P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

Chapter 27

Genetics of Migraine

Michel D. Ferrari, Joost Haan, and Aarno Palotie

Anyone can experience an occasional migraine attack without necessarily being a migraine patient. Not the attack itself, but the repeated occurrence of attacks, is abnormal. In this respect, migraine is very similar to other paroxysmal disorders, such as epilepsy. Migraine often runs in families, suggesting that genetic factors, among others, influence the individual threshold for attacks. Next to genetic factors, other endogenous and exogenous factors modulate this threshold, and migraine is therefore considered a multifactorial disorder (47). Unraveling the genetic basis of migraine should improve our understanding of the pathogenesis of the disease, notably how, why, and when patients experience attacks. This improved insight into the mechanism of the onset of migraine attacks may promote the development of migraine-specific prophylactic drugs. In addition, it may help to establish an objective diagnostic test for (subtypes of) migraine (47). This chapter updates the genetic data on migraine without aura (MO), migraine with aura (MA), familial hemiplegic migraine (FHM), and related disorders.

FAMILY STUDIES

Transmission of migraine from parents to children was reported as early as the seventeenth century (200). Since that time, a large number of studies have reported a positive family history of migraine (reviewed in Russell [149]). Although a positive family history is characteristic of genetic traits, it is obviously not direct evidence for a genetic contribution because families often have a shared environment. Moreover, in very common traits such as migraine (lifetime prevalence of 16 to 21% in the general population (145,153), the chance of a positive family history increases by itself. Therefore, to provide evidence for a genetic contribution, a positive family history should include more stringent criteria than only affected first-degree relatives. In addition, the method of recording family history can also influence the result.

Despite the fact that familial aggregation of migraine is a well-recognized clinical observation and that many studies in the past have supported this empirical observation, there are few studies that meet modern methodologic standards. Apart from problems in collecting data (e.g., questionnaires, interviews), most studies lack validated diagnostic criteria, like those of the International Headache Society (IHS). Two population-based studies randomly selected individuals who were subsequently interviewed (152,162). Russell and Olesen (152) selected 4,000 (3,000 male and 1,000 female) 40-year-old individuals from the Danish Central Person Registry. On the basis of a questionnaire, these authors selected those with self-reported migraine and invited them for a headache interview and a physical and neurologic examination. Spouses and first-degree relatives were interviewed by phone and classified according to IHS criteria. This resulted in 270 probands with migraine: 126 had MO, 127 MA, and 17 had both types of migraine. Interestingly, a different pattern of familial risk was observed for MA and MO. Compared with the general population, the first-degree relatives of probands with MO had 1.9 times the risk for MO but only 1.4 times the risk for MA. On the other hand, first-degree relatives of probands with MA had almost 4 times the risk for MA but no increased risk for MO. The authors concluded that MO was caused by a combination of genetic and environmental factors, whereas MA was determined largely by genetic factors.

A population-based study by Stewart et al. (162) collected a random sample of households in Baltimore County, Maryland, using a random-digit dialing method. The survey was based on either a telephone interview or a self-administered questionnaire. Individuals with probable migraine were invited for a clinic visit for interview and general medical and neurologic examinations. This resulted in 73 migraine probands and 511 first-degree relatives. Probands were stratified into those having more disabling symptoms, missing work or school, and those who only rarely had to skip work or school because of migraine.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

The risk for migraine was considerably higher among relatives of probands with disabling migraine (relative risk [RR] 2.17) compared to relatives of probands with minimal disability (RR 1.20). This risk was not influenced by the type of the proband's migraine. An increased risk for both types of migraine was found in family members, regardless of whether the proband had MA or MO. The authors concluded that familial factors contribute to less than 50% of all migraine cases.

Noble-Topham et al. estimated the genetic load in familial MA, by comparing sibling risk, age at onset, and aura type in 54 MA probands categorized by family history of MA (125). Families with an MA proband were divided into families with MA in three generations ($n = 15$), two generations ($n = 20$), and one generation, so only the proband was affected ($n = 19$). The recurrence risk to siblings of probands was 2.7-fold higher in three generation compared with two-generation MA families and 4.8-fold higher in three-generation compared with one-generation MA families. MA probands from three-generation families were significantly younger than probands with no affected family members. The significant difference in genetic load and the earlier age at onset in the three-generation families is further evidence of a genetic basis for MA.

TWIN STUDIES

Several large, population-based twin studies have been published regarding the concordance of migraine in monozygotic twins (54,79,85,102,123,165,205). The older studies were performed before the introduction of the standard IHS criteria for the diagnosis of migraine, but have a trend similar to that of the newer studies, suggesting a higher concordance rate for migraine in monozygotic twins than in dizygotic twins in many populations (193).

Several studies in a Danish twin cohort (54,182) addressed most of the criticisms of older twin studies, because subjects were personally interviewed and IHS criteria were applied. The concordance rate for monozygotic twins indicated that genetic factors are a major contributor to the pathogenesis of both MO and MA. In a Finnish twin study, similar concordance rates were found (85). Mulder et al. (123) compared the prevalence and heritability of migraine across six of the countries that participate in the GenomEUtwin project, including a total of 29,717 twin pairs. The prevalence of migraine was ranging from 10 to 13% in Finland to 32 to 34% in Danish and Dutch women.

Another type of twin study focused on twins who had been raised apart. This setting provides an even more direct estimate of genetic influence because the effect of a shared environment is excluded. A drawback of these studies, however, is that the sample size is inevitably small because of the few individuals available. A study by Ziegler et al. (205) found that, in general, monozygotic twins had a higher concordance rate for migraine than dizygotic twins (total of 197 twin pairs) but did not find statistically significant evidence that monozygotic twins raised apart (23 pairs) would have a higher concordance rate for migraine than dizygotic twins raised apart (20 pairs). A small case-type study reported that two sets of monozygotic twins raised apart were concordant not only for migraine but also for the age at onset of the attacks (68). Svensson et al. studied a cohort of twins aged 42 to 81 years, including a subsample of 314 pairs reared apart and 364 matched control pairs reared together (165). They found no significant shared rearing environmental influences on migraine. The heritability of migraine was estimated at 38% for men and 48% for women. Interestingly, among monozygotic twins reared apart, those separated at 3 years of age or earlier were more similar for lifetime migraine than those separated later, and this was especially true for women. Svensson et al. suggested that family "resistance" in migraine is mainly caused by genetic factors, whereas environmental influences make family members different, not similar.

PREVALENCE OF MIGRAINE IN ETHNICALLY DIFFERENT POPULATIONS

The prevalence of migraine in African and Asian populations appears lower than in European and North American populations (134,176). These differences among racial groups may be caused by genetic rather than cultural or environmental factors because they persist in the United States. Stewart et al. (161) randomly selected and interviewed (by telephone) 12,328 individuals 18 to 65 years of age living in Baltimore County, Maryland. IHS criteria were used for the diagnosis of migraine. Migraine prevalence was significantly higher in whites than in African or Asian Americans. African Americans reported a higher level of headache pain but were less likely to report nausea and vomiting with their attacks compared to whites. By contrast, African Americans were less disabled by their attacks than were whites. Asian Americans and white Americans did not have significant differences in associated features.

MODE OF INHERITANCE

A number of attempts have been made to analyze the mode of inheritance of migraine. The early reports resulted in a number of conclusions, from autosomal recessive to autosomal dominant, with or without incomplete penetrance (reviewed in Russell [149]). A number of technical details, such as differences in diagnostic criteria and statistical analyses, contribute to the somewhat contradictory

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

conclusions. Because of the higher prevalence of migraine in women and the often-reported maternal transmission, X-linked and mitochondrial inheritance have been of special interest but were proved to be unlikely (116,138).

Recent studies have been performed with up-to-date diagnostic criteria and statistical tools. Four studies published during the past 10 years have all used the IHS criteria for diagnosis, and all study subjects were individually interviewed. Three (83,151,183) of these four studies suggested a multifactorial inheritance. The other (116) suggested a recessive inheritance. A multifactorial inheritance was suggested regardless of whether the families were recruited from headache clinics (83,183) or from a population survey (151). Although various criticisms can be applied to all of these studies, there is a nearly 100% consistency of the results, suggesting a multifactorial mode of inheritance for migraine.

MOLECULAR STUDIES IN MIGRAINE

The search for genetic risk factors in paroxysmal diseases, such as migraine, is complicated by a number of clinical, genetic, and statistical problems. Major clinical issues are how to determine whether or not a person is affected and how to distinguish likely gene carriers from possible phenocopies. Another inherent problem is the high likelihood of locus heterogeneity. Although hard data are scanty, most linkage and association studies suggest that multiple genes contribute to the genetic susceptibility for migraine. Although early onset and severe clinical course are traditionally regarded as indicators of a genetic factor, it is unclear how one should deal with paroxysmal disorders. Are the number of attacks or their severity indicators of the presence of genetic risk factors, or are these merely a consequence of the frequency and intensity of the exposure to environmental triggers? The genetic strategy depends on the available patients, family material, and knowledge of likely candidate genes. When family material is abundant and candidate genes are scarce, a random genome screening for linkage is the method of choice. The preferred statistical method of analysis is debated, namely, parametric versus nonparametric, and the statistical thresholds that provide optimal distinction between linkage and background noise. Linkage findings may lead, after independent confirmation, to identification of positional candidate genes as opposed to the functional candidate genes that originate from insights into the biochemical pathways underlying the disease. The involvement of such functional candidates can be evaluated via functional assays and also by means of linkage tests in multiply affected families. A third, less commonly practiced method of identifying candidate genes for multifactorial disorders is localization of genes that cause rare Mendelian variants of that disorder. Such loci can then be evaluated as possible susceptibility loci, assuming that mutations that convey susceptibility to a complex disease are allelic to more serious gene defects leading to Mendelian segregation. Tentatively, one might call such candidate genes phenotypic candidates. Such rare variants (e.g., in the case of migraine FHM, or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoen cephalopathy [CADASIL]; see below) usually have a clear inheritance pattern, and candidate loci can be identified by using regular logarithm of the odds (LOD) score analyses. With respect to functional candidates, one might object that their number is a priori not strictly defined and that different investigators may favor different functional candidates. In contrast, for phenotypic candidates the number of alternatives is usually limited. A fourth approach is investigating association with genetic markers. The rationale of such studies is that genetic markers, such as DNA polymorphisms, may occur in disequilibrium with genes, various alleles of which may lead to differences in the phenotype. Such linkage disequilibrium may have two possible reasons. Either the time that elapsed to separate the suspect genes from the tightly linked DNA polymorphism by recombination may not have been sufficient for the disequilibrium to disappear, or the marker allele itself influenced the phenotype to be studied.

FAMILIAL HEMIPLEGIC MIGRAINE

The only true molecular insight into migraine pathophysiology is provided by the isolation of the gene for a rare subtype of MA. FHM, a rare autosomal dominantly inherited subtype of MA, was first reported early in the twentieth century (26). A complete list of the early FHM literature is provided elsewhere (reviewed in Russell [149]). Attacks of FHM usually consist of a phase with hemiparesis in addition to at least two typical (visual) aura symptoms with a mean duration of 60 minutes, followed by a headache phase. FHM attacks resemble those of basilar migraine (61), and the headache and aura symptoms, apart from the hemiparesis, are identical to those of MA (173). Some patients have atypical attacks, either with a prolonged aura lasting up to 5 days or with signs of diffuse encephalopathy, expressed as confusion or coma, fever, and sometimes seizures. Atypical attacks are often the first symptoms of the disease and may be triggered by head trauma.

Patients with FHM and their unaffected relatives may also have attacks of MO or "nonhemiplegic" typical MA. Thomsen et al. studied the prevalence of MO and MA in probands with FHM and their first-degree relatives (174). Compared to the general population, FHM probands had virtually no increased risk of MO but a significantly increased risk of almost 8 times of MA. In total, 65% of FHM patients also have attacks of "normal" migraine: with aura 61%, without aura 18%, or with both types 21%. A similar pattern was seen among their first-degree relatives, who had no increased risk of MO, whereas the risk of

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

MA was significantly increased; 7.6 times in FHM-affected first-degree relatives and 2.4-times in non-FHM–affected first-degree relatives. These results suggest that the genetic abnormality resulting in FHM may also cause attacks with the symptomatology of MA. Thus, FHM and MA seem to be part of the same spectrum and FHM may be a good model to study the genetics of "normal" migraine.

An increased risk might suggest that genes involved in FHM are candidate genes for MO and "nonhemiplegic" typical MA. Sporadic cases with FHM symptomatology exist (10,42,64,169), but they are not classified as FHM because this requires at least one affected first- or second-degree relative with identical attacks (63).

GENETIC STUDIES OF FHM

In 1993, linkage of FHM to chromosome 19p13 was reported (76), soon followed by proof of genetic heterogeneity, because only about 50% of the families appeared to be linked to this locus (77,132). Only a few clinical differences have been found between chromosome 19-linked and unlinked families (171), the most striking exception being cerebellar ataxia, which occurs in approximately 50% of the chromosome 19-linked but in none of the unlinked families (42,44,76,77,133). Another difference is that patients from chromosome 19-linked families are more likely to have attacks triggered by minor head trauma and associated with coma (42,170,171).

The human gene originally designated *CACNL1A4*[39] has since been renamed *CACNA1A* (105). The gene encodes for the α1A subunit of voltage-gated P/Q-type neuronal calcium channels. The first missense mutations in the *CACNA1A* gene were found in FHM in 1996 (132). Since that time, several other mutations have been found (Fig. 27-1). There are mutations that cause pure FHM and others that are associated with FHM with ataxia. Ducros et al. (42) presented an extensive study on 21 FHM families

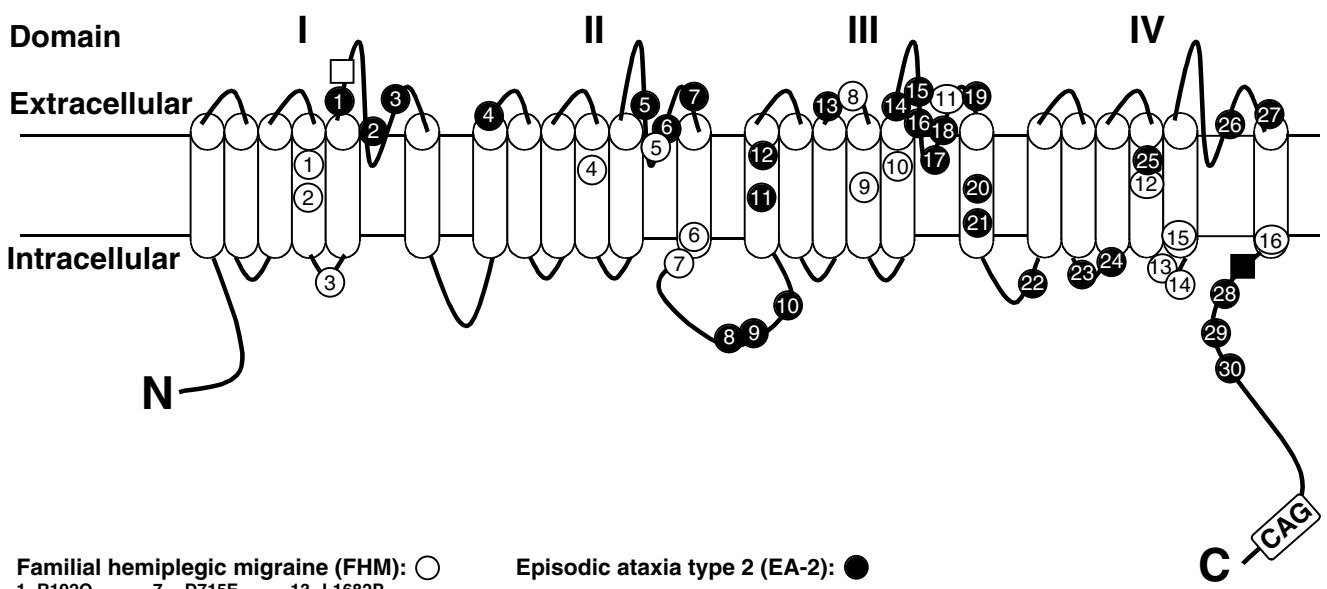

FIGURE 27-1. The *CACNA1A* gene with mutations. The α1A pore-forming subunit of P/Q-type voltage-gated calcium channels is located in the neuron membrane and contains four repeated domains. Each domain includes six membrane-spanning segments and a so-called P-loop between the fifth and sixth segments. Positions of mutations identified in this gene are given, including those identified in mice.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

with eight different mutations. With a few exceptions, mutations were found in single, often small families. Only the *T666M* and the *R385Q* mutation were identified in 10 and 3 families, respectively. The *T666M* mutation appears to be the most common mutation worldwide, being found in several families from several countries (41,42,92,132,166,195). The finding of recurrent mutations allowed a comparison of all clinical features in mutation carriers. Of all mutation carriers, those with the *T666M* mutation showed the greatest frequency of hemiplegic migraine (98%), severe attacks with coma (50%), and nystagmus (86%). Thirteen subjects with mutations had no attacks of hemiplegic migraine, and some had MA (five subjects) or MO (one subject). A total of 66 atypical FHM attacks were reported in 44 mutation carriers. Some of these attacks were found to be prolonged (seven attacks in six patients), and most attacks were associated with encephalopathy (59 attacks in 38 patients).

At the far end of the FHM *CACNA1A* spectrum is the clinical presentation of affected members of two families with an *S218L* missense mutation (48,93). These patients had recurrent atypical attacks, often triggered by trivial head trauma. The proband of the second family died after a period of coma following a symptom-free period of several hours after a mild head trauma. She had never experienced an attack of (hemiplegic) migraine. It appears that the S218L (and possibly other) *CACNA1A* calcium-channel mutations put persons at risk for uninhibited cerebral edema and fatal coma after minor head trauma.

Two studies point to the association of the *CACNA1A* gene with generalized epilepsy (25,78). Of four single-nucleotide polymorphisms (SNPs) and one microsatellite marker within the gene that were tested, one showed a significant association with epilepsy (25). However, because this SNP-8, located in exon 8, does not result in structural changes of the *CACNA1A*-encoded protein, it is unlikely that it is the causative mutation. Instead, SNP-8 is expected to be in linkage disequilibrium with such mutation. In another family, a missense mutation in the *CACNA1A* gene was associated with both episodic ataxia and epilepsy (78). These studies provided first evidence of the involvement of the *CACNA1A* locus in epilepsy in humans, which is of interest in view of the epileptic phenotype observed in *CACNA1A* mutant mice (see below).

Some years ago, two separate groups reported linkage of FHM to chromosome 1 (43,53). A North American group showed, in one large family, an LOD score of 3.04 at $\theta = 0.09$ with marker *D1S249* on chromosome 1q31 (53). Although suggestive evidence for linkage appeared to confirm this locus in one large Australian pedigree classified as "typical migraine" (103), the 1q31 locus was recently considered unlikely by the original investigators (90). Another group found linkage to chromosome 1q21-q23 in three FHM families (43), confirmed in other families (21).

One of the most important breakthroughs in the genetics of headache of the last 2 years is the identification of the second FHM gene (FHM2). This turned out to be the *ATP1A2* gene, encoding the α_2 subunit of sodium potassium pumps (30,107). Missense mutations were identified in two families (Fig. 27-2) and functional assays in cell lines suggested a loss of function as the underlying mechanism. Of interest, three subjects reported a history of seizures similar to migraine-triggered seizures observed in FHM1 patients. Two novel missense mutations in the *ATP1A2* gene confirmed these results: one mutation was identified in a small family with pure FHM, the second in a large FHM family with benign familial infantile convulsions (BFIC), expanding the clinical phenotype associated with *ATP1A2* mutations (189) (see Fig. 27-2). BFIC is a rare autosomal-dominant benign form of epilepsy, with strictly partial, nonfebrile, convulsions that begin at age 3 to 12 months and disappear after the first year. All BFIC persons tested had the missense mutation, but BFIC and FHM only partially cosegregated. It seems that migraine and epilepsy have partially overlapping mechanisms related to dysfunction of ion transport. Importantly, the discovery of the *ATP1A2* gene opens up a new perspective on migraine mechanisms and therapies and resulted in a boost of genetic research (9,190).

Because some FHM families could not be linked to either chromosome 1 or 19, at least a third FHM gene must exist (43).

SPORADIC HEMIPLEGIC MIGRAINE AND THE *CACNA1A* GENE

The etiology of sporadic hemiplegic migraine (SHM), that is, hemiplegic migraine without affected family members, is unknown. Several studies searched for *CACNA1A* mutations in patients with SHM. In one study, two of three SHM patients with cerebellar signs had a mutation: a *T666M* mutation in a patient with cerebellar ataxia and a *Y1384C* mutation in a mentally retarded woman with recurrent prolonged attacks of hemiplegic migraine, coma, and seizures associated with permanent cerebellar ataxia and atrophy (184,185). Studies of small series of SHM patients showed mutations in the *CACNA1A* gene in two of three SHM patients with permanent cerebellar ataxia, but no mutations in eight patients without ataxia (19,41,42). In a recent study of 27 SHM patients, *CACNA1A* mutations were found in two of the patients (169). A patient carrying the *T666M* mutation was distinct from the others by showing permanent cerebellar ataxia and atrophy on computed tomography (CT) scan. Unfortunately, no DNA from the parents of this patient was available. Remarkably, the other mutation (*R583Q*) was found in a patient without cerebellar symptoms. This *R583Q* mutation had been reported previously in four families with FHM and associated ataxia (5,42).

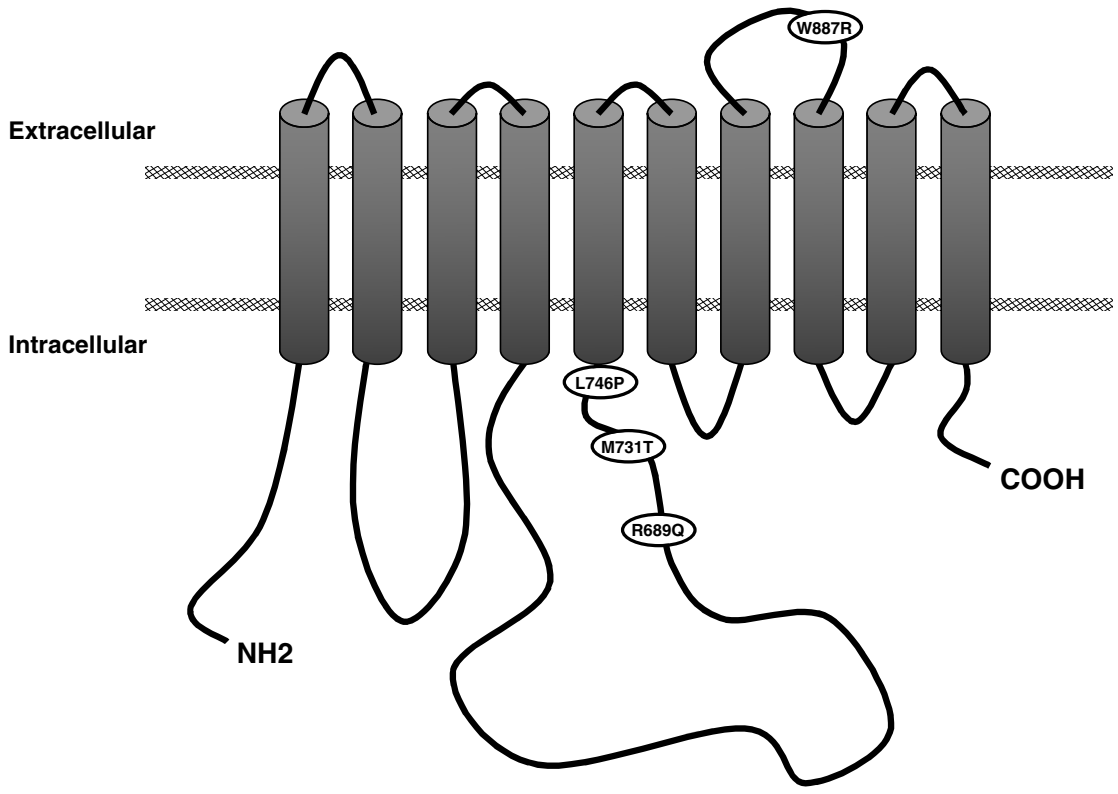

FIGURE 27-2. Predicted transmembrane model of Na^+, K^+-ATPase α_2-subunit. The location of the various mutations is indicated.

A study in a group of 105 SHM patients and their first-degree family members showed that more than half of the SHM patients had also nonhemiplegic MA attacks, and one third had additional MO attacks (175). First-degree family members of "pure SHM" patients had an increased risk of MA, whereas family members of all SHM patients together had an increased risk of both MO and MA. Another study showed that the clinical symptoms of SHM patients were more similar to FHM than MA (174).

EPISODIC ATAXIA TYPE 2 AND SPINOCEREBELLAR ATAXIA TYPE 6

Episodic ataxia type 2 (EA-2) is also referred to as acetazolamide-responsive paroxysmal cerebellar ataxia, paroxysmal vestibulocerebellar ataxia, or hereditary paroxysmal cerebellar ataxia (11). Onset is usually in childhood or early adulthood. Attacks are characterized by generalized ataxia lasting minutes to hours that may occur spontaneously or can be provoked by stress, exertion, alcohol, fever, and heat. Many patients also have interictal nystagmus and may display mild cerebellar atrophy. Up to 50% of patients experience migraine(like) symptoms during or in between attacks, or both. Magnetic resonance imaging (MRI) often reveals cerebellar atrophy (192). Attacks can be precipitated by emotional stress, exercise, or alcohol, and acetazolamide is often effective in preventing attacks. EA-2 appeared to be linked to the same interval on chromosome 19p as FHM (96,167,186,194) and was finally proved to be caused by mutations in the *CACNA1A* gene. Mutation analysis has revealed various different mutations in the *CACNA1A* calcium-channel gene in EA-2 families (see Fig. 27-1), including truncating mutations, resulting in premature stops and leading to putative aberrant CACNA1A proteins, and missense mutations (32,33,51,69,70,78,132,155,187). After several reports of new EA-2 mutations the total number is now over 20 (71,89,112,164). No *CACNA1A* mutation was identified in a family with episodic ataxia indistinguishable from EA-2, which suggests that EA-2 is a heterogeneous disorder and that other genes causing EA-2 should exist (65).

One of the EA-2 missense mutations caused additional generalized epilepsy (78), and another such mutation caused episodic weakness years before the onset of EA-2 attacks (69).

Spinocerebellar ataxia type 6 (SCA6) differs clinically from EA-2 by the presence of progressive rather than episodic ataxia (55). Six different cDNA isoforms of the *CACN1A1* gene have been reported, of which three contained a 5-nucleotide insertion before the stop codon, resulting in a shift of the open reading frame in which the

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

CAG repeat is predicted to encode a polyglutamine stretch (204). Small triplet expansions of the intragenic *CAG* repeat, ranging from 21 to 30 repeat units, were observed in SCA6 patients, whereas normal chromosomes displayed 4 to 20 repeats (68,111,148,204). The *CAG* repeat length is inversely correlated with age at onset of ataxia (68, 111,148). Anticipation of the disease was observed clinically, but intergenerational allele size change was not observed, in contrast to other SCAs, which are also caused by *CAG* repeats. Two homozygotic cases of SCA6 have been reported. The first case could not demonstrate an unequivocal gene dosage effect on age at onset (111). The second case showed an earlier age of onset and more severe clinical manifestations than her sister, a heterozygote carrying an expanded allele with the same repeat length as the homozygote. SCA6 has been estimated to occur in 10% of Germans and 30% of Japanese with SCAs (111,148).

FHM missense mutations seem by themselves (without *CAG* repeat expansions) sufficient to cause cerebellar ataxia (42,172,203). In contrast, two families with small *CAG* expansions showed paroxysmal symptoms (72). In one family with a clinical diagnosis of EA-2, a *CAG23* repeat allele gave different interictal symptoms, ranging from nystagmus only to severe progressive cerebellar ataxia. In another family, initially classified as autosomal dominant cerebellar ataxia of unknown type, an intergenerational allele size change showed that a *CAG20* allele was associated with an EA-2 phenotype and a *CAG25* allele with progressive cerebellar ataxia.

FUNCTIONAL STUDIES OF *CACNA1A* MUTATIONS

Voltage-dependent Ca^{2+} channels are key protein structures in neuronal cell membranes (reviewed in Plomp et al. [141]). They transduce electrical signals into a cellular influx of Ca^{2+}, which acts as a second messenger in many processes such as regulation of excitability, transmitter release, gene regulation, and axon growth. Ca^{2+} channels consist of a pore-forming, voltage-sensing α_1-subunit, and auxiliary β-, α_2 δ-, and γ-subunits. Several subtypes of heteromultimeric channels exist, which can be differentiated by pharmacologic and electrophysiologic criteria (i.e., N-, P/Q-, L-, R-, and T-types). The α_1-subunit consists of four homologous repeats (I to IV), each with six transmembrane segments (S1 to S6; see Fig. 27-1). The so-called P-loop between S5 and S6 is believed to form the inner lining of the ion pore. The S4 segments have been shown to be involved in voltage sensing.

The *CACNA1A* gene encodes for the pore-forming subunit, α_{1A}. Alternative splicing of *CACNA1A* yields either P- or Q-type channels (8). P/Q-type Ca^{2+} channels are widely expressed in the central nervous system (CNS), especially in the cerebellum. In cell bodies, P/Q-type Ca^{2+} channels play a role in excitability, presumably via Ca^{2+}-dependent K^+ channels. Furthermore, Ca^{2+} influx stimulates intracellular signaling pathways, mostly involving kinases, which can influence gene expression, for example. During development, P/Q-type Ca^{2+} channels appear to participate in the process of neurite initiation. At mature synaptic terminals, their main function is to mediate transmitter secretion by allowing Ca^{2+} to stimulate the release machinery complex at so-called active zones, resulting in exocytosis of synaptic vesicles. The α_{1A}-subunit contains defined sites that interact with specific presynaptic proteins (see Fig. 27-1), presumably required for targeted presynaptic localization and specific presynaptic function of P/Q-type Ca^{2+} channels. Other specific sites for interaction with β-subunits and G-proteins have been identified.

Several missense mutations associated with FHM have been analyzed with electrophysiologic techniques in neuronal and non-neuronal expression cells (reviewed in Pietrobon [140]). In earlier studies, in human and nonhuman and in neuronal and non-neuronal expression cells, FHM mutations appeared to have different effects on channel conductance, kinetics, and expression depending on the model system in which these were investigated (62,97,98). The inconsistency of the effects of mutations is illustrated by the observation that mutations *T666M* and *R192Q* induced a decreased or increased calcium influx, respectively (62). In addition, mutant *T666M* and *V714A* channels have a low-conductance mode that sometimes switches to the wild-type state (98). In a recent study, single-channel analysis with mutation *V1457L* was extended (178). This mutation increased the channel open probability by shifting its activation to more negative voltages and reduced both the unitary conductance and the density of functional channels in the membrane. To investigate the possibility of changes in channel function common to all FHM mutations, the product of single-channel current and open probability as a measure of Ca^{2+} influx through single channels was measured, and all five FHM mutants analyzed (*T666M, V714A, I1815L, R192Q,* and *V1457L*) showed a single-channel Ca^{2+} influx larger than wild-type in a broad voltage range around the threshold of activation. FHM mutations were also expressed in mouse cerebellar granule cells, and here the FHM mutations invariably led to a decrease in the maximal current density in neurons. It was concluded that mutational changes of functional channel densities can be different in different cell types, and that two functional effects common to all FHM mutations analyzed exist: increase of single-channel Ca^{2+} influx and decrease of maximal $Ca_V2.1$ current density in neurons (178).

The missense mutations in FHM suggest a molecular mechanism similar to what is found in other human channelopathies. Both alleles are likely to be expressed, with the allele harboring the missense mutation resulting in loss- or gain-of-function variants of the P/Q-type

calcium channels. Such mutations have been described in the α-subunit of the skeletal muscle sodium channel, resulting in hyperkalemic periodic paralysis, paramyotonia congenita, and the sodium channel myotonias (reviewed in Kullmann [99]).

Several EA-2 mutations have recently been studied in expression systems (57,69,78,197). Both truncating and missense mutations induced a dramatic reduction or even complete loss of current density. For *F1491S*-mutated channels, it was shown by immunohistology that this was not from a lack of membrane expression (57). Interestingly, *R1820X*-mutated channels, lacking the complete carboxyterminal intracellular domain, have a dominant-negative mode of action, presumably by disturbing the incorporation of wild-type $Ca_v2.1$ protein in the cell membrane, resulting in less functional channels (78). In contrast, CACNA1A protein harboring the *AY1593/1594D* mutation was able to form calcium channels in *Xenopus laevis* oocytes, but with pronounced loss of function (197).

The effects of SCA6-related polyglutamine expansions of $Ca_v2.1$ on the function of P/Q-type channels have also been recently analyzed (139,147,177). Shifts in (in)activation voltage were observed, of which the direction and extent depended on the used splice-variant (P- or Q-type), the length of glutamine expansion, and the presence of β_4-subunits. Immunohistochemical analysis showed an increase in intracellular and plasma membrane expression of SCA6-mutated $Ca_v2.1$ protein (139). A more than twofold increase in current density was observed, along with small hyperpolarizing shifts in activation voltage. As in FHM, a complicated pattern appears to emerge for SCA6-mutated channels, resulting in either an increased or a decreased cellular calcium influx.

STUDIES OF *CACNA1A* IN MICE AND IN NEUROMUSCULAR JUNCTIONS

A number of mammalian models with ion channel mutations exist. The animals typically exhibit a combination of seizures and ataxia. Whether any of these animal models exhibit migraine-like symptoms is obviously impossible to determine. The fact that even the nematode *Caenorhabditis elegans* genome contains close to 200 ion channel genes (4) reflects the diversity of specific signaling needs and the complexity of the family of these molecules. One might speculate that, in a multifactorial disorder such as migraine, a complex combination of seemingly minor variations in ion channel genes, combined with variations in other molecules of downstream signaling pathways, might predispose to the migraine attack. On the other hand, studies in families with a strong inheritance pattern of migraine may reveal individual genes with major influences on the predisposition.

The excitement over *CACNA1A* mutations in migraine was heightened by the discovery of mouse models that carry mutations in the corresponding mouse gene (14,40, 49,206). Unlike FHM and EA-2, which are autosomal dominant traits, the mouse traits are recessive. "Tottering" mice have motor seizures and slowly progressive ataxia beginning around the third postnatal week, whereas "leaner" mice have absence spells (brief seizures) and are severely ataxic, often not surviving past weaning. Tottering mice have a missense mutation resulting in a nonconservative (Pro600Leu) amino acid change near the second p-domain, a site putatively involved in channel formation. The more severe phenotype, leaner, is caused by a splice donor mutation, which results in truncation of the normal transcribed sequences and expression of multiple aberrant transcripts and novel C-terminal sequences in the polypeptide. This is analogous with the human mutations in which missense mutations have been detected in FHM, and the more severe phenotype EA-2 tends to have truncating mutations.

Tottering, leaner, and "rolling Nagoya" mutated P/Q-type channels have been studied in cerebellar cells and in expression/transfection systems (39,104,120,196). The main effect appears to be reduction of calcium current density. Furthermore, leaner and rolling Nagoya channel kinetics are changed, although there is some inconsistency among the leaner studies (39,104,120). Reduced calcium current in rolling Nagoya Purkinje cells aborts action potential firing, presumably resulting from insufficient recruitment of calcium-activated potassium channels for repolarization (39).

In addition, two *CACNA1A-null* mutant (knockout) mice were independently generated, showing a lethal phenotype at young age (50,81). Total calcium current density in cerebellar cells was found to be decreased. P-/Q-type currents were abolished and appeared to be partly compensated for by N- and L-type current. Cerebellar granule cells of heterozygous mice from one of the two *null* mutants displayed a 50% reduction in P-/Q-type current density (50), whereas no reduction was observed in the other model (81).

It is now generally accepted that migraine aura is caused by cortical spreading depression, a depolarization wave associated with temporary disturbance of ion balances (101). Recently it was shown that aura symptoms in some FHM patients can be abolished by the glutamate receptor antagonist ketamine (88). Because glutamate release is mediated by P-/Q-type calcium channels, it is well conceivable that *CACNA1A* mutations will influence cortical spreading depression (129). Indeed, experimentally induced cortical spreading depression in tottering and leaner mice was found altered, in parallel with a reduced release of cortical glutamate (2,16,81).

Very recently, a knockin mouse model was generated carrying the human pure *FHM-1 R192Q* mutation (188).

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

Multiple gain-of-function effects were found, including increased $Ca_v2.1$ current density in cerebellar neurons, enhanced neurotransmission at the neuromuscular junction (NMJ) and, in the intact animal, a reduced threshold and increased velocity of cortical spreading depression. These very important data show that the increased susceptibility for cortical spreading depression and aura in migraine may be due to cortical hyperexcitability. The *R192Q FHM-1* mouse appears to be a promising animal model to study migraine mechanisms and treatments.

The NMJ is a suitable model synapse in which to study *CACNA1A* mutations because motor nerve terminals contain P-type calcium channels that are responsible for acetylcholine release. Transmitter release is decreased during high-rate nerve stimulation in tottering NMJs in vitro (142). Interestingly, spontaneous quantal transmitter release was doubled. Leaner and rolling Nagoya NMJs showed a reduction of about 30% and 60%, respectively, of low-rate stimulation-evoked acetylcholine release. Similar changes may occur at brain synapses in humans with mutated *CACNA1A*-encoded protein. Furthermore, in vivo neuromuscular transmission may be compromised. Indeed, recent clinical electrophysiologic studies showed NMJ malfunction in three EA-2 patients with *CACNA1A* missense and truncation mutations (70). Single-fiber electromyography (SFEMG) demonstrated increased jitter and the occurrence of blockings in these patients. Similar findings were observed in patients with MA (1). Surprisingly, SFEMG of three SCA6 patients was unremarkable (69). In the paralytic autoimmune disorder Lambert-Eaton myasthenic syndrome, P-type Ca^{2+} channels at the NMJ are the target of autoantibodies. Interestingly, some of these patients also have ataxia and cerebellar degeneration.

OTHER HEREDITARY DISEASES FREQUENTLY ASSOCIATED WITH MIGRAINE

Several hereditary diseases are associated with migraine and can serve as models in which to search for and study migraine genes (58,119).

CADASIL is characterized by recurrent subcortical ischemic strokes, extensive white matter abnormalities on MRI, progressive subcortical dementia, and mood disorders with severe depressive episodes (23,29,37,84). Up to one third of the patients have MA (23,34,37,82,191). In one CADASIL family, 4 of 10 affected members demonstrated by MRI had cooccurrence with FHM, and one member unaffected on MRI had FHM (67). Initially, CADASIL and FHM were considered to be allelic because the CADASIL locus was mapped to chromosome 19p12 (179). Further linkage studies revealed that the loci were separate (36), and later studies showed mutations in the *NOTHC3* gene in CADASIL (75,84,108). Although CADASIL and FHM are genetically unrelated, the question remains of why MA occurs so frequently in CADASIL. The relation of migraine and CADASIL is further underlined by the finding of families linked to the CADASIL locus, in which patients have MRI white matter lesions and attacks of MA, but without ischemic stroke (20,22).

Migraine was one of the prominent features in a large family with vascular retinopathy and Raynaud phenomenon (168). The disease was recently linked to chromosome 3p21.1-p21.3 (131).

Mosewich et al. (121) reported a family with a typical mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (*MELAS*) point mutation, with migraine, rather than stroke-like episodes, as the major finding. Sano et al. (154) reported a Japanese family with features from both *MELAS* and mitochondrial disease, myoclonic epilepsy with ragged-red fibers (*MERRF*), with migraine as one of the prominent symptoms. Migraine has been associated more often with *MELAS* and *MERRF* (91). A recent description of segregation of familiar cases of migraine in a family with the Leber *T14484C* mutation (27) adds to these previous clinical observations of migraine in patients with various mitochondrial DNA mutations. However, no point mutations or large-scale deletions were found in 23 Germans with sporadic MA (91), excluding a significant role of mitochondrial genome mutations in white patients with migraine. A point mutation in mitochondrial nucleotide 11084 was found in 25% (13 of 53) of Japanese migraineurs but in none of 39 normal subjects or 60 tension-type headache sufferers (157). This, but no other mutation, was detected in several other studies from different countries (59,60,150). Mitochondrial mutations might therefore explain some cases of migraine in Japanese but is unlikely to play an important role worldwide.

An interesting observation was made in the so-called cyclic vomiting syndrome (CVS), which is recently included in the second edition of the international classification of headache disorders as one of the childhood periodic syndromes that are commonly precursors of migraine. The origin is thought to be mitochondrial. A survey of parents of 62 children with a severe form of CVS showed that migraine, myopathy, seizures, and dysautonomia-like symptoms were far more common in matrilineal versus nonmatrilineal relatives (7). Mitochondrial DNA sequence variants are probable risk factors in most children at this "severe" end of the CVS spectrum, and migraine appears to be part of the phenotype (28).

Pseudomigraine with lymphocytic pleocytosis is characterized by episodic neurologic dysfunction associated with headache and cerebrospinal fluid lymphocytic pleocytosis. Because cerebrospinal fluid lymphocytic pleocytosis can occur in atypical FHM attacks and both

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

pseudomigraine and FHM can be triggered by angiography, the *CACNA1A* gene was studied as a candidate gene (24). No mutation, however, was found in eight patients.

LINKAGE AND ASSOCIATION STUDIES OF MO AND MA

The inherent feature of locus heterogeneity in complex traits contributes to the fact that linkage studies for migraine are challenging. Several studies assigning susceptibility loci for common forms of migraine have been published, but none of these studies has provided as conclusive evidence for a true susceptibility gene as *CACNA1A* in the case of FHM (Table 27-1). Study samples in attempts to find linkage for more common forms of migraine have varied significantly. Some of the studies have focused on one or only a few large families, whereas others have used relatively large numbers of medium-sized families. Moreover, phenotypic information is scanty in all these studies, and they are therefore difficult to compare. It is noteworthy that none of the loci assigned by linkage studies in common forms of migraine (MA, MO, or MA/MO) has thus far been independently unambiguously replicated, nor have any gene mutations from these loci been published. Despite these caveats, well-designed linkage studies performed with critical statistical analyses provide a powerful tool to tackle susceptibility loci for migraine and potentially to identify susceptibility genes and novel metabolic pathways.

Association studies have used polymorphisms of candidate genes and have looked for overrepresentation of specific alleles in migraine samples from the general population. Many studies have provided significant or suggestive associations. However, none of them has provided conclusive evidence of a specific risk allele for MA or MO. Several groups have performed linkage and association studies of the *CACNA1A* gene, serotonin transporter gene, and dopamine receptor gene, which are discussed separately.

TABLE 27-1 Migraine Genes or Loci With Significant Linkage or Mutations

Genes/Loci	*Reference*
CACNA1A (chromosome 19p13)	132
Chromosome 1q	43
NOTCH3 CADASIL gene	75
Neurovascular gene 3p21	131
4q24/4q21	6,198
6p12.2-p21.1	18
14q21.2-q22.3	159
11q24	17

TABLE 27-2 Positive Association Studies in Migraine

Locus/Gene	*Reference*
Group-specific component locus	135
Esterase D locus	135
HLA-DR2	110
Tumor necrosis factor B gene	109,180
Angiotensin-converting enzyme gene	136
Methylenetetrahydrofolate reductase gene	86,95
Endothelin type A receptor gene	181
Catechol-*O*-methyltransferase gene	46
Interleukin-1α gene	143
Xq24-28-linked gene	127
Insulin receptor gene	74,115
LDRL gene	117
Glutathione S-transferase gene	100
Tumor necrosis factor gene	144
Serotonin receptor gene	See text
Dopamine D_2 receptor gene	See text

For an overview of the many other association studies in migraine, see Table 27-2.

THE *CACNA1A* GENE

After the identification of the *CACNA1A* gene, the more challenging step has been investigation of its role in the common types of migraine. As mentioned, some mutation carriers in FHM families have attacks of MA or MO (42,170).

Several classical linkage studies have been performed. A Finnish study did not find linkage to chromosome 19 in four multigenerational families with MO and MA (66). An Australian study included several multigenerational families (128). One large tested family showed both cosegregation and significant allele sharing for markers located in or adjacent to the FHM migraine locus. Other tested families showed neither cosegregation nor excess allele sharing to chromosome 19 markers. An American family with dominantly inherited migraine, episodic vertigo, and essential tremor that responded to acetazolamide did not link to chromosome 19p13 (3). A recent Canadian study found no evidence for linkage in 64 MA families (124). It is therefore very unlikely that *CACNA1A* mutations will be found in many families with MO or MA. However, this does not exclude at all the hypothesis that dysfunction of biochemical pathways in which the gene product (neuronal calcium-channel subunit) is involved may also be involved in the mechanisms for migraine in general.

A German–Dutch affected sibling-pair analysis of 28 families suggests that the *CACNA1A* gene on chromosome 19p13 is involved in MO and MA (114). The maximal multipoint LOD score was 1.29 ($P \approx .013$), but the major

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

contribution was made by one large family. The results were inconclusive with respect to the relative importance in MO and MA, respectively. Subsequently, a larger second and independent affected sibling-pair analysis involving 36 extended Dutch families with MO and MA showed significant increased sharing of the marker alleles in sibs with MA (172). No such increased sharing was found for MO. A combined analysis for both migraine types, including sibling pairs in which one had MO and the other MA, resulted in increased allele sharing. The relative risk ratio for a sibling (λ_s) to suffer from MA, defined as the increase in risk for the trait attributable to the 19p13 locus, was $\lambda_s = 2.4$. When MO and MA were combined, λ_s was 1.25. When the results of both studies were combined, the maximal multipoint LOD score increased to 2.27 ($P \approx .001$).

A recent mutation analysis in an Australian family with MA and MO linked to the *CACNA1A* region revealed no disease-causing mutation or associated polymorphism in the *CACNA1A* gene (102), nor did an Italian study in sporadic migraine patients (12). In the Australian study, association was tested with two microsatellite markers within the gene, but no significant association was found. This study, however, does not exclude involvement of *CACNA1A* in typical migraine, because the gene is very large and a significant positive association is found only if the marker is in linkage disequilibrium and thus closely linked to the disease-causing mutation. Not surprisingly, the *T666M* mutation and five other FHM mutations were not identified in a group of 143 "normal," nonhemiplegic migraine patients (199).

Recently, two studies focusing on the dissection of the chromosome 19p area in MA were published (74,115). These studies suggest that the locus linked to MA is distinct from the FHM locus and that specific alleles in the insulin-receptor gene would be associated with MA. In a set of 16 families, the maximal LOD score peaked at the insulin-receptor locus. Surprisingly for a complex trait, the authors found that the θ value, reflecting the locus homogeneity of the study sample, was 0.99, indicating that all families contribute to the linkage in this region. This is uncommon in any complex trait and has not been found in any other studies in any non-Mendelian disorder. McCarthy et al. (115) found some evidence for association of migraine with aura with polymorphisms in the insulin receptor gene in two United States populations from the San Francisco area. However, these associations were inconsistent, found only for one SNP and only for MO in an Australian control sample and not found at all in an independent British control sample. Furthermore, there was no check for the Hardy–Weinberg equilibrium nor correction for multiple testing. A confirmation of this potentially interesting finding would be welcome.

Future direct mutation analysis of persons with MO and MA will establish the precise role of the calcium-channel gene in these conditions.

THE SEROTONIN SYSTEM

Serotonin is implicated in migraine pathophysiology (158). More than a dozen different 5-HT signal-mediating receptors have been described. Most of them belong to the metabotropic type of receptor, being composed of a single polypeptide that transmits their action through G-proteins. The only exception is the 5-HT_3 receptor type, which is a ionotropic receptor permeable to sodium and potassium ions. Interestingly, this receptor is coded by a single gene on chromosome 11q22 and forms a homomeric complex composed of five copies of the same subunit, a relatively unique structure for neurotransmitter receptors.

Several studies investigated an association between 5-HT genes and migraine. Most of the studies were negative. No association was found with receptor-type 5-HT_{2A} (13,80,118,126), 5-HT_{2C} (13,15,73), 5-HT_{1D} (118), 5-HT_{1B} (106,118), 5HT_{SERT} (118), and 5-HT_{1F} (106).

On the other hand, a Danish–Scottish association study found an association of MO and MA with 5-HT_{SERT}(130), and Turkish studies found an association between a *T102C* polymorphism in the 5-HT_{2A} receptor gene (45), and with the serotonin transporter 2.10 allele (201). A short/short type 5-HTTLPR polymorphism in the 5-HT transporter gene was associated with frequency of attacks in migraine patients, whereas the short/long and long/long types were not (94).

DOPAMINE D_2 RECEPTOR GENE

A number of data support a role for dopamine in the pathophysiology of certain subtypes of migraine (163). Moreover, many symptoms, such as nausea, vomiting, and hypotension, suggest that brainstem dopaminergic neurotransmission is involved in the migraine attack. Further support for the involvement of the dopaminergic system in migraine has evolved from the finding that dopamine antagonists are effective in the treatment of migraine symptoms.

Peroutka et al. (137,138) studied the association of an intragenic polymorphism in the dopamine D_2 receptor (DRD_2) in 129 unrelated MO (77) and MA (52) patients and 121 controls, and in MA patients with anxiety and depression. These investigators found an excess of an Nco I polymorphic allele in MA, with or without anxiety and depression, compared to controls and MO. Del Zompo et al. (31) studied 50 nuclear families affected with MO from the island of Sardinia, divided into nondopaminergic (35) and dopaminergic (31) probands, and analyzed them by the Transmission Disequilibrium Test (TDT) to dopamine receptors D_2, D_3, and D_4 (31). The subgroup of dopaminergic migraineurs was selected on the basis of both yawning and nausea immediately before or during the pain phase of migraine. No association was detected

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

with intragenic polymorphisms in DRD_3 or DRD_4 to MO. However, in the dopaminergic subgroup of migraine, an allelic association to DRD_2 was detected. The association vanished when the DRD_2 polymorphism was analyzed in the entire set of MO individuals. Both of these studies have their merits as well as methodologic weaknesses. In the study by Peroutka et al. (137,138), only scanty information was provided about patient phenotypes and genetic background. On the other hand, the study by Del Zompo et al. (31) had an almost optimal population design utilizing a genetic isolate and modern methodology, but subgrouping of patients resulted in quite small patient sets. A German group found no association of MA with DRD_2 Nco I (35), and another group did not find an association with the DRD_2–141C Ins/Del polymorphism (113). Therefore, it is not possible to make a definitive conclusion about the role of the DRD_2 locus on the basis of these studies. Sheperd et al. (156) found no association between migraine and DRD_1, DRD_3, and DRD_5.

THE X CHROMOSOME

An unequal gender distribution with a female dominance is a well-known finding in both MA and MO (146,160). There is also evidence of a higher frequency of migraineurs in first-degree relatives of male probands (152,162). These findings have stimulated studies of a possible involvement of X-chromosomal loci in migraine etiology. Nyholt et al. (127) reported on a limited genome scan using 28 X-chromosomal markers. In four large Australian migraine families, these authors found a significant excess of allele sharing and suggestive evidence for linkage on a relatively large area on chromosome Xq. Although the clinical information provided was limited, the families represented rather common migraine forms with both MA and MO individuals. Interestingly, one family also showed linkage to the 1q31 FHM locus. Further studies are necessary to confirm the role of X-chromosomal loci in genetic predisposition to migraine.

GENOME-WIDE SCANS

During the last 2 years, several successful linkage studies have been conducted in migraine. First, a genome-wide scan of MA was performed, using 50 medium-sized families from Finland (198). The families were selected on the basis of strong representation of MA in all generations. Although MA was the overwhelmingly predominant phenotype, many families had some members with MO. In selecting families for this study, there was a strong bias toward severe phenotypes because the probands were identified from headache clinics rather than from the general population or from general practitioner offices. A linkage for the MA phenotype to a rather broad region on chromosome 4q24 was detected. The α value, reflecting the number of families contributing to the linkage, was 30 to 50%. In subsequent family samples an α value of about 30% has been observed, suggesting that about one third of the families might have a predisposing variant in this region (unpublished data). This chromosomal area does not contain any known ion channel genes, which would be obvious candidates in which to search for predisposing sequence variants. However, several genes localized to this region are expressed in the CNS and are therefore candidates for further research. Bjornsson et al. (6) were able to confirm linkage to chromosome 4q21 in Icelandic MO families. By combining their impressive patient resources and unique Icelandic genealogy database, they were able to identify 103 families with 289 MO patients. Genome-wide scanning revealed a locus on chromosome 4q21 that shows overlap with the Finnish locus. Interestingly, the LOD score increased when the sample set was reanalyzed using affected females only, and allowing a relaxed definition of MO. This might be explained, according to the researchers, by the higher preponderance in females. Future identification of one or two migraine genes on 4q21 will have to show the contribution to MO and MA.

In a Canadian linkage study a genome-wide screen was conducted in 43 MA families that were selected because of an apparent autosomal-dominant pattern of transmission (17). A novel susceptibility locus was identified on chromosome 11q24. No evidence was obtained for linkage to any of the known migraine loci on chromosomes 1, 4, and 19, confirming that there is genetic heterogeneity for MA.

In addition to linkage analysis in multifamily studies, two mapping studies were reported in single families. A large Italian MO pedigree revealed significant evidence of linkage on chromosome 14q22 (159). In a large Swedish family with MO and MA, linkage was obtained for a novel locus on chromosome 6p12.2-p21.1 (18). Like the Icelandic study, they allowed a relaxed definition of MO in about half of the MO patients. Additional studies should investigate the contribution of both loci to migraine in the general population.

IS MIGRAINE A CHANNELOPATHY?

Although still circumstantial, there is some striking clinical, genetic, neurophysiologic, and neuropharmacologic evidence that typical migraine might be, at least in part, a channelopathy (122). Migraine shares with proven neurologic and neuromuscular channelopathies a number of clinical characteristics: both are present in attacks of usually several hours to days that may be provoked by specific trigger factors; there is a gender-related expression; onset usually is around puberty, and amelioration after the age of 40; finally, migraine, basilar migraine, and the

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

TABLE 27-3 Genetics of Migraine: Summary of Main Findings

Family and twin studies point to genetic contribution
Multifactorial mode of inheritance
Only migraine gene thus far is *CACNA1A,* in FHM, but probably also in MO and MA
FHM is allelic with EA-2 and SCA6
Functional studies with *CACNA1A* mutations still inconclusive
Many other genes are suggested (see Tables 27-1 and 27-2)
Much research is still needed

proven channelopathic FHM have identical headache and aura symptoms (apart from the hemiplegia) and coexist in patients (61,173). Genetic evidence includes the demonstrated involvement of the *CACNA1A* gene in at least subpopulations of migraine: classical linkage in an Australian family (128), FHM *CACNA1A* mutations in patients with migraine but without FHM (42,170), and increased sharing of the *CACNA1A* locus with migraine in two independent sibling-pair analyses (114,172). Neurophysiologic evidence includes the demonstration of subclinical single-fiber abnormalities (1). Finally, neuropharmacologic evidence comes from the observations that certain P-/Q-type calcium-channel blockers interfere with putative basic migraine mechanisms: α-eudesmol blocks the release of calcitonin gene-related peptide and neurogenic plasma extravasation, and administration of Ω-agatoxin in the periaquaductal gray facilitates firing of the trigeminal nucleus caudalis.

CONCLUSIONS

The identification of the first "migraine gene," *CACNA1A* in FHM, has introduced a new point of view into the area of migraine research, characterizing migraine as a channelopathy in at least some subtypes (Table 27-3). In the spectrum of *CACNA1A* -related disorders, FHM is only one of many neurologic (paroxysmal) disorders. Although MO and MA can be considered part of this *CACNA1A* spectrum, there have been conflicting results about the precise role of the *CACNA1A* gene in susceptibility to typical migraine.

REFERENCES

1. Ambrosini A, Maertens De Noordhout, et al. Neuromuscular transmission in migraine: a single-fiber EMG study in clinical subgroups. *Neurology*. 2001;56:1038–1043.
2. Ayata C, Shimizu-Sasamata M, Lo EH, et al. Impaired neurotransmitter release and elevated threshold for cortical spreading depression in mice with mutations in the alpha1A subunit of P/Q type calcium channels. *Neuroscience*. 2000;95:639–645.
3. Baloh RW, Foster CA, Yue Q, et al. Familial migraine with vertigo and essential tremor. *Neurology*. 1996;46:458–460.
4. Bargmann CI. Neurobiology of the *Caenorhabditis elegans* genome. *Science*. 198;282:2028–2033.
5. Battistini S, Stenirri S, Piatti M, et al. A new CACNA1A gene mutation in acetazolamide-responsive familial hemiplegic migraine and ataxia. *Neurology*. 1999;53:38–43.
6. Bjornsson A, Gudmundsson G, Gudfinnsson E, et al. Localization of a gene for migraine without aura to chromosome 4q21. *Am J Hum Genet*. 2003;73:986–993.
7. Boles RG, Adams K, Ito M, et al. Maternal inheritance in cyclic vomiting syndrome with neuromuscular disease. *Am J Med Genet*. 2003;120A:474–482.
8. Bourinet E, Soong TW, Sutton K, et al. Splicing of alpha 1A subunit gene generates phenotypic variants of P- and Q-type calcium channels. *Nat Neurosci*. 1999;2:407–415.
9. Bradbury J. Second gene identified for familial hemiplegic migraine. *Lancet Neurol*. 2003;2:137.
10. Bradshaw P, Parsons M. Hemiplegic migraine, a clinical study. *Q J Med*. 1965;34:65–85.
11. Brandt T, Strupp M. Episodic ataxia type 1 and 2 (familial periodic ataxia/vertigo). *Audiol Neurootol*. 1997;2:373–383.
12. Brugnoni R, Leone M, Rigamonti A, et al. Is the CACNA1A gene involved in familial migraine with aura? *Neurol Sci*. 2002;23: 1–5.
13. Buchwalder A, Welch SK, Peroutka SJ. Exclusion of 5-HT2A and 5-HT2C receptor genes as candidate genes for migraine. *Headache*. 1996;36:254–258.
14. Burgess DL, Jones JM, Meisler MH, et al. Mutation of the Ca2+ channel beta subunit gene Cchb4 is associated with ataxia and seizures in the lethargic (lh) mouse. *Cell*. 1997;88:385–392.
15. Burnet PW, Harrison PJ, Goodwin GM, et al. Allelic variation in the serotonin 5-HT2C receptor gene and migraine. *Neuroreport*. 1997;18:2651–2653.
16. Caddick SJ, Wang C, Fletcher CF, et al. Excitatory but not inhibitory synaptic transmission is reduced in lethargic (Cacnb4(Lh)) and tottering (Cacna1atg) mouse thalami. *J Neurophysiol*. 1999;81:2066–2074.
17. Cader ZM, Noble-Topham S, Dyment DA, et al. Significant linkage to migraine with aura on chromosome 11q24. *Hum Mol Genet*. 2003;12:2511–2517.
18. Carlsson A, Forsgren L, Nylander PO, et al. Identification of a susceptibility locus for migraine with and without aura on 6p12.2-p21.1. *Neurology*. 2002;59:1804–1807.
19. Carrera P, Piatti M, Stenirri S, et al. Genetic heterogeneity in Italian families with familial hemiplegic migraine. *Neurology*. 1999;53:26–33.
20. Ceroni M, Poloni TE, Tonietti S, et al. Migraine with aura and white matter abnormalities: Notch3 mutation. *Neurology*. 2000;54:1869–1871.
21. Cevoli S, Pierangeli G, Monari L, et al. Familial hemiplegic migraine: clinical features and probable linkage to chromosome 1 in an Italian family. *Neurol Sci*. 2002;23:7–10.
22. Chabriat H, Tournier Lasserve E, Vahedi K, et al. Autosomal dominant migraine with MRI white-matter abnormalities mapping to the CADASIL locus. *Neurology*. 1995;45:1086–1091.
23. Chabriat H, Vahedi K, Iba Zizen MT, et al. Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [see comments]. *Lancet*. 1995;7:934–939.
24. Chapman KM, Szczygielski BI, Toth C, et al. Pseudomigraine with lymphocytic pleocytosis: a calcium channelopathy? Clinical description of 10 cases and genetic analysis of the familial hemiplegic migraine gene CACNA1A. *Headache*. 2003;43:892–895.
25. Chioza B, Wilkie H, Nashef L, et al. Association between the alpha(1a) calcium channel gene CACNA1A and idiopathic generalized epilepsy. *Neurology*. 2001;56:1245–1246.
26. Clarke JM. On recurrent motor paralysis in migraine. *BMJ*. 1910;1:1534–1538.
27. Cupini LM, Massa R, Floris R, et al. Migraine-like disorder segregating with mtDNA 14484 Leber hereditary optic neuropathy mutation. *Neurology*. 2003;60:717–719.
28. Cupini LM, Santorelli FM, Iani C, et al. Cyclic vomiting syndrome, migraine, and epilepsy: a common underlying disorder? *Headache*. 2003;43:407–409.
29. Davous P. CADASIL: a review with proposed diagnostic criteria. *Eur J Neurol*. 1998;5:219–233.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

30. De Fusco M, Marconi R, Silvestri L, et al. Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nat Genet*. 2003;33: 192–196.
31. Del Zompo M, Cherchi A, Palmas MA, et al. Association between dopamine receptor genes and migraine without aura in a Sardinian sample. *Neurology*. 1998;51:781–786.
32. Denier C, Ducros A, Durr A, et al. Missense CACNA1A mutation causing episodic ataxia type 2. *Arch Neurol*. 2001;58:292–295.
33. Denier C, Ducros A, Vahedi K, et al. High prevalence of CACNA1A truncations and broader clinical spectrum in episodic ataxia type 2. *Neurology*. 1999;52:1816–1821.
34. Desmond DW, Moroney JT, Lynch T, et al. The natural history of CADASIL: a pooled analysis of previously published cases. *Stroke*. 1999;30:1230–1233.
35. Dichgans M, Forderreuther S, Dieterich M, et al. The D2 receptor Nco1 allele: absence of allelic association with migraine with aura. *Neurology*. 1998;51:928.
36. Dichgans M, Mayer M, Muller Myhsok B, et al. Identification of a key recombinant narrows the CADASIL gene region to 8 cM and argues against allelism of CADASIL and familial hemiplegic migraine. *Genomics*. 1996;15:151–154.
37. Dichgans M, Mayer M, Uttner I, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol*. 1998;44:731–739.
38. Diriong S, Lory P, Williams ME, et al. Chromosomal localization of the human genes for alfa1A, alfa1B, and alfa1E voltage-dependent Ca2+ channel subunits. *Genomics*. 1995;30:605–609.
39. Dove LS, Abbott LC, Griffith WH. Whole-cell and single-channel analysis of P-type calcium currents in cerebellar Purkinje cells of leaner mutant mice. *J Neurosci*. 1998;18:7687–7699.
40. Doyle J, Ren X, Lennon G, et al. Mutations in the Cacnl1a4 calcium channel gene are associated with seizures, cerebellar degeneration, and ataxia in tottering and leaner mutant mice. *Mammal Genome*. 1997;8:113–120.
41. Ducros A, Denier C, Joutel A, et al. Recurrence of the T666M calcium channel CACNA1A gene mutation in familial hemiplegic migraine with progressive cerebellar ataxia. *Am J Hum Genet*. 1999;64:89–98.
42. Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *N Engl J Med*. 2001;345:17–24.
43. Ducros A, Joutel A, Vahedi K, et al. Mapping of a second locus for familial hemiplegic migraine to 1q21-q23 and evidence of further heterogeneity. *Ann Neurol*. 1997;42:885–890.
44. Elliott MA, Peroutka SJ, Welch S, et al. Familial hemiplegic migraine, nystagmus, and cerebellar atrophy. *Ann Neurol*. 1996;39:100–106.
45. Erdal ME, Herken H, Yilmaz M, et al. Association of the T102C polymorphism of 5-HT2A receptor gene with aura in migraine. *J Neurol Sci*. 2001;188:99–101.
46. Erdal E, Herken H, Yilmaz M, et al. Significance of the catechol-O-methyltransferase gene polymorphism in migraine. *Brain Res Mol Brain Res*. 2001;94:193–196.
47. Ferrari MD. Migraine. *Lancet*. 1998;351:1043–1051.
48. Fitzsimons RB, Wolfenden WH. Migraine coma. *Brain*. 1985;108: 555–577.
49. Fletcher CF, Lutz CM, O'Sullivan TN, et al. Absence epilepsy in tottering mutant mice is associated with calcium channel defects. *Cell*. 1996;87:607–617.
50. Fletcher CF, Tottene A, Lennon VA, et al. Dystonia and cerebellar atrophy in Cacna1a null mice lacking P/Q calcium channel activity. *FASEB J*. 2001;15:1288–1290.
51. Friend KL, Crimmins D, Phan TG, et al. Detection of a novel missense mutation and second recurrent mutation in the CACNA1A gene in individuals with EA-2 and FHM. *Hum Genet*. 1999;105:261–265.
52. Gardner K. The genetic basis of migraine: how much do we know? *Can J Neurol Sci*. 1999(Suppl 3);S37–43.
53. Gardner K, Barmada MM, Ptacek LJ, et al. A new locus for hemiplegic migraine maps to chromosome 1q31. *Neurology*. 1997;49: 1231–1238.
54. Gervil M, Ulrich V, Kyvik KO, et al. Migraine without aura: a population-based twin study. *Ann Neurol*. 1999;46:606–611.
55. Geschwind DH, Perlman S, Figueroa KP, et al. Spinocerebellar ataxia type 6. Frequency of the mutation and genotype-phenotype correlations. *Neurology*. 1997;49:1247–1251.
56. Griffiths LR, Nyholt DR, Curtain RP, et al. Migraine association and linkage studies of an endothelial nitric oxide synthase (NOS3) gene polymorphism. *Neurology*. 1997;49:614–617.
57. Guida S, Trettel F, Pagnutti S, et al. Complete loss of P/Q calcium channel activity caused by a CACNA1A missense mutation carried by patients with episodic ataxia type 2. *Am J Hum Genet*. 2001;68: 759–764.
58. Haan J, Terwindt GM, Ferrari MD. Genetics of migraine. *Neurol Clin*. 1997;15:43–60.
59. Haan J, Terwindt GM, Maassen JA, et al. Screening for mtDNA mutations in migraine patients. *Cephalalgia*. 1997;17:329–330.
60. Haan J, Terwindt GM, Maassen JA, et al. Search for mitochondrial DNA mutations in migraine subgroups. *Cephalagia*. 1999;19: 20–22.
61. Haan J, Terwindt G, Ophof R, et al. Is familial hemiplegic migraine a hereditary form of basilar migraine? *Cephalalgia*. 1995;15:477–481.
62. Hans M, Luvisetto S, Williams ME, et al. Functional consequences of mutations in the human alpha1A calcium channel subunit linked to familial hemiplegic migraine. *J Neurosci*. 1999;19:1610–1619.
63. Headache Classification Committee of the International Headache S. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*. 1988;8:1–96.
64. Heyck H. Varieties of hemiplegic migraine. *Headache*. 1973;12:135–142.
65. Hirose H, Arayama T, Takita J, et al. A family of episodic ataxia type 2: no evidence of genetic linkage to the CACNA1A gene. *Int J Mol Med*. 2003;11:187–189.
66. Hovatta I, Kallela M, Farkkila M, et al. Familial migraine: exclusion of the susceptibility gene from the reported locus of familial hemiplegic migraine on 19p. *Genomics*. 1994;23:707–709.
67. Hutchinson M, O'Riordan J, Javed M, et al. Familial hemiplegic migraine and autosomal dominant arteriopathy with leukoencephalopathy (CADASIL). *Ann Neurol*. 1995;38:817–824.
68. Ishikawa K, Tanaka H, Saito M, et al. Japanese families with autosomal dominant pure cerebellar ataxia map to chromosome 19p13.1-p13.2 and are strongly associated with mild CAG expansions in the spinocerebellar ataxia type 6 gene in chromosome 19p13.1. *Am J Hum Genet*. 1997;61:336–346.
69. Jen J, Wan J, Graves M, et al. Loss-of-function EA2 mutations are associated with impaired neuromuscular transmission. *Neurology*. 2001;57:1843–1848.
70. Jen J, Yue Q, Nelson SF, et al. A novel nonsense mutation in CACNA1A causes episodic ataxia and hemiplegia. *Neurology*. 1999; 53:34–37.
71. Jen J, Kim GW, Baloh RW. Clinical spectrum of episodic ataxia type 2. *Neurology*. 2004;62:17–22.
72. Jodice C, Mantuano E, Veneziano L, et al. Episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) due to CAG repeat expansion in the CACNA1A gene on chromosome 19p. *Hum Mol Genet*. 1997;6:1973–1978.
73. Johnson MP, Lea RA, Curtain RP, et al. An investigation of the 5-HT2C receptor gene as a migraine candidate gene. *Am J Med Genet B Neuropsychiatr Genet*. 2003;117:86–89.
74. Jones KW, Ehm MG, Pericak-Vance MA, et al. Migraine with aura susceptibility locus on chromosome 19p13 is distinct from the familial hemiplegic migraine locus. *Genomics*. 2001;78:150–154.
75. Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383:707–710.
76. Joutel A, Bousser MG, Biousse V, et al. A gene for familial hemiplegic migraine maps to chromosome 19. *Nature Genet*. 1993;5: 40–45.
77. Joutel A, Ducros A, Vahedi K, et al. Genetic heterogeneity of familial hemiplegic migraine. *Am J Hum Genet*. 1994;55:1166–1172.
78. Jouvenceau A, Eunson LH, Spauschus A, et al. Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. *Lancet*. 2001;358:801–807.
79. Juel-Nielsen N. Individual and environmental. A psychiatric investigation of monozygotic twins reared apart. *Acta Psychiatr Scand*. 1964;40:1–292.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

80. Juhasz G, Zsombok T, Laszik A, et al. Association analysis of 5-HTTLPR variants, 5-HT(2A) receptor gene 102T/C polymorphism and migraine. *J Neurogenet*. 2003;17:231–240.
81. Jun K, Piedras-Renteria ES, Smith SM, et al. Ablation of P/Q-type Ca(2+) channel currents, altered synaptic transmission, and progressive ataxia in mice lacking the alpha(1A)-subunit. *Proc Natl Acad Sci U S A*. 1999;96:15245–15250.
82. Jung HH, Bassetti C, Tournier Lasserve E, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: a clinicopathological and genetic study of a Swiss family. *J Neurol Neurosurg Psychiatry*. 1995;59:138–143.
83. Kalfakis N, Panas M, Vassilopoulos D, et al. Migraine with aura: segregation analysis and heritability estimation. *Headache*. 1996;36: 320–322.
84. Kalimo H, Ruchoux MM, Viitanen M, et al. CADASIL: a common form of hereditary arteriopathy causing brain infarcts and dementia. *Brain Pathol*. 2002;12:371–384.
85. Kallela M, Wessmann M, Farkkila M, et al. Clinical characteristics of migraine concordant monozygotic twin pairs. *Acta Neurol Scand*. 1999;100:254–259.
86. Kara I, Sazci A, Ergul E, et al. Association of the C677T and A1298C polymorphisms in the 5,10 methylenetetrahydrofolate reductase gene in patients with migraine risk. *Brain Res Mol Brain Res*. 2003;111:84–90.
87. Karger AG, Alonso I, Barros J, et al. Basel. Phenotypes of spinocerebellar ataxia type 6 and familial hemiplegic migraine caused by a unique CACNA1A missense mutation in patients from a large family. *Arch Neurol*. 2003;60:610–614.
88. Kaube H, Herzog J, Kaufer T, et al. Aura in some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. *Neurology*. 2000;55:139–141.
89. Kaunisto MA, Harno H, Kallela M, et al. Novel splice site CACNA1A mutation causing episodic ataxia type 2. *Neurogenetics*. 2003;5:69–73.
90. Keryanov S, Gardner KL. Physical mapping and characterization of the human Na, K-ATPase isoform, ATP1A4. *Gene*. 2002;292: 151–166.
91. Klopstock T, May A, Seibel P, et al. Mitochondrial DNA in migraine with aura. *Neurology*. 1996;46:1735–1738.
92. Kors EE, Haan J, Giffin NJ, et al. Expanding the phenotypic spectrum of the CACNA1A gene T666M mutation: a description of five FHM families. *Arch Neurol*. 2003;60:684–688.
93. Kors E, Terwindt GM, Vermeulen FLMG, et al. Delayed cerebral edema and fatal coma after minor head trauma: role of the CACNA1A calcium channel subunit gene and relationship with familial hemiplegic migraine. *Ann Neurol*. 2001;49:753–760.
94. Kotani K, Shimomura T, Shimomura F, et al. A polymorphism in the serotonin transporter gene regulatory region and frequency of migraine attacks. *Headache*. 2002;42:893–895.
95. Kowa H, Yasui K, Takeshima T, et al. The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. *Am J Med Genet*. 2000;96:762–764.
96. Kramer PL, Yue Q, Gancher ST, et al. A locus for the nystagmus-associated form of episodic ataxia maps to an 11-cM region on chromosome 19p. *Am J Hum Genet*. 1995;57:182–185.
97. Kraus RL, Sinnegger MJ, Glossmann H, et al. Familial hemiplegic migraine mutations change alpha1A Ca2+ channel kinetics. *J Biol Chem*. 1998;6:5586–5590.
98. Kraus RL, Sinnegger MJ, Koschak A, et al. Three new familial hemiplegic migraine mutants affect P/Q-type Ca2+ channel kinetics. *J Biol Chem*. 2000;275:9239–9243.
99. Kullmann DM. The neuronal channelopathies. *Brain*. 2002;125: 1177–1195.
100. Kusumi M, Ishizaki K, Kowa H, et al. Glutathione S-transferase polymorphisms: susceptibility to migraine without aura. *Eur Neurol*. 2003;49:218–222.
101. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. *Brain*. 1994;117:99–210.
102. Lea RA, Curtain RP, Hutchins RP, et al. Investigation of the CACNA1A gene as a candidate for typical migraine susceptibility. *Am J Med Genet*. 2001;105:707–712.
103. Lea RA, Sheperd AG, Curtain RP, et al. A typical migraine susceptibility region localizes to chromosome 1q31. *Neurogenetics*. 2002;4:17–22.
104. Lorenzon NM, Lutz CM, Frankel WN, et al. Altered calcium channel currents in Purkinje cells of the neurological mutant mouse leaner. *J Neurosci*. 1998;18:4482–4489.
105. Lory P, Ophoff RA, Nahmias J. Towards a unified nomenclature describing voltage-gated calcium channel genes. *Hum Genet*. 1997;100:149–150.
106. Maassen VanDenBrink A, Vergouwe MN, et al. Chromosomal localization of the 5-HT1F receptor gene: no evidence for involvement in response to sumatriptan in migraine patients. *Am J Med Genet*. 1998;77:415–20.
107. Marconi R, De Fusco M, Aridon P, et al. Familial hemiplegic migraine type 2 is linked to 0.9Mb region on chromosome 1q23. *Ann Neurol*. 2003;53:376–81.
108. Markus HS, Martin RJ, Simpson MA, et al. Diagnostic strategies in CADASIL. *Neurology*. 2002;59:1134–1138.
109. Martelletti P, Brioli G, Lulli P, et al. Tumor necrosis factor B gene polymorphism contributes to susceptibility to migraine without aura. *J Headache Pain*. 2000;2:119–122.
110. Martelletti P, Lulli P, Morellini M, et al. Chromosome 6p-encoded HLA-DR2 determinant discriminates migraine without aura from migraine with aura. *Hum Immunol*. 1999;60:69–74.
111. Matsuyama Z, Kawakami H, Maruyama H, et al. Molecular features of the CAG repeats of spinocerebellar ataxia 6 (SCA6). *Hum Mol Genet*. 1997;6:1283–1287.
112. Matsuyama Z, Murase M, Shimizu H, et al. A novel insertion mutation of acetazolamide-responsive episodic ataxia in a Japanese family. *J Neurol Sci*. 2003;210:91–93.
113. Maude S, Curtin J, Breen G, et al. The–141C Ins/Del polymorphism of the dopamine D2 receptor gene is not associated with either migraine or Parkinson's disease. *Psychiatr Genet*. 2001;11:49–52.
114. May A, Ophoff RA, Terwindt GM, et al. Familial hemiplegic migraine locus on 19p13 is involved in the common forms of migraine with and without aura. *Hum Genet*. 1995;96:604–608.
115. McCarthy LC, Hosford DA, Riley JH, et al. Single-nucleotide polymorphism alleles in the insulin receptor gene are associated with typical migraine. *Genomics*. 2001;78:135–149.
116. Mochi M, Sangiorgi S, Cortelli P, et al. Testing models for genetic determination in migraine. *Cephalalgia*. 1993;13:389–394.
117. Mochi M, Cevoli S, Cortelli P, et al. A genetic association study of migraine with dopamine receptor 4, dopamine transporter and dopamine-beta-hydroxylase genes. *Neurol Sci*. 2003;23:301–305.
118. Monari L, Mochi M, Valention ML, et al. Searching for migraine genes: exclusion of 290 cM out of the whole human genome. *Ital J Neurol Sci*. 1997;1:277–282.
119. Montagna P. Molecular genetics of migraine headache: a review. *Cephalalgia*. 2000;20:3–14.
120. Mori Y, Wakamori M, Oda S, et al. Reduced voltage sensitivity of activation of P/Q-type Ca2+ channels is associated with the ataxic mouse mutation Rolling Nagoya (Tg(Rol)). *J Neurosci*. 2000;20:5654–5662.
121. Mosewich RK, Donat JR, DiMauro S, et al. The syndrome of mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes presenting without stroke. *Arch Neurol*. 1993;50:275–278.
122. Moskowitz MA, Bolay H, Dalkara T. Deciphering migraine mechanisms: clues from familial hemiplegic migraine genotypes. *Ann Neurol*. 2004;55:276–280.
123. Mulder EJ, Van Baal C, Gaist D, et al. Genetic and environmental influences on migraine: a twin study across six countries. *Twin Res*. 2003;6:422–431.
124. Noble-Topham SE, Dyment DA, Cader MZ, et al. Migraine with aura is not linked to the FHM gene CACNA1A or the chromosomal region, 19p13. *Neurology*. 2002;59:1099–1101.
125. Noble-Topham SE, Cader MZ, Dyment DA, et al. Genetic loading in familial migraine with aura. *J Neurol Neurosurg Psychiatry*. 2003;74:1128–1130.
126. Nyholt DR, Curtain RP, Gaffney PT, et al. Migraine association and linkage analyses of the human 5-hydroxytryptamine (5HT2A) receptor gene. *Cephalalgia*. 1996;16:463–467.
127. Nyholt DR, Dawkins JL, Brimage PJ, et al. Evidence for an X-linked genetic component in familial typical migraine. *Hum Mol Genet*. 1998;7:459–463.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

128. Nyholt DR, Lea RA, Goadsby PJ, et al. Familial typical migraine: linkage to chromosome 19p13 and evidence for genetic heterogeneity. *Neurology*. 1998;50:1428–1432.
129. Obrenovitch TP, Zilkha E. Inhibition of cortical spreading depression by L-701,324, a novel antagonist at the glycine site of the N-methyl-D-aspartate receptor complex. *Br J Pharmacol*. 1996;117:931–937.
130. Ogilvie AD, Russell MB, Dhall P, et al. Altered allelic distribution of the serotonin transporter gene in migraine without aura and migraine with aura. *Cephalalgia*. 1998;18:23–26.
131. Ophoff RA, DeYoung J, Service SK, et al. Hereditary vascular retinopathy, cerebroretinal vasculopathy, and hereditary endotheliopathy with retinopathy, nephropathy and stroke map to a single locus on chromosome 3p21.1-p21.3. *Am J Hum Genet*. 2001;69:447–453.
132. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. *Cell*. 1996;1:543–552.
133. Ophoff RA, van Eijk R, Sandkuijl LA, et al. Genetic heterogeneity of familial hemiplegic migraine. *Genomics*. 1994;1:21–26.
134. Osuntokun B, Adeuja AO, Nottidge VA, et al. Prevalence of headache in Nigerian Africans: a community-based study. *East Afr Med J*. 1992;69:196–199.
135. Pardo J, Carracedo A, Munoz I, et al. Genetic markers association study in migraine. *Cephalalgia*. 1995;15:200–204.
136. Paterna S, Di Pasquale P, Dángelo A, et al. Angiotensin-converting enzyme gene deletion polymorphism determines an increase in frequency of migraine attacks in patients suffering from migraine without aura. *Eur Neurol*. 2000;43:133–136.
137. Peroutka SJ, Price SC, Wilhoit TL, et al. Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI alleles. *Mol Med*. 1998;4:14–21.
138. Peroutka SJ, Wilhoit T, Jones K. Clinical susceptibility to migraine with aura is modified by dopamine D2 receptor (DRD2) NcoI alleles. *Neurology*. 1997;49:201–206.
139. Piedras-Renteria ES, Watase K, Harata N, et al. Increased expression of alpha 1A Ca2+ channel currents arising from expanded trinucleotide repeats in spinocerebellar ataxia type 6. *J Neurosci*. 2001; 21:9185–9193.
140. Pietrobon D. Calcium channels and channelopathies of the central nervous system. *Mol Neurobiol*. 2002;25:31–50.
141. Plomp JJ, van den Maagdenberg AMJM, Molenaar PC, et al. Mutant P/Q-type calcium channel electrophysiology and migraine. *Curr Opin Invest Drugs*. 2001;2:1250–1260.
142. Plomp JJ, Vergouwe MN, Van den Maagdenberg AM, et al. Abnormal transmitter release at neuromuscular junctions of mice carrying the tottering alpha(1A) Ca(2+) channel mutation. *Brain*. 2000;123:463–471.
143. Rainero I, Pinessi I, Salani G, et al. A polymorphism in the interleukin-1 alpha gene influences the clinical features of migraine. *Headache*. 2002;42:337–340.
144. Rainero I, Grimaldi LME, Salani G, et al. Association between the tumor necrosis factor-α-308 G/A gene polymorphism and migraine. *Neurology*. 2004;62:141–143.
145. Rasmussen BK, Jensen R, Schroll M, et al. Epidemiology of headache in a general population—a prevalence study. *J Clin Epidemiol*. 1991;44:1147–1157.
146. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia*. 1992;12:221–228.
147. Restituito S, Thompson RM, Eliet J, et al. The polyglutamine expansion in spinocerebellar ataxia type 6 causes a beta subunit-specific enhanced activation of P/Q-type calcium channels in Xenopus oocytes. *J Neurosci*. 2000;20:6394–6403.
148. Riess O, Schols L, Bottger H, et al. SCA6 is caused by moderate CAG expansion in the alpha1A-voltage-dependent calcium channel gene. *Hum Mol Genet*. 1997;6:1289–1293.
149. Russell MB. Genetic epidemiology of migraine and cluster headache. *Cephalalgia*. 1997;17:683–701.
150. Russell MB, Diamant M, Norby S. Genetic heterogeneity of migraine with and without aura in Danes cannot be explained by mutation in mtDNA nucleotide pair 11084. *Acta Neurol Scand*. 1997;96: 171–173.
151. Russell MB, Iselius L, Olesen J. Investigation of the inheritance of migraine by complex segregation analysis. *Hum Genet*. 1995;96:726–730.
152. Russell MB, Olesen J. Increased familial risk and evidence of genetic factor in migraine. *BMJ*. 1995;311:541–544.
153. Russell MB, Rasmussen BK, Thorvaldsen P, et al. Prevalence and sex-ratio of the subtypes of migraine. *Int J Epidemiol*. 1995;24:612–618.
154. Sano M, Ozawa M, Shiota S, et al. The T-C(8356) mitochondrial DNA mutation in a Japanese family. *J Neurol*. 1996;243:441–444.
155. Scoggan KA, Chandra T, Nelson R, et al. Identification of two novel mutations in the CACNA1A gene responsible for episodic ataxia type 2. *J Med Genet*. 2001;38:249–253.
156. Sheperd AG, Lea RA, Hutchins C, et al. Dopamine receptor genes and migraine with and without aura: an association study. *Headache*. 2002;42:346–351.
157. Shimomura T, Kitano A, Merukawa H, et al. Mutation in platelet mitochondrial gene in patients with migraine [Abstract]. *Cephalalgia*. 1995;15(Suppl 14):10.
158. Sicuteri F, Testi A, Anselmi B. Biochemical investigations in headache: increase in the hydroxyindoleacetic acid excretion during migraine attacks. *Int Arch Allergy*. 1961;19:55–58.
159. Soragna D, Vettori A, Carraro G, et al. A locus for migraine without aura maps on chromosome 14q21.2-q22.3. *Am J Hum Genet*. 2003;72:161–167.
160. Stewart WF, Linet MS, Celentano DD, et al. Age- and sex-specific incidence rates of migraine with and without visual aura. *Am J Epidemiol*. 1991;134:1111–1120.
161. Stewart WF, Lipton RB, Liberman J. Variation in migraine prevalence by race. *Neurology*. 1996;47:52–59.
162. Stewart WF, Staffa J, Lipton RB, et al. Familial risk of migraine: a population-based study. *Ann Neurol*. 1997;41:166–172.
163. Stochino ME, Asuni C, Congiu D, et al. Association study between the phenotype migraine without aura-panic disorder and dopaminergic receptor genes. *Pharmacol Res*. 2003;48:531–534.
164. Subramony SH, Schott K, Raike RS, et al. Novel CACNA1A mutation causes febrile episodic ataxia with interictal cerebellar deficits. *Ann Neurol*. 2003;54:725–731.
165. Svensson DA, Larsson B, Waldenlind E, et al. Shared rearing environment in migraine: results from twins reared apart and twins reared together. *Headache*. 2003;43:235–244.
166. Takahashi T, Igarashi S, Kimura T, et al. Japanese cases of familial hemiplegic migraine with cerebellar ataxia carrying a T666M mutation in the CACNA1A gene. *J Neurol Neurosurg Psychiatry*. 2002;72:676–677.
167. Teh BT, Silburn P, Lindblad K, et al. Familial periodic cerebellar ataxia without myokymia maps to a 19-cM region on chromosome 19p13. *Am J Hum Genet*. 1995;56:1443–1449.
168. Terwindt GM, Haan J, Ophoff RA, et al. Clinical and genetic analysis of a large Dutch family with autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon. *Brain*. 1998;121:303–316.
169. Terwindt GM, Kors EE, Haan J, et al. Mutation analysis of the CACNA1A calcium channel subunit gene in 27 patients with sporadic hemiplegic migraine. *Arch Neurol*. 2002;59:1016–1018.
170. Terwindt GM, Ophoff RA, Haan J, et al. Variable clinical expression of mutations in the P/Q-type calcium channel gene in familial hemiplegic migraine. Dutch Migraine Genetics Research Group. *Neurology*. 1998;50:1105–1110.
171. Terwindt GM, Ophoff RA, Haan J, et al. Familial hemiplegic migraine: a clinical comparison of families linked and unlinked to chromosome 19. *Cephalalgia*. 1996;16:153–155.
172. Terwindt GM, Ophoff RA, van Eijk R, et al. Involvement of the P/Q type calcium channel α1A-subunit (CACNA1A) gene region on 19p13 in migraine with and without aura. *Neurology*. 2001;56:1028–1032.
173. Thomsen LL, Eriksen MK, Roemer SF, et al. A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. *Brain*. 2002;125:1379–1391.
174. Thomsen LL, Olesen J, Russell MB. Increased risk of migraine with typical aura in probands with familial hemiplegic migraine and their relatives. *Eur J Neurol*. 2003;10:421–427.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-27 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:58

175. Thomsen LL, Ostergaard E, Olesen J, et al. Evidence for a separate type of migraine with aura: sporadic hemiplegic migraine. *Neurology* 2003;60:595–601.
176. Tokio S, Hisanori K, Toshiya H, et al. Prevalence of migraine in western Japan [Abstract]. *Cephalalgia*. 1993;13(Suppl 13):10.
177. Toru S, Murakoshi T, Ishikawa K, et al. Spinocerebellar ataxia type 6 mutation alters P-type calcium channel function. *J Biol Chem*. 2000;275:10893–10898.
178. Tottene A, Fellin T, Pagnutti S, et al. Familial hemiplegic migraine mutations increase Ca2+ influx through single human Cav2.1 channels and decrease maximal Cav2.1 current density in neurons. *Proc Natl Acad Sci U S A*. 2002;99:13284–13289.
179. Tournier Lasserve E, Joutel A, Melki J, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps to chromosome 19q12. *Nature Genet*. 1993;3:256–259.
180. Trabace S, Brioli G, Lulli P, et al. Tumor necrosis factor gene polymorphism in migraine. *Headache*. 2002;42:341–345.
181. Tzourio C, El Amrani M, Poirier O, et al. Association between migraine and endothelin type A receptor (ETA–231 A/G) gene polymorphism. *Neurology*. 2001;56:1273–1277.
182. Ulrich V, Gervil M, Kyvik KO, et al. Evidence of a genetic factor in migraine with aura: a population based Danish twin study. *Ann Neurol*. 1999;45:242–246.
183. Ulrich V, Gervil M, Kyvik KO, et al. The inheritance of migraine with aura estimated by means of a structural equation modelling. *J Med Genet*. 1999;36:225–227.
184. Vahedi K, Denier C, Ducros A, et al. Sporadic hemiplegic migraine with de novo CACNA1A missense mutation [Abstract]. *Neurology*. 1999;52(Suppl 2):A274.
185. Vahedi K, Denier C, Ducros A, et al. CACNA1A gene de novo mutation causing hemiplegic migraine, coma, and cerebellar atrophy. *Neurology*. 2000;55:1040–1042.
186. Vahedi K, Joutel A, Van Bogaert P, et al. A gene for hereditary paroxysmal cerebellar ataxia maps to chromosome 19p. *Ann Neurol*. 1995;37:289–293.
187. van den Maagdenberg AMJM, Kors EE, Brunt ER, et al. Three novel truncating mutations and one novel missense mutation in the CACNA1A gene causing episodic ataxia type 2. *J Neurol*. 2002;249:1515–1519.
188. Van den Maagdenberg AMJM, Pietrobon D, Pizzorusso T, et al. A *Cacna1a* knockin migraine mouse model with increased susceptibility to cortical spreading depression. *Neuron*. 2004;41: 701–710.
189. Vanmolkot KR, Kors EE, Hottenga JJ, et al. Novel mutations in the Na+, K+-ATPase pump gene ATP1A2 associated with familial hemiplegic migraine and benign familial infantile convulsions. *Ann Neurol*. 2003;54:360–366.
190. Vanmolkot KR, van den Maagdenberg AM, Haan J, et al. New discoveries about the second gene for familial hemiplegic migraine, ATP1A2. *Lancet Neurol*. 2003;2:721.
191. Verin M, Rolland Y, Landgraf A, et al. New phenotype of the cerebral autosomal dominant arteriopathy mapped to chromosome 19: migraine as the prominent clinical feature. *J Neurol Neurosurg Psychiatry*. 1995;59:579–585.
192. Vighetto A, Froment JC, Trillet M, et al. Magnetic resonance imaging in familial paroxysmal ataxia. *Arch Neurol*. 1988;45:547–549.
193. Vogel F, Motulsky AG. Human genetics. Berlin: Springer Verlag; 1986.
194. von Brederlow B, Hahn AF, Koopman WJ, et al. Mapping the gene for acetazolamide responsive hereditary paroxysmal cerebellar ataxia to chromosome 19p. *Hum Mol Genet*. 1995;4:279–284.
195. Wada T, Kobayashi N, Takahashi Y, et al. Wide clinical variability in a family with a CACNA1A T666M mutation: hemiplegic migraine, coma, and progressive ataxia. *Pediatr Neurol*. 2002;26:47–50.
196. Wakamori M, Yamazaki K, Matsunodaira H, et al. Single tottering mutations responsible for the neuropathic phenotype of the P-type calcium channel. *J Biol Chem*. 1998;273:34857–34867.
197. Wappl E, Koschak A, Poteser M, et al. Functional consequences of P/Q-type Ca2+ channel Cav2.1 missense mutations associated with episodic ataxia type 2 and progressive ataxia. *J Biol Chem*. 2002;277:6960–6966.
198. Wessman M, Kallela M, Kaunisto MA, et al. A susceptibility locus for migraine with aura, on chromosome 4q24. *Am J Hum Genet*. 2002;70:652–662.
199. Wieser T, Mueller C, Evers S, et al. Absence of known familial hemiplegic migraine (FHM) mutations in the CACNA1A gene in patients with common migraine: implications for genetic testing. *Clin Chem Lab Med*. 2003;41:272–275.
200. Willis T. *Opera omnia*. Amstelaedami: Henricum Wetstenium; 1682.
201. Yilmaz M, Erdal ME, Herken H, et al. Significance of serotonin transporter gene polymorphism in migraine. *J Neurol Sci*. 2001;186:27–30.
202. Yue O, Jen JC, Nelson SF, et al. De novo mutation in CACNA1A caused acetazolamide-responsive episodic ataxia. *Am J Med Genet*. 1998;77:298–301.
203. Yue Q, Jen JC, Thwe MM, et al. De novo mutation in CACNA1A caused acetazolamide-responsive episodic ataxia. *Am J Med Genet*. 1998;26:298–301.
204. Zhuchenko O, Bailey J, Bonnen P, et al. Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel. *Nature Genet*. 1997;15:62–69.
205. Ziegler DK, Hur YM, Bouchard TJ Jr, et al. Migraine in twins raised together and apart. *Headache*. 1998;38:417–422.
206. Zwingman TA, Neumann PE, Noebels JL, et al. Rocker is a new variant of the voltage-dependent calcium channel gene Cacna1a. *J Neurosci*. 2001;21:1169–1178.