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EDITORIAL

Pasquale Montagna
Pietro Cortelli
Mirella Mochi

The "typical" migraines: genetic studies and some practical considerations

P. Montagna (✉) • M. Mochi
Department of Clinical Neurosciences,
University of Bologna Medical School,
Via Ugo Foscolo 7, I-40123 Bologna, Italy
e-mail: pmontagna@neuro.unibo.it
Tel.: +39-051-6442179
Fax: +39-051-6442165

P. Cortelli
Department of Neurology,
University of Modena and Reggio Emilia,
Modena, Italy

Abstract Epidemiological genetic, family and twin studies show that the typical migraines carry a substantial genetic risk; they are currently conceptualized as complex genetic diseases. Several genetic association and linkage studies have been performed in the typical migraines. Candidate gene studies based on "a priori" pathogenic models of migraine (migraine as a calcium channelopathy; a mitochondrial DNA disorder; a disorder in the metabolism of serotonin or dopamine; in vascular risk factors or in the inflammation cascade; etc.) did not result in uniformely accepted findings. Linkage and genome wide scans gave evidence for several genetic susceptibility loci, still however in need of confirmation. Careful dissection of the clinical phenotypes and trigger factors shall greatly help future efforts in the quest for the genetic basis of the typical migraines.

Key words Migraine • Aura • Genetics • Cardiovascular risk

"Typical" migraine as a complex disease: genetic epidemiology, twin and segregation analysis studies

That migraine runs in families is an ancient observation. Familiarity however is not synonymous with heritability, especially given the wide prevalence of migraine and the possibility that familial occurrence is due to chance. In order to assess the heritability of migraine, e.g. the rate of variance attributable to genetic factors, the disease risk of relatives of migraine probands is determined and compared to that found in the general population. Several surveys indicated that first- and sometimes also second-degree relatives of migraine probands show increased risk for migraine: a two-fold increased risk for migraine without aura (MO) and 1.4 for migraine with aura (MA) in the case of first-degree relatives of MO probands, and a 4-fold risk for MA in the case of first- degree relatives of MA probands [1]. An increased disease risk does not however prove heritability, since it may result from shared environmental factors. It is therefore interesting to note that at least one genetic epidemiology survey found an increased disease risk for migraine in first-degree relatives compared to spouses of migraine probands, who presumably share environmental factors at least for some time in their lives. Notably however, the relative risk for spouses was increased compared to the general population, which implies some degree of assorted mating or shared environmental influences [1]. Studies of heritability performed according to disease risk comparisons came to high rates of genetic determination, e.g. 60%–80% for MO and MA [2].

Better ways of analysing heritability of migraine are studies of monozygotic versus dizygotic twins, especially when reared-together and reared-apart (adopted) identical twins are considered. Several twin studies have been performed in migraine [3] (and tetrachoric correlations in female Danish twins [4]) and gave heritability estimates

of about 50% for MO and MA, without important sex differences. They implied significant heritability rates for migraine with the remainder of variance being due to unshared environmental influences between twins [3]. It is likely however that such twins studies, performed in genetically and environmentally rather uniform populations, underestimate the role of environmental factors, or that at least they come close to the upper limit of heritability of the disease.

Even though they establish that migraine is heritable, these approaches cannot determine the pattern of heritability. Simple inspection of pedigrees was unable to determine the mode of hereditary transmission [5]. More recently, classic and complex segregation analysis of migraine pedigrees has shown that patterns of inheritance do not fit with simple mendelian rules of transmission, say an autosomal dominant with reduced penetrance or an autosomal recessive model, and that, even in families with an apparently autosomal dominant multigenerational pattern, a multifactorial inheritance is likely [6]. In some instances however, the influence of a single major gene or even hereditary patterns of sex-linked transmission or matrilinear heredity could not in principle be excluded [7]. Multifactorial inheritance implies that numerous genes, each having a small effect, segregate to produce the phenotype. In such a case, the result is a quantitative trait, e.g. a continuous varying character, to which each different gene or locus contributes in part (quantitative trait locus). There is, however, no evidence that migraine is a quantitative character, and indeed, it may be wrong to assume that complex human traits must all be the result of segregation at numerous interacting, rather than at a single or few major genetic liability loci; even complex animal behaviours have been shown to be regulated by a single major gene [8].

The typical migraines: candidate-gene studies

Candidate-gene studies are widely performed in the genetic analysis of complex traits, since the power of detecting genes involved in the etiopathogenesis of complex diseases is small with linkage studies. Association studies look at statistical correlation between some genetic variants and a phenotypic trait, and, if a candidate gene approach is chosen, a pathogenic hypothesis must first be generated in which genes involved in specific metabolic pathways or cellular functions are selected for analysis. This is understandably tricky however, and constitutes one of the difficulties with association studies, since an a priori assumption must be made, based on current fashionable but sometimes erroneous pathogenetic theories. Association studies also suffer from limitations common to epidemiological surveys, such as small sizes and selection bias in patient and control populations. As a result, these studies are often difficult to replicate. Moreover, genetic association is not proof of pathogenesis, and the involvement of the genetic variant must also be demonstrated on expression patterns and functional consequences. Pathogenetic theories of migraine abound, and many genes have consequently been subjected to association studies. These shall be examined according to the pathogenic model implicated.

Migraine as a channelopathy

The concept of migraine as a channelopathy was proposed by the Leiden school after the seminal genetic works on familial hemiplegic migraine (FHM) clarified FHM as a calcium channelopathy. The genetics of FHM are outside the scope of this review; they bear however on the genetics of the typical migraines, since FHM is considered a variety of migraine with aura, according to the IHS classification [9], and since it is clear, from detailed analysis of FHM pedigrees, that obligate carriers of the FHM mutation may display migraine with aura or without aura only, e.g. without hemiplegia. Several searches have therefore been made in order to assess the role of the FHM locus or the FHM mutations in the CACNA1A gene located on chromosome 19p13 in the genetics of the more common migraine types.

In 1995, May et al. tested the involvement of the 19p13 chromosomal region in 28 families with migraine with and without aura [10]. Sib-pair analysis showed that affected siblings shared the same highly informative marker allele (D19S394) more frequently than expected by chance, suggesting the involvement of 19p13 in the etiology of the common forms of migraine. Positive results were reported in 1998 also by Nyholt et al. [11] who studied one large family showing both cosegregation and significant allele sharing for markers situated across a 12.6-cM region containing the FHM Ca2+ channel gene. They concluded that mutations either in the CACNA1A gene or a closely linked gene were implicated in some pedigrees with familial typical migraine. As recently as 2001, Terwindt et al. [12] assessed the involvement of the 19p13 FHM locus in migraine with and without aura by analysing affected sib-pairs from 36 extended families with typical migraine with or without aura using flanking and CACNA1A intragenic markers. They found that sibling pairs with MA inherited the same 19p13 CACNA1A containing region significantly more frequently than expected by chance, consistently with an important involvement of this region in migraine, especially MA. Such results had led previously to the contention that the typical migraines could be conceptualized as calcium channelopathies, a concept useful also in

explaining their co-morbidity with ataxia and epilepsy, and applicable also to the animal models displaying mutations in the murine homologue of the human CACNA1A gene [13].

These positive studies, confirming the involvement of CACNA1A in the etiology of the more common forms of migraine, have been disputed. Thus, Hovatta et al. [14], studying typical migraines in a genetic isolate such as the Finnish population, did a linkage study on four families with multiple cases of migraine to markers on chromosome 19p. They excluded a region of 50 cM, flanking the FHM locus as a site of migraine liability. In our own study of 14 Italian families with MO and MA, we performed association, linkage and sib-pair analyses to markers near the CACNA1A region, with negative results [15]. In another study of Italian familial cases of "complicated" migraine, migraine stroke and MA [16], we reported the absence of the four original CACNA1A mutations described in FHM by Ophoff et al. [17]. Moreover, in their search for mutations in CACNA1A in nine families with migraine and episodic vertigo inherited in an autosomal dominant pattern, Kim et al. analysed all 47 exons and flanking introns of CACNA1A without finding any mutations, thus concluding that mutations in CACNA1A are not common in families with migraine headaches [18]. Even more recently, Jones et al. [19] analysed 16 families with MA for co-segregation with markers on 19p13, and obtained a lod score of 4.79 near D19S592, to a locus which however proved distinct from CACNA1A. Such a locus, distinct from CACNA1A and implicated in the genetics of MA, was later mapped, by the same group, to the insulin receptor gene, located on 19p13.3/2 [20]. It remains to be seen whether these latter results can explain the positive but controversial findings described previously. It appears that the 19p13 chromosomal region may contain several genes implicated in migraine genetics. Until now, however, no mutations in the CACNA1A gene have been described in families with migraine without hemiplegia, and therefore the purported role of CACNA1A in the typical migraine must be considered as still putative.

Migraine and the mitochondrial genome

The rationale for searching for mitochondrial DNA mutations in the typical migraines is based on the several striking similarities between some mtDNA diseases, the MELAS syndrome in particular [21], and MA or "complicated" migraine, on the prophylactic efficacy of riboflavin [22], and on several reports of abnormal mitochondrial metabolism detected in muscle and platelets and on ^{31}P magnetic resonance spectroscopy of the brain and muscle in migraineurs [23]. We hypothesized that abnormalities of oxidative energy metabolism play some role in the pathogenesis of migraine [24]. Mitochondrial biochemical abnormalities do not however necessarily imply the mtDNA (which codes for only 13 mitochondrial proteins) and, moreover, in a segregation study of MO and MA families we could not detect any hint of matrilinear transmission [2], making it doubtful that mtDNA has a role in the more common forms of migraine. Indeed, the several searches for mtDNA mutations, even though plagued by shortcomings (e.g. analysis of blood cells only, search for selected mutations without sequencing of the entire mtDNA), have been uniformly negative in the typical migraines, even when multigenerational families have been analysed with an apparently matrilinear type of transmission (Table 1). The situation is different when complicated migraine is considered, in particular migraine stroke: 6% of juvenile migraine strokes harbour the MELAS mtDNA mutation [31], and accumulation of so-called secondary Leber hereditary optic neuropathy mutations occurs in juvenile migraine stroke [32]; more interestingly, a particular mtDNA haplotype, subcluster U5, has been linked to migraine stroke [29, 33], and an mtDNA 8.1 kb deletion has been reported in cyclic vomiting syndrome, a migraine equivalent [34]. It appears therefore that, though not a liability for the typical migraines, mtDNA plays a role in the genetics of complicated migraine, especially migraine stroke, and of some migraine equivalents (Table 2).

Table 1 mtDNA studies in migraine with negative results

Klopstock et al. (1996) [25]	3243 MELAS, 8344 MERRF, mtDNA deletions absent in MA
Haan et al. (1999) [26]	3243 MELAS, 3271, 11084, mtDNA deletions absent in matrilinear migraines
Russell et al. (1997) [27]	11084 mutation absent in Danish migraineurs
Cortelli et al. 1995 [28]	No tRNA Leu (UUR) mutation in cluster headache
Majamaa et al. (1998) [29]	8344, 8993, 11778, mtDNA deletions absent in migraine stroke
Buzzi et al. (2000) [30]	3243 MELAS mutation absent in multigenerational matrilinear migraine

MA, migraine with aura

Table 2 mtDNA studies in migraine with positive results

Bresolin et al. (1991) [23]	MtDNA deletion in 1 case with migraine stroke
Shimomura et al. (1995) [35]	11084 mtDNA mutation in 25% of 53 Japanese migraineurs
Ojaimi et al. (1998) [32]	4216 and 13708 LHON secondary mutations in juvenile stroke
Majamaa et al. (1997) [31]	MELAS mutation in 6% of juvenile migraine stroke
Majamaa et al. (1998) [29]	MtDNA U haplotype in migraine stroke
Finnila et al. (2001) [33]	MtDNA U5 haplotype and tRNA mutations in migraine stroke
Ohno et al. (1998) [36]	tRNA Glu and 12SrRNA mutations in matrilinear FHM
Shimomura et al. (1994) [37]	tRNA Leu UUR mutation in cluster headache
Odawara et al. (1997) [38]	mtDNA deletion in cluster headache
Boles et al. (1999) [34]	8.1 kb mtDNA deletion in cyclic vomiting syndrome

Table 3 Serotonin metabolism genes in migraine

Gene (chromosome)	Phenotype	Reference
5-HTSERT (17q11.2-12)	Allelic association with MO (increased ST in 2.12 and decreased ST in 2.10 alleles) and MA (idem and increased Stin 2.9 alleles)	[39]
	Allelic association with migraine (increased Stin 2.10 allele)	[40]
	No association or linkage with migraine	[15, 41]
5-HT2A (13q14-21)	Allelic association (C allele) with aura but not with migraine	[42]
	No association or linkage with migraine	[15, 43, 44]
5-HT1B (6q13), *5-HT1D* (1p36.3-34.3), *5-HT2B* (2q36.3-q37.1), *5-HT2C* (Xq22-25)	No association or linkage with migraine	[15, 43, 45]
5-HT1B (6q13), *5-HT1F* (3p12)	Not associated with therapeutic response to triptans	[46, 47]

Migraine and serotonin metabolism genes

The rationale for exploring serotonin (5-HT) metabolism genes is based on the pathogenetic role assigned to serotonin in the migraine attack and on the documented efficacy of the several triptan drugs, which act at serotonin receptors 5-HT1B, D and F. Accordingly, serotonin metabolism genes have been considered promising candidate genes, but with scant success until now. All the studies performed on these receptors, including those with the aim of exploring whether the variable therapeutic response to triptans could be linked to genetic variations in these receptors, failed to detect any significant association or linkage (Table 3). Similar negative results were obtained for the 5-HT receptors 2A, 2B and 2C, the site of action of several prophylactic antimigraine drugs. The only study to report a significant association with migraine involved genetic variants of the 5-HT transporter SERT gene, in which an overrepresentation of allele Stin2.12 and a reduction of allele Stin2.10 were found in MO, with an additional trend to overrepresented Stin 2.9 allele in MA [39]. Exactly the opposite (increased Stin2.10 allele in migraine) was found by Yilmaz et al. [40], however, and negative findings were reported both by us in our sample of 14 Italian families with migraine [15] and by Lea et al. [41].

Migraine and dopamine metabolism genes

Here again the rationale depends on the features of dopaminergic hypersensitivity found in migraineurs and taken to explain symptoms such as yawning, nausea and vomiting, and hypotension during the attack, and on pharmacological evidence of increased dopamine receptors (DR) D2 and D4 on the surface of blood cells in migraineurs. However, the genetic evidence is murky, since positive studies of association with dopamine receptors genes, in particular DRD2, have been contradicted in other populations. NcoIC allele of the DRD2 gene was found associated with MA, and in particular with MA co-morbid with anxiety and depression, by

Peroutka et al. [48, 49], and Del Zompo et al. [50] found an association between DRD2 (but not DRD1 and DRD3) and MO in a sample of Sardinian families analysed by means of transmission dysequilibrium test: allele I of DRD2 was associated with yawning and nausea during the migraine attack, though not with migraine itself. Dichgans et al. [51], however, questioned these DRD2 findings: in their own population no particular association of NcoI allele with MA was found; moreover they pointed out that the allele is not functional, meaning that the particular DNA transition results in the same aminoacid and protein and therefore does not change the function of the dopamine receptor. In addition, NcoIC allele is the most frequent allele, and it is difficult to envisage that a disease is associated with the most frequent allele in the population. In our own study of dopamine metabolism genes [52], we performed an association study in MO and MA Italian patients with markers in the DRD2, DRD3 and COMT and MAO-A genes: all studies gave negative results. Again negative results with DRD2 markers were obtained by Lea et al. [41] and, more recently, Shepherd et al. [53] also reported negative association of migraine with DRD1, DRD3 and DRD5 genes. A positive association with a dopamine-beta-hydroxylase (DBH) intragenic dinucleotide polymorphism, with an altered allelic distribution between migraine and controls was found and confirmed by transmission dysequilibrium test implemented on the family data; DBH codes for an enzyme which catalyzes the transformation of dopamine into norepinephrine [41]. Like all of the previously mentioned studies on dopamine metabolism genes, this last finding has not been replicated yet, and the provisional conclusion must therefore be that no unequivocal role for dopamine metabolism genes has been ascertained in the typical migraines to date (Table 4).

Migraine and prothrombotic and vascular risk factor genes

Migraineurs carry a significant cardiovascular risk, and accordingly several investigators have explored genetic risk factors as candidate genes for migraine co-morbidity (Table 5). Overall, no significant association was found for genetic risk factors such as the Leiden factor V mutation (even though a single study reported positive findings), protein C and S deficiencies, factor II 20210 G/A mutation, factor XIII Val34Leu polymorphism, the decanucleotide insertion/deletion in the factor VII promoter, and the platelet HPA-1 and HPA-2 alloantigenic systems. Likewise, association of migraine with the endothelial nitric oxide synthase (NOS3) and inducible nitric oxide synthase (iNOS) genes was negative, a rather dispiriting finding in view of the pathogenetic role attributed to nitric oxide metabolism in migraine [63, 64]. Positive findings were instead obtained with the angiotensin-converting enzyme gene deletion polymorphism, thought to be implicated in hypertension and cardiovascular risk, in which allele D was found significantly related to the frequency of the migraine attacks in 302 patients with MO [62], and with the endothelin type A receptor, in which allele G was shown to have a protective role against migraine [65]. This was a population based study, and the association was stronger in migraineurs with a family history of severe headaches. Finally, the homozygous C677T mutation in the methylenetetrahydrofolate reductase gene, which is responsible for hyperhomocysteinemia, was associated with migraine, especially MA [66]. These studies are intriguing but it must be remarked that not all of them have yet been replicated in independent populations.

Table 4 Dopamine metabolism genes and migraine

Gene	Phenotype	Reference
DRD2	Allelic association (NcoI allele) with MA	[48]
	Allelic association (NcoI allele) with MA co-morbid with anxiety/depression	[49]
	Allelic association (allele 1) with yawning/nausea during MO attack	[50]
	No allelic (NcoI allele) association with MA	[51]
	No allelic association with MO/MA	[52]
	No allelic association with migraine	[41]
DRD1, DRD3, DRD4, DRD5 COMT, MAO-A	No association with typical migraine	[41, 52, 53]
DBH	Allelic association with typical migraine	[41]

MA, migraine with aura; *MO*, migraine without aura; *DBH*, dopamine beta-hydroxylase

Table 5 Prothrombotic and vascular risk genetic factors and migraine

Gene or mutation	Phenotype	Reference
Factor V R/Q (Leiden mutation)	Associated with MA	[56]
	No association with migraine stroke	[57]
	No association with MA/MO	[58]
	No association with juvenile MA	[59]
Factor II 20210 G/A	No association with MA or MO	[60]
	No association with migraine stroke	
Factor XIII Val34Leu polymorphism	No association with migraine	[61]
Decanucleotide insertion/deletion in the factor VII promoter	No association with MA or MO	[58]
Platelet HPA-1 and HPA-2 alloantigenic systems	No association with MA or MO	[58]
Protein S deficiency	Associated with MA	[56]
Angiotensin-converting enzyme (ACE)	D allele associated with MO and higher frequency of attacks	[62]
Endothelial/inducible nitric oxide synthase (NOS3; iNOS)	No linkage/association with migraine	[63, 64]
Endothelin type A receptor (ETA –231 A/G) polymorphism	G allele associated with protection from migraine	[65]
MTHFR (methylenetetrahydrofolate reductase) C677T mutation	Homozygous mutation associated with migraine, especially MA	[66]

MA, migraine with aura; *MO*, migraine without aura

Migraine and genes involved in inflammation

A few studies have addressed the problem of the role of genes coding for cytokines and other proteins involved in the inflammatory cascade. Peroutka et al. [54] studied polymorphism frequencies for complement C3F and C3S in a sample of 137 migraineurs and found that this common polymorphism had no association with migraine susceptibility. Trabace et al. [67] found that the frequency of TNFB*2 allele, located in the HLA class III region, was significantly increased and that of TNFB1 decreased in MO, suggesting that the TNFB*2 allele confers a high risk for MO. The same group had previously observed a protective role for the HLA-DR2 antigen in MA [68]. Finally, a polymorphism in the interleukin-1alpha gene was found to influence age at onset of migraine and was associated with MA [69].

Genetics of the typical migraines: other linkage studies

Other genetic studies have investigated some chromosomal regions chosen either for their involvement in FHM or for considerations derived from the genetic epidemiology of the disease. Thus, considering the increased prevalence of migraine among females and in first-degree relatives of male probands affected with migraine, Nyholt et al. [70] performed linkage studies looking for an X-linked component in migraine. Of three large multigenerational migraine pedigrees, two showed significant excess allele sharing to Xq markers. In a later more detailed study, they were able to establish significant linkage to Xq24-28 [71] in two large Australian pedigrees, thus providing compelling evidence for a migraine susceptibility locus on chromosome Xq24-28. Taking into consideration the recently reported linkage of FHM to chromosome 1, Lea et al. [55]

explored the possibility that such chromosomal region was also implicated in typical migraines. In a migraine Australian pedigree, they found strong evidence for linkage to chromosome lq31 markers, with the interval for suggestive linkage spanning approximately 18 cM and a maximum allele sharing LOD score of 3.36 for marker D1S2782. Linkage was validated in an independent sample of 82 affected pedigrees, giving evidence for a typical migraine locus near chromosome lq3l and suggesting that the second locus for FHM may contribute to susceptibility to the more common forms of migraine. In regard instead to the first FHM locus at 19p13, we saw before how Jones et al. [19] were able to identify a suceptibility locus for the typical migraines at 19p13 but distinct from CACNA1A. In a later refinement of this work, McCarthy et al. [20] investigated this migraine locus by means of linkage and association analysis with 48 single-nucleotide polymorphisms (SNIPs) within the locus in a population of 827 migraineurs and 765 controls. Five SNIPs within the insulin receptor gene INSR showed significant association with migraine, and the association was independently replicated in a separate case-control population. This association of migraine with the INSR could explain the epidemiological association between migraine and diabetes mellitus/hypertension, and why fasting is a migraine trigger factor. However, the role of INSR remained unclear, since the study showed that INSR mRNA levels (in blood) were no different between phenotypes, and that there were no aberrant transcripts, implying normal expression of the gene; moreover binding of ^{125}I-insulin (in mononuclear cells) was also unaffected, and there were no differences in clinical parameters among controls and migraineurs. These caveats notwithstanding, the INSR represents an intriguing associated gene since it is present in brain cells and may regulate energy metabolism; however, if not functional, it could still be in linkage dysequilibrium with a yet unidentified gene.

Genetics of the typical migraines: genome-wide scans

Genome-wide scans are performed to dissect multilocus inheritance into quantitative trait loci (QTLs) and to map them to specific chromosomal regions. They rely on markers that are evenly spaced throughout the genome, and, in contrast to the candidate genes approach, have no regard to their function or the context within a specific gene (they need no a priori hypothesis). This makes genome-wide scans particularly useful in complex diseases. A kind of genome-wide scan, though rather simple in conception, was the work of Pardo et al. [72], who utilized eleven genetic blood markers typed in 112 migraineurs and compared with a random sample of healthy individuals. Strong associations were found between migraine and group-specific component GC 1F-1F and esterase-D ESD 2–2, located on chromosomes 4 and 13, respectively. Wessman et al. [73] performed a genome-wide screen of 50 multigenerational Finnish families with MA, using 350 polymorphic microsatellite markers with an average intermarker distance of 11 cM. They found significant linkage with D4S1647 on 4q24 and no other chromosomal region.

Genetics of the typical migraines: conclusive considerations

Even this short exposition of the principal genetic investigations performed in the typical migraines demonstrates the bewildering array of results obtained, and how most of them are plagued by a frequent problem in the studies of complex diseases, i.e. non-replication. Other results still await confirmation in independent population samples. Therefore it is safe to assume that there is still no confirmed genetic liability locus for the "typical" migraine headaches. Non-replication is so frequently encountered in the genetic studies of complex diseases that widespread scepticism surrounds association studies especially when performed with the candidate-gene approach. Are we therefore dealing with faulty methodology?

Several problems concur in non-replication: definition of phenotype may vary across different populations and different studies; most studies have been performed on small numbers, without consideration of the power necessary for significant results and without considering that migraine is very prevalent and carries a relatively small magnitude of relative risk (association studies give difficult results when the relative risk is less than 10); moreover, no study has taken into consideration of environmental factors modifying the relationship between genotype and disease; some studies selected polymorphisms either too rare (<5%) in the general population, or that were not functional, leading to overreliance on linkage dysequilibrium; many studies do not entertain the expression of the genes investigated. To these methodological shortcomings must be added the lack of some rigorous epidemiological principles: use of inappropriate control groups, patient cohorts selected from tertiary care centers and not from the general population, etc. To all of these methodological problems we could add some erroneous assumptions that we make in the genetics of migraine. The assumption that migraine results from the interaction of tens or even hundreds of genes each carrying a small genetic load and interacting, intercalated in metabolic pathways so diverse and ranging from ion channels to inflammatory proteins and mitochondrial DNA does not make much clinical sense. Such a view of migraine as a genetic "fruit salad" is moreover rather dispiriting: since each gene carries a small genetic risk, it does not represent a worthwile target for therapeutic modifications, which would only marginally

affect the phenotypic expression of the disease. Migraine is, however, internally consistent in its phenotypic expression through age, sex, census and populations, and deserves consideration as a disease with intrinsic pathogenetic autonomy. We must remember that even complex diseases may stem from the effects of a few major single genes. Probably, a more careful distillation of the phenotypic expression of migraine and of its trigger factors, e.g. more clinical ingenuity and judgement, shall serve the quest for the genetic basis of the typical migraines better.

The typical migraines: a time for pharmacogenetics?

Much hype has been afforded by the possible developments in pharmacogenetics. In the case of the typical migraines, where we have still no definite genes in our hands, the time for pharmacogenetics has yet to come. Still, it is possible to make conjectures and to envisage possible avenues for pharmacological research. Knowledge of the genetics of FHM makes the P/Q calcium channels possible targets for new drugs even for the typical migraines; moreover, we can expect useful information from studies of channel characteristics in mouse mutants and in channels expressed in oocytes or in cultivated cells. Pharmacogenetics could also take advantage of gene polymorphisms to tailor pharmacological treatment, and in this regard several examples are possible, for instance taking note of polymorphisms in the 5-HT1B receptor gene (the Cys124 polymorphism) and in the 5-HT2C gene (the Cys23-Ser23) which are already known to affect negatively the binding of dyhydroergotamine, sumatriptan and serotonin [74, 75]. Finally, we could discern and take into consideration the role of modifying genes (e.g. 5-HT and dopamine metabolism genes, prothrombotic/vascular risk factors) in the treatment of migraine attacks and migraine co-morbidity. All of this is for the future. At the moment, the only two works that studied the therapeutic response to sumatriptan in migraineurs found no association with genetic variation at the 5-HT receptor 1B and 1F genes [46, 47].

Post-scriptum Recently, other susceptibility loci for migraine have been identified on 6p12.2-p21.1 (Carlsson et al. Neurology 2002;59:1804–7) and 14q21.2-q22.3 (Soragna et al. Am J Hum Genet 2003;72:161–7), and the gene (ATP1A2) for FHM2 has been identified (De Fusco et al. Nat Genet 2003;33:192–6).

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