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Review

The search for migraine genes: an overview of current knowledge

N. J. Colson [a], F. Fernandez [a], R. A. Lea [a, b] and L. R. Griffiths [a, *]

[a] Genomics Research Centre, School of Medical Science, Griffith University, Gold Coast, Queensland (Australia), 9726, Fax: +61 7 55948908, e-mail: l.griffiths@griffith.edu.au
[b] Institute of Environmental Science and Research, Wellington (New Zealand)

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Abstract. Migraine is a complex familial condition that imparts a significant burden on society. There is evidence for a role of genetic factors in migraine, and elucidating the genetic basis of this disabling condition remains the focus of much research. In this review we discuss results of genetic studies to date, from the discovery of the role of neural ion channel gene mutations in familial hemiplegic migraine (FHM) to linkage analyses and candidate gene studies in the more common forms of migraine. The success of FHM regarding discovery of genetic defects associated with the disorder remains elusive in common migraine, and causative genes have not yet been identified. Thus we suggest additional approaches for analysing the genetic basis of this disorder. The continuing search for migraine genes may aid in a greater understanding of the mechanisms that underlie the disorder and potentially lead to significant diagnostic and therapeutic applications.

Keywords. Migraine, gene, susceptibility, linkage, association.

Introduction

Migraine is a primary headache disorder characterised by recurrent attacks of disabling head pain, which may be accompanied by nausea and emesis, and in some sufferers, neurological disturbances. Migraine imparts a significant burden on society, both socially and financially. The World Health Organization has identified migraine among the world's top 20 leading causes of disability, with an impact that extends far beyond individual suffering [1]. The lack of clear symptom definitions and precise diagnostic criteria has led to variability in diagnosis. In 1988 the Internal Headache Society published a system of classification with specific definitions of migraine syndromes. This system requires that certain attributes be present to establish a diagnosis for migraine headaches [2]. This classification has recently been updated [3]. The two most frequent subtypes are migraine with aura (MA), previously known as classic migraine, and migraine without aura (MO), previously known as common migraine. Migraine without aura, which occurs in ~77% of migraineurs [4], is characterised by moderate to severe head pain that is generally unilateral and pulsating, and exacerbated by physical activity. Nausea, along with phonophobia and photophobia, may occur [3]. Migraine with aura, which occurs in ~31% of sufferers [4], is classified by the existence of focal neurological symptoms preceding or accompanying the headache [3]. Neurological symptoms may include focal paresthesia or weakness, visual or auditory hallucination, vertigo, fainting or a confusional episode. Some sufferers undergo a premonitory phase and a resolution phase, in which they may experience food cravings, depression, excessive yawning or hypo/hyperactivity [3]. Some individuals experience both types of attack during their life [4].

* Corresponding author.

Family and twin studies have provided evidence for a genetic component in migraine. In 1996 Russel et al. compared the risk of migraine in 44 families to the general population. It was found that first-degree relatives of probands with MO had a 1.9-fold increased risk of MO, and first-degree relatives of probands with MA had a 4-fold increased risk of MA. It was concluded that both genetic and environmental factors are important in MO and that MA is determined largely by genetic factors [5]. In a 1997 population-based study Stewart et al. investigated the risk of migraine in first-degree relatives of 73 migraineurs and 72 matched controls. It was found that the risk of migraine was 50% more likely in relatives of migraine probands than in relatives of controls [6]. Numerous twin studies have also shown a role for both genetic and environmental components and furthermore provided evidence that there is no simple inheritance of migraine since concordance does not reach 100% in monozygous twins [7–10]. A 2003 study looking at genetic variance across six countries reported heritability estimates ranging from 34 to 57% [11].

Migraine molecular genetics

The identification of susceptibility genes for complex traits such as migraine can be challenging, in particular due to the contribution of multiple and potentially interacting genetic loci, as well as the confounding influence of environmental factors. In the search for genes involved in migraine, a number of researchers have focused on familial hemiplegic migraine (FHM) a rare subtype of MA with an autosomal dominant inheritance pattern. FHM attacks involve neurological symptoms similar to MA with additional motor involvement. Sufferers of FHM can also experience attacks of non-hemiplegic migraine [12]. The discovery of several genetic defects associated with FHM has provided some interesting insights into the role of genetic defects in this type of disorder. The first FHM gene was located by pedigree linkage analysis to chromosome 19p13 [13], and was later identified as *CACNA1A* coding for the α1A subunit of Cav2.1 channels. Four missense mutations were originally reported [14]. Mutations in this gene, capable of modulating neurotransmitter release, have also been implicated in episodic ataxia type 2 and spinocerebellar ataxia type 6 [14, 15]. The α1 subunit forms the ionic pore of the P/Q type neuronal calcium channel and plays a major role in voltage sensitivity and ionic selectivity. A 2002 study expressing FHM mutations in cultured cells revealed an increased open probability for calcium influx and a decrease in density of functional calcium channels [16]. The overall impact of these effects in the human brain is not known. Nervous system alterations in knockout mice deficient in P/Q-type calcium channel genes range from absence seizures, and ataxia, to selective degeneration of the cerebellum if the mouse survives past weaning [17]. Loss-of-function mutations in the α1 subunit lead to tottering, leaner [18] and rocker mouse [19]. A *CACNA1A* knockin mouse carrying the R192Q FHM1 mutation showed increased Cav2.1 current density, enhanced neurotransmission and lowered threshold for cortical spreading depression (CSD) [20], a depolarisation wave that propagates across the brain cortex and is speculated to cause the neurological symptoms that present in MA [21]. A second FHM locus has been subsequently mapped to chromosome 1q21–23 [22], where loss of function mutations in the *ATP1A2* gene which encodes a P-type Na+, K+ ATPase have been found [23, 24]. This ATPase may play a role in Na+/Ca2+ exchange following activation of voltage-gated Ca2+ channels resembling the effect of *CACNA1A* mutations and thus potentially facilitating CSD [25]. A third locus for FHM has recently been identified on chromosome 2q24, the implicated gene being *SCN1A*, which encodes a neuronal voltage-gated sodium channel. The specific mutation is a missense mutation in the so-called hinged-lid domain of the protein, which is critical for fast inactivation of the channel. Mutations of this gene have also been associated with epilepsy [26].

The involvement of FHM genes in the more common forms of migraine has been the focus of much research. A 1998 study performed in our laboratory reported the region around the FHM1 gene at 19p13 as being implicated in familial typical migraine, which includes MA and MO, in some families although not all, indicating the genetic heterogeneity of the disorder [27]. Others have also suggested involvement of this locus in typical migraine [28, 29]; however, not all studies agree [30–32]. Although the *CACNA1A* gene cannot be completely ruled out as contributing to the overall genetic risk of the common forms of migraine, it is possible that variations within an adjacent gene on 19p13 may confer a more substantial risk to the disorder. This idea is supported by a 2001 migraine linkage study which incorporated haplotype analysis of 16 pedigrees affected with MA. Results of this work suggest an MA susceptibility gene on chromosome 19p13 in a region distinct from (and telomeric to) the FHM1 (*CACNA1A*) locus [33]. With regard to other genes in this region, McCarthy et al. (2001) reported positive association of several single-nucleotide polymorphisms (SNPs) in the Insulin Receptor gene (*INSR*) located at 19p13 in typical migraine [34], although in a more recent study Kaunisto et al. (2005) found no evidence for a susceptibility region at this locus using both parametric and non-parametric linkage analyses in 72 Finnish MA families [35]. In 2002 we published a study providing evidence for genetic linkage of 1q31 to migraine, close to the second FHM susceptibility locus, in a single large multigenerational pedigree. We further analysed an independent sample of 82 affected pedigrees by family-based asso-

ciation test, adding support to the initial findings [36]. A follow-up study showed evidence for linkage at 1q23 to markers spanning the *ATP1A2* gene; however, testing all known FHM mutations of *ATP1A2* in common migraine probands of pedigrees showing excess allele sharing was negative [37]. These results will require further clarification, as other candidate genes may lie within the 1q23-q31 chromosomal region.

Several other loci have been identified in genome-wide linkage analyses. Table 1 summarizes all those with statistically significant (logarithm of the odds) LOD scores. The first genome-wide linkage analysis was conducted in 2002 in 50 Finnish families with MA, implicating 4q24 [38]. A region close by, 4q21, was implicated in 103 Icelandic families with MO [39]. In a Swedish family with MA and MO there was significant linkage to 6p12.2–21.1 [40]. There was also significant linkage to 14q21.2–22.3 in an Italian pedigree with MO [41], and 11q24 in 43 Canadian families with MA [42]. In a 2005 study performed at our laboratory, significant linkage to 18p11 and 3q-tel for a more severe heritable form of migraine was shown. Excess allele sharing was also seen in previously implicated regions at 1q23 and 14q22 in an analysis of 92 pedigrees with the MA/MO phenotype [43]. Nyholt et al. (2005) performed a genome-wide linkage analysis on 756 twin families. Results showed significant linkage for latent class analysis (LCA)-derived migraine to 5q21 and replication of previously reported susceptibility loci at 6p12.2-p21.1 and 1q21-q23, close to the FHM2 locus [44]. In earlier studies performed in our laboratory, Nyholt et al. had also implicated a region on Xq24–28 after scanning the X chromosome in 3 large Australian pedigrees [45, 46]. Russo et al. (2005) recently investigated and implicated a region at 15q11-q13 in 10 families with MA [47]. This particular chromosome 15 region contains three GABA-A receptor subunit genes [47]. Interestingly, three others are located at Xq28 [48, 49]. GABA is the major inhibitory neurotransmitter of the brain, occurring in 30–40% of all synapses in regions such as the cerebral cortex, hippocampus, thalamus, basal ganglia, cerebellum, hypothalamus and brainstem [50]. Notably, studies have reported higher GABA levels in blood platelets [51] and saliva [52] in patients suffering migraine compared with controls. Recently, Vieira and colleagues reported an increase of GABA levels in the cerebrospinal fluid in depressed patients during headache attacks [53]. These findings suggest that GABA could be involved in the pathophysiology of migraine. In addition, GABAergic drugs can modulate biochemical and physiological events in the disorder. In fact cortical events that underlie MA may be suppressed by an increase of inhibitory GABAergic neurotransmission induced for example, by valproate [54]. In addition, the concept of migraine as a result of CNS hyperexcitability [55] has led to the use of GABAergic anticonvulsant medications as efficient therapy for prevention of migraine [56]. Thus further investigation of chromosomal regions harbouring GABA-related genes may be worthwhile.

Candidate gene studies

A further approach in complex disease gene mapping is targeted candidate gene analysis using association studies. Selection of genetic markers for this type of analysis is based on the hypothesis of the marker being functionally relevant, or in linkage disequilibrium with a causal variant [57]. This type of approach has been employed by numerous research groups and tests for differences in allele frequencies between affected individuals (cases) and migraine unaffected individuals (controls). Genetic association studies have suggested a role of numerous candidate genes in migraine susceptibility, although follow-up confirmatory studies are limited and none have yet been functionally linked. As case-control analyses have a history of spurious and controversial results, independent replication is now considered a key factor in evaluating the validity of significant results [58]. Table 2 summarises results of published association studies in the past 10 years. Positive results of association studies to date can be grouped into broad subcategories that are either well-known migraine triggers, or implicated in migraine pathophysiology. These subcategories include genes involved in neurotransmitter function, vascular function and a more recent addition, hormonal function.

Table 1. List of migraine genome-wide linkage studies showing significant LOD scores.

Authors	No. of families/patients studied	Phenotype	Region detected
Nyholt et al. 2005	756 families	LCA diagnosis	5q21
Lea et al. 2005a	92 pedigrees	MA MO	18p11, 3qtel in severe heritable form
Bjornsson et al. 2003	289 patients	MO	4q21
Cader et al. 2003	43 families	MA	11q24
Soragna et al. 2003	large pedigree	MO	14q21.2–22.3
Carlsson et al. 2002	large pedigree	MA MO	6p12–21
Wessman et al. 2002	50 pedigrees	MA	4q24

LCA = Latent Class Analysis; MA = migraine with aura; MO = migraine without aura.

Table 2. List of published association studies on migraine in the past 10 years.

Authors	Gene/s analysed	Chromosomal location	*n* MIG/MA/MO	Results
Scher et al. 2006	MTHFR	1p36.3	187MA/226MO 1212C	significant association (p = 0.006)
Colson et al. 2005	AR	Xq11.2-q12	275MA/MO 275C	no association
	PGR	11q22-q23	575MA/MO 575C	significant association (p = 0.017), PGR/ESR1 interaction
Kowa et al. 2005	ACE	17q23	54MA/122MO 248C	significant association MA (p < 0.01)
Lea et al. 2005b	ACE, MTHFR	17q23, 1p36.3	270MA/MO 270C	ACE, MTHFR interact to increase MA risk (p = 0.018)
Oterino et al. 2005	MTHFR, TS, MS, MTHFD1	1p36.3, 18p11.32, 5p15.3-p15.2 14q24	138MA/191MO 237C	MTHFR, TS, MTHFD1 interact to increase migraine risk
Marziniak et al. 2005	HSERT	17q11.1-q12	197MA/MO 115C	significant association MA (p < 0.001)
Filic et al. 2005	MAO-A	Xp11.4	30MA/80MO 150C	weak association in male MO
	MAO-B	Xp11.23	30MA/80MO 150C	no association
Marziniak et al. 2004	MAO-A	Xp11.4	119MIG 229C	no association
Curtain et al. 2004	LDLR	19p13.3	244MA/MO 244C	no association
Rainero et al. 2004	TNF alpha	6p21.3	299MA/MO 306C	significant association (p < 0.001)
Colson et al. 2004	ESR1	6q25.1	575MA/MO 575C	significant association (p = 0.003)
Otterino et al. 2004	MTHFR	1p36.3	78MA/152MO 204C	no overall association but higher allele frequency in MA
Lea et al. 2004	MTHFR	1p36.3	275MA/MO 275C	significant association (p = 0.017)
Racchi et al. 2004	5-$HT_{1B/1D}$, 5-HT_{2C}	6q13, Xq24	44MA 33C	no association
Johnson et al. 2003	5-HT_{2C} receptor	Xq24	275MA/MO 275C	no association
Juhasz et al. 2003	5-HT_{2A} receptor	13q14-q21	126MA/MO 101C	no association
	HSERT	17q11.1-q12	126MA/MO 101C	borderline association
Kusumi et al. 2003	GST	11q13	174MA/MO/TT 372C	significant association (p < 0.01)
Kara et al. 2003	MTHFR	1p36.3	23MA/70MO 136C	significant association (p < 0.01)
Mochi et al. 2003a	LDLR	19p13.3	140MA/220MO 200C	significant association (p = 0.017)
Mochi et al. 2003b	DRD4 DAT DBH	11p15.5, 5p15.3, 9q34	93MA/101MO 117C	significant association DRD4 in MO (p = 0.0009)
Rainero et al. 2002	APOE	19q13.2	241MA/MO 587C	no association

These and other implicated genes that do not fall into these broad categories are also discussed.

Neurotransmitter function

There is some evidence that the neurotransmitter system plays a key role in migraine pathophysiology. During migraine attacks, activation of the cerebral structures of the thalamus in response to excessive afferent stimulation, or of the hypothalamus in response to changes in the internal environment are believed to occur [59, 60]. These responses involve modulation of the intracranial perivascular nerve, initiating neurogenic inflammation and causing an increase in the diameter of the meningeal blood vessels. The vasodilatation, in turn, allows propagation of nociceptor factors (liberated in blood circulation), causing headache pain. Several neurobiological systems are part of these events, including the serotoninergic, acetylcholinergic and catecholaminergic systems. Norepinephrine can mediate many important functions in the central and peripheral nervous systems. It is the major neurotransmitter of the sympathetic division of the autonomous nervous system, where its release regulates vascular tone and cardiac contractility among other vital functions. In the central nervous system, norepinephrine

Table 2. (Continued).

Authors	Gene/s analysed	Chromosomal location	*n* MIG/MA/MO	Results
Shepherd et al. 2002	DRD1 DRD3 DRD5	5q35.1, 3q13.3, 4p16.1	275MA/MO 275C	no association
Trabace et al. 2002	TNF	6p21.3	32MA/47MO 101C	significant association TNFβ in MO ($p = 0.004$)
McCarthy et al. 2001	INSR	19p13.3-p13.2	827MA/MO 765C	significant association ($p < 0.05$)
Yilmaz et al. 2001	HSERT	17q11.1-q12	52MA/MO 80C	significant association Stin 2.10 ($p = 0.01$)
Lea et al. 2001b	iNOS	17q11.2-q12	262MA/MO 252C	no association
Lea et al. 2001a	CACNA1A CACNA1A	19p13	177MA/MO 182C 81 families (TDT)	no association no association
Maude et al. 2001	DRD2	11q23	200MA/MO 464C	no association
Erdal et al. 2001	5-HT_{2A} receptor	13q14-q21	61MA/MO 41C	significant association codon 102 in migraine subtypes
Tzourio et al. 2001	endothelin receptors	13q22	140MA/MO	significant association ETA ($p < 0.001$)
Kowa et al. 2000	MTHFR	1p36.3	22MA 52MO 261C	significant association ($p < 0.0001$)
Lea et al. 2000	DBH DBH	9q34 82 families (TDT)	177MA/MO 182C Disequilibrium	significant association ($p = 0.019$)
Paterna et al. 2000	ACE	17q23	302MO 201C	significant association ($p <0.05$)
Peroutka et al. 1999	DRD2	11q23	52MA 121C	significant association ($p <0.005$)
Del Zompo et al. 1998	DRD2 DRD3 DRD4	11q23, 3q13.3, 11p15.5	50 families MO (TDT)	disequilibrium in DRD2
Dichgans et al. 1998	DRD2	11q23	47MA/55MO 145C	no association
Ogilvie et al. 1998	HSERT	17q11.1-q12	173MO/94MA 133C	significant association ($p = 0.025$)
Griffiths et al. 1997	eNOS	7q36	91MA/MO 85C	no association
Burnet et al. 1997	5-HT_{2C} receptor	Xq24	73MA/169MO 129C	no association codon 23
Peroutka et al. 1997	DRD2	11q23	129MA/MO 121C	significant association MA ($p <0.005$)
Paterna et al. 1997	ACE	17q23	191MO 201C	significant association ($p <0.05$)
Nyholt et al. 1996	5-HT_{2A} receptor	13q14-q21	96MA/MO 91C	no association

M = migraine (no MA/MO specified), MA = migraine with aura, MO = migraine without aura, TT = tension-type headache, C = control, AR = androgen receptor gene, PGR = progesterone receptor gene, ACE = angiotensin converting enzyme gene, MTHFR = 5,10-methylenetetrahydrofolate reductase gene, TS = thymidylate synthase gene, MS = methionine synthase gene, MTHFD1 = methylenetetrahydrofolate dehydrogenase, methylenetetrahydrofolate cyclohydrolase formyltetrahydrofolate synthetase gene, MAO = monoamine oxidase gene, TNF = tumour necrosis factor gene, HSERT = serotonin transporter gene, GST = glutathione S-transferase, LDLR = low-density lipoprotein gene, DRD = dopamine receptor gene, APOE = apolipoprotein E gene, INSR = insulin receptor gene, iNOS = inducible NOS gene, CACNA1A = calcium channel subunit gene, TDT = transmission disequilibrium test, DBH = dopamine beta hydroxylase gene, eNOS = endothelial nitric oxide synthase gene, DAT = dopamine transporter gene.

is localised within several neurons in the hindbrain and midbrain and participates in the regulation of several vital physiological functions (e.g. cardiac rhythm, awake-sleep cycle and cognition) [61]. Disturbances in the noradrenergic system can contribute to pathologies such as hypertension [62], hyperactivity sleep disorders [63] and migraine [64]. In some migraineurs, the level of plasma noradrepinephrine has been measured as significantly lower in patients compared with controls [65], indicating a sympathetic dysfunction.

A role for central dopamine hypersensitivity in migraine has also been proposed. A lower threshold for dopamine receptor activation [66, 67] and increased expression of certain dopamine receptors in lymphocytes [68] has been found in migraineurs compared with controls. Furthermore, d'Andrea and colleagues have showed that platelet levels of dopamine in migraine patients are higher than those found in healthy control subjects [69]. Investigations into genes involved in dopaminergic pathways, have shown interesting, although at times conflicting, results. Peroutka et al. (1997) showed a role for the *Noc* I allele of the D_2 dopamine receptor (*DRD2*) gene in MA susceptibility [70], although Dichgans et al. (1998) was unable to confirm this result in a smaller German group [71], as

did Maude et al. testing a different polymorphism in the same gene [72]. Del Zompo et al. (1998) tested a different intragenic polymorphism within the gene in a subgroup of migraineurs with specific 'dopaminergic' symptoms (yawning and nausea during migraine) from 50 families by transmission disequilibrium testing (TDT), providing evidence for a role of the *DRD2* gene in MO [73]. Unlike traditional case-control analyses, the TDT is quite robust to population stratification [74]. Population stratification is a limitation of case-control analysis if the study groups are not carefully selected to be ethnically homogenous, therefore follow-up studies of this gene in a large study group may be warranted. More recently, Mochi et al. (2003b) showed association of the D_4 dopamine receptor (*DRD4*) gene with MO [75].

Several functional polymorphisms have been reported for the dopamine beta hydroxylase (*DBH)* gene. The first association between *DBH* alleles of a short tandem repeat (STR), and DBH plasma concentration was observed in a unrelated British population [76]. This functional *DBH* polymorphism (STR) has been confirmed by Cubells et al. (1998), who also showed an influence of *DBH* polymorphisms on plasma and CSF DBH levels [77]. A 19-bp insertion/deletion (indel), also located in the *DBH* promoter [78], was associated with phenotypic variation in DBH activity in plasma [79]. At our laboratory the prevalence of different alleles of both markers, the *DBH* STR and *DBH* insertion/deletion, was examined by association study in 177 unrelated migraineurs and 182 controls plus a TDT analysis of 296 subjects (263 affected) from 82 families of migraineurs. The results showed a distortion of allele transmission of the microsatellite (STR) marker in individuals suffering from both migraine with or without aura [80]. Notably, a single 10-kb block beginning from the indel marker in the *DBH* gene has been recently reported as being highly associated with the phenotype of the enzyme [81]. This block contains in particular the SNP –1021 C→T polymorphism, which accounts for 35–52% of the total phenotypic variance in plasma DBH activity in samples from three different populations [81]. This functional polymorphism has been associated with Parkinson's disease [82]. A new intragenic non-synonymous SNP polymorphism (+1603 C→T) has also been recently identified in exon 11 of the *DBH* gene and has been associated with the phenotype of the enzyme as well [83]. Interestingly, significant differences in serum DBH have been observed in migraine patients compared with healthy control subjects [84, 85] and during a migraine attack [86]. DBH plays an important role in the noradrenergic system. This enzyme is localised within the membrane fraction of norepinephrine and epinephrine-producing neurons and neurosecretory cells, where it catalyses the conversion of dopamine to norepinephrine [87, 88]. DBH may be as important as dopamine and norepinephrine in dysfunction of the catecholamine pathway, notably in nervous and mental disorders.

Scientific support has implicated the brain neurotransmitter 5-hydroxytryptamine (5-HT; serotonin) as being involved in the pathophysiology of migraine, supporting a proposed serotonergic theory of migraine. Documented evidence of increased serotonin activity associated with a corresponding decrease in nociception and decreased serotonin activity levels with a subsequent increase in nociception is indicative of the role of serotonin in pain modulation [89]. Changes in serotonin serum levels during migraine attacks [90] and disruptions within the synthesis of serotonin [91] all substantiate the pathophysiological role of serotonin in migraine pathogenesis. Hypermetabolism within the brain stem region of serotonergic raphe nuclei has also been documented in migraineurs [92]. The role of serotonin in migraine is further suggested by its involvement in therapy. Triptans, selective serotonin 5-HT1B/1D agonists, are very effective acute migraine drugs [93, 94]. Although conflicting results have been reported about the use of SSRIs (selective serotonin reuptake inhibitors) in migraine prevention [95–98], trycyclic antidepressants such as amitriptyline are currently employed in migraine prophylaxis with evidence supporting their effectiveness for use [99, 100]. Thus genes in the serotonergic system have been investigated as potential candidates to mediate susceptibility to migraine. One of them is the human serotonin transporter gene (*5-HTT/HSERT/STG*) located on chromosome 17q11.1-q12. This gene contains a 44-bp insertion/deletion functional polymorphism in the promoter region, which regulates the expression and function of the serotonin transporter gene [101]. Another polymorphism has been described, a variable-number tandem repeat (VNTR) of the 17-bp sequence in intron 2, which has several alleles: STin 2.7, STin 2.9, STin 2.10, STin 2.11 and STin 2.12 [102]. The function of this VTNR polymorphism is not well known. Ogilvie et al. (1998) investigated the VNTR polymorphism in 266 individuals with migraine, and 133 unaffected controls. Results suggested a role for this marker in migraine [103]. Yilmaz and colleagues (2001) have also reported that the presence of STin 2.10 allele in this marker may increase the risk of migraine, although the specific differences tended to be contradictory to the results of Ogilvie and colleagues [104]. Juhasz et al. (2003) investigated a functional polymorphism in the upstream regulatory region of the serotonin transporter gene in the Hungarian female population. This marker was analysed in 126 migraine sufferers and 101 unrelated healthy controls. A borderline association between the short allele and migraine was found [105]. Marziniak et al. (2005) performed an association study in 197 migraineurs and 115 controls investigating the same functional serotonin transporter gene promoter polymorphism. Results showed that the frequency of the less active short allele was increased in

MA sufferers but not in MO sufferers in comparison with the control population [106]. The serotonin transporter catalyses a high-affinity sodium chloride-dependent process to transport serotonin from the extracellular space into serotonergic neurons and blood platelets, thereby terminating its actions [107]. This key element of serotonergic transmission might be an indicator of genetically driven vulnerability to migraine. Other important components of the serotonergic system are the serotonin receptors, of which there are many subtypes throughout the brain. For example, the 5-HT2C receptor subtype is a metabotropic receptor, able to stimulate several phospholipases (C and A2) and channels (K+, Cl–), where it's expressed nearly exclusively in the brain [108]. Two lines of evidence point to the importance of the 5-HT2 receptor in migraine: several anti-migraine drugs are 5-HT2 receptor antagonists [109–111], and the 5-HT2 receptor agonist meta-chlorophenylpiperazine has been shown to induce a migraine attack [112]. Nonetheless, several studies investigating genes encoding various 5-HT receptor subtypes have shown insufficient evidence for a role in migraine. Buchwalder et al. (1996) failed to find a role for *5-HT2A* and *5-HT2C* in migraine by linkage analysis in 18 pedigrees [113]. Burnet et al. (1997) failed to find an association of a codon 23 variant of *5-HT2C* and migraine in an association study [114]. Similarly, at our laboratory Johnson et al. (2003) found no association with migraine of *5-HT2C* using both a linkage and association approach [115]. Racchi et al. (2004) found no evidence for involvement of *5-HT1B/1D* and *5-HT2C* polymorphisms in migraine with aura [116]. In a 1996 study at our laboratory Nyholt et al. tested two markers in the *5-HT2A* by linkage and association analysis and found no evidence for a role of these loci in migraine [117]. A positive association with the 102T/C polymorphism of *5-HT2A* and MA was reported by Erdal et al. (2001) in a small study group (n = 105) [118]; however, Juhasz et al. (2003) found no association with migraine of this particular locus in a larger study sample [105].

Vascular function

Alterations in vascular function have been noted in migraineurs [119–121]. Thus genes involved in vascular functioning have also been explored as likely migraine candidates. Of particular note is the methylenetetrahydrofolate reductase (*MTHFR)* gene, mutations of which have been implicated in mild hyperhomocysteinemia, a condition which is understood to exert deleterious effects on the vascular endothelium through oxidative damage [122]. Notably, both 677T and 1298C mutations of *MTHFR* have been implicated in reduced enzymatic capacity [123, 124]. 5, 10-methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the metabolism of methionine, and homocysteine is an intermediate of this pathway. Plasma homocysteine levels are determined by both genetic factors (such as mutations in genes involved in the metabolism pathway) and non-genetic factors (e.g. nutritional factors, sex, age). Several studies have investigated plasma homocysteine levels as a cause of vascular disease [125–127], although it has been suggested that hyperhomocysteinemia may in fact be a secondary effect of the disease [128]. Nevertheless, recent meta-analyses have confirmed a significant link between hyperhomocysteinemia and vascular disease and further concluded that individuals with the *MTHFR* 677TT genotype have a modest but significant increased risk of vascular disease [129, 130]. Kowa et al. (2000) provided the first evidence for a role of the T allele of the *MTHFR* C677T mutation in migraine, in particular MA susceptibility. Kara et al. (2003) confirmed these results in an independent study, as well as the C allele of the A1298C mutation in the same gene. We also confirmed a role in MA of the T allele in the C677T mutation [131]. Oterino et al. (2004) were unable to demonstrate a significant difference in frequency of the *MTHFR* 677 genotypes in a Spanish cohort; however, they did report a significant difference in the frequency of TT homozygosis between MA and MO, with the T allele occurring more frequently in MA [132]. More recently, Sher et al. (2006) showed an association of the TT genotype in migraine in a large study group (n = 1625) [133].

Other vascular genes implicated in migraine are the Angiotensin I-converting enzyme (*ACE*) gene and the endothelin type A receptor (*ETA*) gene. The Angiotensin I-converting enzyme is one of the key enzymes in the rennin-angiotensin-aldosterone system and plays an important role in blood pressure regulation [134], while the ETA receptor is involved in vasoconstriction [135]. The *ACE* I/D polymorphism is considered to influence serum enzyme levels [136]. Paterna et al. (1997, 2000) have shown a role for the D allele of this polymorphism in MO in two independent studies [137, 138]. Kowa et al. (2005) have also shown a role for the D allele in MA [139]. Interestingly, Lea et al. (2005) have shown an interacting role for *MTHFR* gene 677T and *ACE* gene D variants, in migraine, with the greatest effect in MA [140]. With regards to the *ETA* gene, in a population-based study in France, Tzourio et al. (2001) found that the A allele in the *ETA* –231 A/G polymorphism was associated with migraine and that the association was stronger in participants with a family history of severe headaches than in those without [141]. Notably the potent vasoconstrictor endothelin 1, whose effect is mediated via endothelin type A and B receptors, has been shown as a potent inducer of CSD [142].

Hormonal function

Hormonal fluctuations have long been known to play a role in migraine susceptibility. Migraine frequency and severity often change during significant hormonal milestones, and it regularly appears for the first time during menarche [143, 144]. Additionally, there is an unequal gender distribution in reported migraine prevalence (18% in females vs. 6% in males) [4, 145]. Stabilization of estrogen levels has been shown to reduce migraine frequency and severity in several small studies [146–149], although larger studies are required for clarification. The ovarian hormones play a complex role in the central nervous system, and their effects appear to be mediated by both genomic and non-genomic mechanisms. Animal studies support interactions with various neurotransmitter systems [150–152] as well as a role in neuronal excitability [153, 154]. Furthermore, estrogens can affect vascular tone [155], most likely through mechanisms involving nitric oxide release [156]. Thus genes involved in hormonal pathways represent likely candidates for migraine susceptibility. In 2004 we investigated the role of the estrogen receptor 1 (*ESR1*) gene in migraine by analysing the G594A SNP in 575 migraineurs and 575 controls (analysed as two independent study groups). Results of both studies showed a significant association of the A allele of the SNP with migraine [157]. More recently, we investigated the progesterone receptor (*PGR*) PROGINS insert in the same two study groups. Results also implicated a role for this gene in migraine in both independent study groups. Analysis of the androgen receptor gene was not significant [158]. We look forward to independent replicates of these analyses, particularly in large carefully selected study groups to clarify the role of hormonal pathways in migraine pathogenesis.

Other implicated candidate genes

Additional genes that have been implicated in migraine susceptibility by association analysis and do not fall into the broad categories above include the insulin receptor gene (*INSR*), tumour necrosis factor-alpha (*TNF*α) and low-density lipoprotein receptor (*LDLR*) genes [34, 159–161]. Plausible hypotheses can be proposed for a role of these genes in migraine. *INSR* is one of the key players in glucose metabolism. Fasting is a well-known migraine trigger [162]. TNFα is a proinflammatory cytokine that has been shown to play a role in nociception [163, 164]. Transitory increases in the levels of TNFα have been observed in the plasma of migraineurs (22 MO, 4 MA) [165] and in the internal jugular blood of migraineurs with aura during an attack [166]. *LDLR* is located in the migraine-implicated region 19p13 and has a role in cholesterol homeostasis. Cholesterol levels have been shown to influence platelet behaviour in migraine patients [167], and migraineurs with aura have been reported to have an increased likelihood of an unfavourable cholesterol profile [168]. Interestingly, in a study performed in our laboratory, a role for the same *LDLR* variant studied by Mochi et al. (2003a) could not be found [169]. Thus a potential role for this gene in migraine susceptibility remains unclear. As discussed earlier, functional analyses of the *INSR* gene variant (at 19p13) associated with migraine were unable to show altered functioning of the receptor when tested in mononuclear cells. However as considered by the authors, limitations of the functional analysis leave open the possibility that *INSR* function could be altered in migraine-relevant cell types such as in neurons or other central nervous system cell types [34]. With regard to TNF genes, Trabace et al. (2002) analysed *TNF*β polymorphisms in 47 patients with MO, 32 patients with MA and 101 controls. Results suggested a role for *TNF*β in MO but not in MA [159]. Rainero et al. (2004) investigated a polymorphism in *TNF*α in 299 migraineurs and 306 controls also showing an association with MO but not MA. Notably, a recent study investigating plasma levels of pro- and anti-inflammatory cytokines in migraineurs and controls showed increased plasma levels of TNFα during migraine attacks in comparison with their levels outside attacks [165].

The future of migraine genetic Research

The advent of powerful new technologies for gene mapping along with the many public access Web-based resources that provide genome-wide sequence and variant data should enable researchers to adopt innovative and effective approaches in the search for genetic determinants of disease. The establishment of the International Hapmap project (www.Hapmap.org), with its detailed information on human genetic variation in diverse population groups that is available for public download, should further accelerate the search for disease causing genes by enabling haplotype analysis and thus fine-tuning the selection of markers for disease gene mapping [170].

Nevertheless, due to the complex polygenic nature of migraine, the search for migraine susceptibility genes will remain challenging. Complicating the issue is the likelihood that many genetic variants may provide a modest yet nonetheless significant contribution to an individual's migraine susceptibility [171]. Additionally, there is likely to be gene-gene interaction as well as gene-environment interactions. Hence standard approaches used to identify single causal genes have their limitations. This could in part explain why investigations of candidate susceptibility genes in case control group studies as well as linkage analyses have at times shown variable results and attempts at independent replication have failed. Case-control studies have received criticism in the past due to a number of factors. They bear the potential for population stratification, where differences in marker allele frequencies may exist due to subpopulation variation in the study

groups, possibly leading to spurious results. Therefore, careful selection to ensure ethnic homogeneity is essential. Deficiencies regarding sample size and lack of statistical power, as well as poor control in type 1 error rate, also impact on the validity of case-control studies [172]. Therefore the use of large study groups and control for multiple testing is important. These issues coupled with the polygenic, multifactorial nature of migraine make it clear that fresh and novel approaches to mapping the genes involved in this disorder are needed.

A future approach to migraine gene studies may be a more in-depth investigation of combinations of genetic and environmental factors. This approach could potentially be initiated by creating multiple risk gene profiles using genes/markers that have shown evidence of modest effects on migraine risk in large population-based study groups that have been replicated in independent study groups or family-based approaches. Additional analyses could focus on clinical profiles, including symptoms, triggers, and successful treatments, thus providing a more comprehensive depiction of interactions between the various components of the disorder.

In this review of migraine gene studies to date, we have identified a number of interesting variants that we believe warrant further investigation in this manner. Studies are already emerging, suggesting a role of gene-gene interactions in migraine. We analysed the interaction of *MTHFR* gene 677T and *ACE* gene I/D variants, showing that alleles of both genes in combination interact to confer a stronger influence on migraine than the independent effect of each allele alone. Oterino et al. (2005) similarly showed that individually various functional polymorphisms in folate-metabolising genes (which may influence homocysteine levels) did not modify migraine risk; however, there was a strong interaction between the *MTHFR* 677T mutation and thymidylate synthase (*TS*), and methylenetetrahydrofolate dehydrogenase, methylenetetrahydrofolate cyclohydrolase formyltetrahydrofolate synthetase (*MTHFD1*) gene variants in migraine [173]. Furthermore, our investigation of hormonal variants showed that the *ESR1* and *PGR* variants act in combination to increase the risk of migraine by a factor of 3, which is greater than the independent effects of these genetic variants on migraine susceptibility [158].

Such investigations provide an interesting insight into the future of genetic analysis of this complex disorder, and hopefully pave the way for further study. It is well known that effective treatment options for migraine sufferers are limited, as are objective guidelines for selection of available treatments. With greater knowledge of the genes and multiple gene profiles involved in migraine susceptibility, future applications may include individual genetic susceptibility profiling and personally tailored pharmacogenetic and/or modulation therapies to abort attacks and control the disorder.

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