

The primary headaches: genetics, epigenetics and a behavioural genetic model

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Abstract The primary headaches, migraine with (MA) and without aura (MO) and cluster headache, all carry a substantial genetic liability. Familial hemiplegic migraine (FHM), an autosomal dominant mendelian disorder classified as a subtype of MA, is due to mutations in genes encoding neural channel subunits. MA/MO are considered multifactorial genetic disorders, and FHM has been proposed as a model for migraine aetiology. However, a review of the genetic studies suggests that the FHM genes are not involved in the typical migraines and that FHM should be considered as a syndromic migraine rather than a subtype of MA. Adopting the concept of syndromic migraine could be useful in understanding migraine pathogenesis. We hypothesise that epigenetic mechanisms play an important role in headache pathogenesis. A behavioural model is proposed, whereby the primary headaches are construed as behaviours, not symptoms, evolutionarily conserved for their adaptive value and engendered out of a genetic repertoire by a network of pattern generators present in the brain and signalling homeostatic imbalance. This behavioural model could be incorporated into migraine genetic research.

Keywords Migraine · Tension-type headache · Cluster headache · Genetics · Epigenetics

Introduction

The genetics of the primary headaches scored recent scientific successes due to the unravelling of the genetics of

FHM. Deciphering of the patho-physiological mechanisms of these common diseases promises to bring the much needed knowledge for pharmacological treatments and therapeutic interventions. There are however also problems and controversies, some not solved by the genetic studies performed to date. The following is a brief subjective review of the available evidence, suggesting a role for epigenetic mechanisms and ending with the proposal of a behavioural model of the primary headaches possibly useful for the genetic studies.

Primary and secondary headaches: symptoms, syndromes or diseases? Idiopathic and syndromic migraines

Headaches/migraines are plagued by problems of definition: these terms describe *symptoms* (a feature which indicates a condition of disease, in particular one apparent to the patient, CED 2003), and at the same time, distinctive *syndromes* (a group of symptoms which consistently occur together) [1] or *diseases* (a disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms) [1] with recognisable diagnostic features, internationally defined [2]. The problems encountered with definitions become evident when dealing with primary or secondary headaches, and when considering idiopathic and syndromic migraines. Secondary headaches are those in which attacks occur due to a recognisable cause or disease, which itself represents the primary cause of the attacks. Syndromic migraines, contrasted with the idiopathic ones, are those in which attacks of migraine, clinically barely or not distinguishable from those occurring in the primary migraines, occur compounded with involvement of other systems. Syndromic migraines are

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often genetically determined. The concept of “syndromic,” potentially useful in the exploration of headache pathogenesis, has been applied to conditions such as deafness, visual loss and epilepsy, but has no place in the HCS classification that classifies headache attacks and not diseases, albeit distinguishing between primary and secondary headaches. These considerations may apply to the genetics of the primary headaches, since by adopting the HCS (2004), we consider symptoms, not diseases (much as if, studying the genetics of diabetes mellitus, we adopted a classification of the hyperglycemias).

Genetic epidemiology of the typical migraines

The typical primary migraines (MO and MA) all have a substantial risk of familial recurrence. When estimating the population relative risk of migraine in specified groups of relatives (i.e. the ratio between the probability that a relative versus a random member of the population is affected), first-degree relatives of migraine without aura probands have 1.9 times the risk of MO and 1.4 times the risk of MA, whereas first-degree relatives of MA probands have nearly four times the risk of MA and no increased risk of MO [3]. Since a family aggregation is implied when the risk ratio exceeds one, this confirms the familial liability for the migraines, even though familiarity is not yet heredity. A further analysis showed however that spouses of MO probands have 1.4 times the risk of MO, and spouses of MA probands have no increased risk of MA [3], thus backing a hereditary liability for MO and especially MA. Twin studies concur with this increased familial liability. Concordance rates for migraine are consistently higher among monozygotic (MZ) than dizygotic (DZ) twins. In particular, heritability estimates were around 52% in female twin pairs raised together or apart since infancy. In MZ Danish twin pairs, liability to MO resulted from additive genetic effects (61%) and from individual-specific environmental effects (39%), while in MA, correlation in liability was 0.68 in MZ and 0.22 in DZ, with heritability estimated at 0.65. Therefore, twin studies reveal that approximately one-half of the variation in migraine is attributable to additive genes, while the remainder is caused by unshared rather than shared environmental factors between twins [4, 5]. Several studies have analysed pedigrees with migraine, segregation analysis being performed to discover the genetic transmission pattern. Studies at first envisioned migraine as a simple mendelian disorder, inherited according to monogenic rules of transmission. Various modes of inheritance, autosomal dominant with female preponderance, possibly sex determined; autosomal recessive with 70% penetrance; polygenic; maternal and X-linked transmissions have been proposed, or rejected

[6, 7]. Finally, based on complex segregation analysis, a multifactorial inheritance was considered the most likely pattern even in high-risk families with MA [8]. A single gene was considered unlikely, but, notably, in some families, a mendelian or mitochondrial inheritance could not be excluded [3]. Currently, migraine is widely considered a complex disease with multifactorial inheritance. This type of inheritance applies to many complex/quantitative traits, i.e. traits that vary continuously in a phenotypic range, and in which variation is quantitative, not qualitative. Examples of quantitative traits are height, body weight, etc. Such traits are influenced by multiple genes (each a quantitative trait locus QTL), each having a small quantitative effect and interacting with the environment. However, there is still no unequivocal evidence that migraine as a quantitative trait varies continuously in the general population, and moreover, genetic variation underlying a continuous character distribution can result from segregation at a single locus too. Therefore, considering migraine as a quantitative trait may still be unwarranted.

The primary headaches also display considerable comorbidity, rarely incorporated into genetic studies. MA is comorbid with hypomania, depression and anxiety, and MO with phobia, panic and major depression. Other comorbidities are stroke, dyslipoproteinemias, essential tremor, paroxysmal dyskinesia and epilepsy. Merikangas et al. in a longitudinal genetic epidemiology study found that migraine was associated with mood disorders and drew attention to the fact that age at onset of anxiety disorders preceded, while onset of affective disorders followed that of migraine, findings consistent with a syndromic relationship between migraine and anxiety/depression [9].

These findings have been replicated, maternal depression being significantly associated with development of migraine in children [10]. Asthma, rhinitis and allergic bronchitis are also important comorbidities recurring in migraine families [11–13]. These comorbid clinical features should be properly incorporated in the genetic studies of the primary headaches.

Mendelian migraines? The genetics of FHM and their putative relationship with the typical migraines MA/MO

Migraines may be multifactorial, but mendelian migraines, i.e., migraines that conform to a mendelian type of genetic transmission, do exist. FHM is classified as a subtype of migraine with aura in the HCS (2004), and it conforms to an autosomal dominant pattern of hereditary transmission. Joutel et al. mapped FHM to chromosome 19, and in 1996 the first FHM gene, *CACNL1A4*, later termed *CACNA1A*, encoding the alpha1A subunit of the P/Q neural calcium

channel, was discovered, accounting for both FHM 1 and episodic ataxia type 2 (EA2) phenotypes [14, 15]. Spinocerebellar atrophy type 6 (SCA6) was added to the FHM and EA2 phenotypes in 1997 [16]. Thus, FHM 1, EA2 and SCA6 are all allelic channelopathies, with missense mutations mostly accounting for FHM, mutations disrupting the reading frame for EA2 and polyglutamine expansions in the COOH gene terminal for SCA6. The phenotypic spectrum of the *CACNA1A* mutations was at first believed to consist either of pure FHM or of FHM associated with cerebellar atrophy. Why some mutations originate pure FHM while others elicit progressive or intermittent cerebellar features remains unclear [17]. Ictal coma after trivial trauma and essential tremor were associated clinical features in families harbouring particular *CACNA1A* mutations. The phenotypic spectrum of the *CACNA1A* mutations has further expanded to include ataxia induced by fever or high temperature [18], childhood epilepsy [19,20] and status epilepticus [21], paroxysmal paranoid psychosis with anxiety [22], benign paroxysmal torticollis of infancy, considered a migraine equivalent [23], and even myasthenic syndrome [24], since *CACNA1A* is also expressed on presynaptic neuromuscular junction terminals where it modulates transmitter release [25] even in the absence of any morphological changes in the junction or muscle weakness [26].

The paroxysmal clinical features of migraine, ataxia and epilepsy, together with the consideration that *CACNA1A* specifies for a calcium channel and that in the tottering and leaner mouse with epilepsy and ataxia, similar mutations are found in the mouse homologue of the calcium channel $\alpha 1A$ subunit gene, led to the proposal that migraine be considered a calcium channelopathy [27]. The concept of migraine as a brain channelopathy fits well with the phenomenon of spreading depression [28], implicated in migraine attack pathophysiology. It is now accepted by the scientific community as an explicative model for migraine. However, the available genetic evidence is controversial or negative (see below).

FHM was soon proved to be genetically heterogeneous, some families linking to chromosome 1 [29,30], and a second gene, *ATP1A2*, encoding the $\alpha 2$ subunit of the Na/K ATPase, was discovered in Italian families and accounting for a phenotype of pure FHM (FHM 2) [31]. New mutations were found in FHM 2 pedigrees [32], and soon the phenotypic spectrum of FHM 2, initially thought to be confined to pure FHM, broadened to include such features as coma, triggered by minor head trauma and angiography [33], recurrent comas [34] and epilepsy, namely benign familial infantile febrile convulsions [35]. Finally, cerebellar ataxia associated with epilepsy and mental retardation was described in an Italian FHM 2

family [36,37], findings later confirmed by Spadaro et al. and Vanmolkot et al. in other families [38, 39]. Phenotypes of alternating hemiplegia of childhood [40–42] and basilar migraine [43] described with *ATP1A2* mutations further enlarged the clinical spectrum of FHM 2. Variability within the same family is notable, with FHM, cerebellar ataxia, recurrent paroxysmal dystonia and mental retardation all recurring together [42].

Lastly, mutations in the neuronal voltage-gated sodium channel *SCN1A* were reported by Dichgans et al. [44] to account for a phenotype of pure FHM (FHM 3), and there are still FHM families without mutations in any of the previously described genes, implying further genetic heterogeneity. Sporadic patients with HM, more common in clinical practice, also present problems, since mutations in the known FHM genes are only rarely encountered in this population [45].

An important corollary of the genetic discoveries obtained in the FHM was the proposal to consider FHM as a model for the typical migraines MO and MA [27]. This spurred the search for the involvement of FHM genes in MO/MA. Up to now the effort has been largely unrewarding. This in our opinion is also due to the misclassification of FHM as a subtype of MA [2], whereas FHM represents a syndromic migraine (see below). Some evidence in favour of linkage of typical migraines to the FHM locus on chromosome 19 was initially offered by May et al. [46], Nyholt et al. [47] and Terwindt et al. [48]. However, early negative studies [49–51] were later substantiated by systematic screening investigations of the *CACNA1A* in families with MO and/or MA [52–55], and to date, mutations in *CACNA1A* have never been demonstrated in kindreds without hemiplegic migraine, with or without aura. The same negative considerations apply to *ATP1A2*. Earlier evidence in favour of a role of the Chr1q31 locus or *ATP1A2* gene in the typical migraines [56, 57] was superseded by negative findings and absent *ATP1A2* mutations in typical migraine only pedigrees, even those displaying an apparently autosomal dominant mode of inheritance [58–61]. The FHM 3 *SCN1A* gene was discovered too recently for any conclusive study. Von Brevern et al. [62] however failed to find any *CACNA1A*, *ATP1A2* or *SCN1A* mutations in patients with migrainous vertigo. Thus, there is no current evidence that the genes causing FHM represent major susceptibility loci for the typical migraines.

Does such negative genetic evidence imply that FHM is not a useful model for migraine etiology? Several reviews of migraine pathogenesis apply the FHM model of neural channelopathy to the typical migraines. While such models are not justified genetically, it may be contended that FHM is nonetheless helpful in elucidating the pathophysiology of

Table 1 A list of proposed (and provisional) syndromic migraines

Syndromic migraines	Genes (chromosome) involved	Migrainous features (references)
MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes)	<i>MTTL1</i> , <i>MTTQ</i> , <i>MTHH</i> , <i>MTTK</i> , <i>MTTS1</i> , <i>MTND1</i> , <i>MTND5</i> , <i>MTND6</i> , and <i>MTTS2</i> (mtDNA)	Most frequent symptom: episodic sudden headache with vomiting and convulsions [63, 64]
CADASIL (cerebral arteriopathy, autosomal dominant, with subcortical infarcts and leukoencephalopathy)	<i>NOTCH 3</i> (19p13.2–p13.1)	MA in 22% [65]; migraine in 38% [66]
HERNS (retinopathy, vascular, with cerebral and renal involvement and Raynaud and migraine phenomena)	<i>TREX1</i> (3p21.3–p21.2)	Migraine in 70% [67]
CCM (familial cerebral cavernous malformations)	<i>KRYT 1</i> (7q11.2–q21)	Convulsions and migraine attacks [68, 69]

the migraine attacks. This consideration however is likely to apply to several clinical conditions all characterised by headache attacks of the migraine type. Migraine-like attacks indeed are found not only in the typical migraines, but also in other conditions, diseases or syndromes, in which they occur together with symptoms and signs of multisystem nervous or extra-nervous involvement. These “syndromic migraines” thus display bona fide migraine headache attacks at some times in their clinical course, and most of them have a genetic basis (Table 1). FHM is also characterised by multisystem neurologic involvement (migraine, hemiplegia, ictal recurrent comas, cerebellar atrophy, mental retardation, epilepsy, movement disorders, myasthenic syndrome, etc.), and therefore we make a plea for FHM to be considered more appropriately as a syndromic migraine and not a subtype of MA, as with the current HCS classification (2004).

Linkage and association studies in the typical migraines

Several studies on the genetics of the typical migraines MO and MA applied genetic association, linkage and genome wide scanning methods. Most of these studies resulted in findings that either lack verification or are controversial. For MA, a genome wide scan on 50 multigenerational families in Finland identified a susceptibility locus on chromosome 4q24 [70]. Other loci for MA have been reported on chromosome 11q24 in Canadian families with an autosomal dominant transmission pattern [71], and on chromosome 15q11–q13 to a genomic region containing genes encoding for GABA-A receptors in ten Italian families again displaying an autosomal dominant transmission pattern [72].

For MO, or for pedigrees with MO mixed with MA, susceptibility loci have been reported on chromosome 6p12.2–p21.1 in Sweden [73], chromosome 5q21 [74], chromosome 14q21.2–q22.3 in an Italian family with MO [75], chromosome Xq24–28 in two large Australian

pedigrees [76] and chromosome 19p13.3/2 to the insulin receptor gene *INSR* [77]. While many of such findings have still to be replicated, in some cases (the *INSR* gene) sequence studies have given negative results [78].

Other studies have examined candidate genes, implying that a pathogenetic (and a priori) hypothesis was formulated beforehand. This may be risky, considering that the pathogenesis of the migraine headaches is still imperfectly understood. Candidate genes explored were the mitochondrial DNA (mtDNA), or genes involved in prothrombotic or cardiovascular disease, or in the metabolism of biologic amines such as dopamine or serotonin, or in a variety of other metabolic systems. Several of the studies applied to mtDNA genes have yielded negative results, even though in some families migraine was reported to segregate with the Leber mtDNA 14484 mutation [79], and mtDNA mutations and haplotypes (haplotype U) have been associated with juvenile migraine stroke [80, 81] and with cyclic vomiting, considered a migraine equivalent in the pediatric population [82–84]. Contrasting results for genes involved in prothrombotic/cardiovascular risk, and for those involved in the metabolism of the biological amines serotonin and dopamine, or in several other metabolic pathways are summarised in Tables 2, 3, 4, and 5.

Finally, a few studies have focused on the genetics of the chronic headaches, a major social problem, since these chronic headaches are often associated with drug abuse and afflict a remarkable percentage of the general population. Chronic tension-type headache displays a substantial familial recurrence, with lifetime relative risk estimated at 3.87 for parents and 3.53 for children of probands; the risk is greater for females (3.35) than for males (2.59) [85]. A genetic association study of chronic headache with drug abuse versus the dopamine metabolism genes by Cevoli et al. [86] found that allele 4 of the exon III VNTR polymorphism of the dopamine receptor 4 gene *DRD4* was associated with chronic daily headache, and allele 9 of the dopamine transporter gene *SLC6A3* was more common in

Table 2 Prothrombotic and cardiovascular risk genes and typical migraine genetics

Prothrombotic/vascular risk genes or mutations examined	Phenotypes
LDL receptor (19p13.2)	Associated with MO [87]; not associated [88]
Factor V R/Q 506 (Leiden mutation)	Associated with MA [89] Not associated with migraine stroke [90]; not associated with MA/MO [91]; not associated with juvenile MA [92]
Factor II 20210 G/A	Not associated with MA/MO [91] Not associated with migraine stroke [93]
Factor XIII Val 34 <i>Leu</i>	Not associated with migraine [94]
Decanucleotide insertion/deletion factor VII promoter	Not associated with MA/MO [91]
Alloantigenic platelet systems HPA-1 and HPA-2	Not associated with MA/MO [91]
Deficit of protein S	Associated with MA [89]
Angiotensin converting enzyme (<i>ACE</i>)	Allele D associated with MO and more frequent migraine attacks [95]
Endothelial NO synthase inducible (<i>NOS3</i> ; <i>iNOS</i>)	Not associated with migraine [96, 97]
Endothelin receptor A (<i>ETA-231 A/G</i>) polymorphism	Allele G protecting from migraine [98]
<i>MTHFR</i> (methylene-tetra-hydrofolate reductase) C677T/A1298C	Homozygous mutation associated with MA [99], associated with MA [100]; risk for MA, modulated by thymidilate synthase gene [101]

Table 3 Serotonin metabolism genes and typical migraine genetics

Serotonin metabolism genes examined	Phenotypes
<i>5-HTSERT</i> (17q11.2–12)	Allelic association with MO (increase of allele STin2.12 + decrease of allele STin2.10) and MA (same + increase of allele Stin2.9) [102]; 5HT-TLPR with MA [103] Allelic association with migraine (allele Stin2.10) [104]; borderline association with migraine [105] No association/linkage with migraine [106, 107]
<i>5-HT2A</i> (13q14–21)	Allelic (allele C) association with migraine aura [108] No association with migraine [105, 106, 109, 110]
<i>5-HT1B</i> (6q13)	No association with migraine [106, 110, 111]
<i>5-HT1D</i> (1p36.3–34.3)	No association with migraine [106, 110, 111]
<i>5-HT2B</i> (2q36.3–q37.1)	No association with migraine [106, 110, 111]
<i>5-HT2C</i> (Xq22–25)	No association with migraine [106, 110, 111]
<i>5-HT1B</i> (6q13)	No association with therapeutic response to triptans [112, 113]
<i>5-HT1F</i> (3p12)	No association with therapeutic response to triptans [112, 113]

chronic daily headache associated with drug abuse than in episodic migraine.

Genetics of tension-type headache

Remarkably, apart from an epidemiological genetic study that demonstrated a familial aggregation for chronic tension-type headache [85], there are no other genetic studies of this common disorder.

Genetics of cluster headache

Cluster headache (CH) has long been considered a sporadic disease. In recent decades, however, a familial recurrence has been appreciated, and the new HCS classification (2004) now states that CH may be transmitted as an autosomal dominant disease in about 5% of cases. Several CH cases have been reported among monozygotic twins and in family pedigrees [129–137], and family studies indicate that I-degree relatives of CH probands carry a 5- to 18-fold, and

Table 4 Dopamine metabolism genes and typical migraine genetics

Genes examined	Phenotypes
Dopamine receptor 2 (<i>DRD2</i>)	Allelic association (allele NcoI) with MA comorbid with anxiety/depression [114] Allelic association (allele 1) with yawning/nausea during attack of MO [115] No allelic association (allele NcoI) with MA [116] No allelic association with MO/MA [107, 117, 118, 119]
Dopamine receptors 1, 3, 4, 5 (<i>DRD1, DRD3, DRD4, DRD5</i>)	No allelic association with migraine [115, 117, 120]
Dopamine transporter (<i>DAT</i>)	Association with chronic daily headache with drug abuse [86]
<i>COMT; MAO-A</i>	No association with migraine [117, 121]
Dopamine-beta-hydroxylase (<i>DBH</i>)	Association with migraine [107], especially males with MA [122] No association [123]

Table 5 Other genes implicated in typical migraine genetics

Genes examined	Phenotypes
Androgen/progesterone receptors	Androgen receptor not associated; progesterone receptor associated with migraine [124]
K channel <i>KCNN3</i>	Allelic association (CAG repeats) with MO/MA [125] Not associated (CAG repeats) [126]
Cytotoxic T lymphocyte antigen 4 (<i>CTLA-4</i>)	Not associated with migraine [127]
<i>HLA-DRB1</i>	Allelic association with MA [128]

II-degree relatives a 1- to 3-fold increased relative risk of the disease [138–141]. CH has been considered a probable autosomal dominant disease with a penetrance of 0.3–0.34 in males and 0.17–0.21 in females [142]. The exact transmission pattern is however still debated [143, 144], and an autosomal recessive pattern has been advocated in certain families [137]. Several candidate genes have been analysed, in particular mtDNA mutations [145–148], HLA antigens [149–151] and *CACNA1A* polymorphisms [152, 153], usually with negative or controversial results. Other genes, such as the NO synthases *NOS1*, *NOS2A* and *NOS3* [154], the elusive amine gene cluster [155], the *CLOCK* gene involved in the regulation of circadian rhythms [156, 157] and the hemochromatosis gene [158], have been found not associated with CH. Recently, an association between CH and a polymorphism in the hypocretin receptor 2 gene *HCRTR2* was reported by Rainero et al. [159], possibly accounting for the circadian recurrence of the CH attacks. Such an association, while confirmed by Schürks et al. [160], was rejected in a European multicentric study [161]. Recently, reports of CH associated with hemiparesis during the attacks suggested a relationship with FHM and ionic channelopathies [162]. Preliminary genic expression studies instead documented the activation of proinflammatory genes during the CH attack [163].

Genetics and epigenetics

Epigenetics is the study of the changes in DNA and DNA-binding proteins that, albeit altering the structure of chromatin, do not modify the nucleotide sequence of DNA. The remarkable feature here is that some of these modifications may be associated with heritable changes in gene function.

Commonly held concepts of heredity indeed pit environmental influences (nurture) against genetic background (nature) as totally separate causative factors. Genetic advances themselves have however demonstrated that the hereditary transmission of biological changes not encoded in the DNA sequence and dictated by environmental influences is possible. This part of genetics, called epigenetics, has received little or no attention in the genetic studies of the primary headaches. It is the contention of the author however that future epigenetic studies will account for several hereditary features of the primary headaches, in particular their comorbidities.

All those (meiotic and mitotic) modifications in gene expression that are heritable but not encoded in the DNA sequence are defined as epigenetic. Molecular mechanisms implicated include (1) methylation of cytosine residues at C5 in dinucleotide CpG sites (localised especially in promoters of well over 40% of the genes and that, when

methylated, cause silencing of the gene); (2) mechanisms of RNA interference, whereby microRNAs silence gene expression; (3) histone (DNA associated proteins) changes: activation or inactivation of genomic regions according to the “histone code”. All of these mechanisms result in the expression or silencing of genes, and underlie such phenomena as inactivation of the X chromosome and genomic imprinting. Several epigenetic diseases are already known that may be inherited through the somatic and the germinal line: fragile X syndrome, in which *ATRX* gene mutations modify the methylation pattern of ribosomal RNA and, by methylation of CGG expansions in the *FMR1* gene, silence the gene; the Angelman and Prader-Willi, and Rett syndromes; also, many colonic cancers and leukemias. Important epigenetic differences that increase with age are found even between monozygotic twins [164]. Notably, epigenetic modifications may increase with age and may also be prevented through interventions directed at DNA or histone methylation (with azanucleotides, antisense oligonucleotides, histone deacetylase). Even more remarkably, there is some evidence that lifestyles and even diet may play a role [165].

Epigenetic models for the primary headaches?

There is consistent evidence that behavioural differences typical of specific inbred animal strains are the consequence of environmental influences acting especially during development rather than DNA changes. Mice strains with decreased environmental exploration behaviour (B6 strain) develop enhanced exploratory behaviour if nurtured in their first 3 months of life by BALB dams, a strain displaying intense exploratory behaviour; changes in behaviour appear to be linked to the type of maternal care, particularly licking of the pup by the mother, a behaviour demonstrated to affect the status of the endocrine stress system in mice [166]. Weaver et al. [167] showed how maternal care in the rat (licking and grooming the pup) modifies the methylation pattern of the promoter of the glucocorticoid receptor gene in the hippocampus; such epigenetic changes, evident from the first week of life, persist throughout the animal’s life but are reversible upon treatment with histone deacetylase inhibitors or upon intracerebral administration of methionine (an intervention that modifies the methylation pattern) [168].

Stress plays a remarkable role in the development of the nervous system: removal of rat pups from the mother causes reduced neurogenesis in the adult hippocampus through steroid-dependent mechanisms [169], and alters serotonergic transporter densities and serotonergic 1A receptors in the rat brain [170]. Administration of steroids to the mother before delivery causes changes in behavioural patterns in

juvenile rats [171], and maternal deprivation in the immediate post-natal period modifies locomotor and steroid release patterns in the adult rat [172]. Epigenetic mechanisms also seem relevant for the formation of memory traces [173] and more generally for cognitive development [174]. Epigenetic mechanisms have been hypothesised for psychiatric disorders [175, 176] and many complex and multifactorial diseases affecting the brain or the inflammatory and immune systems [177–179].

There are still no studies of epigenetic mechanisms in the primary headaches. When considering, however, the important maternal influence in migraine genetics; the consistent and inherited co-morbidities especially for psychiatric and inflammatory-immune disorders; twin studies documenting that only about half of the variability is due to “genetic” factors; it is possible to envision that epigenetic mechanisms, especially those acting during nervous system development in early infancy and childhood, play a role in the heritability and pathophysiology of the primary headaches. Preliminary studies have already analysed attachment styles in adult migraineurs [180, 181], and a prospective investigation demonstrated correlations between events suffered during pregnancy and early life, and quality of adult life 31–33 years later [182]. It is reasonable to suggest that early life factors and attachment styles between mother and child represent determinants of epigenetic changes relevant in migraine pathogenesis. Such early pre- and post-natal environmental behavioural factors could be usefully analysed to define endophenotypes of adaptive behaviour useful in the genetic studies of the primary headaches.

Final comments: a behavioural model of the primary headaches as fight-or-flight response and sickness behaviour to be incorporated into genetic research

Consideration of epigenetic mechanisms may help in analysing behaviours during the headache attacks. Any genetic studies are ultimately dependent upon the definition of the phenomenon taken into consideration, and on how it is conceptualised. Therefore, studies have to rely upon conventional diagnostic criteria, in turn based on a priori interpretations. Most genetic studies have been performed within the frame of migraine interpreted simply as a “pain” trait with multifactorial inheritance. In a “harlequin” model, several genetic factors, each one having a small specific weight, interact with environmental factors to determine the migraine attack. Such a model should however be better tailored to suit phenomena such as the migraine attack and the migraine diseases that are really behavioural “processes” with an intrinsic logic of their own [183], one that is consistent within attacks, within

patients and within populations. There is a need to conceive of the primary headaches along more useful scientific lines. Consistently lacking in the genetic studies is for instance any consideration of migraine as a behavioural response to environmental and/or endogenous triggers, a view that has scientific support [184] and that we recently revised to accommodate a Darwinian perspective [185]. According to our view, migraine and other primary headaches such as CH are behaviours, not symptoms, evolutionarily conserved for their adaptive value and engendered out of a genetic repertoire by networks of pattern generators present in the brain. These neural networks serve the homeostasis of the brain, with migraine pain considered a kind of visceral pain signalling homeostatic imbalance. The behavioural repertoire enacted during the migraine attack, complete with its full panoply of pain, cognitive, autonomic, motor, etc., symptoms and signs, is comparable to that defined as *sickness behaviour* and already known to develop in all mammals and other animals following challenge with infective and other pathogenic agents [186]. In contrast, behaviour during the CH attacks [187] resembles the *fight-or-flight response* of hypothalamic animals. These behaviours during the headache attacks really represent “healing” processes, and migraine may even be evolutionarily advantageous [188]. Thus, what is relevant in this new behavioural model is not the manifestations of the attack, but the factors triggering it, that, migraine being of the brain, must relate to still unknown disturbances of brain homeostasis [185]. Accordingly, it is these triggering factors rather than the manifestations during the attacks that may represent the features most relevant for a true dissection of the genetics of the primary headaches.

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