Epilepsia, **45**(5):479–487, 2004
Blackwell Publishing, Inc.

Autosomal Recessive Idiopathic Epilepsy in an Inbred Family from Turkey: Identification of a Putative Locus on Chromosome 9q32-33

*Betül Baykan, †Francesca Madia, *‡Nerses Bebek, †Stefania Gianotti, §Ahmet Ilter Güney, ‡Naci Cine, ‖Amedeo Bianchi, *Ayşen Gökyiğit, and ¶Federico Zara

*Department of Neurology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey; †Laboratory of Human Genetics, E.O. Ospedali Galliera, Genova, Italy; ‡Institute for Experimental Medicine (DETAE), Istanbul University, §Department of Medical Biology and Genetics, Marmara University Medical Faculty, Istanbul, Turkey; ‖Unit of Neurology, Ospedale S. Donato, Arezzo, and ¶Laboratory of Neurogenetics, Unit of Neuromuscular Disease, Gaslini Institute and University of Genova, Genova, Italy

Summary: *Purpose:* The study describes the clinical features of an inbred family from Turkey with three members affected by seizures and tests possible autosomal recessive (AR) inheritance by means of linkage analysis.

Methods: Personal and family history was obtained from each subject, and general physical, neurologic, and EEG examinations were performed. A set of 382 fluorescence-labeled markers was used for the initial genome-wide search. A further set of 83 markers was used to map the locus precisely and to exclude the remaining genome.

Results: Twelve individuals from three generations were examined. Two subjects were affected by idiopathic epilepsy, whereas, their brother experienced a single unprovoked generalized seizure. Two siblings affected by idiopathic epilepsy and their unaffected sister showed a photoparoxysmal response to photic stimulation. Nine family members reported migraine. The genome-wide search led to the identification of a unique homozygous, 15.1-cM region shared by subjects with seizures on chromosome 9q32-33 and providing a lod score of 2.9. This locus, however, was not associated with migraine in this pedigree.

Conclusions: The study suggests that idiopathic epileptic traits with AR inheritance might be underestimated in the general population and that inbred pedigrees may represent powerful tools for the identification of AR genes. **Key Words:** Idiopathic epilepsy—Autosomal recessive inheritance—Inbred families.

Genetic factors play an important role in the etiology of idiopathic epilepsy (IE). However, epidemiologic studies indicate that IE often manifests as a sporadic condition, sometimes in small familial aggregates, usually phenotypically heterogeneous. Accordingly, it has been hypothesized that several genes with variable effect, possibly interacting with each other and environmental factors, could be responsible for the phenotypic variability and complex inheritance of this group of disorders (1,2).

Conversely, large pedigrees with several affected cases have consistently been described worldwide, suggesting mendelian inheritance for a subset of epileptic syndromes.

So far, most mendelian IEs are autosomal dominant (AD) traits showing reduced penetrance and variable clinical expression (3–9). Although uncommon, AD idiopathic epilepsies have been extensively investigated, leading to the identification of a cohort of epileptogenic genes, most of them encoding for neuronal ion-channel subunits (10).

Conversely, only a few IEs with autosomal recessive (AR) inheritance have been described.

AR inheritance was first proposed for a subset of families affected by familial rolandic epilepsy with linkage detected on chromosome 15q (11). Consistent with the previous report, Guerrini et al. (12) described an inbred family segregating AR rolandic epilepsy in association with paroxysmal exercise-induced dystonia and writer's cramps and mapped the gene on chromosome 16p12-11.2.

Apart from these focal forms of IEs, AR inheritance was proposed for juvenile myoclonic epilepsy by Panayiotopoulos and Obeid (13). AR inheritance also was reported in a large kindred segregating generalized tonic–clonic and myoclonic seizures (14), and the gene mapped on chromosome 16p13.3 (15).

So far, however, no genes responsible for AR idiopathic epilepsies have been identified, and the pathogenesis of these disorders remains unknown.

Accepted December 26, 2004.
Address correspondence and reprint requests to Dr. F. Zara at Laboratorio di Neurogenetica, U.O.Malattie Neuro-Muscolari, Istituto "G. Gaslini" - Università di Genova, Largo Gaslini, 5, 16100 Genova, Italy. E-mail: federicozara@ospedale-gaslini.ge.it

In the present report, we describe the clinical features of an inbred family from Turkey and the identification of a candidate locus for AR idiopathic epilepsy on chromosome 9q32-33.

METHODS

Subjects

This family was identified in a prospective study aiming to investigate Turkish families with IE. The female proband, followed up since 1997, had IGE with photosensitivity and migraine without aura, both easily controlled with valproate (VPA) treatment. The family descends from a common ancestor who had married twice. Consanguineous marriages were an important feature in the pedigree (Fig. 1). Twelve individuals from three generations were directly examined (II:4, III:1, III:2, III:3, III:4, III:5, IV:6, IV:7, IV:8, IV:9, IV:10, and IV:11). Personal and family history was obtained from each subject, and general physical and neurological examinations were performed. Each individual underwent at least one EEG recording including hyperventilation (HV) and intermittent photic stimulation (IPS).

Epilepsy and migraine were diagnosed and classified according to the International League Against Epilepsy (ILAE) and International Headache Society (IHS) criteria, respectively (16,17).

Photoparoxysmal response (PPR) was subclassified into four types of abnormal response to IPS, according to Doose and Waltz (18): type 1 includes spikes within the occipital rhythm; type 2 indicates parietooccipital spikes with a biphasic slow wave; type 3 means parietooccipital spikes with a biphasic slow wave and spread to the frontal region; and type 4 includes generalized spikes and waves or polyspikes and waves.

Nonspecific EEG abnormalities such as irregularities of the background or isolated paroxysms of theta waves were not considered to be indicative of pathological status. Neurologic examination, seizure types and headache characteristics, neuropsychological tests, EEG and magnetic resonance imaging (MRI) findings, and response to therapy were assessed in patients with seizures. More than three EEGs were performed in a 3- to 5-year period, including sleep and sleep deprivation in subjects showing seizures, and at least one EEG was done in the other available subjects (Table 1). Cases II:5 and II:6 live in a distant

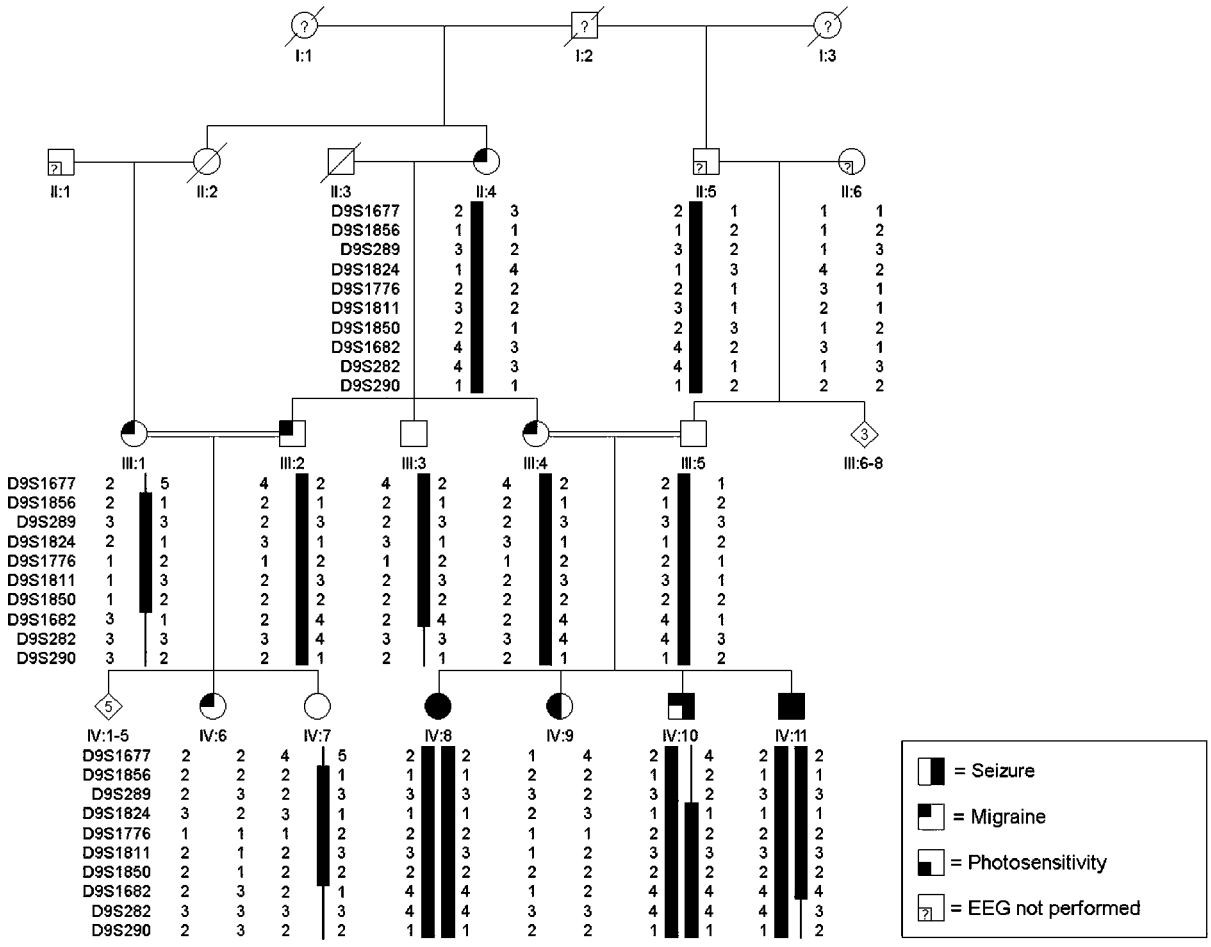

FIG. 1. Pedigree and chromosome 9q haplotypes of the investigated family.

TABLE 1. *Clinical features of the investigated family members*

			GTCS			Headache		EEG findings (no. of recordings)		
ID	Age (yr)	Sex	Age at onset (yr)	Timing	No.	Type	Frequency	At rest and during HV	Photo-sensitivity (a)	MRI findings
II:4	70	F	–	–	–	Migraine without aura	3–4/wk	Normal (1)	–	Not done
III:1	52	F	–	–	–	Migraine without aura	2/mo	Normal (1)	–	Not done
III:2	54	M	–	–	–	Migraine without aura	1/mo	Normal (1)	–	Not done
III:3	44	M	–	–	–	–	–	Normal (1)	–	Not done
III:4	43	F	–	–	–	Migraine without aura	1–2/wk	Nonspecific theta paroxysms (1)	Type 1 (?)	Not done
III:5	46	M	–	–	–	–	–	Nonspecific slow waves during HV (1)	–	Not done
IV:6	28	F	–	–	–	Migraine without aura	1–2/mo	Normal (1)	–	Not done
IV:7	20	F	–	–	–	–	–	Nonspecific slow waves during HV (1)	–	Not done
IV:8	25	F	15	During the day, IPS	2 1	Migraine without aura	1–2/mo	Nonspecific, short, slow-wave paroxysms (5)	Type 4	Left frontal venous angioma, pericerebellar arachnoid cyst
IV:9	23	F	–	–	–	Migraine without aura	1–2/mo	Nonspecific slow-wave paroxysms (2)	Type 3	Not done
IV:10	18	M	16	Early stages of sleep	1	Migraine without aura	1/mo	Nonspecific slow-wave paroxysms during HV (4)	–	Normal
IV:11	15	M	7	On awakening	5	Migraine without aura	3/wk	Nonspecific, short, slow-wave paroxysms (5)	Type 2	Normal

a = grouped according to Doose and Waltz (18); GTCS: generalized tonic-clonic seizure; HV: hyperventilation, IPS: Intermittent photic stimulation.

village of Northern Turkey and could not come to the clinic for neurologic examination and EEG recordings. Clinical information for these individuals was obtained with direct telephone interviews.

The study was approved by the ethical committee of Istanbul Medical Faculty (01.03.2000/79), and all investigated subjects gave written informed consent.

Genotyping and linkage analysis

Three hundred eighty-two fluorescence-labeled markers of the ABI Prism linkage-mapping set version 2 (PE Biosystems) were typed by polymerase chain reaction (PCR) for the genome-wide search. Genotypes were analyzed with GENESCAN 2.0 and GENOTYPER 3.0 software on a 377 ABI Prism Genetic Analyzer all from (Applied Biosystems, Foster City, CA, U.S.A). A further set of 83 ^{32}P-labeled primers from the Genethon linkage map was used for fine mapping (19). Simulations, multipoint lod scores, and haplotypes were performed by using the ALLEGRO 1.1b program (20). Lod scores were calculated assuming a fully penetrant AR epileptic trait with a prevalence of 1×10^{-5} and an AD migraine trait with a prevalence of 0.01, 0.90 penetrance, and 0.1 phenocopy rate. Equifrequent marker alleles were used throughout the analysis.

RESULTS

Pedigree and clinical presentation

Figure 1 shows the pedigree structure of the investigated family, and Table 1 summarizes the clinical and laboratory features of the family affected by epilepsy and migraine.

Neurologic and general examinations were normal in all of the examined family members. The cranial MRIs were normal in two siblings showing seizures. In the index case, cranial MRI disclosed venous angioma at the left frontal deep white matter and pericerebellar arachnoid cyst interpreted as coincidental findings not related to epilepsy. The neuropsychological tests of the index case and case IV:11 revealed normal findings.

Epilepsy features

The family members of generations 1, 2, and 3 did not report seizures. The individuals III:4 and III:5 had a consanguineous marriage, and all but one of their four

children had epileptic seizures. The 25-year-old female proband (case IV:8) had two generalized tonic–clonic seizures (GTCSs) during daytime, with onset at age 15 years. Myoclonic jerks were recorded once during a video-EEG investigation in the IPS period and disappeared after VPA treatment. This case was given a diagnosis of juvenile myoclonic epilepsy.

Her 18-year-old brother (case IV:10) was admitted with a single nocturnal GTCS after fasting for a considerable time at age 16 years. He was followed up without treatment and had no recurrence to date. This patient could not be considered to have epilepsy, as he had only one unprovoked seizure and a nonspecific EEG.

The youngest (15-year-old) male sibling (case IV:11) had a total of five GTCSs on awakening; the first episode occurred at age 7 years. He also had weekly episodes of headache, and one of his GTCSs coincided with one of his headache attacks. He also described a visual aura, characterized by colored, round hallucinations moving across the visual field and usually triggered by television. This description did not resemble the classic appearance of fortification spectra with squared borders, and it is much more in keeping with visually evoked occipital lobe seizures than with a typical migraine aura. His GTCSs, however, were not triggered by visual stimuli, and four of them were not related to any visual aura. Moreover, he did not have any isolated visual aura without succeeding pulsating headaches. We think that he had idiopathic epilepsy with photosensitivity, besides migraine.

The outcome of the seizures was favorable in all the cases. The index case was seizure free during last 5 years with VPA treatment. Case IV:10 did not use any drugs and had no further seizures in the follow-up period. Case IV:11 experienced a GTCS under treatment with 1,250 mg VPA. After the increase of the dosage to 1,500 mg VPA, no other seizures occurred.

EEG findings

In all the investigated subjects (12 family members), the background activity was normal.

In the proband, interictal EEGs showed nonspecific slow-wave paroxysms of short duration at resting condition (Fig. 2a). Nonspecific slow-wave paroxysms were accentuated during hyperventilation. Generalized polyspike-and-wave discharges (GSWs) were observed during IPS, indicating a type 4 PPR response. A prolonged video-EEG investigation was performed to evaluate the occurrence of myoclonic jerks. In this examination, myoclonic jerks were recorded at the time of eye closure during IPS (Fig. 2b). Unfortunately, her third GTCS occurred in the same video-EEG examination (at 15-Hz IPS). She had an ictal EEG pattern with a generalized onset (Fig. 2c).

EEG of case IV:10 showed generalized theta waves 2 min after the onset of hyperventilation (Fig. 3a). Repeated EEGs including short daytime sleep and 24-h sleep deprivation revealed no evidence of photosensitivity and of other specific changes in that case, although it was done without treatment.

The EEGs of case IV:11 showed irregular spikes and waves prominent on posterior regions elicited by IPS at 14 to 18 Hz, diagnosed as type 2 PPR (Fig. 3b).

The EEGs of the asymptomatic sibling (case IV:9) demonstrated rare theta waves over both hemispheres and type 3 PPR during IPS in a prolonged EEG (Fig. 4a).

The EEG of the mother showed questionable findings that could be interpreted either as a mild PPR type 1 or a photic driving response (Fig. 4b), whereas the father

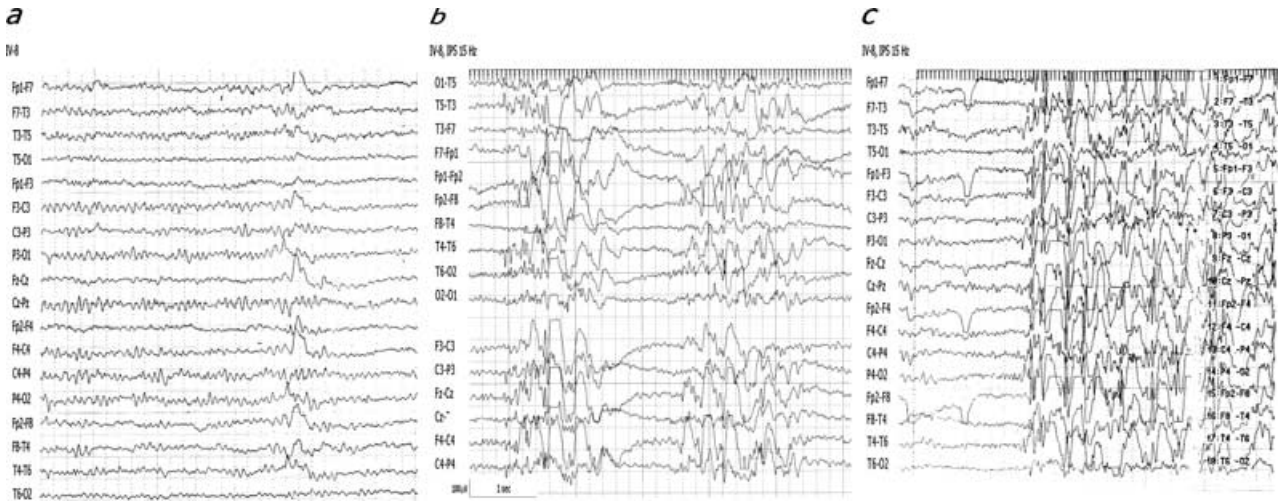

FIG. 2. EEG findings of the index patient (case IV:8). **a:** Resting EEG showing a nonspecific slow-wave paroxysm. **b:** Generalized polyspikes-and-waves during 15 Hz of intermittent photic stimulation (IPS). **c:** Onset of a generalized convulsion during IPS.

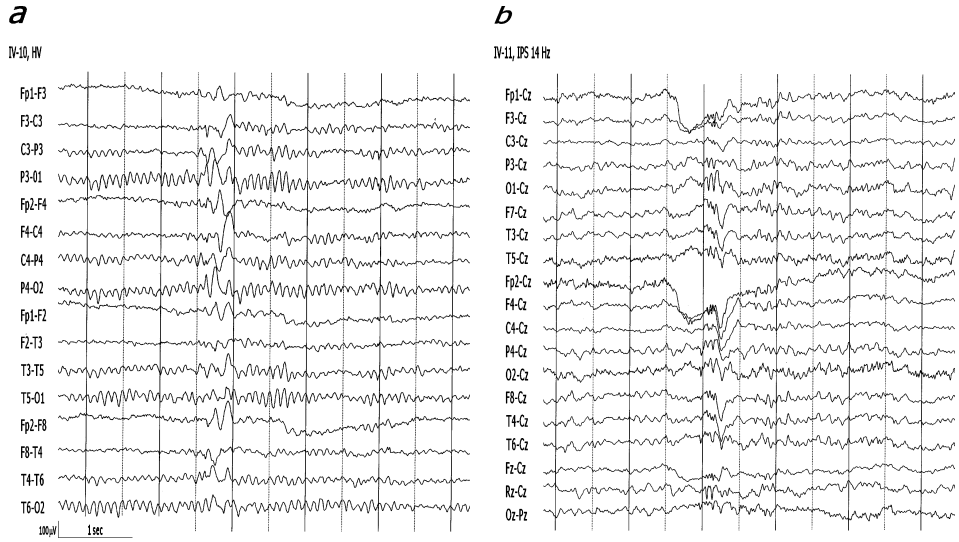

FIG. 3. EEG findings of other cases with seizures. **a:** EEG of case IV:10 demonstrating a short nonspecific slow-wave paroxysm during hyperventilation (HV). **b:** Photoparoxysmal response (PPR) elicited with 14 Hz of intermittent photic stimulation in IV:11.

showed nonspecific slow-wave changes during hyperventilation (Fig. 4c).

EEG examinations in all five other investigated relatives revealed normal results except nonspecific slow-wave changes during hyperventilation in case IV:7, aged 20 years.

Other neurologic features

Migraine was a common clinical condition in the family. Family members from three generations reported headaches diagnosed as migraines (Fig. 1).

The index case had monthly episodes of one-sided (left or right) severe headache without aura, which had a throbbing quality, lasting >4 h. Nausea or vomiting did not occur. Noisy and overcrowded situations and head movements worsened the headache. Sunlight also could trigger headaches. She reported inability to look at the sun for a relatively long period. To relieve the headache, she took analgesic drugs and went to sleep. VPA made her life more comfortable. She had also mild to moderate, nonthrobbing tension headache episodes localized on the neck as a second type of headache.

Her 23-year-old sister without seizures (case IV:9) also had typical characteristics of the headache, diagnosed as migraine without aura.

Case IV:10 also complained of severe and right-sided throbbing headache episodes lasting 6 h, relieved with analgesic drugs and accompanied by nausea and vomiting. He reported aggravation with physical activity and phonophobia. His single GTCS occurred shortly after a migraine attack, during the early hours of night sleep.

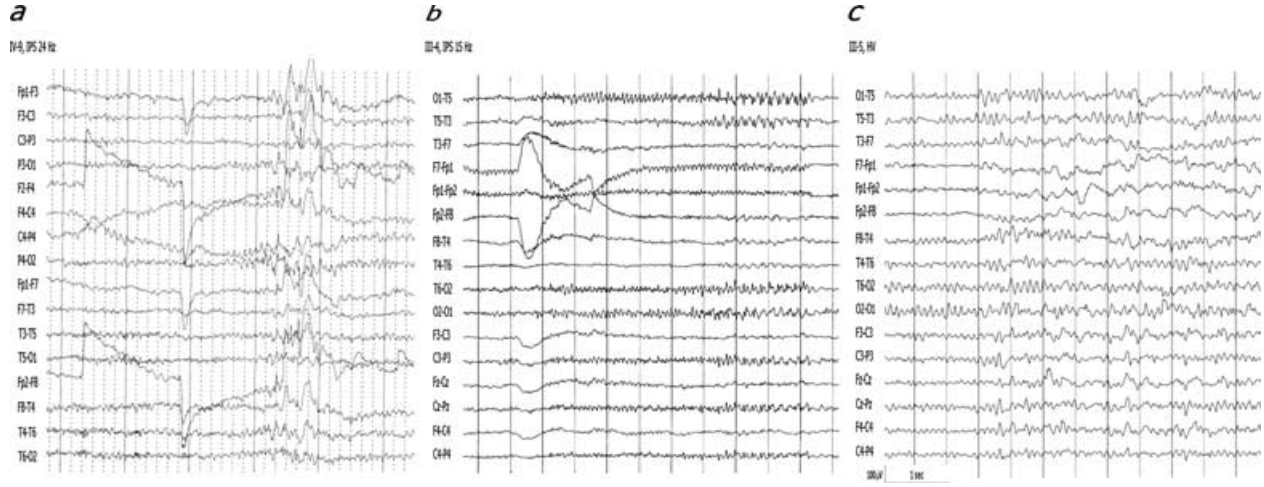

FIG. 4. EEG features of the members without epilepsy. **a:** Photoparoxysmal response (PPR) of case IV:9 during 24 Hz of intermittent photic stimulation (IPS). **b:** EEG of the proband's mother, suggesting a mild PPR type I elicited by 15 Hz of IPS or a photic driving with alpha rhythm subharmonics. **c:** Mild generalized slow-wave activity after the hyperventilation period of the father (case III:5).

Case IV:11 had the worst headaches among his siblings, according to the mother. They occurred one to three times weekly. Nausea was always present. The previously mentioned visual aura characterized by white–blue moving spots, was triggered by TV or bright light and was not present on every occasion (one to two monthly) of the headaches. The headache localized mainly to the frontal and eye regions on both sides, with a throbbing quality and aggravated with physical activity. The episodes lasted nearly 1 day if he did not use analgesic drugs. VPA clearly reduced the quality and quantity of the headaches.

Their mother (case III:4) had both migraines without aura and tension headaches as did the index case, whereas their father (case III:5) denied having any prominent headache episodes. The grandmother (case II:4), cases III:1 and III:2 with a consanguineous marriage, and one of their children were diagnosed also as having migraine without aura (IV:7).

All of the subjects with migraine reported inability to look at the sun. The distribution of migraine in the family is compatible with AD inheritance.

Linkage analysis

Simulations were carried out to determine whether the family could provide the statistical power to map loci for both the AR epileptic trait and AD migraine. Maximum expected multipoint were 2.9 for seizures and 2.3 for migraine. According to this, we focused our study on the localization of the gene responsible for seizures. A genome-wide screening was undertaken on the family branch affected by seizures (II:4, II:5, II:6, III:4, III-5, IV:8, IV:9, IV:10, and IV:11) by using 382 microsatellite markers covering 3.379 cM autosomal DNA at an average spacing of 8.8 cM.

The screening led to the identification of a unique homozygous segment on chromosome 9q32-33. A further set of 83 markers was used to fine-map the 9q locus and to follow up regions that were not excluded by the initial screening.

When using all available family members, multipoint lod scores reached 2.9 along a 15.1-cM interval between markers D9S289 and D9S282 (Table 2). The analysis of haplotypes revealed a large region of homozygosity in all subjects affected by seizures (Fig. 1), indicating that they inherited the same DNA segment from individual I:2.

To determine whether the heterozygosity at the chromosome 9q locus was associated with migraine in the family, we performed linkage analysis assuming an AD trait with 0.90 penetrance, as suggested by the transmission pattern observed in the family. The phenocopy rate was set to 0.1, according to the high prevalence of migraine in the population. However, lod scores were negative along the region due to the presence of three male carriers without migraine (II:5, III:3, and III:5) and two female individuals with migraine not carrying the putative disease haplotype (IV:6 and IV:9).

TABLE 2. *Multipoint Lod scores for epilepsy and migraine versus chromosome 9q32-33 markers*

Marker	Location (cM)	Lods	
		Epilepsy (AR)	Migraine (AD)
D9S1677	0	$-\infty$	−1.2
D9S1856	2.6	$-\infty$	−2.4
D9S289	3.3	$-\infty$	−2.4
D9S1824	4.8	2.9	−2.5
D9S1776	6.4	2.9	−2.5
D9S1811	10.2	2.9	−2.5
D9S1850	15.1	2.8	−2.3
D9S1682	18.3	2.8	−2.1
D9S282	18.4	$-\infty$	−1.3
D9S290	23.3	$-\infty$	−1.3

AD, autosomal dominant; AR, autosomal recessive.

DISCUSSION

Epilepsy

We describe an inbred family from Turkey with two members affected by IE with photosensitivity and one individual showing a single unprovoked generalized seizure.

The clinical features of the epileptic phenotype we observed in the family are not uniform and do not fit traditional clinical classification precisely, as reported for other familial IEs (7–9). IEs are characterized primarily by age at onset, absence of structural brain damage, lack of neurologic signs and symptoms, and by the seizure types. In this family, only the index case had documented generalized myoclonia precipitated by IPS, and none of the other patients had myoclonic jerks. Furthermore, they had GTCSs at any time of the day. The differences found with respect to the age at onset (7 vs. 15–16 years), to the diurnal distribution of GTCSs (during night sleep, during the daytime, or on awakening), to the frequency of GTCSs (single seizure vs. five GTCSs) and to the presence or absence of myoclonus, are all consistent with intrafamilial phenotypic variability observed for many IEs (5,7,9,21), as a result of the interaction between high penetrant inherited mutations and the individual genetic background.

The clustering of epileptic seizures in a single generation and the presence of documented consanguinity suggest an AR mode of inheritance and prompted us to attempt the localization of the putative gene by homozygosity mapping.

A unique, large, homozygous region was identified in all patients on chromosome 9q. Maximum lod scores along the critical region (2.9) fall just below the threshold of "3" traditionally used to declare linkage for mendelian traits. However, we could exclude the presence of alternative homozygous regions in the remaining genome by

typing an additional set of densely spaced markers. Thus we consider our data highly suggestive of the presence of a gene for AR-IE on chromosome 9q32-33.

Epilepsy and photosensitivity

While collecting EEG data of the family, we detected photosensitivity in two siblings with seizures (IV:8 and IV:11), the unaffected sister (IV:9), and questionable findings in their mother, who was quite old for a definitive photosensitive response on the EEG (III:4).

Photosensitivity is defined by the occurrence of spikes or spikes-and-waves in response to IPS. The EEG pattern can show a wide range of expression from occipital spikes to generalized irregular spikes-and-waves (18). Epidemiologic studies showed that photosensitivity is a common condition occurring in ~7% of healthy children aged from 1 to 16 years. Girls are more often affected than boys, and PPR is associated with epilepsy in only 3% of subjects (18). Thus photosensitivity is not observed in most patients affected by epilepsy. According to this, epilepsy and PPRs have different genetic etiologies, even though they may share some genes (22). Based on a family study, Waltz and Stephani (23) proposed an AD transmission with age-dependent penetrance. However, the variable expressivity of the trait and the high prevalence of PPR in the population suggest a more complex inheritance and some caution in the interpretation of family data.

Our findings fit these observations well. The lack of photosensitivity in one male sibling (IV:10) with epilepsy and its presence in the sister without seizures indicate that seizure susceptibility and PPR are likely to be independent manifestations in this family.

Epilepsy and migraine

A further peculiar clinical feature of the family is the presence of several individuals with migraine without aura. Epilepsy and migraine are definitely different disorders, although connections may exist for specific conditions.

The aura with visual symptoms is the complex of neurologic symptoms, which occurs just before or at the onset of the migraine headache, but is also common in patients with occipital lobe epilepsy (24). Furthermore, in some patients, the migraine precedes complex partial seizures as a triggering factor (25,26). In the youngest brother, one GTCS was preceded by his typical headache attack after a visual aura resembling mostly a simple partial seizure of occipital onset. The subject did not report isolated visual auras without succeeding headaches, and four other GTCSs did not relate to any aura or any visual trigger. This patient might have a form of photosensitive occipital lobe epilepsy besides migraine.

When large populations are considered, the link between migraine and epilepsy becomes looser and controversial. Marks and Ehrenberg (25) found that ~20% of epilepsy patients had the migraine syndrome. Conversely, the study of Ottman and Lipton (27) failed to detect any association between migraine and epilepsy.

Genetic factors play an important role in the etiology of both epilepsy and migraine, particularly when an aura is present (28). A genetic overlapping between epilepsy and migraine has been found in rare families with familial hemiplegic migraine and epilepsy for a P/Q-type calcium channel α1-subunit gene (CACNA1A) and a sodium/potassium pump α2-subunit (ATP1A2) (29,30). However, a causative role of these genes in common forms of migraine and epilepsy has not been demonstrated.

In this family, migraine spans three generations and affects all patients with seizures ($n = 3$) and six additional individuals without epilepsy. Therefore we hypothesized that the chromosome 9q locus might be responsible for migraine in heterozygous subjects and for a more severe phenotype (migraine + seizures) in homozygous individuals. However, our data indicate that migraine is not determined by the chromosome 9 locus.

The clustering of migraine in this family could either occur as a coincidence because of the high prevalence of migraine in the population, or be determined by another gene with a dominant effect.

Photosensitivity and migraine

We cannot exclude that migraine and photosensitivity might share a genetic basis in this family. In our family, three individuals showing a PPR have migraines, but the sample is too limited to address the issue.

The development of migraine after intense visual stimulations, such as bright sunlight or the flash of headlights, is well recognized (31). So far, however, the link between migraine and EEG changes induced by photic stimuli has been poorly investigated.

CONCLUSIONS

Although AR inheritance has been proposed for different forms of human IE (11,13), robust genetic evidence has been provided for two rare phenotypes to date: rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp, and familial myoclonic epilepsy of infancy (12,15).

This finding apparently conflicts with the observation that epileptic traits are often transmitted as AR disorders in other mammals [dogs (32), rats (33), mice (34–36) and more distant species such as chickens (37) and *Drosophila* (38). This discrepancy may be partially due to the high inbreeding rate of specific animal populations or to bias in the evaluation of phenotypes toward more severe AR traits.

We believe, however, that AR traits in human IE are underestimated as a consequence of (a) phenotypic and genetic variability of epilepsies; (b) the lower clustering of cases in families affected by AR traits compared with AD traits; and (c) the demographic structure of populations in which most family studies are carried on. Within

the European Community, for instance, the average number of offspring for a woman is 1.47 (2001 data from Eurostat), and recessive traits are expected to manifest as sporadic conditions at most. If we take into account phenotypic and genetic heterogeneity of epilepsy, we can assume that several AR traits may be present in the general population as clinically and genetically distinct sporadic phenotypes.

Under this scenario, the analysis of AR traits cannot rely on large pools of nuclear families, whereas inbred families will play an essential role (11,12).

We describe a family affected by AR idiopathic epilepsy, and we identify a candidate locus for IE on chromosome 9q32-33. So far, no genes have been associated with AR idiopathic epilepsies. Thus candidate genes cannot be easily selected among a hundred of transcripts mapped within the critical region. A few genes, however, show a strong preferential expression in the brain: brain-specific spectrin (SPAN1), syntaxin-binding protein 1 (STXBP1), and paralemmin 2 (PALM2). It is still unknown whether this locus underlies a very rare phenotype or a more common condition. Recent studies indicate that genes initially associated with rare traits turned out to be involved in rather frequent disorders (39,40). Thus in the absence of novel methodologic approaches, the genetic analysis of sporadic cases and families that are uninformative for linkage analysis will probably require the identification of several candidate genes—maybe hundreds—through the study of familial phenotypes.

Acknowledgment: We honor the family whose openness and cooperation made this study possible. We thank Dr. Ugur Ozbek for his contributions to the study. We also thank the members of the Turkish League Against Epilepsy, Commission on Genetics, for their valuable comments. This work was supported by the Research Fund of the Istanbul University (Project number 910/061296) and the "Pierfranco e Luisa Mariani" Foundation (F.Z.) and the Italian Ministry of Health (Project RF 3/00 to F.Z.).

REFERENCES

1. Anderson VE, Hauser WA, Rich SS. Genetic heterogeneity and epidemiology of the epilepsies. In: Delgado-Escueta AV, Wilson WA, Olsen RW, et al., eds. *Jasper's basic mechanisms of the epilepsies: advances in neurology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999:59–73.
2. Prasad AN, Prasad C, Stafstrom CE. Recent advances in the genetics of epilepsy: insights from human and animal studies. *Epilepsia* 1999;40:1329–52.
3. Bjerre I, Corelius E. Benign familial neonatal convulsions. *Acta Paediatr Scand* 1968;57:557–61.
4. Vigevano F, Fusco L, Di Capua M, et al. Benign infantile familial convulsions. *Eur J Pediatr* 1992;151:608–12.
5. Scheffer IE, Bhatia KP, Lopes-Cendes I, et al. Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder. *Lancet* 1994;343:515–7.
6. Scheffer IE, Jones L, Pozzebon M, et al. Autosomal dominant rolandic epilepsy and speech dyspraxia: a new syndrome with anticipation. *Ann Neurol* 1995;38:633–42.
7. Ottman R, Risch N, Hauser WA, et al. Localization of a gene for partial epilepsy to chromosome 10q. *Nat Genet* 1995;10:56–60.
8. Scheffer IE, Berkovic SF. Generalized epilepsy with febrile seizures plus: a genetic disorder with heterogeneous clinical phenotypes. *Brain* 1997;120:479–90.
9. Xiong L, Labuda M, Li DS, et al. Mapping of a gene determining familial partial epilepsy with variable foci to chromosome 22q11-q12. *Am J Hum Genet* 1999;65:1698–710.
10. Roll P, Szepetowski P. Epilepsy and ionic channels. *Epileptic Disord* 2002;4:165–72.
11. Neubauer BA, Fiedler B, Himmelein B, et al. Centrotemporal spikes in families with rolandic epilepsy: linkage to chromosome 15q14. *Neurology* 1998;51:1608–12.
12. Guerrini R, Bonanni P, Nardocci N, et al. Autosomal recessive rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp: delineation of the syndrome and gene mapping to chromosome 16p12-11.2. *Ann Neurol* 1999;45:344–52.
13. Panayiotopoulos CP, Obeid T. Juvenile myoclonic epilepsy: an autosomal recessive disease. *Ann Neurol* 1989;25:440–3.
14. de Falco FA, Majello L, Santangelo R, et al. Familial infantile myoclonic epilepsy: clinical features in a large kindred with autosomal recessive inheritance. *Epilepsia* 2001;42:1541–8.
15. Zara F, Gennaro E, Stabile M, et al. Mapping of a locus for a familial autosomal recessive idiopathic myoclonic epilepsy of infancy to chromosome 16p13. *Am J Hum Genet* 2000;66:1552–7.
16. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389–99.
17. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;8:1–96.
18. Doose H, Waltz S. Photosensitivity: genetics and clinical significance. *Neuropediatrics* 1993;24:249–55.
19. Dib C, Faure S, Fizames C, et al. A comprehensive genetic map of the human genome based on 5.264 microsatellites. *Nature* 1996;380:152–4.
20. Gudbjartsson DF, Jonasson K, Frigge ML, et al. Allegro, a new computer program for multipoint linkage analysis. *Nat Genet* 2000;25:12–3.
21. Singh R, Scheffer IE, Crossland K, et al. Generalized epilepsy with febrile seizures plus: a common childhood-onset genetic epilepsy syndrome. *Ann Neurol* 1999;45:75–81.
22. Zifkin BG, Kasteleijn-Nolst Trenite D. Reflex epilepsy and reflex seizures of the visual system: a clinical review. *Epileptic Disord* 2000;2:129–36.
23. Waltz S, Stephani U. Inheritance of photosensitivity. *Neuropediatrics* 2000;31:82–5.
24. Andermann F, Zifkin B. The benign occipital epilepsies of childhood: an overview of the idiopathic syndromes and the relationship to migraine. *Epilepsia* 1998;39(suppl 4):S9–23.
25. Marks DA, Ehrenberg BL. Migraine-related seizures in adults with epilepsy, with EEG correlation. *Neurology* 1993;43:2476–83.
26. Niedermeyer E. Migraine-triggered epilepsy. *Clin Electroencephalogr* 1993;24:37–43.
27. Ottman R, Lipton RB. Is the comorbidity of epilepsy and migraine due to a shared genetic susceptibility? *Neurology* 1996;47:918–24.
28. Russell MB, Iselius L, Olesen J. Migraine without aura and migraine with aura are inherited disorders. *Cephalalgia* 1996;16:305–9.
29. Ophoff RA, Terwindt G, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type 2 are caused by mutations in the Ca^{++} channel gene CACNL1A4. *Cell* 1996;87:543–52.
30. Fusco MD, Marconi R, Silvestri L, et al. Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump $\alpha 2$ subunit associated with familial hemiplegic migraine type 2. *Nat Genet* 2003;33:192–6.
31. Debney LM. Visual stimuli as migraine trigger factors. In: Clifford Rose F, ed. *Progress in migraine research*. London: Pitman, 1984:30–54.
32. Hall SJ, Wallace ME. Canine epilepsy: a genetic counseling program for keeshonds. *Vet Rec* 1996;138:358–60.
33. Noda A, Hashizume R, Maihara T, et al. NER rat strain: a new type of genetic model in epilepsy research. *Epilepsia* 1998;39:99–107.
34. Fletcher CF, Lutz CM, O'Sullivan TN, et al. Absence epilepsy in tottering mutant mice is associated with calcium channel defects. *Cell* 1996;87:607–17.

35. Burgess DL, Jones JM, Meisler MH, et al. Mutation of the Ca^{2+} channel beta subunit gene Cchb4 is associated with ataxia and seizures in the lethargic (lh) mouse. *Cell* 1997;88:385–92.
36. Letts VA, Felix R, Biddlecome GH, et al. The mouse stargazer gene encodes a neuronal Ca^{2+}-channel gamma subunit. *Nat Genet* 1998;19:340–7.
37. Nunoya T, Tajima M, Mizutani M. A hereditary nervous disorder in Fayoumi chickens. *Lab Anim* 1983;17:298–302.
38. Wang XJ, Reynolds ER, Deak P, et al. The seizure locus encodes the *Drosophila* homolog of the HERG potassium channel. *J Neurosci* 1997;17:882–90.
39. Escayg A, MacDonald BT, Meisler MH, et al. Mutations of SCN1A encoding a neuronal sodium channel, in two families with GEFS+2. *Nat Genet* 2000;24:343–5.
40. Claes L, Del-Favero J, Ceulemans B, et al. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. *Am J Hum Genet* 2001;68:1327–32.