of the right and left vertebral arteries, usually at the pontomedullary junction. The basilar artery usually terminates into the right and left posterior cerebral arteries ***(Rowland, 2005).***

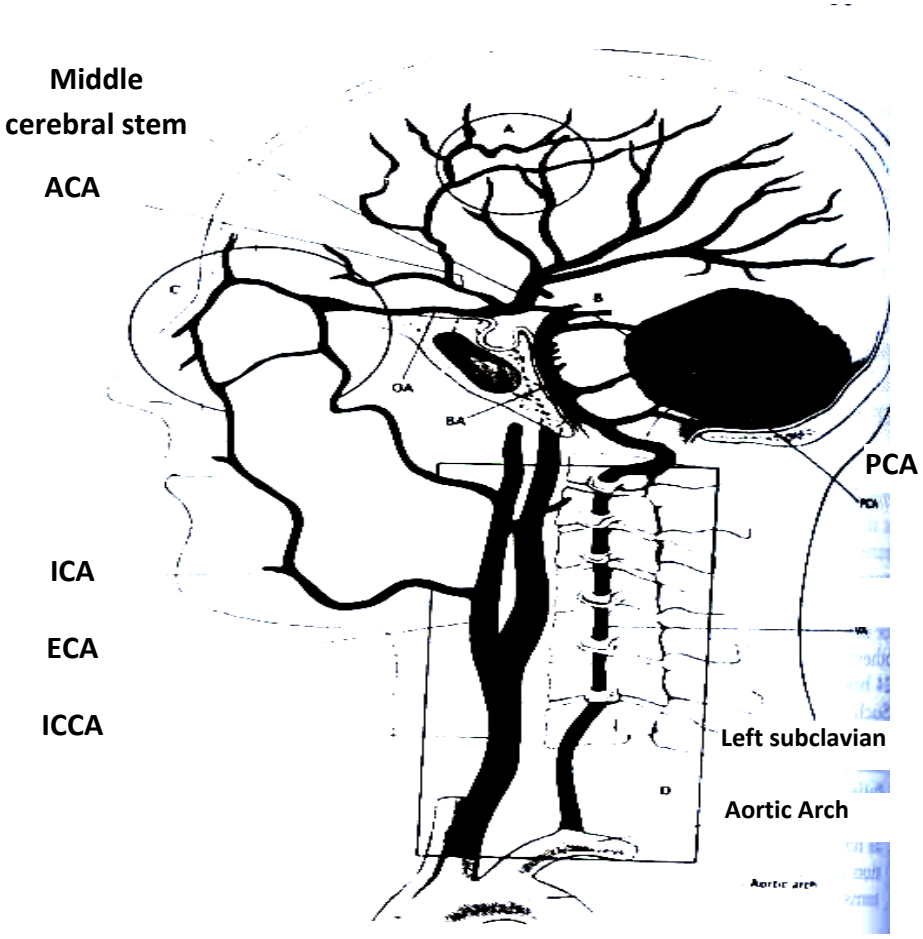


**Figure (1):** Show the vascular supply of the brain ***(Rowland, 2005)***

## Pathophysiology of Migraine

### *Genetics of migraine*

Genetic epidemiology has shown that risk to first–degree relative of probands with migraine with aura is four fold,whereas in migraine without aura, is 1.9 fold. Clearly indicating that genetic influence is stronger in migraine with