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Four New Families with Autosomal Dominant Partial Epilepsy with Auditory Features: Clinical Description and Linkage to Chromosome 10q24

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Summary

Purpose—Autosomal dominant partial epilepsy with auditory features (ADPEAF) is a rare form of nonprogressive lateral temporal lobe epilepsy characterized by partial seizures with auditory disturbances. The gene predisposing to this syndrome was localized to a 10-cM region on chromosome 10q24. We assessed clinical features and linkage evidence in four newly ascertained families with ADPEAF, to refine the clinical phenotype and confirm the genetic localization.

Methods—We genotyped 41 individuals at seven microsatellite markers spanning the previously defined 10-cM minimal genetic region. We conducted two-point linkage analysis with the ANALYZE computer package, and multipoint parametric and nonparametric linkage analyses as implemented in GENEHUNTER2.

Results—In the four families, the number of individuals with idiopathic epilepsy ranged from three to nine. Epilepsy was focal in all of those with idiopathic epilepsy who could be classified. The proportion with auditory symptoms ranged from 67 to 100%. Other ictal symptoms also were reported; of these, sensory symptoms were most common. Linkage analysis showed a maximum 2-point LOD score of 1.86 at ($\theta = 0.0$ for marker D10S603, and a maximum multipoint LOD score of 2.93.

Conclusions—These findings provide strong confirmation of linkage of a gene causing ADPEAF to chromosome 10q24. The results suggest that the susceptibility gene has a differential effect on the

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lateral temporal lobe, thereby producing the characteristic clinical features described here. Molecular studies aimed at the identification of the causative gene are underway.

Keywords

Epilepsy; Epidemiology; Focal; Auditory; Genetics; Linkage; Phenotype

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Epilepsy is one of the most common neurologic disorders, affecting ~3% of individuals at some time in their lives (1). Genetic susceptibility clearly contributes to the etiology of many forms of epilepsy, but the extreme clinical and etiologic heterogeneity of the disorder presents constant challenges for genetic research. Through the increasingly collaborative efforts of neurologists, genetic epidemiologists, and molecular biologists, specific susceptibility genes that raise risk for certain epilepsy syndromes have been localized and identified.

As of November 2001, causative genes have been identified in three nonprogressive human epilepsy syndromes: benign familial neonatal convulsions (2,3), autosomal dominant nocturnal frontal lobe epilepsy (4,5), and generalized epilepsy with febrile seizures plus (6–9). Interestingly, all of these genes encode voltage-gated or ligand-gated ion channels. In addition, localization of susceptibility genes to specific chromosomal regions has been reported in 11 nonprogressive epilepsy syndromes (10–31), including autosomal dominant partial epilepsy with auditory features (ADPEAF) (32–37).

We localized the gene for ADPEAF to a 10-cM interval on chromosome 10q24 in an analysis of a single large pedigree with apparently autosomal dominant inheritance with 71% penetrance (32). In this family (family 6610; Table 1), six of 11 family members with epilepsy that could not be attributed to an identified environmental insult described auditory auras at seizure onset. Other sensory symptoms (visual, olfactory, vertiginous, and cephalic) also were reported frequently, but autonomic, psychic, and motor symptoms were less common. The clinical seizure manifestations suggested that the effect of the mutation is localized to the lateral temporal lobe(35).

In 1999, a large Basque family was reported with clinical features very similar to those of ADPEAF (33). Affected individuals reported auditory and visual ictal symptoms. The partial seizure manifestations suggested a lateral temporal lobe origin near the temporo-occipital junction, and EEG and single-photon emission computed tomography (SPECT) abnormalities also pointed to the temporal lobe as an area of dysfunction. A susceptibility gene was localized to a 15-cM interval on chromosome 10q that overlaps with the ADPEAF region by a common 3-cM core. Because of the great similarity in clinical features in our original linkage family and that described by the Basque group, we believe it is likely that the same gene underlies epilepsy in the two families. If this is true, then the linkage evidence in the Basque pedigree helps to narrow the region from 10 to 3 cM. Two other families with clinical features similar to ADPEAF also were reported by other investigators, with linkage evidence consistent with the same localization on 10q, but too few affected family members to reach statistical significance (34,36).

The Basque group called the syndrome they described “autosomal dominant lateral temporal epilepsy.” However, we prefer to denote the syndrome by our original name, which emphasizes the auditory symptoms rather than brain localization. Although the seizures in ADPEAF probably do originate from the lateral temporal lobe, the genetic contributions to epilepsies with this brain localization may be very heterogeneous. Restriction to epilepsies involving specific auditory symptoms may reduce genetic heterogeneity somewhat (although the possibility of heterogeneity cannot be excluded in this subgroup either). We used the characteristic auditory features described in our original family to identify new families with

ADPEAF and define the phenotype for subsequent linkage analysis. Here we describe clinical features and evidence for linkage to chromosome 10q24 in four newly identified families with ADPEAF.

The confirmation of linkage in these four families is important because it validates their suitability for studies aimed at identifying the causative gene for ADPEAF. Use of these families for gene identification requires strong evidence—both clinical and genetic—that they are likely to represent the same syndrome. This linkage finding provides that evidence, while supplying a phenotype description that will facilitate recognition of the syndrome by other clinicians and investigators.

METHODS

Clinical data collection

Since publication of our original linkage finding, we have been searching for additional families with the same syndrome to be used to refine the localization. Given the distinct auditory symptoms in the original family (and the relative rarity with which they are generally reported), we have tried to find families containing four or more individuals with auditory symptoms. We have found two additional families that meet this criterion, and also have collected data from two smaller families that appear to have the same phenotype (Fig. 1). We describe the clinical characteristics of all four families and the results of linkage analysis in three of them. The remaining family (family D; Fig. 1) is uninformative for linkage because only an affected parent–child pair could be sampled.

Each subject was screened for occurrence of seizure disorders through a telephone interview administered either directly or to a close relative. Screening interviews also were administered to a parent whenever possible, to ensure complete ascertainment of childhood seizures. Subjects reported to have had afebrile seizures were given a diagnostic evaluation that included a semistructured diagnostic interview administered either in person or over the telephone by a neurologist or physician with specialized training in epilepsy. The diagnostic interview, a revised version of that used in the original phase of the study (38,39), obtained information on seizure semiology through both verbatim descriptions and structured questions about signs and symptoms, and on seizure etiology through questions about history and timing of specific risk factors previously demonstrated for epilepsy.

Medical records were requested when information from the diagnostic interview was ambiguous or further clarification was needed. Data from neurologic examinations, EEGs, and neuroimaging were not obtained systematically because they seldom contributed significantly to the diagnosis in an earlier phase of the study in which they were systematically obtained. However, information from the medical records on the results of EEGs, imaging studies, neurologic examinations, and histories were used to supplement the information from the diagnostic interview when available.

Final diagnoses were assigned by the senior neurologists (W.A.H., T.A.P.), based on review of all of the data collected on each subject. Epilepsy was defined as a lifetime history of two or more unprovoked seizures. Subjects with epilepsy who had a history of an insult to the central nervous system (CNS) occurring ≥7 days before the first unprovoked seizure were classified as *remote symptomatic;* those with no identified cause were classified as *idiopathic*. Seizures precipitated by acute alterations in homeostasis or insults to the CNS (including febrile seizures) were excluded from the definition of epilepsy and classified as *acute symptomatic.* Seizures were classified according to the 1981 criteria of the International League Against Epilepsy (ILAE) (40), and epilepsies according to the 1989 ILAE criteria for classification of epileptic syndromes (41). To ensure that diagnoses were made blindly with

respect to those of other family members, identifying information was removed before consensus review, and subjects from different families (including many with epilepsies other than ADPEAF) were reviewed in random order.

Genotype determination

In families A, B, and C, 41 individuals were genotyped for seven microsatellite markers spanning the 10 cM minimal genetic region defined by our original linkage report. All the markers were screened by using a semiautomatic fluorescence-labeled genotyping system (42,43). In brief, polymerase chain reaction (PCR) reactions were performed in 384-well PCR plates (Marsh Bio Products, Rochester, NY U.S.A.) and PTC 225 thermocyclers (MJ Research, Inc., Waltham, MA U.S.A.) with a total volume of 10 μ1 containing 50 ng of genomic DNA, 0.15–0.2 m *M* $MgCl_2$, 0.2 m *M* dNTPs and 0.5 units of platinum Taq DNH polymerase (Gibco Life Tech, Invitrogen Corporation, Carlsbad, CA U.S.A.). Markers were typed by using Applied Biosystems 377 DNA sequencers and the GENESCAN 2.0/GENOTYPER 1.1.1 software (PE Applied Biosystems, Foster City, CA, U.S.A.). Two independent researchers who were blind to disease phenotypes checked the computer-generated genotypes.

Linkage analysis

All of the assumptions regarding phenotype definition and genetic parameters (mode of inheritance, and penetrance and frequency of the susceptibility allele) were made *a priori*, without any information about the genetic marker phenotypes, and were the same as those used in our original linkage report (32). Only individuals with idiopathic epilepsy were classified as affected; those with acute symptomatic seizures, remote symptomatic epilepsy, or uncertain diagnoses were classified as unknown. The marker frequencies used for linkage analysis were estimated from the data on typed individuals within the three families. For analyses with an assumed mode of inheritance, we used an autosomal dominant model with a frequency of 0.001 for the susceptibility allele, and a risk of 1% in noncarriers of the gene. In the original linkage family (32), lifetime cumulative incidence of idiopathic epilepsy in gene carriers was estimated to be 71%. All but one of those affected with idiopathic epilepsy were aged ≥20 years at observation (current age or age at death), and none had onset after age 20 years. The age-at-onset distribution was similar in the families described here. Thus as in the original analysis, for simplicity we assumed a uniform penetrance of 71% in gene carriers 20 years or older, and classified those younger than 20 years who were currently unaffected as unknown.

Initially, we conducted two-point linkage analysis using the ANALYZE package (44). Subsequently, we conducted multipoint parametric and nonparametric linkage analyses as implemented in GENEHUNTER2 (45). For the GENEHUNTER analysis, we used the scoring function based on allele sharing among all affected relatives simultaneously. Some of the nonfounders who were uninformative (e.g., unaffected children) were dropped from the analysis to circumvent the computational limitations of the software. For locus order and intermarker distance, we used the maps from the Marshfield Medical Research Foundation.

RESULTS

Description of the families

Family A—Five individuals in the family have had seizures, including one married-in person (II:4; Fig. 1). Of these, four had idiopathic epilepsy and one (II:4) had febrile seizures. The age at onset of idiopathic epilepsy ranged from 9 to 10 years. Epilepsy was clearly focal in all four individuals with idiopathic epilepsy. All of them had secondarily generalized tonic–clonic seizures, and all reported auditory auras. The auditory symptoms varied among affected family members (Table 2). All four individuals described unformed sounds such as whistling, clicking, or popping, but one individual also reported formed auditory auras of “a phrase being repeated

over and over." One subject's description suggested reflex seizures precipitated by auditory stimuli ("a surprising noise or racket from behind could kick off the aura").

As in the original reported ADPEAF family (35), other auras also were described (Table 1). Three individuals reported other sensory symptoms (visual, gustatory, and vertiginous), and one described psychic symptoms (derealization/depersonalization and déjà vu) at seizure onset.

Results of interictal EEGs or imaging could be obtained on only a few individuals in the family. One subject's (III:7) medical record contained an EEG report that indicated generalized mild slowing without epileptiform activity. Affected individuals were not reported to be neurologically abnormal (other than having seizures), although formal neurologic examination results were available on only one subject (II:3).

Family B—Eleven individuals in the family have had definite seizures, and two additional individuals were classified as having "possible" seizures. Of these, nine had idiopathic epilepsy with onset ranging from 11 to 23 years. One individual had remote symptomatic epilepsy associated with head trauma and infection (V:1), and one individual had febrile seizures (V:7). Two individuals were classified as having "possible" epilepsy because of limited information (V:8, IV:11). In one subject (V:8), the screening interview produced vague reports of an unexplained fall in childhood and one staring episode in adolescence; a full diagnostic interview could not be obtained. In the second (IV:11), the diagnosis was unclear because the single event described was reported only by an uncle of the subject (who was 3 years old at the time of occurrence), and was not reported by either the parents or the subject. These individuals were classified as "unknown" in the linkage analysis.

Among the nine individuals with idiopathic epilepsy, seizures had clearly focal onset in seven; in two individuals, the types of seizures could not be determined. Six (67%) subjects reported auditory auras: formed, unformed, and reflex (Table 2). Other sensory symptoms (vertiginous) also were described, as were motor (clonic unilateral movements in one individual and automatisms in another) and autonomic (visceral/epigastric) symptoms (Table 1). As in the original family (35), one subject reported ictal inability to speak.

As in family A, limited EEG or imaging results were available. Magnetic resonance imaging (MRI) results were obtained from one individual (IV:1) and CT results from one individual (V:4). Both were normal. No EEG results were obtained. Neurologic examination was documented on subject III:4, and was normal. Formal examination results were not available on other subjects, but no abnormalities were reported.

Family C—Four individuals in the family have had definite seizures. Three of these had idiopathic epilepsy, and one (I:1) had remote symptomatic focal epilepsy, beginning at age 78 years, presumed secondary to Parkinson disease. The onset of idiopathic epilepsy ranged from 13 to 21 years. Of the three subjects with idiopathic epilepsy, two (III:1 and II:3) had clear focal onset with auditory auras (Table 2). Subject III:1 described only partial seizures with secondary generalization, whereas II:3 reported both simple partial seizures and secondarily generalized tonic–clonic seizures. The third individual (II:1) was diagnosed with idiopathic epilepsy of unknown type. This individual had generalized tonic–clonic seizures preceded by a nonspecific brief "buzzing in (the) head," which was *"not like a sound,"* and also episodes of vaguely described "blank staring." In our diagnostic review process, which is blind to the diagnoses of other family members, these descriptions did not clearly distinguish between complex partial accompanied by secondarily generalized seizures, and absence accompanied by primary generalized tonic–clonic seizures.

The two individuals with clearly focal epilepsy also reported other nonauditory auras (Table 1). Subject III:1 reported preictal vertigo, a visual aura "like…watching TV…like a glass panel," and a tingling in the feet rising up the whole body. Subject II:3 described unilateral hand numbness and paresthesias, as well as a vague premonitory sensation: "…you know they're coming—your head just…and you know it's going to happen."

EEG, imaging, and neurologic examination results were available only for subject I:1, who had remote symptomatic epilepsy. The EEG revealed generalized slowing and disorganization, periodic bifrontal slowing, and right temporal slowing, with no epileptiform activity. CT scan showed only atrophy, and neurologic examination was notable for parkinsonism.

Family D—Three individuals in the family have had seizures; all of these were classified as idiopathic epilepsy. Two (II:2 and III:3) had complex partial seizures with auditory auras, which sometimes secondarily generalized; one had only nocturnal tonic–clonic seizures, which were classified as unknown whether primary or secondarily generalized. The age at onset of epilepsy in this family ranged from 12 to 30 years. (Two had onset at age 12 years; the individual with onset at age 30 years was deceased at the time of the interview; this individual's offspring, who provided the information, was unsure of the exact age at onset.)

An addition to the auditory symptoms, subjects described visual and epigastric auras (Table 1). Subject III:3 also reported ictal dyspnea, headache, eyelid fluttering, and manual automatisms, and was thought to have "partial epilepsy with migrainous features" by a physician whose medical records were available.

EEG, imaging, and neurologic examination data were available only for subject III:3. One of several interictal EEGs showed right posterior temporo-occipital spikes; the rest were normal. However, ictal EEG identified left mid- and anterior temporal onset. MRI and neurologic examination were normal.

Linkage analysis

Two-point linkage analysis showed a maximum LOD score of 1.86 at $\theta = 0.0$ for D10S603 (Table 3). Within each family, all individuals with idiopathic epilepsy carried a haplotype defined by the seven markers examined. The LOD score for D10S192, which is located <1 cM telomeric to D10S603, was 1.60. Both the multipoint parametric analysis and nonparametric analysis strengthened the findings from the 2-point analysis. The strongest support for linkage was observed for D10S603 (multipoint LOD = 2.93; NPL = 8.06, p value = 0.001354); the support for linkage for adjacent markers declined but not substantially.

The two individuals in family B who were classified as having "possible" epilepsy because of limited information (and classified as "unknown" in the linkage analysis) both carried the disease-linked haplotype. Two individuals with symptomatic epilepsy, who also were classified as "unknown" in the linkage analysis, also carried the haplotype. In family 6610, one person who had epilepsy attributed to severe head trauma (i.e., in our study, head trauma accompanied by ≥30 min of unconsciousness) was not typed in the original study but was later discovered to carry the disease-linked haplotype in that family. This person also had reported auditory symptoms, like those reported by family members with idiopathic epilepsy (35,37). In family B, one person with symptomatic epilepsy caused by a combination of severe head trauma and meningitis also carried the disease-linked haplotype. Conversely, in family C, an individual with epilepsy associated with neurodegeneration (Parkinson disease) did not appear to carry the haplotype.

These families contain few individuals with febrile seizures (total of four in all four families, two of whom are married in), and those with febrile seizures did not carry the haplotype.

However, one person with an alcohol-related seizure (001 in family 6610) was a carrier (35, 37).

DISCUSSION

Our 2-point LOD score of 1.85 and multipoint LOD score of 2.93 in these three additional families with ADPEAF provide strong confirmatory evidence for link age of a gene causing this syndrome to chromosome 10q24. Because replication involves testing an established hypothesis, a lower LOD score is needed to establish statistical significance in a replication study than in a genome-wide scan used to search for linkage. Lander and Kruglyak (46) recommended a nominal p value of 0.01 for *confirmation* of linkage, corresponding to a LOD score of ~1.2 (i.e., lower than their recommended LOD score of 3.3 for *detection* of linkage). Unfortunately, there were no key recombinants in any of these three families that allowed us to narrow the minimal genetic region further. However, if it can be assumed that the Basque family described by Poza et al. (33) harbors the same gene, the region of interest can be narrowed to the 3-cM overlap zone.

Phenotype definition poses a significant problem in the investigation of the genetic basis of epilepsy. We focused on auditory auras as the characteristic symptom to define the ADPEAF phenotype and direct the search for additional families. Our linkage results in these families confirm that this cardinal clinical manifestation has genetic relevance, and merits its place in definition of the ADPEAF phenotype. Although other symptoms are reported in these families, they may not be so specific an indicator of this genetic syndrome. One reason auditory auras are useful for defining a characteristic phenotype is the infrequency with which they are reported. In most studies, elementary auditory auras occur in <3% of patients (35). In addition, auditory auras can give insight into an anatomic site of the abnormality produced by mutations in the ADPEAF gene, because they have been shown to be particularly useful in localization to the lateral temporal lobe (35).

Based on our haplotype analysis, it appears that febrile seizures are not part of the ADPEAF phenotype. However, individuals whose epilepsy was attributed to severe head trauma were found to carry the haplotype, suggesting that their epilepsy may have been caused either by the gene or a gene–environment interaction.

ADPEAF appears to be quite rare. The original family in which we found linkage was identified from our database of 1,957 families collected for epidemiologic purposes without regard to family history. Very few of the other families in this database had family histories consistent with autosomal dominant inheritance, and only one other small family (family C, Fig. 1) appeared to have auditory symptoms consistent with ADPEAF. We also solicited referrals of patients with the syndrome in a mailing to the membership of the American Epilepsy Society, and many members said that none had been seen in their practices.

Despite the probable rarity of this syndrome, identification of the causative gene on chromosome 10q would have broad, important implications. Discovery of the gene, its product, and its pathophysiologic mechanism would elucidate the way in which a genetic defect can produce abnormalities that differentially affect the lateral temporal lobe, and may give insight into the pathophysiology of focal epilepsy, or epilepsy overall.

We have been performing molecular studies aimed at identification of the causative gene, focusing on the 3-cM overlap region between our original linkage family and that described by Poza et al. (33). These studies indicate that the overlap region (between markers D10S185 and D10S577) is approximately four megabases in size. The region does not appear to contain any obviousion channels, but several genes contain membrane-spanning regions and may be

reasonable candidates. Recently mutation screening for one of these has produced promising results, which we will describe separately.

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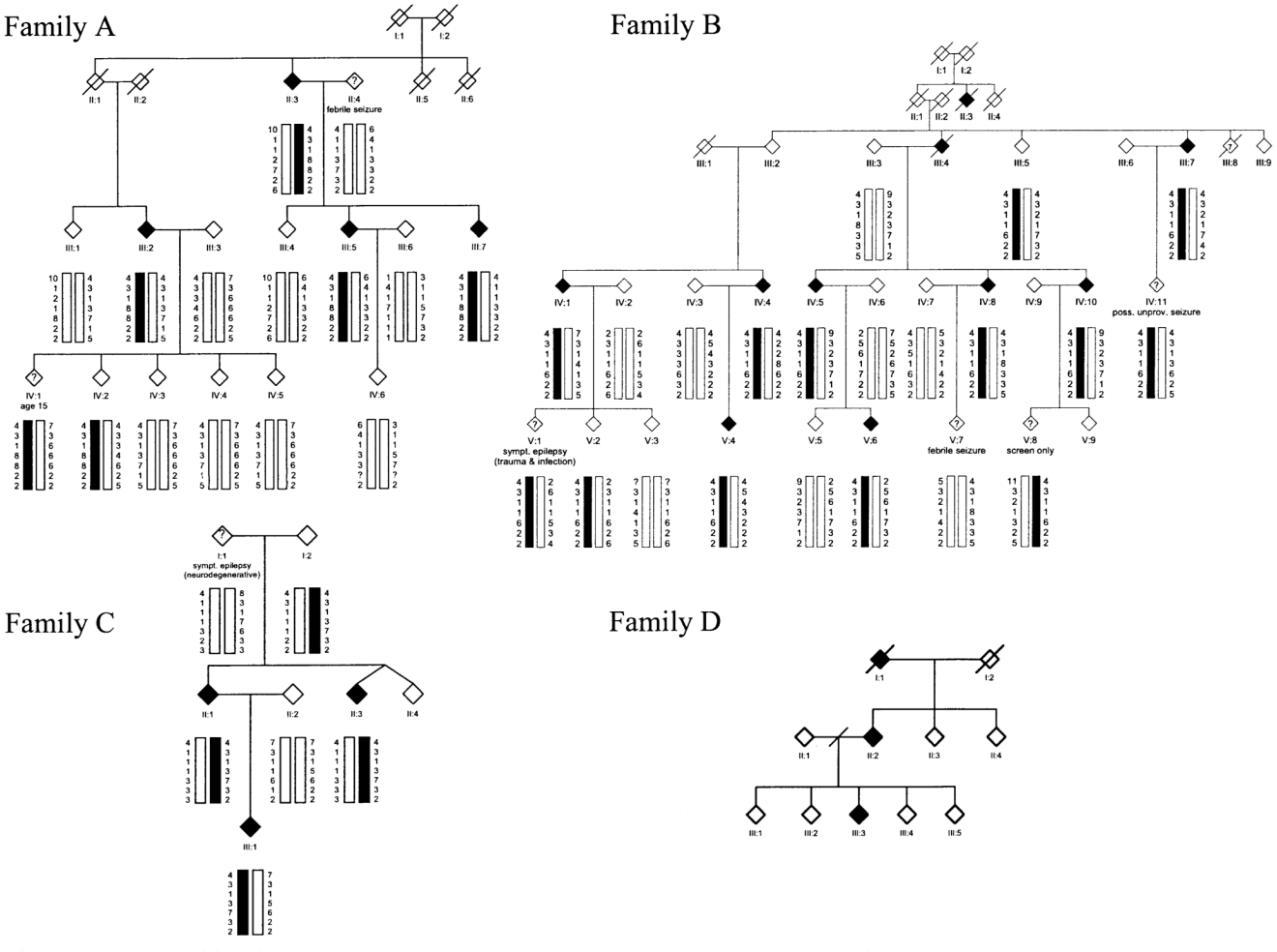

FIG. 1.

Pedigrees of four families with autosomal dominant partial epilepsy with auditory features. Individuals with idiopathic epilepsy are denoted by solid symbols; those with symptomatic epilepsy, febrile seizures, other acute symptomatic seizures, isolated unprovoked seizures, or uncertain diagnoses are denoted by "?" and classified as unknown in the linkage analysis. Haplotypes defined by cosegregation of alleles at the seven markers D10S185, D10S200, D10S198, D10S603, D10S192, D10S222, and D10S566 on chromosome 10q are indicated by black bars. Haplotypes of individuals marrying into the family are shown as open bars, although phase cannot be assigned unambiguously. Genders have been hidden and birth orders changed to protect confidentiality.

TABLE 1

Comparison of clinical features in the five families

No. of individuals with	Family 6610	Family A	Family B	Family C	Family D
Idiopathic focal epilepsy	10	4	7	2	2
Idiopathic generalized epilepsy	0	0	0	0	0
Idiopathic epilepsy, unknown type	1	0	2	1	1
Possible epilepsy	0	0	2	0	0
Symptomatic epilepsy	3[a]	0	1[b]	1[c]	0
Febrile seizure	2	1	1	0	0
Other acute symptomatic seizure	1[a]	0	0	0	0
Age at onset of idiopathic epilepsy: average (range)	12 (8–19)	10 (9–10)	17 (11–23)	17 (13–21)	18 (12–30)
No. (%) of individuals with idiopathic epilepsy with specific symptoms					
Auditory	6 (55%)	4 (100%)	6 (67%)	2 (67%)	2 (67%)
Other sensory	6 (55%)	3 (75%)	3 (33%)	2 (67%)	2 (67%)
Motor	2 (18%)	0	2 (22%)	0	1 (33%)
Autonomic	5 (45%)	0	1 (11%)	0	1 (33%)
Psychic	5 (45%)	1 (25%)	0	0	0

[a] Family 6610, three individuals had symptomatic epilepsy associated with head trauma, brain tumor, and cerebral palsy, respectively. One individual had an acute symptomatic seizure related to alcohol.

[b] Family B, one individual had symptomatic epilepsy associated with head trauma and infection.

[c] Family C, one individual had late-onset symptomatic epilepsy associated with Parkinson disease.

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TABLE 2

Verbatim descriptions of auditory symptoms in newly ascertained families

Family ID	Subject ID	Verbatim description
A	II:3	All at once, in my left ear, I hear a motor, quite similar to a motor to run a washing machine. First it was a click like valve springs—adink, adink, adink—it started going faster and louder… a whackety-whack.
	III:2	It was a popping noise that could get louder and louder until I black out… I would have a grand mal seizure if the sound was particularly loud. It sounds like a pop gun… the popping noise would drown out all other sound—I couldn't hear well … it would sound like I was in a vacuum.
	III:5	I usually have a high-pitched whistling in my left ear, which would be either preceded or followed by a sound like my heartbeat in my ears … the intensity of the sound grows as I get close to the big seizure.
	III:7	I hear a very subtle clicking noise, like horses' hooves from left ear, then ~10 s later, loss of consciousness … hearing a phrase, word for word … often followed by a similar clicking sound before loss of consciousness … a déjà vu of a phrase being repeated over and over.
B	III:7	I hear a sound like bells ringing before some of the seizures.
	IV:4	My co-worker and I were sitting at a table drinking coffee and suddenly I couldn't hear—like when you ride up in the mountains and your ears pop. She said I looked at her and tried to speak. I don't know if you'd call it a sound—lack of sound, I guess. Pressure, sort of.
	IV:5	(They) usually start with a buzzing or ringing in the right ear, I hear a radio jingle—an advertisement of a local radio station on the radio 10 years before the big seizures started. It gets louder and louder, sometimes goes away. It gets so loud that I black out. I close my eyes and tell people to shut up because as soon as I begin to talk, I could have a big seizure.
	IV:8	I hear helicopters … the helicopter sound gets really loud—like it's landing next to (my) ears, and it's like (my) whole head is vibrating with the noise—then I black out … I always hear the same thing. It lasts ~30 s.
	IV:10	Sometimes when it starts I hear helicopters ringing in my ears … it starts soft, gets louder … I hear ringing, I can't stand it; I put my hands over my ears. One time … I could hear people talking around me but I couldn't answer. I stopped eating and put my hands over my ears.
	V:6	I heard ringing in my ears, both ears … it was loud, I was afraid to move.
C	II:3	I hear a buzzing, like a buzz siren.
	III:1	Like there's fluid blocking my ears, and it's hard to hear sometimes.
D	II:2	Smooth static, sometimes, as if I was hard of hearing. Sounds were softer, less loud.
	III:3	I would start to get intense and distorted sound. Voices get distorted. A sharp ringing in my left ear … high-pitched ring. Then it stops all of a sudden.

TABLE 3

Results of two-point linkage analysis in families A, B, and C

Marker	Map position[b]	LOD score at θ = 0.0[a]			
		Family A	Family B	Family C	Total
D10S185	116.34	0.939	0.193	0.241	1.372
D10S200	117.42	0.878	0.286	−0.304	0.861
D10S198	121.98	0.063	0.342	0.000	0.405
D10S603	123.70	1.147	0.742	−0.034	1.855
D10S192	124.27	0.729	0.907	−0.034	1.602
D10S222	125.41	0.085	0.756	0.292	1.133
D10S566	127.11	0.576	−0.144	−0.322	0.109

[a] LOD scores computed by using the ANALYZE package under the same model of inheritance used in the original linkage article; autosomal dominant inheritance with susceptibility allele frequency = 0.001, penetrance in individuals carrying 0, one, and two copies of the susceptibility allele = 0.01, 0.71, 0.71, respectively.

[b] Map positions in centimorgans (cM) from centromere, based on Marshfield map.