BACKGROUND: Two forms of familial temporal lobe epilepsy (FTLE) have been described: mesial FTLE and FTLE with auditory auras. The gene responsible for mesial FTLE has not been mapped yet, whereas mutations in the LGI1 (leucine-rich, glioma-inactivated 1) gene, localized on chromosome 10q, have been found in FTLE with auditory auras.

OBJECTIVE: To describe magnetic resonance imaging (MRI) findings in patients with FTLE with auditory auras.

DESIGN AND METHODS: We performed detailed clinical and molecular studies as well as MRI evaluation (including volumetry) in all available individuals from one family, segregating FTLE from auditory auras.

RESULTS: We evaluated 18 of 23 possibly affected individuals, and 13 patients reported auditory auras. In one patient, auditory auras were associated with déjà vu; in one patient, with ictal aphasia; and in 2 patients, with visual misperception. Most patients were not taking medication at the time, although all of them reported sporadic auras. Two-point lod scores were positive for 7 genotyped markers on chromosome 10q, and a Zmax of 6.35 was achieved with marker D10S185 at a recombination fraction of 0.0. Nucleotide sequence analysis of the LGI1 gene showed a point mutation, IVS7-2A>G, in all affected individuals. Magnetic resonance imaging was performed in 22 individuals (7 asymptomatic, 4 of them carriers of the affected haplotype on chromosome 10q and the IVS7-2A>G mutation). Lateral temporal lobe malformations were identified by visual analysis in 10 individuals, 2 of them with global enlargement demonstrated by volumetry. Mildly reduced hippocampi were observed in 4 individuals.

CONCLUSIONS: In this family with FTLE with auditory auras, we found developmental abnormalities in the lateral cortex of the temporal lobes in 53% of the affected individuals. In contrast with mesial FTLE, none of the affected individuals had MRI evidence of hippocampal sclerosis.

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THE FAMILIAL occurrence of temporal lobe epilepsy (FTLE) was first described as a benign clinical form of TLE.1 Magnetic resonance imaging (MRI) studies in mesial FTLE demonstrated signs of hippocampal sclerosis, not only in patients with refractory seizures, but in patients with good seizure control and seizure remission. These findings indicate a strong genetic factor for the development of hippocampal sclerosis in some families.2,3

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Another form of familial TLE was first reported by Ottman et al4 and later by other authors.5-7 Seizure semiology pointed to an extrahippocampal epileptogenic area, and characteristically, most patients reported auditory auras. Patients had good seizure control, and epileptiform discharges were observed in the posterior temporal regions. Molecular studies identified linkage to chromosome 10q,4-7 and the gene has recently been cloned (leucine-rich, glioma-inactivated 1 gene [LGI1]).8 No MRI abnormalities have been described in these patients so far.5-7 The objective of this study was to investigate MRI abnormalities in a large kindred with familial TLE with auditory auras, linked to chromosome 10q.

METHODS

We studied one large family, segregating TLE from auditory auras by detailed clinical and MRI evaluation. Molecular studies were performed in all available family members after informed consent was obtained. A family pedi-
Informed consent was obtained, and all possibly affected individuals were clinically assessed by at least one of us. Seizures and epilepsy syndromes were determined according to the recommendations of the International League Against Epilepsy, and all affected individuals were genotyped at markers on chromosome 10q.

Figure 1. Summarized pedigree of the family with temporal lobe epilepsy and auditory auras, with haplotypes for markers on chromosome 10q.
affected individuals were also classified by the clinical outcome.

Genomic DNA was extracted from blood samples and genotyped for 7 dinucleotide repeat markers (D10S583, D10S185, D10S574, D10S1680, D10S577, D10S192, and D10S566),\(^1\) which flank the 15-centimorgan (cm) candidate interval on ch10q. We calculated 2-point lod scores using the MLINK program of the Linkage package (Centre d’Etude des Polymorphismes Humaines, Paris, France; University of Utah, Salt Lake City\(^1\) and Columbia University, New York, NY, assuming an autosomal dominant inheritance with 80% penetrance. For mutation analyses, we screened the entire coding region of the LGI1 (leucine-rich, glioma-inactivated 1) gene by polymerase chain reaction, using primers that flanked all intron-exon junctions.

Nucleotide sequences were analyzed using dye-terminator chemistry for megaBACE 1000 (Amersham Pharmacia Biosciences UK Ltd, Buckinghamshire, England).

Magnetic resonance imaging was performed by a 2-T scanner, with T1- and T2-weighted images in 3 orthogonal planes, including thin coronal (3 mm) T1 inversion recovery images perpendicular to the long axis of the hippocampus. In addition, a 3-dimensional T1 acquisition was obtained for multiplanar reconstruction.

Magnetic resonance imaging acquisition parameters were: (1) sagittal T1 spin-echo (6-mm thick; flip angle, 180°; repetition time [TR], 430 milliseconds; echo time [TE], 12 milliseconds; matrix, 200×350; field of view [FOV], 25×25 cm); (2) coronal, perpendicular to the long axis of the hippocampus, defined by the sagittal images: [a] T2-weighted fast spin-echo (4-mm thick; flip angle, 120°; TR, 4800 milliseconds; TE, 129 milliseconds; matrix, 252×320; FOV, 18×18 cm); [b] T1-weighted inversion recovery (3-mm thick; flip angle, 200°; TR, 2800 milliseconds; TE, 14 milliseconds; inversion time, 840 ms; matrix, 130×256; FOV, 16×18 cm); (3) axial images parallel to the long axis of the hippocampi: [a] T1-weighted gradient echo (3-mm thick; flip angle, 70°; TR, 200 milliseconds; TE, 5 milliseconds; matrix, 180×232; FOV, 22×22 cm); [b] T2-weighted fast spin-echo (4-mm thick; flip angle, 120°; TR, 6800 milliseconds; TE, 129 milliseconds; matrix, 252×328; FOV, 21×23 cm); (4) T1-weighted 3-dimensional gradient echo, acquired in the sagittal plane (1-mm thick; flip angle, 35°; TR, 22 milliseconds; TE milliseconds, 9°; matrix, 236×220; FOV, 23×25 cm).

Visual analyses were performed using a workstation (OMNIPRO; Elscint, Haifa, Israel) for multiplanar reconstruction.

Independent analyses were performed by 2 investigators (E.K. and F.C.) who were blinded to clinical status, and both agreed with the conclusion. Quantitative analyses of hippocampal formation and the anterior aspect of the temporal lobes (volumetry) were done according to a standardized protocol,\(^1\) using thin coronal T1 inversion recovery images and the National Institutes of Health Image program (http://rsb.info.nih.gov/nih-image/). Volumes were compared with those in a control group of 20 healthy adult volunteers, and data were transformed into z scores (number of SDs from the mean of control group).

We identified 23 possibly affected subjects (5 were deceased) in the pedigree (Figure 1). We evaluated 18 of them: 11 men and 7 women. The mean age at seizure onset was 19 years (range, 10-35 years). None of the evaluated individuals who met the clinical criteria for TLE with auditory auras had a history of risk factors (febrile convulsions, head trauma, or meningitis). All patients had a benign clinical course.

Auditory auras were reported by 12 (66%) of 18 patients, and were described as a radio sound or a motorcycle running by most of them (Table 1). Other reported symptoms are presented in Table 1, and included déjà vu, visual misperception, with distortion of faces or objects, and episodes in which they suddenly were unable to hear or understand what people said (aphasic aura). There was only 1 patient (III-22) who did not report auras, but she had only a few generalized tonic-clonic seizures during sleep. Secondarily generalized tonic-clonic seizures were reported as a rare manifestation by 12 patients. One individual (V-6) had only recurrent febrile seizures during childhood but no clinical findings of TLE with auditory auras.

Two-point lod scores were greater than Zmax=3.0 for all 7 markers genotyped on chromosome 10q (Table 2):
showed a point mutation, IVS7-2A

Zmax = 5.61 at θ = 0 for D10S583; Zmax = 6.35 at θ = 0 for D10S185; Zmax = 4.79 at θ = 0 for D10S574; Zmax = 4.77 at θ = 0 for D10S1680; Zmax = 4.26 at θ = 0 for D10S577; Zmax = 5.55 at θ = 0 for D10S192; and Zmax = 4.26 at θ = 0.05 for D10S566. Nucleotide sequence analysis of the LGII gene showed a point mutation, IVS7-2A>G, that was likely to abolish the splicing site. We predict that this mutation results in exon 8 skipping, thus producing a truncated protein. The point mutation was present in all affected individuals and in 1 asymptomatic carrier of the haplotype. Although 4 individuals had mildly reduced hippocampal volumes on volumetry, this was not sufficient to define MRI evidence of mesial temporal sclerosis on visual analysis, as commonly encountered in mesial FTLE.2

**COMMENT**

Although the description of auditory auras in FTLE is remarkable, some patients also report other sensory and psychic symptoms, in isolation or accompanying the auditory symptoms.14 Auditory features may vary among affected family members, from undefined sounds to auditory illusions, such as distortions and volume changes. In addition, some patients had an ictal aphasia. All of these positive and negative manifestations suggest a lateral temporal lobe seizure focus involving the cortex of posterior temporal regions.

The identification of temporal lobe abnormalities on MRI in patients with this specific form of TLE, linked to chromosome 10q, has not been reported so far. We found clear-cut signs of lateral temporal malformations in 53% of affected individuals and in 1 asymptomatic carrier of the haplotype. Although 4 individuals had mildly reduced hippocampal volumes on volumetry, this was not sufficient to define MRI evidence of mesial temporal sclerosis. However, this mild volume loss and altered shape of the hippocampus and parahippocampal gyrus may influence the pattern of propagation of ictal discharges and seizure semiology.

### Table 3. Visual and Volumetric Data on the 22 Individuals Who Underwent Magnetic Resonance Imaging

<table>
<thead>
<tr>
<th>Individual Number</th>
<th>Chromosome 10q Haplotype</th>
<th>Status</th>
<th>Hippocampal Volumetry</th>
<th>Temporal Lobe Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-4 +</td>
<td>Affected</td>
<td>Normal</td>
<td>LTLM, with LTL enlargement* and fusiform gyrus malformation</td>
<td></td>
</tr>
<tr>
<td>IV-8 +</td>
<td>Nonaffected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-7 +</td>
<td>Affected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-9 -</td>
<td>Nonaffected</td>
<td>Normal</td>
<td></td>
<td>LTLM, with LTL enlargement*</td>
</tr>
<tr>
<td>IV-24 +</td>
<td>Affected</td>
<td>Normal</td>
<td></td>
<td>LTLM, with LTL encephalocele</td>
</tr>
<tr>
<td>IV-17 +</td>
<td>Affected Reduced at left</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-11 +</td>
<td>Affected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-7 +</td>
<td>Nonaffected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-15 +</td>
<td>Affected</td>
<td>Normal</td>
<td></td>
<td>LTLM, with LTL enlargement and absence of 1st and 2nd temporal sulcus. Abnormal shape of left fusiform gyrus</td>
</tr>
<tr>
<td>IV-5 +</td>
<td>Nonaffected Reduced at right</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-13 +</td>
<td>Affected Reduced at left/mild increased T2 signal</td>
<td>Normal</td>
<td>LTLM, with LTL enlargement and absence of 1st and 2nd temporal sulcus, abnormal shape and axis of hippocampus, and mild hemispheric asymmetry (left &gt; right) (Figure 2)</td>
<td></td>
</tr>
<tr>
<td>IV-10 +</td>
<td>Affected</td>
<td>Normal</td>
<td>LTLM, with hippocampus showing abnormal shape and axis, and widened fusiform gyrus</td>
<td></td>
</tr>
<tr>
<td>III-24 +</td>
<td>Affected</td>
<td>Normal</td>
<td>LTLM, with LTL enlargement</td>
<td></td>
</tr>
<tr>
<td>III-10 +</td>
<td>Affected</td>
<td>Normal</td>
<td>LTLM, with LTL enlargement and hippocampus showing abnormal shape and axis</td>
<td></td>
</tr>
<tr>
<td>V-6 -</td>
<td>Febrile seizures Reduced at left/mild increased T2 signal</td>
<td>Normal</td>
<td>LTLM, with abnormally rounded hippocampus, fusiform and parahippocampal gyrus malformation</td>
<td></td>
</tr>
<tr>
<td>III-20 +</td>
<td>Affected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-9 +</td>
<td>Affected</td>
<td>Normal</td>
<td></td>
<td>LTLM, with LTL enlargement</td>
</tr>
<tr>
<td>IV-4 +</td>
<td>Affected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-16 -</td>
<td>Nonaffected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-1 +</td>
<td>Affected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-22 +</td>
<td>Affected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-3 +</td>
<td>Nonaffected</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** LTL, left temporal lobe; LTLM, left temporal lobe malformation; ellipses, not applicable; minus sign, absent; plus sign, present.

*Confirmed by volumetry.

Although the description of auditory auras in FTLE is remarkable, some patients also report other sensory and psychic symptoms, in isolation or accompanying the auditory symptoms.14 Auditory features may vary among affected family members, from undefined sounds to auditory illusions, such as distortions and volume changes. In addition, some patients had an ictal aphasia. All of these positive and negative manifestations suggest a lateral temporal lobe seizure focus involving the cortex of posterior temporal regions.

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Twenty-two family members underwent MRI (7 asymptomatic, 4 of them haplotype carriers). In Table 3, we present the affected status, the presence of the chromosome 10q haplotype, and the visual and quantitative MRI studies for each subject. Visual analysis showed lateral temporal lobe dysgenetic features (Figure 2 and Figure 3) in 10 (45%) of 22 patients. Their left temporal lobes seemed enlarged, sometimes with protrusion of brain parenchyma with an encephalocelelike appearance (Figure 2). However, anterior temporal lobe volumetry showed a significant global increase in volumes in only 2 individuals.

Volumetric studies revealed mildly reduced hippocampi in 4 individuals, with z scores ranging from –2.0 to –2.5. In 2 of them, a mildly increased hippocampal T2 signal was also observed on visual analysis. However, none of these 4 patients fulfilled the criteria for determining MRI evidence of mesial temporal sclerosis on visual analysis, as commonly encountered in mesial FTLE.2
The relationship of the mesial and lateral aspects of the temporal lobe has been extensively studied. Although it is well recognized that in mesial TLE, the main structures implied in the pathogenesis of epilepsy are the hippocampus, amygdala, and other mesial temporal lobe structures, the lateral temporal cortex may also play an important role in this scenario. The subcortical connections of mesial temporal structures are bidirectional, and include afferents from the hypothalamus, the auditory system, and the lower brainstem nuclei involved in viscerosensory and gustatory functions.

Several types of perceptual phenomena can occur in temporal lobe seizures. Visual and auditory hallucinations and illusions are commonly elicited by temporal lobe seizure discharge. Auditory illusions are usually changes in the loudness of perceived sounds. Most of these changes are attributable to discharge in the auditory association cortex, but occasionally they can be reproduced by amygdaloid stimulation. These illusions frequently have experiential qualities. Elementary auditory and visual hallucinations indicate discharge in the primary auditory and visual cortices. The stimulation response map of Penfield and Perot shows that the points in the temporal isocortex from which auditory experiential phenomena could be elicited occupy the first temporal convolution. Experiential phenomena with auditory features may be elicited by stimulation with intracranial electrodes of several temporal lobe structures. These have been observed with an afterdischarge beyond the stimulated site in 22 (29%) of 75 individuals. In addition, there were reports of auditory hallucinations/illusions (one with associated visual

Figure 2. A, T1-weighted inversion recovery coronal magnetic resonance images from patient III-13 show left temporal lobe dysgenesis, characterized by enlargement of the lateral temporal lobe, with small gyri (although not characterizing polymicrogyria). B, T1 sagittal images from the same patient show the absence of the first and second temporal sulci on the anterior and middle portions of the left temporal lobe. The posterior basolateral aspect of the left temporal lobe is also abnormal, with a downward protrusion of parenchyma, exhibiting an encephalocele-like appearance (arrow).

Figure 3. T1-weighted inversion recovery coronal magnetic resonance images from patients III-4 (A) and IV-11 (B) show left temporal lobe malformation, with a disgenetic aspect of temporal gyri and enlargement of the lateral aspect of the temporal lobe.
hallucination) in 3 patients after hippocampus stimulation. Experiential phenomena without an afterdischarge or with discharges limited to the stimulated site were elicited in 20 (27%) of 75 patients, and 3 of them had auditory hallucinations/illusions combined with visual features (one from temporal isocortex stimulation and 2 from amygdala stimulation).  

At this point, we cannot be sure that the development structural abnormalities in the temporal lobes found in our patients are directly implicated in seizure origin. However, the MRI findings in this family with TLE with auditory auras are clearly distinct from the MRI findings in mesial FTLE, and these different abnormalities are consistent with the distinct seizure semiology in these 2 forms of familial TLE.

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