Chapter 1

Genetic Aspect of Headache

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Additional information is available at the end of the chapter

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Abstract

Headache is a multifactorial disease and the genetic basis is not clear yet. We review recent findings about molecular basis of subtypes of headache. The fundamentals of molecular genetics and the recent advances in this area are important for clinicians to understand the pathogenesis of the disorder. Recent studies provide a foundation for critical appraisal of the literature, unprecedented insights and reveal promising treatment targets for future drug development. This chapter provides an overview of molecular genetics, epigenetic and genome-wide association studies on headache. In summary, we try to explain the state-of-the-art molecular basis of headache and the possible future direction in this field of research studies. According to recent studies the main types of are evaluative, exploratory about molecular basis of headache. In recent years, new studies have been designed to provide an update and understanding of the modern day genetics, the advances in genetic research and methods and a basis for understanding the strategy by which advances in molecular genetics can be applied for understanding complex polygenetic diseases such as migraine.

Keywords: headache, genetic, epigenetic, cluster type headache, tension type headache, migraine

1. Molecular basis of headache subtypes

Recently, researchers have identified the gene variations that increase the susceptibility to develop headaches. To analyze the cause, clinical history of headaches is very important. While headaches can be caused by medical conditions, injuries, or infections, sometimes they are not due to any specific disease or other identified medical conditions. The three most common of those types of primary headaches are tension, cluster and migraine headaches (**Figure 1**). Tension-type headache (TTH) brought on by stress or depression, so everyone has

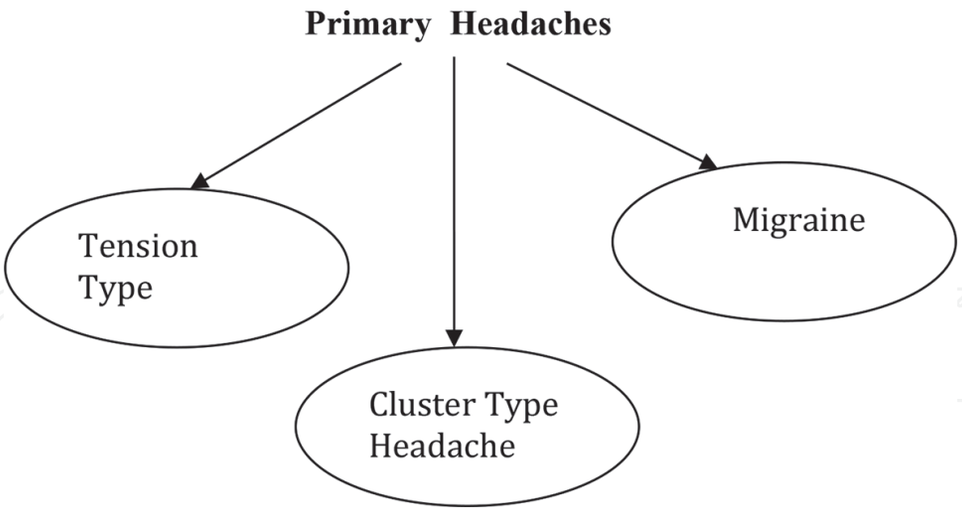

Figure 1. Diagram of primary headaches subtypes.

experienced TTH. TTH can be brief, episodic or continuous. According to some researchers, TTH could be secondary to the vasoconstriction, rather than dilatation [1–3].

The neurobiological mechanisms of tension-type headache are concerning. Central sensitization plays a major role in chronic TTH. Whether peripheral mechanisms or central mechanisms are primarily responsible for TTH is an important issue to differentiate it pathophysiologically from migraine. The literature suggests that migraine and tension-type headache may have the similar pathophysiology. Moreover, exact mechanism for both the disorders is still to be elucidated [4–6].

The prevalence of migraine has been shown to be increasing. The researchers have suggested that the central nervous system (CNS) susceptible to headache has been linked to an important survival or reproductive advantage. Some possible reasons are determined; one of these says that migraine is a defense mechanism; the other one consider it as a result of novel environmental factors; the next one regards migraine as a compromise between genetic harms and benefits. Genetic epidemiological studies are necessary to prove the involvement of genetic factors. Twin studies have been used to assess the respective roles of genetic and environmental factors in migraine [7, 8].

We briefly mention here the headache types and characteristics. The first title is TTH. Biological mechanisms of TTH are yet to be explained. This disease usually is associated with depression and anxiety. In addition, the genetic factors are most important for TTH pathogenesis. The neurological mechanisms of TTH are not known clearly. Genetic and neurobiological research studies have increased our understanding of the complex mechanisms that may lead to TTH. There is strong evidence for a genetic predisposition for TTH. Moreover pain pathways in the central nervous system are positively associated with TTH. Research has enhanced our current understanding regarding the means through which psychological factors lead to TTH, suggesting sympathetic hyperactivity as a possible mechanism [9, 10].

The etiology of cluster-type headache (CH) is still unknown. Until recently, researchers thought that CH was not an inherited disorder; however, several new studies have suggested

that genetic factors play an important role in the CH. Some studies show that CH phenotype is inherited such as in autosomal dominant disease [11, 12]

To identify genetic factors that confer susceptibility to migraine, many studies have been conducted on the genetic basis of migraine types. First approach on this is classical linkage analysis. This approach aims to identify affected segments of chromosomes in individuals using a family-based approach. For monogenic migraine types, this approach has been particularly successful. A second commonly used strategy to identify gene variants involves candidate-gene association studies. These studies are determinate with alleles and genotype frequencies in control and case groups. Recently, DNA variants have advanced spectacularly, allowing the cost-effective analysis of DNA variants in patients in so-called genome-wide association studies (GWAS). Also, GWAS included hundreds of genes for many complex diseases. To determine the size of rarer gene variants is too expensive and takes more time. Instead, methods such as next-generation sequencing of exons (exome sequencing) and whole-genome sequencing can be used [13].

2. Genetic aspects of tension-type headache

While tension-type headaches (TTH) are the most common primary headache disorder it has not been as thoroughly investigated as migraine headaches. A lifetime prevalence of TTH has been seen in the general population ranging between 30 and 78% in different studies [13]. Nevertheless, 24–37% had TTH several times a month, 10% had it weekly and 2–3% of the population had chronic TTH, usually lasting for the greater part of their lifetime [14] According to the second edition of the International Classification of Headache Disorders, TTH is classified into three subtypes according to headache frequency: infrequent episodic TTH, frequent episodic TTH and chronic TTH [13]. The female-to-male ratio of TTH is 5:4 indicating that, unlike migraine, women are affected only slightly more than men [15]. The average age of onset of TTH is higher than in migraine, namely 25 to 30 years in cross-sectional epidemiologic studies [16].

Many studies probably provide a valid measure of the major etiologic role that genetic or environmental factors play in TTH. **Table 1** shows the genetic association studies in TTH. In a study of twins from the New Danish Twin Registry, it was found that the concordance rates were significantly higher in MZ than same-gender DZ twin pairs with no or frequent episodic TTH, while the difference was not significant in chronic TTH due to small number of twin pairs. In monozygotic (MZ) and same-gender DZ twin pairs, the concordance rates of infrequent episodic tension-type headache was significantly different in women but not in men, although the difference was small in both genders. It was suggested that genetic factors play a role in no and frequent episodic tension-type headache, while infrequent episodic TTH is caused primarily by environmental factors [17]. However, differently Ulrich et al. suggested that an environmental influence was of major importance for episodic TTH and a genetic factor had minor contribution [18] but in chronic tension-type headache, the genetic factor may be more important.

When the population-relative risk in first- degree relatives compared with normal controls has been calculated in a Danish study, it was shown that first-degree relatives of 122 probands with chronic tension headache had more than three times the risk of chronic tension

Gene	Genetic variants	Results	Reference
Monoamine oxidase (MAO)	rs1799836 G/A promoter polymorphism of a variable number of tandem repeats (VNTR)	No association	[21]
Catechol-O-methyltransferase (COMT)	Val158Met	may be involved in the phenotypic expression	[25]
Tumor necrosis factor (TNF)	TNFA 308G > A and TNFB 252G > A	No association	[40]
Estrogen receptor (ESR1) progesterone receptor (PROGINS)	ESR1 PvuII (rs2234693), ESR1 325 C→G (rs1801132)] and [(rs1042838)	No association	[119]
Apolipoprotein E (APOE)		Association	[28]
Serotonin (5-hydroxytryptamine, 5HT) transporter gene	the variable number of tandem repeats (VNTR) and 5'-flanking promoter region (5-HTTLPR)	Association	[33]
Serotonin transporter gene	5-HTTLPR)	Association	[34]
Serotonin transporter gene	5-HTTLPR	Association	[35]
Serotonin transporter gene	5HTR2c-Cys23Ser	No association	[36]
Glutathione S-transferase (GST) M1, T1, P1	GST M1 and T1 null polymorphism GSTP1 $Ile^{105}Val$	No Association	[42]
Methylenetetrahydrofolate reductase gene (MTHFR)	C677T and A1298C	Association	[38]
Methylenetetrahydrofolate reductase gene (MTHFR)	C677T	No association	[39]

Table 1. The genetic association studies in TTH.

headache than the general population. An increased family risk can be caused by genetic or environmental factors because probands and spouses share their environment, the risk of chronic tension headache in spouses is used to elucidate the relative role of genetic and environmental factors. As first-degree relatives had a significantly increased risk of chronic tension headache and spouses had no increased risk, this result supports the importance of genetic factors in chronic tension headache. [19]. For investigation of the mode of inheritance of chronic tension-type headache complex segregation analysis was performed in 122 Danish families. The complex segregation analysis indicates that chronic tension-type headache has multifactorial inheritance [20].

Because TTH treatment features medication with inhibitors for selective reuptake of serotonin and monoamine oxidase inhibitors, The polymorphic patterns of MAOA and MAOB, both in TTH patients and the healthy population were addressed in our previous study. MAO gene polymorphisms were examined in a group of 120 TTH patients and in another 168 unrelated healthy volunteers (control group). MAOA promoter and MAOB intron 13 polymorphisms were genotyped using PCR-based methods. But an overall comparison between genotype and allele frequencies of the patients and the control group did not reveal any statistically significant difference between the patients and the control group [21].

The catechol-O-methyltransferase (COMT) is an enzyme involved in the metabolic degradation of dopamine, norepinephrin and epinephrine [22]. It is accepted that COMT gene is one of the several potential headache genetic determinants. Several studies indicate that the genetic polymorphism due to a G→A substitution at codon 158 of the COMT gene, which leads to the formation of a heat-stable, high-activity COMT variant (Val/Val) and heat-labile, low-activity variants (Val/Met or Met/Met) [23]. Zubieta et al. demonstrated that a measure of pain sensitivity paralleled the COMT activity of the genotypes and individuals with Val/Val genotype have reduced pain sensitivity compared with those with the Met/Met genotype [24]. And also, Fernández-de-las-Peñas C et al. investigate the relationship between Val158Met polymorphisms, headache and pressure hypersensitivity in children with chronic tension-type headache (CTTH). But it was reported that the Val158Met COMT polymorphism does not appear to be involved in predisposition to suffer from CTTH in children; nevertheless, this genetic factor may be involved in the phenotypic expression, as pressure hypersensitivity was greater in those CTTH children with the Met/Met genotype [25]. Nitric oxide has an important role in the pathophysiology of tension-type headache. It is suggested nitric oxide synthetase inhibitors are helpful in the management of chronic tension-type headache by reducing the central sensitization [26]. Besides nitric oxide synthetase, nitric oxide production is also dependent on apolipoprotein E (APOE) polymorphism and this production is gene specific [27]. And it was investigated that APOE polymorphism may be associated with migraine as well as tension-type headache. And the results of the study showed that APOE epsilon2 gene increases the risk of migraine, while APOE epsilon4 gene is protective against migraine and tension-type headache [28].

As other neurotransmitters, serotonin have a role in pain mechanisms, selective serotonin re-uptake inhibitors (SSRIs) reduce the symptomatic/analgesic medication use for acute headache attacks of tension-type headache [29]. Serotonin is taken up from the synaptic space regularly with a 5-hydroxytryptamine transporter (5-HTT) [30, 31]. Two polymorphic sites in 5-HTT gene was studied in various studies: different numbers of variable-number-tandem-repeat (VNTR) region of 16-17 base-pair (bp) in the second intron of 5-HTT gene leads several alleles such as STin 2.7, STin 2.9, STin 2.10, STin 2.11, STin 2.12 and a 44-base pair insertion/deletion in the 5'--flanking promoter region (5-HTT gene-linked polymorphic region-5-HTTLPR) creating a short (S) and a long (L) allele [32]. The possible role of 5-HTTLPR and VNTR polymorphisms was evaluated individually and in combination in risk of CTTH. Moreover, the relationship between the clinical response of the drugs or analgesic overuse and the serotonin transporter (5-HTT) gene polymorphisms was investigated [33, 34]. Park et al. reported that S/S genotype frequency was significantly higher in patients with CTH (76%) than in those with controls (59%; P =.02). The authors suggested that 5-HTTLPR might be one of the genetically contributing factors [35].

But differently in another study any statistically significant results based on the 5-HTTLPR gene alleles and CTTH risk were not found. Only, when it was investigated the combined effect of the two polymorphic loci of the 5-HTT gene, genotypes S/S-12/10 and L/S-12/10 displayed statistically significant frequency in the CTTH group than in the control group. Aylin et al. reported that the presence of homozygous L and STin12 alleles may play a protective role against CTTH [33]. Also in a different study showed that the S/S genotype frequency

was significantly higher in CTTH patients with analgesic overuse. And it was suggested that serotonergic activity may be involved in the development of analgesic overuse in CTTH and that 5-HTTLPR might be one of the genetically contributing factors [34]. But no significant differences were noticed between the 5-HTTLPR and VNTR haplotype groups and success in treatment. 5HT2c-receptor (5HTR2c) is another subtypes of 5HT2 families. The relationship between 5HTR2c Cys23Ser polymorphism and TTH was also investigated. However, there were no differences found among TTH and control groups [36].

Increased homocysteine levels are associated with various pathological conditions in humans, including stroke and cardiovascular disorders. So vasodilation of cerebral blood vessels may result in headache, or high levels of homocysteine may cause temporary thrombosis of cerebral blood vessels, allowing less oxygen into the brain thus possibly causing headache. Frosst et al. reported an association between the homozygous C677T mutation in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene and serum homocysteine levels [37]. In a case-control study, the prevalence of two common MTHFR polymorphisms, C677T and A1298C, in tension-type headache patients and healthy controls was compared. And it was suggested that patients with C1298C and C677C/C1298C genotypes may predispose to tension-type headache [38]. On the contrary, the study of Kowa et al. could not reach the same results. It was reported that MTHFR gene polymorphisms was not a genetic risk factor for TTH in their study [39].

Also it was investigated the relationship between TTH and tumor necrosis factor (TNF) gene polymorphisms (TNFA 308G > A and TNFB 252G > A) [40] and also estrogen receptor [ESR1 PvuII (rs2234693), ESR1 325 C→G (rs1801132)] and progesterone receptor [PROGINS (rs1042838)] polymorphisms [41]. But no risk was observed when TTH patients were compared with HC. Similarly, in a study that evaluates the relationship between GSTM1, T1 and P1 gene polymorphism and TTH, no difference was found between two groups in the genotype and allele distribution [42].

3. Genetic aspects of cluster-type headache

Cluster headache (CH), the most severe primary headache, is characterized by recurrent, unilateral attacks of headache of great intensity and brief duration, accompanied by local signs and symptoms of autonomic dysfunction. In about 80% of the patients, the attacks occur in series lasting weeks or months, so-called cluster periods [3]. The disease has an estimated prevalence of 1/500 and displays marked sex bias (female:male ratio 1:2.5 to 1:3.5) [43, 44].

Twin studies represent one of the simplest ways to unravel the relative importance of genetic and environmental effects. Much of the available literature on CH is reported in numerous concordant monozygotic twin pairs [45–48]. However, other studies demonstrated discordant twin pairs showed the importance of both genetic and individual specific factors and environmental factors in CH [49]. Beside this, epidemiological surveys indicate that compared with the general population, the first-degree relatives of CH patients had a 14 fold increase in the disease risk in affected Danish probands and 39 fold increase in affected Italian probands.

Also second-degree relatives have two times higher risk in Danish probands and eight times higher risk in Italian probands [50–52]. The different results can be partly explained by methodological differences or selection bias. The increased familial risk of CH strongly suggests a genetic cause for the disease. However, the pattern of inheritance does not appear to be uniform. The familial clustering supports a model of autosomal dominant inheritance with reduced penetrance in some families but autosomal recessive model in others [53, 54] Also a study by Sjöstrand demonstrated a significantly lower mean age of onset in the second/third generation of families with CH than in the first generation. This can be explained by anticipation or selection bias, since individuals with late age at onset from the second/third generation may not yet have symptoms [55, 56].

To date, no clear molecular genetic evidence has been shown for CH. A point mutation was reported in mitochondrial transfer RNAleu(UUR) gene at nucleotide pair 3243 in a Japanese man with sporadic CH [56]. However, this mutation was not detected in Italian and German patients with CH [57, 58] and the involvement of mitochondrial genes in CH remains unproven.

Neuroimaging studies have identified the posterolateral hypothalamic grey matter as the key area for the basic defect in CH [59]. Hypocretin-1 and -2 (also called orexin-A and -B) are newly discovered neuropeptides [60, 61]. Hypocretin-containing cells are located exclusively in the posterolateral hypothalamus, with widespread projections to the entire neuroaxis. Hypocretin-1 and -2 bind to 2 G protein-coupled receptors, termed HCRTR1 and HCRTR2. The peptides of the hypocretin/orexin system influence a wide range of physiologic and behavioral processes in mammals [62, 63]. Some of these, such as sleep, neuroendocrine, locomotor, autonomic regulation, feeding behavior and energy homeostasis, may be of relevance for the pathogenesis of CH. Also a striking feature of CH is its diurnal and seasonal periodicity, suggesting that circadian and infradian rhythms regulate CH attacks. The hypocretin system plays a pivotal role in generating such rhythms and hypocretin-containing neurons originate almost exclusively from the posterolateral hypothalamus [60, 61, 64]. Recent studies suggest a contribution of hypocretin to the pathogenesis of CH. A study among 109 Italian CH patients showed a strong association between the hypocretin type 2 receptor (HCRTR2) G1246A polymorphism and CH [65]. This association was confirmed in a major study from Germany, showing that homozygous carriers of the G-allele had a twofold increase in disease risk [66]. Also in another study among Italian patients five additional intronic polymorphisms was genotyped, covering more than 75% of the entire 108.35 kb sequence of the HCRTR2 gene. And the carriage of the GTAAGG haplotype was shown to be associated with the disease and resulted in a 3.7-fold increased risk for CH [67]. On the contrary, the association was not replicated in a dataset of CH patients of Danish, Swedish and British origin [68]. In addition there are two published meta-analysis studies investigating the association between polymorphisms of the HCRTR2 gene and CH. However, there are conflicting results between two studies, Rainero et al. suggested that the G1246A polymorphism of the HCRTR2 gene may modulate the genetic risk for CH [69] but Weller et al. did not find evidence for association of G1246A polymorphism (rs2653349) [70].

Besides this, the association between CH and a variable number tandem repeat (VNTR) polymorphism of the PER3 clock gene that has been associated to preferred daily rhythm

(chronotype) in several studies was investigated. The hypothalamic biological clock may thus be involved in the pathophysiology and 149 patients were genotyped, but no difference in PER3 VNTR polymorphisms between patients and controls was found. And no association between CH, PER3 VNTR polymorphism and chronotype was found in the study [71].

Also some researchers performed a genetic association study to evaluate the relationship between CH and polymorphisms in the Clock gene, another highly conserved circadian gene, that influence the circadian phase in humans [72]. But they found that phenotype and allele frequencies were similarly distributed in CH patients and controls. Also it was determined that the clinical features of the disease were not significantly influenced by different genotypes. In conclusion, studies reported that the 3092 T-->C polymorphism of the Clock gene is unlikely to play an important role in CH [73, 74].

Recent studies suggested that iron metabolism may be involved in the pathophysiology of primary headaches. The genetic association studies are shown in **Table 2**. In patients with migraine and chronic daily headache, Welch and colleagues [75] reported elevated iron concentrations in the periaqueductal gray matter, one of the pain-modulating centers of the brainstem. To evaluate whether mutations of the HFE gene would modify the occurrence and the clinical features of CH, an association study was performed in a cohort of Italian CH patients and healthy controls. They did not find C282Y mutation in both controls and cases. The prevalence of the H63D mutation was nearly similar in controls and cases so it was suggested that genetic variations within the HFE gene are associated with CH. But the HFE D63D genotype determined showed the onset of the disease at a significantly later age in comparison with both H63H and H63D patients. So they recommended the HFE gene may influence the disease phenotype and may be regarded as a disease modifier gene [76].

Nitric oxide (NO) plays a critical role in the regulation of vasodilation, neurotransmission, inflammation and many other events throughout the body. NO also appears to be an important mediator of vascular headache pathophysiology [77, 78]. And an association analysis of five polymorphic microsatellite markers in the three different NO synthase (NOS) genes; nNOS (NOS1), iNOS (NOS2A) and eNOS (NOS3) was performed. However, it is unlikely that genetic variations within the NOS genes contribute greatly to CH susceptibility [79].

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the remethylation pathway converting homocysteine to methionine. The TT genotype of the common MTHFR 677C>T polymorphism (rs1801133) has been shown to impair enzyme activity and increase homocysteine levels [37]. It was shown that this variant has been linked to migraine in recent meta-analyses [80, 81] Homocysteine and oxidized metabolites like homocysteic acid exert excitatory effects on neurons and homocysteic acid has been shown to increase cell firing of trigeminal neurons [82]. Hence, a link between the MTHFR 677C>T polymorphism and CH is plausible. But in an investigation on the association between the MTHFR 677C>T polymorphism and CH among German patients and controls do not indicate an association between genotypes of the MTHFR 677C>T polymorphism and CH overall [83].

Alcohol is a well-known trigger factor for CH attacks during the active phases of the disease. The alcohol dehydrogenase (ADH) pathway, which converts alcohol to the toxic substance

Gene	Genetic variants	Results	Reference
Alcohol dehydrogenase 4 (ADH4)	rs1800759 (-136AC) rs1126671 (Ile328Val)	No association	[85]
Period (PER3)	VNTR polymorphism	No association	[71]
Hypocretin receptor 2 (HCRTR2)	G1246A (rs2653349)	No association	[70]
5-HTTLPR	rs4795541 (3-bp insdel) rs25531 (A > G)	No association	
Alcohol dehydrogenase (ADH4)	rs1800759 (-136AC) rs1126671 (Ile328Val)	Association	[84]
Methylenetetrahydrofolate reductase gene (MTHFR)	rs1801133 (677C>T)	No association	[83]
Hypocretin Receptor-2 (HCRTR2)	Haplotype of rs10498801, rs3122156, rs9357855, rs2653342, rs3800539, rs2653349	Association	[67]
CLOCK Gene	rs1801260 (T3092C)	No association	[73]
HCRTR2	G1246A (rs2653349)	Association	[69]
HCRTR2	G1246A (rs2653349)	No association with drug responses in CH	
G protein beta3 subunit	rs5443 (C825T)	Association with triptan response	[87]
Hypocretin receptor 2 (HCRTR2)	G1246A (rs2653349)	Association	
Clock gene	rs1801260 (T3092C)	No association	[76]
Calcium channel gene (CACNA1A)	SSCP analysis of all 47 exons	No association	[89]
Calcium channel gene (CACNA1A)		No association	[88]
HFE (hemochromatosis)	C282Y and H63D	No association	[76]
Hypocretin (HCRT) Hypocretin receptor (HCRTR1) Hypocretin receptor 2 (HCRTR2)	-3250CT rs8072081 (-1717CT) rs1056526 (T264C) rs2271933 (C1375T) rs2653349 (G1246A) rs1027650 (IVS4 12.564AC)	Not polymorphic Not polymorphic No association No association Association No association	[65]

Table 2. The genetic association studies in CH.

acetaldehyde, is responsible for most of the alcohol breakdown in the liver. And Rainero and colleagues investigated the association of genetic variants within the ADH4 gene with CH susceptibility and phenotype. They suggested that CH was associated with the ADH4 gene or a linked locus. For rs1126671 polymorphism, the carriage of the AA genotype, in comparison with remaining genotypes, was associated with a significantly increased disease risk of 2.33 times. [84] But the results were not confirmed in Swedish population. The data from this study did not support an association of the ADH4 SNPs rs1126671 and rs1800759 with CH [85].

Only about 70% of migraine and CH patients report significant treatment responses to triptans, which are agonists at 5-HT1B/D receptors belonging to the family of G protein-coupled receptors. A C825T polymorphism identified in the gene for the G protein β3 (Gβ3) subunit (GNB3) has been associated with an enhanced signal transduction via GPCR [86]. It was investigated whether a common polymorphism in the gene for the G protein β3 subunit (GNB3 C825T) modulates responder rates to triptans among a large cohort of Caucasian CH patients. It was suggested that pain relief by triptans is significantly modulated by a common genetic GNB3 variant [88].

Also mutations of the P/Q type calcium channel alpha 1 subunit (CACNA1A) gene on chromosome 19p13 have been shown to cause several neurological disorders with a wide clinical spectrum, mainly episodic diseases. Missense mutations of the gene cause familial hemiplegic migraine (FHM) and it is also likely to be involved in the more common forms of migraine. It was investigated whether the CACNA1A gene is also a candidate gene for CH. In this study an association analysis of an intragenic polymorphic (CA)n-repeat with marker D19S1150 and a (CAG)n-repeat in the 3'UTR region was performed, in 75 patients with CH in Swedish population. But it was found that genotypes and allele frequencies were similarly distributed in patients and controls. Also linkage disequilibrium between the two markers was similar in patients and controls. And it was suggested that any significance of the CACNA1A gene in CH is unlikely [88]. Similarly Haan J et al. suggested that there is no involvement of the calcium channel gene (CACNA1A) mutations in a Dutch family with CH [89].

4. Genetic aspect of migraine

Migraine is an episodic and disabling neurological disorder affecting roughly 14% of the population. The two most prevalent forms are migraine without aura (MO) and migraine with aura (MA). Migraine tends to run in families and has a strong genetic basis, with heritability estimates of 40–57%. In the rare monogenic subtype of migraine, familial hemiplegic migraine (FHM), three causative genes have been identified. There is, however, no significant association between these genes and MO and/or MA. Many linkage studies and candidate gene studies have suggested causative genes in MO and MA, but few have been replicated. Recent attempts using genome-wide association studies (GWAS) have yielded four single nucleotide polymorphisms (SNPs) that are significantly associated with migraine and recently, three additional SNPs have shown convincing association as well [90–93].

Recently, several studies have been used to identify genetic variants either causing migraine or conferring vulnerability to the disease. The array-based technologies and second-generation DNA sequencing has provided novel analysis to genetic database. In general, rare variants

are sought by DNA sequencing in multigenerational families with many affected individuals. These studies were previously performed using a linkage approach, followed by refinement of the linkage region and targeted Sanger sequencing of candidate genes. On the other hand, genome-wide association studies (GWAS) allowed the determination of the case-control or family-based association studies in large samples [93].

Many studies are conducted for understanding of molecular genetic basis of MA, MO and FHM well. Especially GWAS has given very important results for these diseases. The present work does not represent a systematic review but rather aims to provide thorough coverage of this area of investigation. Migraine can be part of known genetic disorders, displaying multiple manifestations and often involving various organs.

Migraine is associated with some of genetic syndromes. These diseases are CADASIL cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, COL4A1 retinal arteriolar tortuosity and leukoencephalopathy, CRV cerebroretinal vasculopathy, CSD cortical spreading depression, FASPS familial anticipated sleep phase syndrome, HERNS hereditary endotheliopathy with retinopathy, nephropathy, stroke, HVR hereditary vascular retinopathy, MELAS mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes, RVCL retinal vasculopathy and cerebral leukodystrophy These disorders, though rare, may lead to a better comprehension of the mechanisms underlying more common forms of idiopathic migraine. Other forms of typical FHM due to mutations in novel FHM candidate genes have been recently described. Mutations resulting in an FHM phenotype have been identified in the PRRT2 (proline-rich transmembrane protein 2) gene, located on human chromosome 16p11 and encoding for an axonal protein associated with the exocytosis protein complex [94–99].

Studies shown that FHM is related to CACNA1A gene which encoded by 19p13, which produces voltage-dependent (P/Q) Cav 2.1 channel, α1A subunit Over 70 missense mutations with "gain of function" effect. ATP1A2 encoded by 1q21-23 that produce to Na^+-K^+ ATPase α2 subunit responsible for FHM 2 disease. FHM3 is related to SCN1A gene. In conclusion, familial forms of MA and in particular FHM, are due to rare inherited or sporadic genetic variants endowed with high penetrance. These mutations are affecting the transmembrane electrochemical gradient by enhancing extracellular glutamate concentrations which are related with neuronal excitability [100, 101]. We can explain migraine-associated genes in four groups and other effective mechanisms (**Figure 2**).

4.1. Candidate genes

(1) Neurological genes: This group candidate genes encode (a)ion channels (calcium channel, voltage-dependent, P/Q type, alpha 1A subunit [CACNA1A], voltage-potassium intermediate/small conductance calcium-activated channel and subfamily N, member 3 [KCCN3]) (b) Na+/K+-ATPase subunits, (c) molecules involved in the synthesis, release and binding of neuropeptides (calcitonin gene-related peptide) or neurotransmitters (glutamate, GABA, dopamine, serotonin) relevant to neuronal excitation and/or to nociception. Some case-control association studies have yielded positive results, as known 5-HT-related genes, MAOA, dopamine-related genes, although most studies have been negative especially for the former two

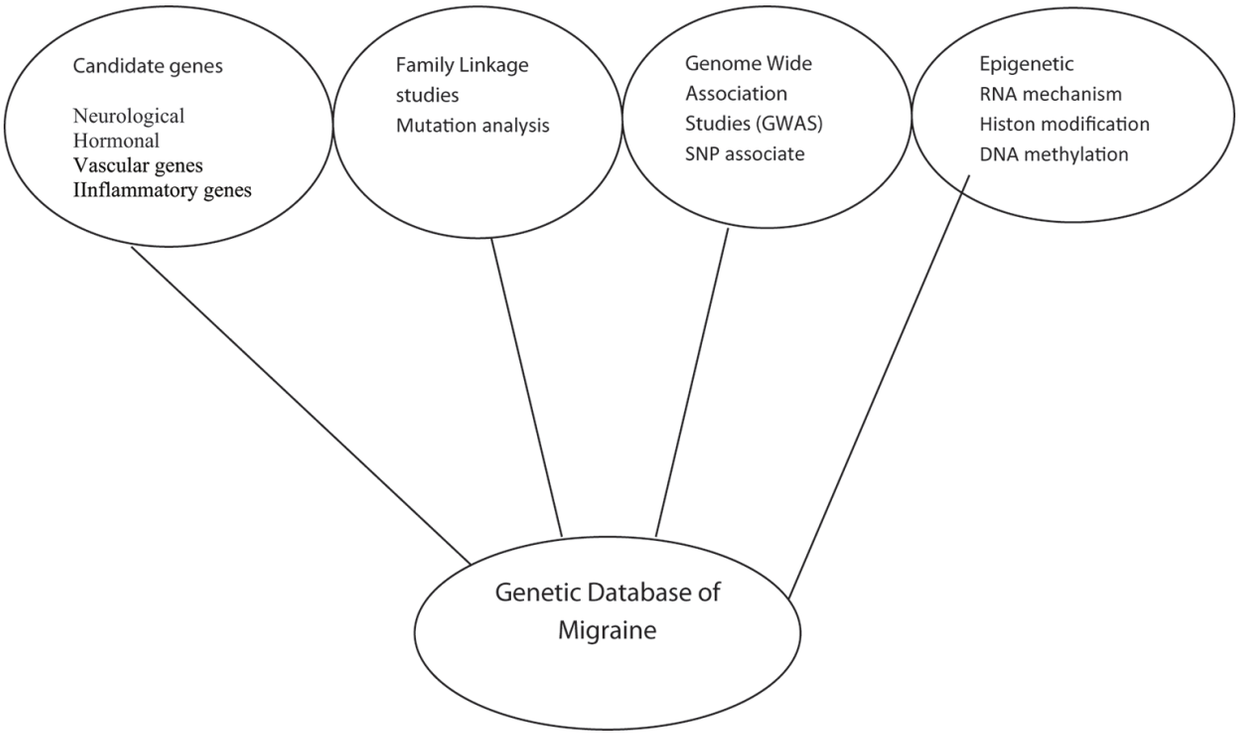

Figure 2. Genetic database of migraine disease.

gene families. Nonetheless, a thorough screening of 150 brain-expressed genes involved in ion homeostasis (channels, transporters, exchangers and accessory subunits) identified three genes encoding potassium channels associated with migraine, namely KCNK18, KCNG4 and KCNAB3 [100, 101].

(2) Vascular genes: These associated genes (ACE, MTHFR, NOTCH3, EDNRA) are involved in blood pressure regulation, endothelial cell function, vasoconstriction and vasodilation. Many vascular genes associated with migraine also confer risk for stroke and heart disease. These functional variants in some of vascular genes may cause migraine. Angiotensin converting enzyme (ACE) plays a key role in the maintenance of blood pressure and vessel wall tension. The D-D ("deletion-deletion") common variant located in the ACE gene (human chr. 17q23) increases ACE enzymatic activity, as well as the frequency and duration of MA attacks. MTHFR is a key component of the remethylation of homocysteine to methionine, as it catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Rare loss-of-function mutations in the MTHFR gene, located in human chromosome 1p36.22, can lead to hyperhomocysteinemia due to decreased enzyme activity [102–109].

NOTCH3 encodes for a transmembrane receptor regulating vascular development and differentiation during embryogenesis, as well as contributing to vascular integrity in adults. In addition to rare NOTCH3 mutations producing MA within the context of CADASIL, also common variants are significantly associated with migraine. Hence, NOTCH3 may play a broader role also in the pathogenesis of common migraine, well beyond rare forms associated with CADASIL. Endothelial genes assessed for association with migraine encode for

endothelin-1 (EDN1), endothelin receptor type A and B (EDNRA and EDNRB), inducible NO synthase (NOS2), endothelial NO synthase (NOS3) and vascular endothelial growth factor (VEGF) [110–114].

(3) Hormonal genes: These group genes are related with estrogen and progesterone metabolism especially relating to menstrual migraine. However, results from studies of genetic association between these genes and migraine were published in the later study, three estrogen receptor 1 (ESR1) haplotypes were significantly associated with the disorder ($P < 0.05$ or 0.01). In addition to ESR1, six other hormonal genes have been investigated, estrogen receptor 2 (ESR2), progesterone receptor (PGR) androgen receptor (AR), follicle stimulating hormone receptor (FSHR), nuclear receptor interacting protein 1 (NRIP1) and cytochrome P450, family 19, subfamily A, polypeptide 1 (CYP19A1) [115–119].

(4) Inflammatory genes: Recent studies shown that neurogenic inflammation, with activation of mast cells and macrophages accompanied by the release of proinflammatory cytokines may play an important role in the pathogenesis of migraine. Especially tumor necrosis factor alfa (TNF-α) gene variants is positive associated with migraine [120, 121]

4.2. Family linkage studies and GWAS

Many GWAS and classical linkage studies have been performed for migraine either using a genome-wide approach or targeting specific regions using microsatellite markers. Also, mitochondrial dysfunction in migraine that increased influx of calcium increases oxidative stress, that muscle biopsy of patients with migraine may show mitochondrial abnormalities, that mtDNA polymorphisms may be increased in migraine patients and that riboflavin, coenzyme-Q, niacin and carnitine, all agents used in the treatment of MIDs, exhibit a beneficial effect for migraine [122].

Recent GWAS studies have shown four SNPs, located on chromosome 8q22.1, 2q37.1, 12q13.3 and 1p36.32, which are associated with MA and/or MO. Although, some meta-analysis confirmed that the same results in independent populations. In another recent GWAS, three additional SNPs located at 1q22 and 3p24. However, all of these associated studies shown that the moderate of change in risk for migraine. On the other hand, the pedigree-based GWAS in an isolated population of Norfolk Island with a high prevalence of migraine and several novel variants in migraine susceptibility were identified [117–120].

4.3. Epigenetic

Epigenetics role of many complex diseases including migraine has aroused curiosity.

The effect of methylated DNA, methylated cytosines in the human D-loop of mitochondrial DNA (mtDNA), acetylation have shown differences between healthy controls and neurodegenerative and age-related diseases. Given comorbidities with migraine and the suggestive link between mitochondrial dysfunction and the lowered threshold for triggering a migraine attack, mitochondrial methylation may be a new avenue to pursue. New epigenetic approach of to solve the complex background of neurological diseases are very important [121–124].

The success of migraine genetic investigations will largely rely upon their capacity on one hand to apply the methodological approaches most apt to respond to each specific experimental question on the other hand, on their capacity to integrate multiple levels of phenotypic, functional and genetic information, in accordance with the complexity of the disorder itself. Environmental factors, such as early and recent life events, hormones and inflammation, can indeed act upon a genetically vulnerable background to trigger the onset and determine the progression of the disease.

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