Chapter 12
Genetic Basis of the Neurophysiological Findings

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Abbreviations

ACE	Angiotensin-converting enzyme
CM	Chronic migraine
CNV	Contingent negative variation
FHM	Familial hemiplegic migraine
IDAP	Intensity dependence auditory evoked cortical potentials
MOH	Medication overuse headache
MRI	Magnetic resonance imaging
MTHFR	5,10-Methylenetetrahydrofolate reductase
nBR	Nociception-specific blink reflex
SSEPs	Somatosensory evoked potentials (SSEPs)
TMS	Transcranial magnetic stimulation
VEP	Visual evoked potential

12.1 Introduction

Migraine is an ictal disorder that is characterised by the recurrence of headache attacks accompanied by autonomic symptoms and sensory hypersensitivity. In about 30% of cases, the headache phase is preceded or accompanied by focal neurological symptoms that characterise the migraine aura [1, 2]. Visual symptoms are the most frequent, followed by somatosensory and language symptoms, as well as symptoms attributable to brainstem involvement and motor symptoms [2]. The motor aura is characteristic of a rare form of migraine with aura called familial

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hemiplegic migraine (FHM) [3]. FHM can be further complicated by epilepsy. Each year, up to 3% of migraineurs progress to having a chronic daily headache, mainly due to medication overuse [4].

The prevalence of migraine in the general population of industrialised countries varies from 4% to 9% in males and 11% to 25% in females. The prevalence of migraine is lower in Africa and Asia, as well as in African and Asian populations living in industrialised countries, suggesting a race-related genetic susceptibility [5, 6]. The prevalence of migraine also varies with age. In pre-puberty it is present in about 3–5% of children with no difference between the two sexes. Then, the prevalence of migraine progressively increases in both sexes between the ages of 12 and 55 years, after which there is a progressive decline, which explains the low prevalence after the age of 70 years (1– 4%) [7]. However, the increase after puberty is much higher in females than in males, with a ratio of about 2–3:1, depending on the different case studies included. In some cases, the natural history of migraine shows that the clinical manifestations remain unchanged over the years. Contrastingly, they can also significantly change regarding the time course of the attacks and their characteristics, sometimes evolving favourably, whilst in other cases worsening.

The clinical, epidemiological and evolutionary variability of migraines seems to be linked both to acquired environmental factors and to certain genetic factors. For instance, higher baseline headache days, acute medication overuse and depression, which are modifiable and unmodifiable risk factors, are associated with migraine progression [8]. The simultaneous presence of multiple comorbidities can further complicate the clinical and prognostic presentation of migraine. Various disorders can occur as comorbidities with migraine and include neurological, psychiatric, cardio- and cerebrovascular, gastrointestinal and immunological conditions. Each of these has its own genetic load and shares some common characteristics with migraine. For these reasons, some researchers believe that there may be a common genetic background that predisposes some people to migraines and other comorbidities [9].

Overall, its considerable clinical variability, relationship with age and sex, progression and relationship to comorbidities elude to migraine being a polyfactorial disorder that may be based on polygenic pathophysiology. Furthermore, it is well known that migraine runs in multiple members of the same family [10]. However, the genetic basis for this remains unclear.

12.2 Link Between the Genetic Load and Nervous System Dysfunction

The polygenic load in migraine can be seen as the determinant of a genetic vulnerability, modulated by multiple endogenous and exogenous factors, such as physical/mental strain, intense light/noise/odours, stress, diet, sleep and acute medication overuse [11]. This suggests that genetic determinants are responsible for the transmission of a predisposition to an increased risk of suffering from a disorder. The

genetic transmission of this risk would result in the presence of abnormalities called biomarkers of vulnerability. The presence of this trait vulnerability does not imply an immediate manifestation of the disease. Migraine is thought to be associated with the presence of vulnerability biomarkers, including electrophysiological markers that could be inherited by a similar multifactorial genetic background. Early evidence of common neurophysiological patterns in multiple members of the same family with a history of migraine was already highlighted in the pre-molecular era [12] and confirmed in more recent studies based on evoked potentials (EPs) and brainstem reflexes. The most frequently detected electrophysiological abnormality in migraine patients is the 'habituation deficit'. This occurs during the pain-free period in response to any sensory stimulus except the olfactory one. All these abnormalities normalise during a migraine attack [13–22]. Cortical responses to painful stimuli, such as laser stimuli, behave differently as they do not become habituated even during the ictal phase, probably because sensitisation mechanisms come into play.

Coherently with the vulnerability model [11], most of these abnormalities develop early in life and would be found in relatives, including those apparently free of migraine pathology.

Between the pre- and post-pubertal age, migraine patients and healthy controls had similar amplitude and habituation at the recording of contingent negative potentials (CNV). This slow cortical potential can be recorded from the scalp in a contingency condition [23]. After that period, when the brain begins to mature and requires more information to be processed, the CNV amplitude increases and the habituation deficit begins to appear in people with migraines, as compared with healthy controls [23]. The same was not found to happen when researchers investigated visual evoked potential (VEP) amplitude and habituation, because both migraineurs and controls did not habituate to the stimulus repetition. Nonetheless, they found a shortened N180 latency from pre- to post-pubertal age in controls but not in the migraineurs [24].

VEP habituation during stimulus repetition and strong intensity dependence during stimulus increase (IDAP) are abnormal both in parents and in their children. Moreover, children tend to have more abnormal values than their parents, both for visual and auditory evoked potentials and in earlier onset of the disease. This finding led the authors to suggest that impaired cortical information processing is present early in the disease course [25]. In other studies, the CNV amplitude and habituation showed a significant correlation between children that suffer from migraines and their affected parents [26], whilst the IDAP increase showed only a tendency towards the same significant correlation [27]. This interrelation was not observed between children with migraines and their healthy parents, or between healthy children and their healthy parents [26, 27]. This confirms that genetic susceptibility can explain part of the variance of electrophysiological response in migraines.

In a multichannel somatosensory evoked potential (SSEP) study, the age of onset of the disease was positively correlated with the power activity of the right brainstem and thalamus, i.e. the earlier the onset, the more pronounced the neurophysiological dysfunctions [28]. By recording VEPs, some authors have found that a

first-degree relative suffering from migraine shows the same significant deficit of habituation and a similar reduction of first block amplitude of migraine without aura patients, compared to controls [29].

As expected from the vulnerability model [11], individuals with a positive family history of migraine, usually defined as 'high-risk', will generally demonstrate the same neurophysiological abnormalities as migraineurs compared to individuals without a family history of the disorder. Siniatchkin et al. found that high-risk subjects and full-blown migraineurs differed significantly from low-risk individuals since the first two groups shared the same increased CNV and lack of habituation [30]. Individuals with a positive family history of migraine were also studied by recording the nociception-specific blink reflex (nBR), reflecting the activity of the trigeminal system area-under-the-curve and habituation. The cortical potentials were found to be reduced interictally in patients with migraines [21, 31]. Di Clemente et al. found that the first block response area was more reduced in people with migraines and high-risk subjects as compared to healthy controls. Moreover, nBR habituation was nonetheless significantly different between groups, since patients with migraines showed a lack of habituation and that subjects were at high risk of potentiation when compared with the habituation curve of healthy controls [32].

Overall, these results suggest that inheritable factors contribute to the typical interictal abnormal sensory information processing at the trigeminal and cortical level seen in migraineurs.

12.3 Monogenic Forms of Migraine and Neurophysiological Responses

The association of one or more neurophysiological abnormalities with one or more genes may explain a person's vulnerability to one or more aspects of the migraine disorder.

Familial hemiplegic migraine (FHM), a rare dominant inherited form of migraine with aura, is an example of a monogenic subtype of migraine which was considered for a long time a model for the common forms of the disease, especially because, except for the motor symptoms, it presents with the same headache and aura features [3]. To date, three genes have been found to underlie dominant inherited forms of FHM [33–35]: voltage-dependent calcium channel, alpha 1A subunit (*CACNA1A*) for FHM1; ATPase Na+/K+ pump, alpha 2 subunit (*ATP1A2*) for FHM2; and voltage-gated sodium channel, type 1 alpha subunit (*SCN1A*) for FHM3. In recent years, the whole genome/whole exome was used to identify additional causal genes in those patients in which no mutation in one of the three genes had been found. Surprisingly, this has not led to undisputed additional genes. All the FHM genes are involved in glutamatergic neurotransmission and cortical excitability. Therefore, their mutations impair these functions, making the brain more susceptible to cortical spreading depression (CSD), the neurophysiologic phenomenon at the base of

migraine aura [10]. Although patients with FHM and those with migraine with aura share many similarities, a more precise genetic link with the common forms of migraine with and without aura has not yet emerged [36–42]. However, one study that examined whether the mutated FHM genes were associated with the same neurophysiological abnormalities found them in the most prevalent forms of episodic migraine. In patients with FHM, non-specific electroencephalographic abnormalities have often been described both during the attacks (unilateral or bilateral delta EEG activity with reduction of alpha [43–52]) and in the interictal phase (theta abnormalities [46, 53]). Some authors measured VEP habituation, IDAP and nBR in a group of genotyped FHM1 and FHM2 patients. They detected more pronounced VEP and nBR habituation in FHM patients than healthy controls, with no significant differences in IDAP parameters [54]. The limitations of this study are the low number of patients and the use of portable equipment. Nonetheless, these results stand in contrast with those obtained in the most prevalent forms of migraine and contradict the assumption that they share the same pathophysiological mechanisms.

This discrepancy between the neurophysiological results obtained from the monogenic forms of migraine and those of common migraine with and without aura was further confirmed using other neurophysiological methods. In a transcranial magnetic stimulation (TMS) study, a group of ten patients with FHM showed higher resting motor threshold, longer central conduction time and lower MEP amplitude on the ictal paretic side than on the non-affected side. In contrast, MEP amplitudes were significantly increased in a group of patients with common migraine with aura [55].

The FHM1 gene is involved in neuromuscular transmission, and researchers have tried to find neuromuscular fingerprints of genetic abnormalities related to P/Q Ca2+ channels in a broad spectrum of patients with migraine aura. Using single-fibre electromyographic (EMG) recordings, they found subclinical abnormalities in a subgroup of patients suffering from the most prevalent forms of migraine with aura [56–58], whilst the EMG results of FHM patients did not differ from those of healthy controls [59].

The TWIK-related spinal cord K+ (TRESK) channel encoded by the *KCNK18* gene is expressed in all primary afferent neurons in trigeminal ganglia and dorsal root ganglia [60], and it is apparently linked to intrafamilial transmission of migraine with aura [61]. Despite the clear interest of this gene in the pathophysiology of migraine pain, to date, there are no neurophysiological data in humans.

12.4 Association Studies Between Genetic Polymorphisms and Neurophysiological Responses

Several single-nucleotide polymorphisms have been found to be more prevalent in the most typical forms of migraine than in controls. Except for 5,10-methylenetetrahydrofolate reductase (MTHFR), an enzyme in folate metabolism, the vast

majority of reported genetic associations with candidate migraine genes have not been convincingly replicated [62]. Few studies have analysed genotype/neurophysiological phenotype correlations in migraineurs (Table 12.1).

Magis et al. searched for a possible correlation between the interictal features of VEPs and the MTHFR C677T polymorphism in people with migraines [63]. The presence of the 677T allele is significantly associated with a lower N1-P1 VEP amplitude both for the grand average of 600 responses and for each of the six blocks of 100 averages. In the CC subgroup and to a lesser extent the CT subgroup, there was a lack of N1-P1 VEP habituation compared to that found in healthy controls. They interpreted these results as due to a mild neurotoxic effect of homocysteine [63]. Similar VEP results were obtained by another group of researchers [64]. In another neurophysiological study, patients with migraine carrying MTHFR C677TT polymorphism exhibited significantly reduced CNV habituation, in respect to both C677TC and C677CC carriers, and the habituation index values correlated positively with the homocysteine levels with no difference in the frequency of the attacks and MRI findings [65].

Other polymorphisms concerning a variety of genes coding for proteins involved in neurotransmission, vascular pathways, inflammation, metal/ion homoeostasis or glucose metabolism have been involved in migraine [10].

According to the definition of central sensitisation (i.e. increased responsiveness not only to noxious but also to innocuous, peripheral stimuli), signs of sensitisation have also been reported in non-painful SSEP studies, in which cortical amplitudes recorded interictally were larger in patients experiencing CM or medication overuse headache (MOH) than in episodic migraines between attacks [17, 19]. In MOH, the initially higher SSEP amplitudes lacked habituation in subsequent block averages, i.e. further increase, resulting in a 'persistent' cortical sensitisation [17].

These abnormalities in cortical responses to somatosensory stimulation appear to be strongly influenced by genetic factors [66]. Angiotensin II, the product of the cleaving activity of the angiotensin-converting enzyme (ACE), functions as a neurotransmitter. The ACE D/D genotype appears to serve as an influencing factor in migraine attack frequency [67], as well as in substance abuse behaviour [68, 69]. Di Lorenzo et al. [66] sought to verify whether the ACE polymorphism could affect neural plasticity, as assessed by SSEP recording, and the clinical features of MOH. They observed that D/D homozygote carriers, with their elevated levels of angiotensin activation, differed from the D/I and I/I carriers in their response to repeated stimulation and to the type of drugs they overused. D/D carriers exhibited the highest averaged SSEP amplitudes (i.e. reflecting sensitisation) and the most severe deficits in habituation, although other MOH patients did not habituate either. This abnormal neurophysiological pattern gradually disappeared in the D/I and I/I carriers, in whom the cortical response normally habituated [66].

The central sensitisation seems to be strongly dependent on glutamate. Therefore, genes that are involved in glutamate signalling may be implicated in migraines [70]. In a preliminary study presented only in abstract form, the *rs3761555* single-nucleotide polymorphism in glutamate receptor ionotropic AMPA 3 (*GRIA3*) influenced SSEP amplitude sensitisation in patients with MOH [71].

Table 12.1 All neurophysiological findings on the genotype/electrophysiological phenotype correlation in migraine

Authors	Subjects	Polymorphism	Methodology	Outcome's variables	Results
Magis et al. [1]	24 MO 28 MA	MTHFR (C677T)	VEP	Amplitude and habituation	Presence of the 677T allele associated with a lower N1-P1 VEP amplitude both for the grand average of 600 responses and for each of the six blocks of 100 averagings. Lack of N1-P1 VEP habituation in the CC subgroup and to a lesser extent in CT subgroup
Azimova et al. [2]	64 MO 19 MA	MTHFR (C677T)	VEP	Amplitude and habituation	Presence of the 677T allele associated with decreased N1-P1 amplitudes and a lack of habituation
de Tommaso et al. [3]	90 MO 15 MA 97 HC	MTHFR (C677T)	CNV	Habituation	Patients with homozygosis (TT) showed significant decrease of CNV habituation which correlates with the homocysteine levels. In patients, the presence of subclinical brain lesions at the MRI was not related with C677T homozygosis
Di Lorenzo et al. [4]	43 MOH	ACE (rs4646994)	SSEP	Amplitude and habituation	Compared with patients carrying II polymorphism, DD carriers showed more pronounced lack of habituation, with those carrying DI falling in between. In DD carriers, the degree of lack of habituation correlated with the duration of overuse phase. Especially in DD carriers, early amplitude responses increased with the type of acute medication
Di Lorenzo et al. [5]	60 MOH	GRIA3 (rs3761555)	SSEP	Amplitude and habituation	TT carriers showed higher amplitudes compared with those of CC carriers, with CT carriers falling in between

MO migraine without aura, *MA* migraine with aura, *MTHFR* 5,10-methylenetetrahydrofolate reductase, *ACE* angiotensin-converting enzyme, *VEP* visual evoked potential, *CNV* contingent negative variation, *SSEP* somatosensory evoked potential

If we regard habituation loss as an endophenotypic characteristic of migraine, it is worth noting that some genetic polymorphisms involved in neural plasticity could modulate behavioural responses in healthy subjects. Both the brain-derived neurotrophic factor (BDNF) Val66Met and the monoamine oxidase type A upstream variable number tandem repeat (MAOA-uVNTR) polymorphism have been associated with the deficit of habituation at pain-related evoked potential elicited by repeated trigeminal painful electrical stimulation [72, 73]. Considering the well-known involvement of the trigeminovascular system in migraines, a similar study focussing on migraines would be worthwhile.

The neurophysiological abnormalities found between attacks are the simplified expression of simple genetic variants, i.e. they are ideally linked to the additive effect of single-gene polymorphisms [74].

12.5 Conclusions

The vulnerability model, commonly used to explain the emergence of psychopathologies such as schizophrenia, major depression and anxiety, postulates that genetic determining factors are responsible for the transmission of a predisposing vulnerability to a higher risk of suffering from a disorder. The genetic transmission of this risk would result in the presence of abnormalities called markers of vulnerability. It does not imply the immediate overt manifestation of the disorder because it depends on the possible co-existence of genetic and environmental factors [11]. Hence, the vulnerability model incorporates the environmental and genetic origin of the disorder and their interaction. With this model of the emergence of a disease as a basis, the search for new tools to dissect the complex phenotypes of functional disorders has revealed the concept of endophenotypes [75]. It has been found that endophenotypic abnormalities that are not clinically apparent but impact on the phenotypes are the simplified expression of genetic variants, i.e. ideally linked to the polymorphism of a single gene. A functional disorder would thus be constituted by the assembly of different simplified phenotypes and simple genetic variations. Beyond the schemes, endophenotypic markers are complex phenotypes that can be influenced by environmental factors. These complex phenotypes may interact with each other and this could be the cause of the disease worsening or improving.

According to the studies revised in this chapter, the vulnerability model can be easily applied to migraine pathology (see Fig. 12.1).

Some authors have proposed the presence of abnormal information processing of sensory stimuli, i.e. the lack of sensory habituation, as a possible marker of vulnerability. This proposed intermediate phenotype was linked to the polymorphism of single genes, such as MTHFR and ACE. In migraines, the neurophysiological endophenotypic marker can interact with several environmental factors, such as sunlight irradiance [76], stress [77], colour lens [78], the number and the type of acute medication intake [17] and

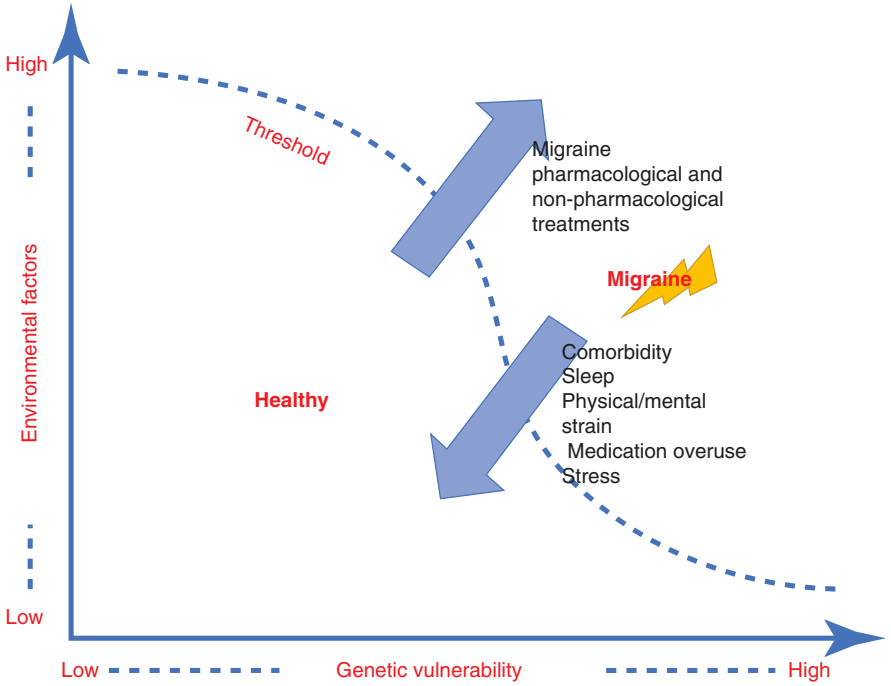

Fig. 12.1 The vulnerability model applied to migraine pathology posits that individuals possess a genetic vulnerability to a migraine that can withstand a certain amount of internal/external stressors due to genes and other biological risk factors and can cope with a certain amount of fluctuations of cortical responsivity. However, once the vulnerability threshold is surpassed, these people may have a higher risk of developing migraines. Comorbidities and other influencing factors lower the migraine threshold by increasing the level of cortical responsivity. Therefore, this may result in the person having a greater susceptibility for migraines. On the other hand, migraine pharmacological and non-pharmacological interventions may increase the vulnerability threshold, preventing the recurrence of migraines (Modified from [11])

migraine preventives [79, 80]. The presence of interictal neurophysiological abnormalities, such as habituation deficit [81], inhibition [82] and thalamocortical activation [83] deficit, has been found to significantly correlate with spontaneous clinical fluctuations in migraine, further confirming this conceptual model.

Therefore, the lack of sensory habituation could be considered a neurophysiological endophenotypic trait associated with the expression of genetic factors that make an individual vulnerable to migraines. This abnormality was found in relatives, including those apparently free of migraine, and thus can be considered a susceptibility marker of possibility.

More studies are needed to verify if this neurophysiological endophenotypic marker is present before the onset of the disease, if it is associated with the disease in the general population and if it can be found in non-affected family members at a higher frequency than that reported in the general population.

It is also of uttermost importance to collect more data on the complex geno- phenotype correlations of clinical and neurophysiological features amongst the different migraine forms. This may help to explain the evolutionary process from episodic to chronic migraine, a debilitating condition in which various polymorphisms have been linked to the disease, its psychiatric comorbidities and dependence behaviour [84–90].

Another possible approach to study migraine vulnerability and its endophenotypic markers is that of epigenetic [91], i.e. verifying whether gene expression patterns change along with a patient's clinic-neurophysiological state.

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