



HAL
open science

Genetics of migraine

Anne Ducros

► **To cite this version:**

Anne Ducros. Genetics of migraine. Revue Neurologique, 2021, 177 (7), pp.801-808.
10.1016/j.neurol.2021.06.002 . hal-03652060

HAL Id: hal-03652060

<https://hal.science/hal-03652060>

Submitted on 16 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Genetics of migraine

Anne Ducros

Affiliation : Neurology Department, Montpellier University Hospital, Montpellier, France

Address : Prof. Anne Ducros, Département de Neurologie, Hôpital Gui de Chauliac, CHU de Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier Cedex 5, France

a-ducros@chu-montpellier.fr

Other email anneducros75@hotmail.fr

Conflicts of interest:

I have no COI to declare pertaining to this review.

Outside of this work, I declare honorarium for board membership from Abbvie/Allergan, Lilly, Lundbeck, Novartis and Teva.

Genetics of migraine

Summary

Migraine is a complex brain disorder explained by the interaction of genetic and environmental factors. In monogenic migraines, including familial hemiplegic migraine and migraine with aura associated with hereditary small-vessel disorders, the identified genes encode proteins expressed in neurons, astrocytes or vessels, which all increase the susceptibility to cortical spreading depression. Study of monogenic migraines showed that the neurovascular unit plays a prominent role in migraine. Genome-wide association studies have identified multiple susceptibility variants that only cause a small increase of the global migraine risk. The variants belong to several complex networks of "pro-migraine" molecular abnormalities, which are mainly neuronal or vascular. Genetics has also underscored the importance of genetic factors shared between migraine and its major co-morbidities including depression and high blood pressure. Further studies are still needed to map all of the susceptibility loci for migraine and then to understand how these genomic variants lead to migraine cell phenotypes. Thanks to the advent of new technologies such as induced pluripotent stem cells, genetic data will hopefully finally be able to lead to therapeutic progress.

Key words: migraine, aura, familial hemiplegic migraine, genetics, comorbidity

1. Migraine is a complex genetic condition

The goal of genetics is to identify key proteins in order to better understand the pathophysiology of a disease, define new therapeutic targets and find possible diagnostic biomarkers.

The existence of hereditary factors in migraine has been demonstrated by twin and family studies in the 1990s [1, 2]. More recent studies indicated a heritability for migraine of about 42% and confirmed that it is a complex disease resulting from interactions between genes and the environment, from interactions between genes themselves, and from factors as yet unknown [3]. Heritability is more important in migraine with aura (MwA) than in migraine without aura (MO) [4].

Migraine is mostly polygenic, due to multiple genetic variants each having a minor-effect accumulating to lead to the disease. A proportion of MwA could be explained by the conjunction of a small number of genetic variants with moderate effect, or by a single variant with a major functional effect as in monogenic migraines [5].

In the much rarer monogenic migraines, a pathogenic mutation in a single gene is sufficient to produce the disease with almost complete penetrance. The main monogenic migraine is familial hemiplegic migraine (FHM) which has an autosomal dominant transmission [6]. Monogenic migraines can also be part of the clinical spectrum of other hereditary neurological and neurovascular conditions.

2. Familial hemiplegic migraine

Hemiplegic migraine (HM) is a rare disorder with an estimated prevalence of 0.01% in the general population [6]. Familial HM, diagnosed when at least one first- or second-degree relative also has HM, represents two thirds of the cases, and sporadic HM (SHM) one third. HM attacks start during youth, and comprise a motor weakness during the aura, which is always associated with at least one other symptom of typical aura (visual, sensory, speech and language) and often with symptoms of brainstem aura (70%) [7]. Duration of aura in HM may be longer than in typical aura (several days to weeks). The headache usually has the characteristics of a MO. Severe attacks with confusion, coma, fever, seizures and reversible brain edema may occur, sometimes after a mild head trauma. HM can be pure or associated with other neurological manifestations including epilepsy, cerebellar ataxia, learning disabilities and mental retardation.

FHM is mostly a monogenic condition, with an autosomal dominant pattern of inheritance and a high penetrance; 70-90% of subjects with a pathogenic mutation clinically express the disease. FHM is subdivided in FHM1, FHM2 and FHM3, according to the presence of mutations in the *CACNA1A*, *ATP1A2* and *SCN1A* genes, respectively [6, 8-10]. The *PRRT2* gene must be added to the

main FHM genes because recent data showed that *PRRT2* is implicated at least as commonly as *SCN1A* [11, 12]. For convenience, we will therefore call FHM4, HM caused by mutations of *PRRT2*. Among the index cases suspected of having HM and referred for genetic diagnosis, only a minority has a mutation in the four major genes, 15% in a French cohort of 697 patients and 21% in a New Zealand and Australian cohort of 230 patients [11, 12]. The most frequent mutations are found in the *ATP1A2* gene (6,3-10%) followed by *CACNA1A* (3.9-7%), *PRRT2* (2.2-2.6%) and finally, *SCN1A* (1.7 -2.3%).

2.1 Genotype-phenotype correlations in FHM

Attacks of HM are similar whatever the type of FHM. Prolonged auras with confusion and association of HM with epilepsy are possible in all types of FHM.

Different mutations of the same gene can influence the phenotype. In FHM1, the two mutations most commonly involved in severe attacks with coma and fever are T666M and S218L.

The nature of the mutated gene also influences the spectrum of manifestations associated with HM attacks [6]. Febrile comas are frequent in FHM1, possible in FHM2, and have not been described in FHM3 and FHM4. Cerebellar ataxia is common in FHM1; a phenomenon of repeated transient blindness was observed only in FHM3; mental retardation has been described in FHM1, 2 and 4; and finally, association of HM with paroxysmal dyskinesia or hypersomnia are suggestive of FHM4 [12].

There is great variability in HM attacks and associated manifestations between individuals who carry different mutations of the same gene, and even between affected family members who carry the same mutation. This variability suggests that other genetic or environmental factors can modulate the clinical phenotype.

2.2 FHM1 and *CACNA1A*

CACNA1A, localized on 19p13, was the first identified HM gene [13]. It encodes the main $\alpha 1$ pore-forming subunit of $\text{Ca}_v2.1$ (or P/Q) neuronal voltage-gated calcium channels. These channels are expressed in brain and cerebellar synaptic endings and play a role in controlling the release of neurotransmitters. More than 25 *CACNA1A* mutations have been identified in FHM1, and most are missense mutations causing a gain of function, which increases Ca^{2+} influxes, glutamatergic neurotransmission and neuronal excitability [14].

Two models of FHM1 knock-in (KI) transgenic mice exist [15, 16]. KI mice for the R192Q mutation, responsible for pure FHM1, did not show any clinical abnormality. KI mice for the S218L mutation, which causes very severe FHM1, have cerebellar ataxia, transient hemiparesis and epilepsy. FHM1-KI mice have increased $\text{Ca}_v2.1$ currents and neurotransmitter release, loss of

balance between excitatory and inhibitory cortical neurotransmissions, and increased susceptibility to cortical spreading depression (CSD). These transgenic mice were also shown to have head pain [17], increased trigeminal activity, tissue anoxia during prolonged aura, increased sensitivity to cerebral ischemia, and a change in trigeminal nociception mediated by calcitonin gene-related protein [18].

Distinct *CACNA1A* mutations have been identified in other neurological disorders. Episodic ataxia type 2 (EA2), characterized by paroxysmal ataxia, dizziness and nausea, is associated with *CACNA1A* mutations responsible for loss of function and decreased Ca^{2+} influxes. Spinocerebellar ataxia type 6 (SCA6), characterized by progressive cerebellar ataxia, is caused by an expansion of a CAG repeat in the terminal part of *CACNA1A*, which causes toxic degeneration of Purkinje cerebellar cells.

2.3 FHM2 and *ATP1A2*

The *ATP1A2* gene on 1q23.2 encodes the α_2 isoform of the catalytic subunit of the ATP-dependent transmembrane A1A2 pump ($\alpha_2 \text{Na}^+/\text{K}^+$ -ATPase) [19]. In the central nervous system, the pump is mainly expressed in astrocytes where it ensures the clearance of extracellular K^+ and produces a Na^+ gradient necessary for the reuptake of glutamate from the synaptic cleft. Over 80 *ATP1A2* mutations have been identified in FHM2. Missense mutations are the most common, but small deletions, a mutation altering the stop codon and an exonic duplication have also been reported. These mutations lead to variable loss of function of the $\alpha_2 \text{Na}^+/\text{K}^+$ -ATPase.

Several models of FHM2-KI transgenic mice exist. Heterozygous transgenic mice show no clinical abnormality. These transgenic mice have an increased susceptibility to CSD due to abnormal astrocyte clearance of K^+ and glutamate [20, 21]. Mice with partially knocked-out (KO) *ATP1A2* also showed increased susceptibility to CSD [22]. Another mouse model where *ATP1A2* was KO in astrocytes showed episodic paralysis and spontaneous waves of CSD with decreased electroencephalographic activity [23]. These animals had brain metabolic abnormalities with increased serine and glycine. A serine- and glycine-free diet suppressed attacks of paralysis in these mutants.

2.4 FHM3 and *SCN1A*

SCN1A on 2q24.3 encodes the pore-forming α_1 subunit of $\text{Na}_v1.1$ channels [24]. These voltage-dependent neural sodium channels are involved in the genesis and propagation of action potentials of cortical neurons, especially in GABAergic inhibitory interneurons [25]. *SCN1A* was already known as an epilepsy gene with over 100 missense and nonsense mutations identified in

various forms of childhood epilepsies. A dozen *SCN1A* mutations have been identified in FHM3. Their functional consequences are complex and there is no animal model of FHM3 [26, 27].

2.5 FHM4 and *PRRT2*

PRRT2 encodes the PRRT2 protein, which plays an important role in brain development, synapse formation, and neurotransmitter release. PRRT2 is expressed in presynaptic termini and interacts with proteins of the exocytosis complex.

PRRT2 mutations have now been identified in several dozen cases of FHM4, of whom two thirds have pure FHM and one third FHM associated with epilepsy, mental retardation or dyskinesia [11, 12, 28-34]. Mutations in *PRRT2* are also associated with several other neurological diseases including benign familial infantile epilepsy (BFIE), infantile seizure syndrome with choreoathetosis (ICCA) and paroxysmal kinesigenic dyskinesia (PKD) [35, 36].

The various *PRRT2* mutations (point duplication, small deletions, missense, total deletions) all induce a loss of function leading to haploinsufficiency. A given *PRRT2* mutation can be associated with several diseases. Indeed, the c.649dupC mutation is common in FHM4, but is also the main causal mutation in PKD and BFIE.

PRRT2-KO mice exhibit paroxysmal abnormal movements upon acquisition of locomotion, develop audiogenic abnormal motor behaviors as they reach adulthood, and have a lowered seizure threshold [37]. Their excitatory hippocampal neurons show increased excitability. Cultured homozygous human and murine KO-*PRRT2* neurons express overactive Nav1.2 and Nav1.6 channels, indicating that PRRT2 inhibits voltage-gated sodium channels.

Other experiments are necessary to understand the factors explaining the great phenotypical variability associated with *PRRT2* mutations, and the potential influence of modifying genes or of the non-mutated allele.

2.6 Other FHM genes

Mutations in several other genes have been identified in HM. All these genes were already known to be involved in other hereditary diseases. In the cohort of 230 index patients from New-Zealand and Australia suspected of HM and referred for genetic diagnosis, 21% had a mutation in the four main above cited genes [11]. Analysis of new HM genes increased the diagnosis rate to 27.8% (*PKND* 0.4%; *SLC4A4* 3.9%; *ATPIA3* 0.9%; *SLC1A3* 0.4%; *SLC2A1* 1.3%).

PKND, the main gene for paroxysmal non-kinesigenic dyskinesia, is rarely involved in HM. It encodes the PKND protein which interacts with proteins of the synaptic termini to modulate the

release of neurotransmitters. *SLC4A4* encodes the Na⁺-HCO³ NBCe1 cotransporter of which certain isoforms, expressed in astrocytes, regulate synaptic pH and neurotransmission. *SLC4A4* is mutated in renal tubular acidosis and in some HM cases [38]. *ATP1A3* encodes the $\alpha 3$ subunit of the Na⁺/K⁺-ATPase pump, which maintains electrochemical gradients across neuronal membranes and regulates excitability at inhibitory synapses. *ATP1A3* is mutated in alternating hemiplegia of childhood and in some cases of HM. *SLC1A3* encodes the EAAT1 transporter, which captures glutamate into astrocytes to terminate its action. *SLC1A3* is mutated in episodic ataxia type 6 and also in some HM cases. *SLC2A1* encodes the glucose transporter GLUT1 (or EAAT2), which enables glucose entry into the brain across the blood-brain barrier. This gene is mutated in paroxysmal exercise-induced dyskinesia, in GLUT1-deficiency syndrome and in some HM cases.

2.7 Sporadic hemiplegic migraine

Sporadic hemiplegic migraine (SHM) is diagnosed when there is no affected relative. SHM can result from a de novo mutation of one of the FHM genes in a subject whose both parents do not have a mutation. These de novo mutations can be transmitted to the offspring, turning SHM into FHM. SHM may also result from mutations in known FHM genes with low penetrance, mosaicism in the transmitting parent, or pathogenic variants in as yet unknown genes. Other SHMs might have a different mode of inheritance, either recessive with double heterozygotes or polygenic [8].

2.8 Links between FHM and common varieties of migraine

The identification of the first FHM genes has initially prompted to consider migraine as a neuronal condition and no more as a vascular disorder. Some authors proposed that the mechanisms of FHM, namely an increased sensitivity to CSD because of glutamatergic synaptic hyperactivity, could be applied to any variety of migraine. Other authors suggested that FHM could be different from the more common migraines, and thus that the identification of genes involved in other monogenic or polygenic migraines was important.

3. Monogenic migraine with aura and TRESK mutations

A frameshift mutation in *KCNK18*, which encodes the TRESK two-pore potassium channel, in a large family where visual MwA was inherited in an autosomal dominant fashion [39]. All affected members had the F139Wfsx24 mutation which was shown to exert a dominant negative effect leading to complete loss of TRESK function [40].

TRESK regulates membrane excitability and plays an important role in nociception. This leakage channel, through which K⁺ passes freely, is the main contributor of leakage currents in the trigeminal ganglion and dorsal root ganglia. TRESK-KO mice have a painful behavioral phenotype,

and show hyperexcitability of the dorsal root and trigeminal ganglia. In the trigeminal ganglion, expression of TRESK is restricted to nociceptive neurons [5, 41].

The causal link between TRESK mutations and migraine has been called into question by the discovery of another mutation with a dominant negative effect, C110R, in persons without migraine [42]. Two recent studies explained this apparent discrepancy, showing that the frameshift (F139Wfsx24), but not the C110R mutation, introduces an alternative start codon that shortens the TRESK protein, causes loss of TRESK currents and significantly increases excitability of nociceptors [40, 43].

These data demonstrated that MwA can be caused by a rare genetic variant inducing a major functional effect. No other family with MwA and a TRESK mutation has been published to date.

4. Other monogenic diseases including migraine

4.1 Familial advanced sleep-phase syndrome (FASPS), migraine, and *CSNK1D* mutations

FASPS, which causes an extreme tendency to wake up early in the morning, can be caused by mutation in a circadian clock gene, *CSNK1D*, which encodes casein kinase 1 delta (CKI δ). In the two large families with a CKI δ mutation, the sleep disorder was associated with migraine [44]. CKI δ -T44A transgenic mice displayed a high propensity for nitroglycerin-induced mechanical hyperalgesia and a reduced threshold for CSD. These data show that migraine can be caused by a mutation in a gene that does not encode an ion channel or a protein involved in glutamatergic signaling. In addition, the link between migraine and FASPS is consistent with the known role of hypothalamus in migraine.

4.2 ROSAH syndrome, migraine and *ALPK1* mutations

ROSAH syndrome (retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis) is an autosomal dominant condition that has a large clinical spectrum which also involves migraine. A missense mutation in the *ALPK1* gene was identified in five families [45]. *ALPK1* encodes alpha kinase 1, which may play a role in inflammation and cellular trafficking. Its role in migraine is unknown.

4.3 Monogenic vascular disorders and migraine

CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a cerebral small-vessel disease responsible for recurrent subcortical infarcts, dementia and premature death [9]. It is the main cause for inherited stroke and vascular dementia. CADASIL is due to *NOTCH3* mutations, which progressively destroy vascular smooth muscle cells

[46]. Migraine is very common in CADASIL (up to 75%), and may include migraine without aura, with typical aura and even with hemiplegic aura. Migraine is often the first manifestation of the disease, 15 to 20 years before cerebral infarctions. Mutant mice, either KI for a CADASIL mutation or NOTCH3-KO, showed an increased sensitivity to CSD [8].

Retinal vasculopathy with cerebral leukodystrophy (RVCL) caused by mutations in *TREX1*, and disorders due to *COL4A1* and *COL4A2* mutations are other small-vessel diseases that frequently involve migraines [9].

The study of these conditions showed that genes expressed in vessels could be implicated in migraine, which was later on confirmed in polygenic migraines.

5. Polygenic migraines and genome-wide association studies

MO and MwA frequently present with multiple familial cases, the distribution of which may suggest Mendelian inheritance. Initial hope, therefore, was that the techniques used successfully in FHM would identify genes for the common migraines. Early studies showed that FHM genes were not involved in common varieties of MO and MwA. Linkage analysis studies have identified dozens of loci that were presented as possibly containing genes involved in migraine, but these have never been discovered [5, 8, 47].

The researchers then turned to genome-wide association study (GWAS) which examines thousands of polymorphisms called SNPs (single nucleotide polymorphisms) in very large cohorts of patients and healthy controls. Each SNP is a variation of the genetic code at a single DNA base pair, and 4 to 5 million SNPs are distributed throughout the genome. A GWAS identifies SNPs significantly associated with the studied disease. For each SNP, the level of significance is very difficult to reach (5×10^{-8}) because of the multiplicity of tests carried out.

In 2010, the first GWAS identified a single migraine-susceptibility locus [48]. Other GWAS followed [49-51], and in 2016, a meta-analysis of GWAS, including 59,674 migraine sufferers and 316,078 controls, identified 38 distinct genomic regions associated with migraine [52]. Each loci explains a small portion of the overall genetic variance, with an odds ratio less than 1.2.

To interpret the GWAS data in migraine, two tissue expression enrichment analyzes clearly demonstrated the enrichment in genes involved in vascular function [52, 53]. The other pathways identified from GWAS were the neuronal pathway [54], and the pathway related to homeostasis of iron ions and other metals [52]. These results show that the vascular theory of migraine is still to be considered and demonstrate that the cerebral neurovascular unit, where neurons and blood vessels are in close structural and functional relationship, plays a prominent role in migraine.

6. Polygenic risk score and genetic architecture of migraine

The 38 variants identified by the GWAS each explain only a small fraction of the genetic risk. Part of the missing heritability may be explained by thousands of variants that probably confer increased risk of migraine but fall below the required levels of significance in GWAS. Another hypothesis is that persons with multiple disease-associated SNPs may have an additive effect conferring a greater overall risk.

The polygenic risk score (PRS) assesses the individual genetic risk of migraine as the sum of all SNPs and alleles that increase the risk of migraine carried by an individual. The PRS may be used to analyze the genetic links between the different primary headaches and the different forms of migraine, and between migraine and its comorbidities. The PRS can also assess pharmacogenetic effects [5].

In a study of 1 589 migraine sufferers from the Finnish population, familial cases had a significantly higher PRS than non-familial cases [55]. The genetic burden was higher in MWA and FHM compared to MO, and was associated with an earlier age of onset of migraine. These data show that migraine is primarily due to an accumulation of minor variants that produce a favorable (pro-migraine) genetic background, and not to highly deleterious single gene mutations.

However, the common variants with minor effect identified by GWAS do not explain the full heritability of migraine. Massive sequencing makes it possible to identify rare variants with minor or moderate effects. A study sequenced the genomic areas associated with migraine in a large cohort of patients and identified four rare variants altering regulatory areas close to four variants discovered by GWAS [56]. The genetics of migraine thus seems very complex, based on the interaction of common variants with minor effects and rare variants affecting regulatory areas.

Finally, rarer and more penetrating mutations can be identified by chance, as in families carrying mutations of TRESK or CKI δ . In these families, the strong penetrance of the migraine phenotype could be determined by interactions between the rare mutation and a pro-migraine genetic background. Most often in the general population, rare mutations would remain silent due to a non-permissive genetic background. Some authors have even hypothesized that FHM would not be truly autosomal dominant but the result of a rare mutation on a pro-migraine background.

7. Other recent genetic findings

7.1 Genetics of headache

A 2018 British GWAS studied 74,461 individuals who had had a headache interfering with daily activities in the previous month and 149,312 controls [57]. The majority of patients probably had tension headache and less often migraine. This study identified 28 headache susceptibility loci of which 14 had already been identified by GWAS in migraine and 14 were new. The majority of the potential headache genes were neuronal and not vascular. This study also found a shared genetic background between the headache phenotype and many psychological traits associated with vulnerability to depression and negative emotions, highlighting the importance of links between psychiatric conditions and painful conditions.

7.2 Genetics of chronic migraine

Chronic migraine is the most disabling form of migraine. According to two large studies, the development of chronic migraine depends on environmental factors, and not on genetic factors [58, 59]. Indeed, no genetic difference was observed between patients with chronic migraine and those with episodic migraine, concerning rare variants identified by exome sequencing or frequent variants identified by GWAS. These data suggest that chronic migraine is acquired and not inherited, and therefore potentially accessible to primary and secondary prevention.

7.3 Genetic factors of response to treatment

One study showed that a polygenic risk score doubling the risk of migraine was associated with a better response to triptans [60]. Genetic factors strongly influence the absorption, distribution, metabolism and excretion of drugs. In the future, determining the genetic profile of an individual could allow the choice of treatments with the best profile of efficacy and tolerance [5].

7.4 Common genetic factors between migraine and its comorbidities

The comorbidities of migraine are diseases whose prevalence is increased in migraine sufferers compared to controls and for which certain pathological mechanisms could be shared. Genetics is a tool to identify some of the common mechanisms. New statistical techniques, including Mendelian randomization (MR), can also estimate the causal links between the genetic background of migraine and its comorbidities [5].

Since 2018, several large studies based on the comparison of GWAS data have shown the existence of a shared genetic susceptibility between migraine and several disorders including psychiatric disorders [61], coronary artery disease [62], hypertension [63], sleep disorders [64], and also endometriosis [65], type 2 diabetes, hyperlipidemia, autoimmune diseases, hemostatic profile [66], asthma and respiratory conditions. In contrast, one study found no causal link between genetic susceptibility to migraine and Alzheimer's disease, intelligence, and brain size [67].

7.5 Mitochondrial genome and migraine

A mitochondrial DNA GWAS in 4,021 migraine sufferers and 14,288 headache-free controls found no migraine-associated variants, ruling out the mitochondrial hypothesis suggested by older studies [68].

8. Conclusions

Genetics of migraine have made significant progress over the past 15 years [5, 10, 47]. The study of monogenic migraines identified key proteins of the susceptibility to CSD and helped to better appreciate the links between migraine and vascular disorders. GWAS have identified multiple susceptibility genes revealing several complex networks of "pro-migraine" molecular abnormalities, mainly neuronal and vascular. Genetics has also underscored the importance of genetic factors shared between migraine and its major co-morbidities including depression and high blood pressure. Very large-scale studies are still needed to map all of the susceptibility loci to migraine and then to understand how these genomic variants lead to migraine cell phenotypes. Thanks to the advent of new technologies such as induced pluripotent stem cells, genetic data will finally be able to lead to therapeutic progress [5]. Ultimately, the main pathophysiological mechanism in a given patient, neuronal or vascular or otherwise, could be determined through its genetic risk profile. Pharmacogenetics could help predict the therapeutic response and thus help prescribe the treatment with the best safety and efficacy profile.

References

- [1] Russell MB, Hilden J, Sorensen SA, Olesen J. Familial occurrence of migraine without aura and migraine with aura. *Neurology* 1993;43(7):1369-73.
- [2] Russell MB, Olesen J. Increased familial risk and evidence of genetic factor in migraine. *Bmj* 1995;311(7004):541-4.
- [3] Polderman TJ, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, et al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet* 2015;47(7):702-9.
- [4] Russell MB, Ulrich V, Gervil M, Olesen J. Migraine without aura and migraine with aura are distinct disorders. A population-based twin survey. *Headache* 2002;42(5):332-6.
- [5] Cader MZ. The genetics of migraine and the path to precision medicine. *Prog Brain Res* 2020;255:403-18.
- [6] Russell MB, Ducros A. Sporadic and familial hemiplegic migraine: pathophysiological mechanisms, clinical characteristics, diagnosis, and management. *The Lancet Neurology* 2011;10(5):457-70.
- [7] The International Classification of Headache Disorders. 3rd edition. ICHD-3. *Cephalalgia : an international journal of headache* 2018.

- [8] Sutherland HG, Albury CL, Griffiths LR. Advances in genetics of migraine. *The journal of headache and pain* 2019;20(1):72.
- [9] de Boer I, Terwindt GM, van den Maagdenberg A. Genetics of migraine aura: an update. *The journal of headache and pain* 2020;21(1):64.
- [10] Bron C, Sutherland HG, Griffiths LR. Exploring the Hereditary Nature of Migraine. *Neuropsychiatr Dis Treat* 2021;17:1183-94.
- [11] Sutherland HG, Maksemous N, Albury CL, Ibrahim O, Smith RA, Lea RA, et al. Comprehensive Exonic Sequencing of Hemiplegic Migraine-Related Genes in a Cohort of Suspected Proband Identifies Known and Potential Pathogenic Variants. *Cells* 2020;9(11).
- [12] Riant F, Roos C, Roubertie A, Barbance C, Hadjadj J, Auvin S, et al. Hemiplegic migraine associated with PRRT2 mutations: a clinical and genetic study. Submitted.
- [13] Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca²⁺ channel gene CACNL1A4. *Cell* 1996;87(3):543-52.
- [14] Tottene A, Fellin T, Pagnutti S, Luvisetto S, Striessnig J, Fletcher C, et al. Familial hemiplegic migraine mutations increase Ca²⁺ influx through single human CaV2.1 channels and decrease maximal CaV2.1 current density in neurons. *Proc Natl Acad Sci U S A* 2002;99(20):13284-9.
- [15] van den Maagdenberg AM, Pietrobon D, Pizzorusso T, Kaja S, Broos LA, Cesetti T, et al. A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. *Neuron* 2004;41(5):701-10.
- [16] van den Maagdenberg AM, Pizzorusso T, Kaja S, Terpolilli N, Shapovalova M, Hoebeek FE, et al. High cortical spreading depression susceptibility and migraine-associated symptoms in Ca(v)2.1 S218L mice. *Annals of neurology* 2010;67(1):85-98.
- [17] Chanda ML, Tuttle AH, Baran I, Atlin C, Guindi D, Hathaway G, et al. Behavioral evidence for photophobia and stress-related ipsilateral head pain in transgenic Cacna1a mutant mice. *Pain* 2013;154(8):1254-62.
- [18] Ferrari MD, Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AM. Migraine pathophysiology: lessons from mouse models and human genetics. *The Lancet Neurology* 2015;14(1):65-80.
- [19] De Fusco M, Marconi R, Silvestri L, Atorino L, Rampoldi L, Morgante L, et al. Haploinsufficiency of ATP1A2 encoding the Na⁺/K⁺ pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nat Genet* 2003;33(2):192-6.
- [20] Leo L, Gherardini L, Barone V, De Fusco M, Pietrobon D, Pizzorusso T, et al. Increased susceptibility to cortical spreading depression in the mouse model of familial hemiplegic migraine type 2. *PLoS Genet* 2011;7(6):e1002129.
- [21] Capuani C, Melone M, Tottene A, Bragina L, Crivellaro G, Santello M, et al. Defective glutamate and K⁺ clearance by cortical astrocytes in familial hemiplegic migraine type 2. *EMBO Mol Med* 2016;8(8):967-86.
- [22] Unekawa M, Ikeda K, Tomita Y, Kawakami K, Suzuki N. Enhanced susceptibility to cortical spreading depression in two types of Na⁽⁺⁾,K⁽⁺⁾-ATPase alpha2 subunit-deficient mice as a model of familial hemiplegic migraine 2. *Cephalalgia : an international journal of headache* 2018;38(9):1515-24.
- [23] Smith SE, Chen X, Brier LM, Bumstead JR, Rensing NR, Ringel AE, et al. Astrocyte deletion of alpha2-Na/K ATPase triggers episodic motor paralysis in mice via a metabolic pathway. *Nat Commun* 2020;11(1):6164.
- [24] Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. *Lancet* 2005;366(9483):371-7.

- [25] Martin MS, Dutt K, Papale LA, Dube CM, Dutton SB, de Haan G, et al. Altered function of the SCN1A voltage-gated sodium channel leads to gamma-aminobutyric acid-ergic (GABAergic) interneuron abnormalities. *J Biol Chem* 2010;285(13):9823-34.
- [26] Cestele S, Scalmani P, Rusconi R, Terragni B, Franceschetti S, Mantegazza M. Self-limited hyperexcitability: functional effect of a familial hemiplegic migraine mutation of the Nav1.1 (SCN1A) Na⁺ channel. *J Neurosci* 2008;28(29):7273-83.
- [27] Bertelli S, Barbieri R, Pusch M, Gavazzo P. Gain of function of sporadic/familial hemiplegic migraine-causing SCN1A mutations: Use of an optimized cDNA. *Cephalalgia : an international journal of headache* 2019;39(4):477-88.
- [28] Cloarec R, Bruneau N, Rudolf G, Massacrier A, Salmi M, Bataillard M, et al. PRRT2 links infantile convulsions and paroxysmal dyskinesia with migraine. *Neurology* 2012;79(21):2097-103.
- [29] Gardiner AR, Bhatia KP, Stamelou M, Dale RC, Kurian MA, Schneider SA, et al. PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. *Neurology* 2012;79(21):2115-21.
- [30] Marini C, Conti V, Mei D, Battaglia D, Lettori D, Losito E, et al. PRRT2 mutations in familial infantile seizures, paroxysmal dyskinesia, and hemiplegic migraine. *Neurology* 2012;79(21):2109-14.
- [31] Riant F, Roze E, Barbance C, Meneret A, Guyant-Marechal L, Lucas C, et al. PRRT2 mutations cause hemiplegic migraine. *Neurology* 2012;79(21):2122-4.
- [32] Dale RC, Gardiner A, Antony J, Houlden H. Familial PRRT2 mutation with heterogeneous paroxysmal disorders including paroxysmal torticollis and hemiplegic migraine. *Dev Med Child Neurol* 2012;54(10):958-60.
- [33] Pelzer N, Haan J, Stam AH, Vijfhuizen LS, Koelewijn SC, Smagge A, et al. Clinical spectrum of hemiplegic migraine and chances of finding a pathogenic mutation. *Neurology* 2018;90(7):e575-e82.
- [34] Suzuki-Muromoto S, Kosaki R, Kosaki K, Kubota M. Familial hemiplegic migraine with a PRRT2 mutation: Phenotypic variations and carbamazepine efficacy. *Brain Dev* 2020;42(3):293-7.
- [35] Ebrahimi-Fakhari D, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2-associated paroxysmal diseases. *Brain : a journal of neurology* 2015;138(Pt 12):3476-95.
- [36] Yang L, You C, Qiu S, Yang X, Li Y, Liu F, et al. Novel and de novo point and large microdeletion mutation in PRRT2-related epilepsy. *Brain Behav* 2020;10(5):e01597.
- [37] Michetti C, Castroflorio E, Marchionni I, Forte N, Sterlini B, Binda F, et al. The PRRT2 knockout mouse recapitulates the neurological diseases associated with PRRT2 mutations. *Neurobiol Dis* 2017;99:66-83.
- [38] Suzuki M, Van Paesschen W, Stalmans I, Horita S, Yamada H, Bergmans BA, et al. Defective membrane expression of the Na⁽⁺⁾-HCO₃⁽⁻⁾ cotransporter NBCe1 is associated with familial migraine. *Proc Natl Acad Sci U S A* 2010;107(36):15963-8.
- [39] Lafreniere RG, Cader MZ, Poulin JF, Andres-Enguix I, Simoneau M, Gupta N, et al. A dominant-negative mutation in the TRESK potassium channel is linked to familial migraine with aura. *Nat Med* 2010;16(10):1157-60.
- [40] Pettingill P, Weir GA, Wei T, Wu Y, Flower G, Lalic T, et al. A causal role for TRESK loss of function in migraine mechanisms. *Brain : a journal of neurology* 2019;142(12):3852-67.
- [41] Weir GA, Pettingill P, Wu Y, Duggal G, Ilie AS, Akerman CJ, et al. The Role of TRESK in Discrete Sensory Neuron Populations and Somatosensory Processing. *Front Mol Neurosci* 2019;12:170.

- [42] Andres-Enguix I, Shang L, Stansfeld PJ, Morahan JM, Sansom MS, Lafreniere RG, et al. Functional analysis of missense variants in the TRESK (KCNK18) K channel. *Sci Rep* 2012;2:237.
- [43] Royal P, Andres-Bilbe A, Avalos Prado P, Verkest C, Wdziekonski B, Schaub S, et al. Migraine-Associated TRESK Mutations Increase Neuronal Excitability through Alternative Translation Initiation and Inhibition of TREK. *Neuron* 2019;101(2):232-45 e6.
- [44] Brennan KC, Bates EA, Shapiro RE, Zyuzin J, Hallows WC, Huang Y, et al. Casein kinase idelta mutations in familial migraine and advanced sleep phase. *Sci Transl Med* 2013;5(183):183ra56, 1-11.
- [45] Williams LB, Javed A, Sabri A, Morgan DJ, Huff CD, Grigg JR, et al. ALPK1 missense pathogenic variant in five families leads to ROSAH syndrome, an ocular multisystem autosomal dominant disorder. *Genet Med* 2019;21(9):2103-15.
- [46] Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996;383(6602):707-10.
- [47] Ducros A. [Genetics of migraine]. *Revue neurologique* 2013;169(5):360-71.
- [48] Anttila V, Stefansson H, Kallela M, Todt U, Terwindt GM, Calafato MS, et al. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. *Nat Genet* 2010;42(10):869-73.
- [49] Chasman DI, Schurks M, Anttila V, de Vries B, Schminke U, Launer LJ, et al. Genome-wide association study reveals three susceptibility loci for common migraine in the general population. *Nat Genet* 2011;43(7):695-8.
- [50] Freilinger T, Anttila V, de Vries B, Malik R, Kallela M, Terwindt GM, et al. Genome-wide association analysis identifies susceptibility loci for migraine without aura. *Nat Genet* 2012;44(7):777-82.
- [51] Anttila V, Winsvold BS, Gormley P, Kurth T, Bettella F, McMahon G, et al. Genome-wide meta-analysis identifies new susceptibility loci for migraine. *Nat Genet* 2013;45(8):912-7.
- [52] Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat Genet* 2016;48(8):856-66.
- [53] Finucane HK, Reshef YA, Anttila V, Slowikowski K, Gusev A, Byrnes A, et al. Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat Genet* 2018;50(4):621-9.
- [54] Eising E, Huisman SMH, Mahfouz A, Vijfhuizen LS, Anttila V, Winsvold BS, et al. Gene co-expression analysis identifies brain regions and cell types involved in migraine pathophysiology: a GWAS-based study using the Allen Human Brain Atlas. *Hum Genet* 2016;135(4):425-39.
- [55] Gormley P, Kurki MI, Hiekkala ME, Veerapen K, Happola P, Mitchell AA, et al. Common Variant Burden Contributes to the Familial Aggregation of Migraine in 1,589 Families. *Neuron* 2018;99(5):1098.
- [56] Techlo TR, Rasmussen AH, Moller PL, Bottcher M, Winther S, Davidsson OB, et al. Familial analysis reveals rare risk variants for migraine in regulatory regions. *Neurogenetics* 2020;21(3):149-57.
- [57] Meng W, Adams MJ, Hebert HL, Deary IJ, McIntosh AM, Smith BH. A Genome-Wide Association Study Finds Genetic Associations with Broadly-Defined Headache in UK Biobank (N=223,773). *EBioMedicine* 2018;28:180-6.
- [58] Louter MA, Fernandez-Morales J, de Vries B, Winsvold B, Anttila V, Fernandez-Cadenas I, et al. Candidate-gene association study searching for genetic factors

- involved in migraine chronification. *Cephalalgia : an international journal of headache* 2015;35(6):500-7.
- [59] Chalmer MA, Rasmussen AH, International Headache Genetics C, andme Research T, Kogelman LJA, Olesen J, et al. Chronic migraine: Genetics or environment? *European journal of neurology : the official journal of the European Federation of Neurological Societies* 2021;28(5):1726-36.
- [60] Kogelman LJA, Esserlind AL, Francke Christensen A, Awasthi S, Ripke S, Ingason A, et al. Migraine polygenic risk score associates with efficacy of migraine-specific drugs. *Neurol Genet* 2019;5(6):e364.
- [61] Brainstorm C, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, et al. Analysis of shared heritability in common disorders of the brain. *Science* 2018;360(6395).
- [62] Daghlas I, Guo Y, Chasman DI. Effect of genetic liability to migraine on coronary artery disease and atrial fibrillation: a Mendelian randomization study. *European journal of neurology : the official journal of the European Federation of Neurological Societies* 2020;27(3):550-6.
- [63] Guo Y, Rist PM, Daghlas I, Giulianini F, International Headache Genetics C, andMe Research T, et al. A genome-wide cross-phenotype meta-analysis of the association of blood pressure with migraine. *Nat Commun* 2020;11(1):3368.
- [64] Daghlas I, Vgontzas A, Guo Y, Chasman DI, International Headache Genetics C, Saxena R. Habitual sleep disturbances and migraine: a Mendelian randomization study. *Ann Clin Transl Neurol* 2020;7(12):2370-80.
- [65] Adewuyi EO, Sapkota Y, International Endogene Consortium I, andMe Research T, International Headache Genetics Consortium I, Auta A, et al. Shared Molecular Genetic Mechanisms Underlie Endometriosis and Migraine Comorbidity. *Genes (Basel)* 2020;11(3).
- [66] Guo Y, Rist PM, Sabater-Lleal M, de Vries P, Smith N, Ridker PM, et al. Association Between Hemostatic Profile and Migraine: A Mendelian Randomization Analysis. *Neurology* 2021;96(20):e2481-e7.
- [67] Daghlas I, Rist PM, Chasman DI. Effect of genetic liability to migraine on cognition and brain volume: A Mendelian randomization study. *Cephalalgia : an international journal of headache* 2020;40(9):998-1002.
- [68] Borte S, Zwart JA, Skogholt AH, Gabrielsen ME, Thomas LF, Fritsche LG, et al. Mitochondrial genome-wide association study of migraine - the HUNT Study. *Cephalalgia : an international journal of headache* 2020;40(6):625-34.