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FULL-LENGTH ORIGINAL RESEARCH

Epilepsy as part of the phenotype associated with *ATP1A2* mutations

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SUMMARY

Purpose: **Mutations in the *ATP1A2* gene have been described in families with familial hemiplegic migraine (FHM). FHM is a variant of migraine with aura characterized by the occurrence of hemiplegia during the aura. Within several FHM families, some patients also had epileptic seizures. In this study we tested the hypothesis that mutations in *ATP1A2* may be common in patients presenting with epilepsy and migraine.**

Methods: **We selected 20 families with epilepsy and migraine and performed mutation analysis of *ATP1A2* in the probands by direct sequencing of all exons and splice-site junctions.**

Results: **Novel *ATP1A2* mutations were found in two of the 20 families (10%). The p.Gly900Arg mutation was present in a family with epilepsy and FHM, and the p.Cys702Tyr mutation occurred in a family with occipitotemporal epilepsy and migraine with and without visual aura. In the two families together, six mutation carriers had the combination of epilepsy and migraine, two had only epilepsy, and six had only migraine.**

Discussion: **This study shows that a history of migraine and a family history of both epilepsy and migraine should be obtained in all patients presenting with epilepsy in the epilepsy clinic. It may be worthwhile to screen patients with a combination of epilepsy and migraine and a positive family history of either migraine or epilepsy for mutations in the *ATP1A2* gene.**

KEY WORDS: **Epileptic seizures, Familial hemiplegic migraine, Na^+, K^+-ATPase.**

Epilepsy and migraine are common chronic disorders characterized by recurrent attacks. Epilepsy has a prevalence of 0.5% (Hauser et al., 1991) and migraine affects 6% of males and 15–18% of females (Lipton & Stewart, 1997). Several studies have reported the comorbidity of both disorders. Six percent of patients with migraine have epilepsy (Andermann & Andermann, 1987) and patients with epilepsy are 2.4 times more likely to have migraine than persons without epilepsy (Ottman & Lipton, 1994). The mechanism underlying both disorders may be a condition of neuronal hyperexcitability resulting from genetic or environmental factors (Ottman & Lipton, 1996).

Cooccurrence of epilepsy and migraine has also been reported in families with familial hemiplegic migraine (FHM). FHM is a rare autosomal dominant subtype of migraine characterized by hemiplegia during the aura. Other reversible neurological symptoms, including visual aura, paresthesias and language impairment, can be observed (Headache Classification Subcommittee of the

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International Headache Society, 2004). Some patients experience severe atypical attacks characterized either by prolonged hemiplegia lasting several days or by signs of diffuse encephalopathy including fever, drowsiness, confusion, and coma (Ducros et al., 2001). Mutations in three genes are known to cause FHM: *CACNA1A*, encoding the α1A-subunit of the P/Q-type calcium channels (FHM1) (Ophoff et al., 1996), *ATP1A2*, encoding the α2-subunit of the Na^+, K^+-ATPase (FHM2) (De Fusco et al., 2003), and *SCN1A*, encoding the neuronal sodium channel α1-subunit (FHM3) (Dichgans et al., 2005). Epileptic seizures occurring independently from the migraine attacks have been reported in families with FHM1 (Kors et al., 2004) and FHM3 (Dichgans et al., 2005) but mainly in families with FHM2. In about 20% of families with an *ATP1A2* mutation, some patients experienced epileptic seizures (De Fusco et al., 2003; Jurkat-Rott et al., 2004). In one of these families, FHM partially cosegregated with benign familial infantile seizures (BFIS) (Vanmolkot et al., 2003). BFIS is an autosomal dominant epilepsy syndrome characterized by partial seizures starting between the age of 3 and 12 months, and spontaneously remitting after 1 year. Most studies performing mutation analysis of *ATP1A2* selected the families through their migraine phenotype. Therefore, epilepsy may be underrepresented in these families.

Within several reported FHM2 families, some members carrying the mutation experienced migraine attacks without motor weakness (De Fusco et al., 2003; Vanmolkot et al., 2003; Thomsen et al., 2007). These individuals had migraine with aura (MA) or migraine without aura (MO), the two most common types of migraine. Mutation analysis of *ATP1A2* in families with MA or MO has led to the identification of two missense mutations possibly involved as susceptibility factor (Todt et al., 2005).

In this study we screened 20 unrelated families with epilepsy and migraine for mutations in *ATP1A2*.

Patients and Methods

Patients

The ethical committees of University Hospital Gasthuisberg and University of Antwerp approved this study and a written informed consent was obtained from all participants or their legal representative. In this study we included 20 unrelated families with epilepsy and migraine. The families were selected through their proband which presented with epilepsy at an epilepsy clinic. History, physical and neurological examinations and brain imaging of the probands did not suggest the presence of an underlying disorder including arteriovenous malformations of the occipital lobe, mitochondrial encephalopathies or celiac disease. All families consisted of at least two patients with epilepsy, migraine or both. The clinical characteristics of these families are summarized in Table 1. Patients with hemiplegic migraine were present in four of the 20 families. Epileptic seizures and syndromes were classified according to the International League Against Epilepsy (ILAE) criteria (Commission on Classification and Terminology of the International League Against Epilepsy, 1981; 1989). The clinical diagnosis of migraine was made according to the International Headache Society (IHS) 2nd edition criteria (Headache Classification Subcommittee of the International Headache Society, 2004). All families were of Belgian origin. DNA was extracted from peripheral blood according to standard procedures. DNA samples of 170 unrelated healthy control individuals, randomly selected form the Belgian population, were also available.

Table 1. Clinical phenotypes of the 20 families with epilepsy and migraine

Family structure	No. of families	No. of patients in total	Phenotypes of patients		
			EPI+MG	Only EPI	Only MG
2 patients	4	8	4	0	4
3 patients	4	12	4	4	4
≥4 patients	12	79	17	47	15

Abbreviations: *EPI* = epilepsy; *MG* = migraine.

Mutation analysis

PCR amplification of the 23 exons and the splice-site junctions of *ATP1A2* was performed in the 20 probands. Intronic primers were designed using the in-house developed software tool SNPbox (Weckx et al., 2005). PCR fragments were sequenced with BigDye Terminator v3.1 Cycle Sequencing kit (PE, Applied Biosytems, Foster City, CA). Sequences were analyzed on an ABI3730 automated sequencer with the Sequencing Analysis 5.0 software. Presence of mutations in patients and absence from control individuals was confirmed using pyrosequencing. Mutations were numbered according to the published cDNA sequence (accession number NM_000702.2) with nucleotide +1 corresponding to the A of the ATG translation initiation codon and the nomenclature followed the MDI/HGVS Mutation Nomenclature Recommendations (http://www.hgvs.org/mutnomen) (den Dunnen & Antonarakis, 2001).

Results

Mutation analysis of *ATP1A2* identified two novel missense mutations: the c.2698G>C mutation predicting the amino acid replacement glycine to arginine on position 900 (p.Gly900Arg) in family A, and c.2105G>A predicting the amino acid replacement cysteine to tyrosine on position 702 (p.Cys702Tyr) in family B.

Clinical data

Family A

The proband (II.3) was a 50-year-old man, who experienced epileptic seizures since the age of 20, 1 year after a

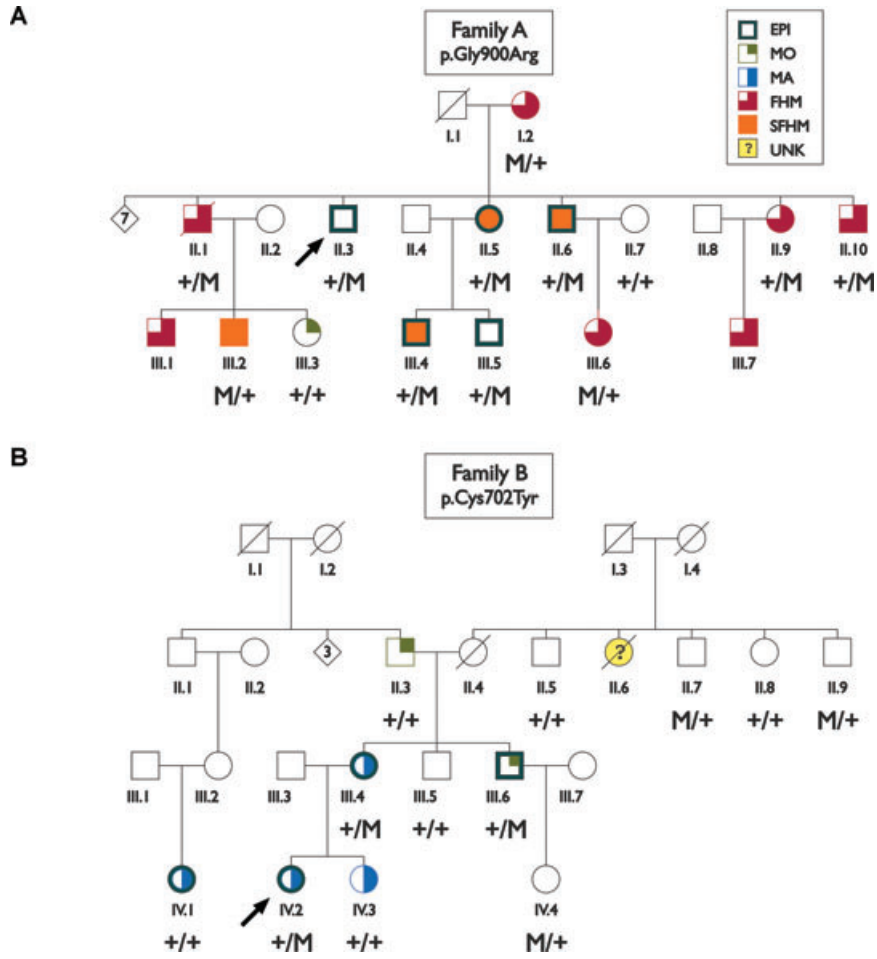

Figure 1.
Pedigrees of family A and B. The arrows indicate the proband. The genotype of the individuals is indicated by (M) for the mutated allele and by (+) for the wild type allele. The numbers in the diamonds indicate the number of unaffected individuals. EPI, epilepsy; MO, migraine without aura; MA, migraine with aura; FHM, familial hemiplegic migraine; SFHM, severe hemiplegic migraine attacks associated with fever, meningism and coma; UNK, unknown status.

traffic accident with cerebral trauma and loss of consciousness (Fig. 1A). Magnetic resonance imaging (MRI) of the brain with gradient echo imaging was normal. A typical seizure started with a visual aura, consisting of a rotating silver ball and was always followed by secondary generalization. A second type of seizures started with dysarthria leading to short complex partial seizures or secondary generalized seizures. Seizures were difficult to control. He had been treated with phenytoin, valproate, carbamazepine, levetiracetam, and phenobarbital. On a combination of carbamazepine and phenobarbital, he was seizure-free. He never had headache episodes.

The proband's mother (I.2) had a history of not further specified psychiatric illness, and according to her children, she had episodes of hemiplegic migraine.

Patient II.6 was a 46-year-old man, who experienced attacks of hemiplegic migraine since the age of 25. The attacks always presented in the same way: hemianopsia with blurred vision, one-sided sensory symptoms, hemiparesis and sometimes speech disturbances. Neurological symptoms, which lasted up to 1 h, were followed by a unilateral pulsating headache, lasting up to 3 days and accompanied by nausea, vomiting, photophobia, and phonophobia. Stress, fatigue, and flickering light were potent triggers. At the age of 29, he experienced an episode of hemiplegic migraine with right hemiparesis, after which he became drowsy and was admitted to the hospital. He had high fever and meningism, and further deteriorated into coma. Computed tomography (CT) of the brain and cerebrospinal fluid (CSF) analysis were normal. EEG showed

slowing over the left temporal lobe. Despite the normal CSF findings, a tentative diagnosis of Herpes simplex virus (HSV) encephalitis was made. His symptoms completely resolved after a few days. Follow-up neurological examination and MRI scan of the brain were normal. In the following year, he experienced three epileptic seizures, which started with a visual hallucination of a black rotating ball, and evolved into secondary generalized tonic–clonic seizures. The epileptic visual aura was different from the visual symptoms he experienced during a migraine attack. Antiepileptic drugs (AEDs) controlled the seizures.

The daughter of patient II.6 (III.6) had attacks of hemiplegic migraine which were triggered by stress, exercise, fatigue, and flickering light, since the age of 11.

Patient II.5 suffered from MO since adolescence. At the age of 22, she was admitted to the hospital with headache, fever, meningism, hemiparesis, aphasia, and somnolence evolving into stupor. At day 5, she developed a generalized tonic–clonic status epilepticus, treated with pentobarbital. Cerebral CT and angiography and repeated lumbar punction were normal. EEG showed slow activity over the left hemisphere. Also in this case, the diagnosis of HSV encephalitis was made. She recovered after some weeks, but developed recurrent right-sided partial motor seizures. EEGs showed epileptic activity over the left frontal and temporal lobe.

Her two sons (III.4 and III.5) both had febrile and afebrile tonic–clonic seizures and were treated with AEDs. Both were mildly mentally retarded. One son (III.4) also had FHM, and at least one episode was triggered by head trauma. At the age of 22, he developed an episode of headache, fever, meningism, and drowsiness, followed 2 days later by a convulsive status epilepticus. CSF and MRI were normal and EEG after treatment with valproate showed generalized slow activity. His symptoms resolved over one week.

Patients II.9, II.10 and III.7 all experienced classical attacks of hemiplegic migraine triggered by stress or exercise.

Patient III.3 suffered from MO. According to family members her father (II.1) and two brothers (III.1 and III.2) had multiple episodes of hemiplegic migraine. Patient III.2 experienced at least one episode of coma with fever, meningism, and epileptic activity of the left hemicorpus triggered by head trauma.

Segregation analysis had previously shown that the inheritance pattern in this family was compatible with a defect on chromosome 1q21-q23 (multipoint lod score 1.17, data not shown).

Family B

The clinical phenotype of the proband was previously reported (Fig. 1B) (Simons et al., 2004). The proband (IV.2), who had a normal birth and early development, had simple febrile seizures at the age of 4. At her menarche, age 12, she developed her first afebrile seizure while watching television. It was a complex partial status epilepticus (CPSE), which started with visual hallucinations characterized by palinopsia, polyopia, tunnel vision, and flashing lights and lasted for more than 1 h. She remained seizure-free until the age of 28. At the birth of her first child, she experienced a second occipital lobe CPSE lasting 1 h and ending with a secondarily generalized tonic–clonic seizure. The first MRI of the brain was normal. Since then, she had recurrent CPSE every 6 months with postictal hemiparesis and severe migraine headache, despite AED treatment. A few months after her second CPSE, she developed a different seizure type characterized by a rising epigastric sensation, fear, hyperventilation, light-headedness, and occasionally inability to speak and diminished awareness, suggesting temporal lobe origin. Initially, these seizures occurred two or three times a month, but after 5 years, seizure frequency was increased to five times a day. MRI of the brain, 5 years after the first MRI, showed left hippocampal sclerosis. Interictal fluorodeoxyglucose positron emission tomography (FDG-PET) showed hypometabolism in the left mesiotemporal region. Substraction ictal single photon emission computed tomography (SPECT) coregistered with MRI showed right occipital hyperperfusion. A second ictal SPECT showed hyperperfusion in the left occipital lobe. The diagnosis of occipitotemporal lobe epilepsy with secondarily developed hippocampal sclerosis was made. Since her first CPSE, the patient also experienced monthly left-sided migraine headaches, usually perimenstrually. Twenty percent of her migraine headaches were preceded by visual aura of flashing lights, similar to the visual hallucinations accompanying her seizures.

The proband's sister (IV.3) suffered from migraine with visual aura consisting of light flashes since puberty. Her migraine attacks occurred usually perimenstrually.

The proband's mother (III.4) experienced an isolated unprovoked epileptic seizure at the time of her menarche, also while watching television. The seizure started with visual hallucinations of flickering images and secondarily generalized. She also had migraine with visual aura, characterized by white or colored stars. Until her menopause, migraine frequency was twice a week. Afterwards, she experienced only five migraine attacks a year.

The proband's grandfather (II.3) had MO, but information concerning the frequency of his migraine attacks was lacking.

A proband's uncle (III.6) suffered from MO once or twice a month. He also experienced every 2 or 3 months a cluster of around five simple partial seizures, characterized by fear, an epigastric rising sensation, piloerection, sweating, staring, and concentration loss. He did not take any AEDs.

A second cousin of the proband (IV.1) experienced two generalized tonic–clonic seizures at the age of 14. Infor-

mation suggesting a focal onset was lacking. EEG, however, showed biposterior epileptic paroxysms after eye closure. Three years later, she experienced a third generalized tonic–clonic seizure and has been seizure-free since. She also had migraine with visual aura characterized by white lights and very bright objects in one visual hemifield. Her migraine attacks occurred premenstrually three or four times a year.

Genetic analyses

In family A the p.Gly900Arg mutation was present in nine patients with FHM of whom four had severe atypical attacks associated with fever, meningism, and coma. Three patients also experienced epileptic seizures independent from migraine attacks. Two family members who had febrile or epileptic seizures without migraine also carried the mutation. The mutation was absent in one individual with MO. No DNA samples were available from two additional individuals with FHM. Therefore, the presence of the mutation could not be confirmed in these individuals.

The p.Cys702Tyr mutation was observed in three patients of family B who had epileptic seizures associated with MA or MO. The mutation was also present in three unaffected individuals. In addition, the pedigree structure suggested that the deceased individual II.4 also carried the mutation since the mutation was present in two of her brothers and two of her children. This person was considered unaffected based on the information obtained by questioning living relatives. The mutation was absent from two migraine patients without epileptic seizures and one patient with epilepsy and migraine more distantly related to the family.

The two mutations were absent from 170 control individuals. At protein level, both mutations were predicted to affect amino acids which were strongly conserved among several α-subunits of Na^+, K^+-ATPase and H^+, K^+-ATPase from different species (Fig. 2).

Discussion

The *ATP1A2* gene on chromosome 1q23 encodes the α2-subunit of the Na^+, K^+-ATPase, an integral membrane protein responsible for maintenance of Na^+ and K^+ gradients across the plasma membrane. Na^+, K^+-ATPase is a member of the large family of P-type ATPases, including other members like H^+, K^+-ATPases and Ca^{2+}-ATPases. The active Na^+, K^+-ATPase is a heteromeric complex formed by a catalytic α-subunit, a regulatory β-subunit and a γ-subunit with unknown function. The α-subunit consists of 10 transmembrane segments (TM1-TM10) and contains the ATP and cation-binding sites. To date, about 30 *ATP1A2* mutations have been reported in families with FHM, FHM associated with BFIS, alternating hemiplegia of childhood, basilar migraine, MA and MO (De Fusco et al., 2003; Vanmolkot et al., 2003; Bassi et al., 2004; Jurkat-Rott et al., 2004; Kaunisto et al., 2004; Spadaro et al., 2004; Swoboda et al., 2004; Riant et al., 2005; Todt et al., 2005; Ambrosini et al., 2005; Pierelli et al., 2006; Vanmolkot et al., 2006a, 2006b; Thomsen et al., 2007). Some patients had additional features, for example mental retardation (De Fusco et al., 2003; Jurkat-Rott et al., 2004; Swoboda et al., 2004; Vanmolkot et al., 2006a) and cerebellar signs like ataxia, nystagmus, and dysarthria (Spadaro et al., 2004). Cooccurrence of epilepsy and migraine has been reported in several families, suggesting that mutations in *ATP1A2* also cause epilepsy (De Fusco et al., 2003; Vanmolkot et al., 2003; Bassi et al., 2004; Jurkat-Rott et al., 2004; Swoboda et al., 2004). The epileptic phenotypes described in these families are summarized in Table 2. However, in most reports the provided clinical information with respect to epilepsy was rather limited.

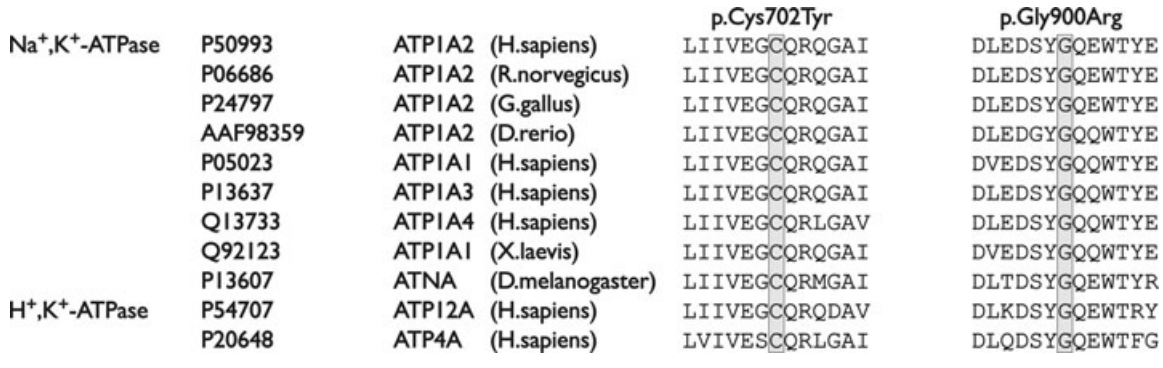

Figure 2.
Amino acid alignment of various ATPase α-subunits from different species for the regions surrounding the mutations. The mutated amino acids are boxed.
Epilepsia © ILAE

Table 2. Literature survey on the epilepsy phenotypes in patients with an *ATP1A2* mutation

Mutation	Proportion mutation carriers with epilepsy	Seizure type	Onset age	Outcome	References
p.Thr378Asn	4/4	Febrile and afebrile GTCS	18 mo-3 y	NS	Bassi et al., 2004
p.Arg689Gln	5/11	BFIS in 2	1.5 mo and 3 mo	Remission	Terwindt et al., 1997; Vanmolkot et al., 2003
		BFIS + FS in 1	BFIS: 3 mo; FS: 4.5 y	BFIS: remission; single FS	
		BFIS + GTCS in 1	BFIS: 4 mo; GTCS: 8 y	BFIS: remission; single GTCS	
		FS in 1	11 mo	Single FS	
p.Asp718Asn	1/7	GTCS	4 y	Only 2x	Jurkat-Rott et al., 2004
p.Leu764Pro	3/22	PE in 1	6 y	Treated with AEDs until 15 y	De Fusco et al., 2003; Marconi et al., 2003
		NS in 2	2 y and 3 y	Benign course with remission	
p.Trp887Arg	2/7	PE with secondary generalization and visual disturbances	NS	Successfully treated with AEDs	De Fusco et al., 2003; Marconi et al., 2003
p.Pro979Leu	1/5	GTCS	8 mo	Remission by 2 y	Cevoli et al., 2002; Jurkat-Rott et al., 2004

Abbreviations: y, year; mo, month; GTCS, generalized tonic–clonic seizures; BFIS, benign familial infantile seizures; FS, febrile seizures; PE, partial epilepsy; NS, not specified; AEDs, antiepileptic drugs.

In this study we analyzed the *ATP1A2* gene in 20 families with epilepsy and migraine. We identified two novel missense mutations, p.Gly900Arg and p.Cys702Tyr, in two Belgian families. Patients in these families had a spectrum of paroxysmal neurological dysfunction, including FHM, common forms of migraine, epileptic seizures, febrile seizures, and status epilepticus. In the first family, the mutation p.Gly900Arg was observed in patients with FHM, epileptic seizures or both, indicating that the mutation underlies both phenotypes. The segregation pattern in this family is compatible with autosomal dominant inheritance and the phenotypical expression of the mutation may depend on genetic or environmental modifiers. The mutation was absent from one individual with MO and therefore, this person is likely to be a phenocopy. The second mutation, p.Cys702Tyr, was detected in three patients with epilepsy and common forms of migraine, suggesting the contribution of the mutation to both phenotypes. None of the patients had hemiplegic migraine, suggesting that *ATP1A2* may also be involved in milder and more common forms of migraine. The identification, in other studies, of *ATP1A2* mutations in patients with nonhemiplegic migraine from FHM families or from families clustering common forms of migraine also supports this hypothesis (De Fusco et al., 2003; Vanmolkot et al., 2003; Todt et al., 2005; Thomsen et al., 2007). The segregation pattern in family B is less clear as the mutation was also present in four unaffected individuals and absent from two patients with only migraine attacks and one distantly related patient with epilepsy and migraine. This observation can be explained in several ways. One explanation could be an autosomal dominant inheritance pattern with a strongly reduced penetrance and the three patients not carrying the mutation could be phenocopies in whom the disease was caused by other genetic or environmental factors. However, an alternative hypothesis of digenic inheritance is also compatible with the segregation pattern in this family. An additional unknown mutation in another migraine susceptibility gene could then be responsible for the migraine phenotype in the grandfather (II.3, Fig. 1B) and the sister (IV.3) of the proband, who did not carry the p.Cys702Tyr mutation. The phenotype of epilepsy associated with migraine in the proband, her mother and her uncle (IV.2, III.4 and III.6) could be due to the combination of the p.Cys702Tyr mutation with the unknown mutation. In this hypothesis, the p.Cys702Tyr mutation alone would be insufficient to cause either epilepsy or migraine. The disease phenotype in the distantly related patient (IV.1) could result from other genetic or environmental factors, possibly including the unknown mutation present in the core family. Todt and colleagues also reported a non-Mendelian inheritance pattern in two families with MA and MO carrying missense mutations in *ATP1A2* (2005).

In our two families, the migraine phenotypes associated with an *ATP1A2* mutation were distinct, that is FHM in family A versus common forms of migraine in family B. However, the epileptic phenotypes showed several similarities. Seizures mainly started in adolescence or early adulthood and semiology suggested onset in the occipital or temporal lobes. Treatment with AEDs was necessary in six of the eight epilepsy patients. In the probands of each

family, seizures were difficult to control. Both underwent a presurgical evaluation, before we fully realized the family history and knew the mutations. Our data stress the importance of obtaining a good history of migraine and a family history of epilepsy and migraine in the presurgical work-up of patients with refractory partial epilepsy with normal MRI of the brain or unilateral hippocampal sclerosis. The epileptic phenotypes of our patients differed from those previously described in patients of FHM families with an *ATP1A2* mutation. The seizures reported in the literature were usually benign, occurred mainly during childhood and remitted spontaneously. In our families, seizures started later in life and were more severe. The difference in epileptic phenotype may be due to differences in selection methods. Our probands were initially collected based on their epileptic phenotype and the families reported in the literature were selected through their migraine phenotype.

Previous studies investigating the role of *ATP1A2* in the etiology of pure epilepsy syndromes, all obtained negative results. Two studies showed no association between common variations in *ATP1A2* and temporal lobe epilepsy or idiopathic generalized epilepsy (Buono et al., 2000; Lohoff et al., 2005). In addition, mutation analysis of *ATP1A2* in 12 families with pure BFIS did not reveal any disease-causing mutation (Martinelli et al., 2005). The patients and families selected for these studies manifested only epilepsy and no migraine. Together with the results of our study, this suggests that *ATP1A2* mainly plays a role in syndromes characterized by the cooccurrence of epilepsy and migraine.

Functional analyses of several reported *ATP1A2* mutations have shown that some mutations cause total loss of function (De Fusco et al., 2003; Bassi et al., 2004; Koenderink et al., 2005; Todt et al., 2005; Vanmolkot et al., 2006a) while others reduce the catalytic turnover or change the kinetic characteristics of the Na^+, K^+-ATPase pump (Segall et al., 2004; Segall et al., 2005; Vanmolkot et al., 2006b). The localization of the two mutations identified in this study suggests that they may also alter the function or the kinetics of the Na^+, K^+-ATPase pump. Both mutations are predicted to affect evolutionary conserved amino acids in functionally important regions of the protein. The p.Gly900Arg mutation is located in the extracellular loop between TM7 and TM8. The affected glycine is part of the four amino acids sequence (SYGQ) which is directly involved in protein-protein interaction between the α-and β-subunits of the Na^+, K^+-ATPase (Colonna et al., 1997). The second mutation, p.Cys702Tyr, affects a conserved cysteine in the loop between TM4 and TM5. This loop harbors critical functional regions of the protein, including the phosphorylation and nucleotide-binding domains, and undergoes major conformational changes during the enzymatic cycle (Moller et al., 1996). Moreover, the majority of the reported FHM2 mutations are located in this loop.

There are four different Na^+K^+-ATPase α-isoforms ($\alpha1$-$\alpha4$) with unique kinetic properties and expression patterns. The $\alpha2$-isoform gene is expressed specifically and abundantly in skeletal muscle, adipose tissue, heart, and brain. In mice, the $\alpha2$-subunit is widely expressed in neurons throughout the brain at the time of birth, whereas in adult brain the expression is primarily located in astrocytes (Moseley et al., 2003). Glial and neuronal Na^+, K^+-ATPase plays an important role in clearance of extracellular K^+ to prevent depolarisation of neurons during high neuronal activity. The Na^+- and K^+- gradients set by the Na^+, K^+-ATPase are also important for reuptake of glutamate from the synaptic cleft via the glutamate transporter and for regulation of intracellular calcium via the Na^+, Ca^{2+}-exchanger. Malfunctioning of the Na^+, K^+-ATPase pump may lead to neuronal hyperexcitability and facilitate both paroxysmal depolarizing shifts (PDS), causing seizures, and cortical spreading depression (CSD), causing migraine, by three synergistic events: elevation of extracellular K^+ levels, accumulation of glutamate in the synaptic cleft, and increase of intracellular Ca^{2+} concentration (Lauritzen, 1994; Pietrobon, 2005). Interestingly, the occipital cortex has the lowest glial to neuronal cell ratio and potassium-buffering capability, potentially making it especially vulnerable to neuronal hyperexcitability, that is PDS and CSD (Lauritzen, 1994). This hyperexcitability in posterior brain regions could explain clinical features of migraine (e.g., visual aura) and epilepsy (e.g., visual hallucinations) in our families.

This study provides additional evidence that *ATP1A2* mutations can cause both epilepsy and migraine and highlights the need to consider analysis of this gene in patients with a combination of migraine and epilepsy and a positive family history of either migraine or epilepsy.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest: The authors report no conflicts of interest.

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