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Seizure semiology in autosomal dominant epilepsy with auditory features due to novel *LGII* mutations

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Abstract

Mutations in *LGII* are found in 50% of families with autosomal dominant epilepsy with auditory features (ADEAF). In ADEAF, family members have predominantly lateral temporal lobe seizures but mesial temporal lobe semiology may also occur. We report here three families with novel *LGII* mutations (p.Ile82Thr, p.Glu225*, c.432-2_436del). Seven affected individuals reported an auditory aura and one a visual aura. A 10-year old boy described a cephalic aura followed by an unpleasant taste and oral automatisms without auditory, visual or psychic features.

Key words: *LGII*, temporal lobe seizures, ADEAF, ADLTE, ADPEAF,

Introduction

Autosomal dominant epilepsy with auditory features (ADEAF) is a distinctive focal genetic epilepsy syndrome previously denoted as autosomal dominant partial epilepsy with auditory features (ADPEAF) or autosomal dominant lateral temporal lobe epilepsy (Berg et al., 2010; Nobile et al., 2009; Ottman et al., 1995). Fifty percent of reported families have mutations in the *LGII* gene which encodes the leucine-rich glioma-inactivated-1 protein (Nobile et al., 2009; Ottman et al., 2004). The hallmark of this disorder is an auditory aura, which occurs in about two third of patients, and is occasionally associated with aphasia or visual phenomena although the latter may occur in isolation (Michelucci, Pasini, & Nobile, 2009; Ottman et al., 2004). To date 33 unique *LGII* mutations have been reported (Ho, Ionita-Laza, & Ottman, 2012).

We report three new families with novel mutations of *LGII* and describe the phenotypes found in these families.

Material and Methods

ADEAF families

ADEAF families were recruited from the investigators' clinical practices. All available family members were phenotyped with seizure and medical history, neurological examination and EEG recordings. Previous medical records were obtained. Informed consent was obtained from all patients or their parents. The local human research ethics committees approved the study.

LGII mutation detection

All *LGII* exons were polymerase chain reaction amplified and sequenced as previously described (Chabrol et al., 2007). Predictions of pathogenicity of the *LGII* mutations were made with Panther (<http://www.pantherdb.org/>) and SIFT (<http://sift.jcvi.org/>).

Results

Families

Family A is from New Zealand, families B and C are Australian. There were 16 individuals with seizures studied in the three families. The average age of onset of *LGII* mutation positive individuals was 17 years (median 16, range 10-27). All individuals were of normal intellect with a normal neurological examination. Case descriptions are summarized in Table 1.

Family A

The proband had a bilineal family history of seizures. Thirteen family members had seizures, of whom we personally evaluated eleven. Four had ADEAF with the *LGII* p.Ile82Thr mutation. Seven had other epilepsies or febrile seizures (FS) and two were deceased and unavailable for study (Figure 1). Individuals A-II-4, A-II-5 and A-III-5 presented at 15 to 18 years with auditory auras, which occasionally evolved, to bilateral convulsive seizures, often during sleep. The individuals had similar auditory auras associated with muffled hearing. Their auras comprised noises described as “a jangle”, “ringing” and an external sound “like two sirens in one – one changing in pitch like a ringing bell and the other subtle, constant and low pitched”.

The proband, A-IV-7, presented at 10 years with clusters of focal seizures which occasionally progressed to bilateral convulsive seizures. A seizure was recorded by the family on a home video. He described an initial feeling of his “brain jumping in his head” followed by a cold tingling feeling spreading from his head to both arms. He experienced an unpleasant bitter taste and swallowed purposefully. He also reported that his right hand hurt during a seizure and remained aware. There was no auditory component. Two interictal EEGs were normal.

He has a strong maternal family history of FS. His mother, A-III-4, had 14 simple FS between 1 and 3.5 years. His aunt, A-III-3, and uncle, A-III-1, had a simple FS at 1 year. His maternal uncle, A-III-2, had several FS over 24 hours at three years and re-presented with infrequent seizures between 30 and 45 years. The seizures consisted of dizziness and blurred vision followed by head and eye deviation and evolved to bilateral convulsive seizures. He has been seizure free on carbamazepine for seven years. EEGs and MRIs

were normal. The maternal grandfather, A-II-2, had three asymmetric nocturnal convulsions between 30 and 80 years. His EEG was normal.

A-IV-17, aged 22 years, and her father were negative for *LGII* mutations. She presented at 6 weeks with seizures several hours after vaccination. The seizures consisted of 1-3 seconds of staring with bilateral arm extension occurring several times per day until 6 months. She was subsequently seizure free with normal development. EEG and cranial ultrasound showed no abnormalities.

Family B

The three individuals studied had auditory auras, which occasionally evolved to convulsive seizures. B-IV-1 described a vibrating sound “like air rushing through an open car window” associated with muffled hearing. B-IV-2 described a “massive” ringing in his ears. B-III-10 described that sounds were distorted and seemed far away. Both B-IV-1 and B-III-10 felt that putting their fingers in their ears would occasionally abort the aura.

Family C

Individual C-IV-4 and her grandfather C-II-1 presented with convulsive seizures usually from sleep. Rarely she had a visual aura of green horizontal stripes progressing downward like the computer screen in the movie “The Matrix”. Her grandfather noted ringing in his ears like the humming of a power station. C-III-3 did not participate in the study.

***LGII* mutations**

Three novel mutations in *LGII* were found. Family A had a missense mutation p.Ile82Thr (exon 2, c.245T>C), which segregated with those with temporal lobe semiology but was not found in A-IV-17 with unclassified epilepsy (Figures 1,2). p.Ile82Thr mutation affects a highly evolutionarily conserved amino acid (Figure 2B) and was predicted to be deleterious by SIFT with a Grantham score of 89 [0-215] and a P-deleterious of 0.991 by Panther. Family B had a stop mutation p.Glu225* (exon 6, c.673G>T) in all tested members (Figures 1,2). Family C had a seven nucleotide deletion that encompassed the acceptor site and beginning of exon 5 (c.432-2_436del), leading to a frameshift starting at Leucine 144, and introducing a stop

codon at 27 amino acids (Figures 1,2). The mRNAs produced with mutations c.432-2_436del or p.Glu225* may be targeted for nonsense mediated decay (NMD). None of these mutations have been reported either as pathogenic or benign polymorphisms in the databases (exome variant server, 1000 Genomes).

Discussion

Here we report 3 novel pathogenic *LGII* mutations with detailed description of their auras. As individuals with ADEAF tend to have infrequent and phamaco-responsive seizures (Berkovic et al., 2004; Bisulli et al., 2004), video-EEG recordings are infrequent and consequently seizure characterization relies on careful clinical descriptions. The pathognomonic feature of ADEAF is the auditory aura consistent with lateral temporal lobe localization (Ottman et al., 1995; Winawer et al., 2002). However, it can occasionally be associated with mesial temporal auras (déjà vu, jamais vu, fear, panic, depersonalization, and epigastric sensations), vertiginous sensations, palpitations, sweating, pallor and olfactory hallucinations (Michelucci et al., 2009; Ottman et al., 2004). In keeping with the literature, we found an auditory aura in the majority (7/9) of our *LGII* mutation positive individuals. One patient had only a visual aura and another patient did not have either a visual or an auditory aura. Other features reported were dizziness or unsteadiness (2/9), tingling in the arms (2/9), and an unpleasant taste (2/9).

The proband of family A had focal seizures with non-localizing semiology one of which was recorded on home video; gustatory features and salivation may have opercular origin but as this is reported later in the seizure, it is likely to represent seizure spread (Hausser-Hauw & Bancaud, 1987; Widdess-Walsh, Kotagal, Jeha, Wu, & Burgess, 2007). He shares some features with his father's seizures as both experience tingling in the limbs and an odd taste. Although the relatives of our proband with a recorded seizure had significant auditory features, he did not. The maternal side of his family has Genetic Epilepsy with Febrile Seizure Plus (GEFS+) with two of the individuals having focal seizures (Scheffer, Zhang, Jansen, & Dibbens, 2009). It is possible that the proband's seizure semiology differs from the other members of his family with *LGII* mutations due to an interaction with epilepsy genes inherited from his mother's side (which are currently unknown) resulting in a modified phenotype.

Genotype-phenotype analysis of *LGII* mutations in ADEAF in 36 families reported that auditory

symptoms were less frequent in individuals with truncation mutations in the C-terminal epitempin (EPTP) domain than other types of mutations or mutations in different domains (Ho et al., 2012) . However, all three individuals in family B with a truncating p.Glu225* mutation, which is located in the first EPTP, had an auditory aura. Interestingly, in our two other families, only some affected individuals have an auditory aura despite sharing the same mutation. It therefore seems unlikely that these mutations per se confer a specific aura semiology.

FIGURE LEGEND

Figure 1: Pedigrees of families with *LGII* mutations.

Figure 2: (A) Representation of the mutations on the gene and protein. (B) Multiple protein alignment showing the conservation of p.Ile82Thr residue.

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Disclosure

None of the authors has any conflict of interest to disclose

REFERENCES

- Berg, A. T., Berkovic, S. F., Brodie, M. J., Buchhalter, J., Cross, H., van Emde Boas, W., . . . Scheffer, I. E. (2010). Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*, 51(4), 676-685.
- Berkovic, S. F., Izzillo, P., McMahon, J. M., Harkin, L. A., McIntosh, A. M., Phillips, H. A., . . . Mulley, J. C. (2004). LGI1 mutations in temporal lobe epilepsies. *Neurology*, 62(7), 1115-1119.
- Bisulli, F., Tinuper, P., Avoni, P., Striano, P., Striano, S., d'Orsi, G., . . . Michelucci, R. (2004). Idiopathic partial epilepsy with auditory features (IPEAF): a clinical and genetic study of 53 sporadic cases. *Brain*, 127(Pt 6), 1343-1352.
- Chabrol, E., Gourfinkel-An, I., Scheffer, I. E., Picard, F., Couarch, P., Berkovic, S. F., . . . Baulac, S. (2007). Absence of mutations in the LGI1 receptor ADAM22 gene in autosomal dominant lateral temporal epilepsy. *Epilepsy Research*, 76(1), 41-48.
- Hausser-Hauw, C., & Bancaud, J. (1987). Gustatory Hallucinations in Epileptic Seizures. Electrophysiological, clinical and anatomical correlates. *Brain* 110, 339-359.
- Ho, Y.-Y., Ionita-Laza, I., & Ottman, R. (2012). Domain-dependent clustering and genotype-phenotype analysis of LGI1 mutations in ADPEAF. *Neurology*, 78(8), 563-568.
- Michelucci, R., Pasini, E., & Nobile, C. (2009). Lateral temporal lobe epilepsies: clinical and genetic features. *Epilepsia*, 50 Suppl 5, 52-54.
- Nobile, C., Michelucci, R., Andreazza, S., Pasini, E., Tosatto, S. C. E., & Striano, P. (2009). LGI1 mutations in autosomal dominant and sporadic lateral temporal epilepsy. [Review]. *Human Mutation*, 30(4), 530-536.
- Ottman, R., Risch, N., Hauser, W. A., Pedley, T. A., Lee, J. H., Barker-Cummings, C., . . . et al. (1995). Localization of a gene for partial epilepsy to chromosome 10q. *Nature Genetics*, 10(1), 56-60.
- Ottman, R., Winawer, M. R., Kalachikov, S., Barker-Cummings, C., Gilliam, T. C., Pedley, T. A., & Hauser, W. A. (2004). LGI1 mutations in autosomal dominant partial epilepsy with auditory features. *Neurology*, 62(7), 1120-1126.
- Scheffer, I., Zhang, Y., Jansen, F., & Dibbens, L. (2009). Dravet syndrome or genetic (generalized) epilepsy with febrile seizures plus? *Brain & Development*, 31, 394-400.
- Widdess-Walsh, P., Kotagal, P., Jeha, L., Wu, G., & Burgess, R. (2007). Multiple auras. Clinical significance and pathophysiology. *Neurology* 69, 755-761.
- Winawer, M. R., Martinelli Boneschi, F., Barker-Cummings, C., Lee, J. H., Liu, J., Mekios, C., . . . Ottman, R. (2002). Four new families with autosomal dominant partial epilepsy with auditory features: clinical description and linkage to chromosome 10q24. *Epilepsia*, 43(1), 60-67.

Family	Seizure Onset	Age Studied/ Gender	Aura	Convulsive seizures
A				
A-II-4	15 yrs	80 yrs Male	Feels dizzy and hears “jangle of noise” for 60 seconds. Aware but aphasic.	Aura may evolve to head deviation and loss of awareness followed by bilateral convulsive movements. Occasionally from sleep.
A-II-5	18 yrs	82 yrs Female Deceased	Ringling noise and other sounds muffled	Usually following aura. When young from sleep.
A-III-5	15 yrs	42 yrs Male	Auditory aura heard outside his head which builds and lasts 10-15 seconds. Two sirens heard together: one changes in pitch like a ringing bell and the other is subtle, constant and low pitched. During the aura normal sounds are distorted. Aware and not aphasic.	8-9 in total. If auditory aura progresses his hands become heavy and arms feel stretched. He develops tingling in his limbs and an odd taste in his mouth. This lasts for 5 seconds and he then becomes unaware with or without head deviation before developing bilaterally convulsive movements. Occasionally from sleep
A-IV-7	10 yrs	13 yrs Male	Clusters. He describes an initial feeling of his brain jumping in his head followed by a cold tingling feeling spreading from his head to his limbs. His arms become “shaky” and he has an unpleasant bitter taste which results in conscious swallowing and mouth movements + salivation. He develops an unpleasant sensation in his right hand. He is completely aware and able to talk with no visual or auditory symptoms. A home video begins shortly after seizure onset. He experiences a bad taste and grimaces. He holds both hands in front of him, appears distressed and has chewing oral automatisms. He remains aware and, although he appears aphasic in the video, he can usually talk through his seizures. He points to his right fingers and nods that they hurt.	Occasional convulsive seizure from sleep. Clusters of convulsive seizures during day with no recollection of aura.
B				
B-IV-1	21 yrs	31 yrs Male	Sounds become muffled and he hears a vibrating sound like air rushing through an open car window. Puts fingers in ears to stop. Sometimes develops chemical taste. Aware.	Auditory aura progresses to become bilaterally convulsive in 10% of seizures.
B-IV-2	27 yrs	28 yrs Male	“Massive” ringing in ears.	Auditory aura progresses to become bilaterally convulsive.
B-III-10	5m – 2 yrs	54 yrs Male	No history available.	
	14 yrs		Sounds distorted and seem very far away – no additional noises. Aware. Puts fingers in ears to stop.	Auditory aura progresses to become bilaterally convulsive.
C				
C-II-1	19 yrs	70 yrs Male	Ringling in ears like the humming of a power station and feels unsteady.	Auditory aura progresses to become bilaterally convulsive. 20 in lifetime.

C-IV-4	16 yrs	30 yrs Female	Visual aura of green horizontal stripes progressing downwards like computer programming on a screen as seen in the movie "The Matrix".	Infrequent usually from sleep Can begin with aura but usually no warning.
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Table 1: Clinical features of the patients of the three families

Convulsive = tonic/clonic. EEG: electroencephalogram, yrs: years, m: months, AED: anti-epileptic drug, MRI: magnetic resonance imaging, LEV: Levetiracetam, R: right, CBZ: Carbamazepine, VPA: Valproate, PHT: Phenytoin, CT: computed tomogram

Figure 1

Figure 2

A

B

<i>Homo Sapiens</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Pan troglodytes</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Pongo pygmaeus</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Macaca mulatta</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Rattus norvegicus</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Mus musculus</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Oryctolagus cuniculus</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Canis familiaris</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Felis catus</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Bos taurus</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Dasyatis novemacinctus</i>	L	S	F	V	R	S	G	F	T	E	I	S	E	G	S	F	L	F	T	P	S	L	O	L	L
<i>Gallus gallus</i>	L	S	F	V	R	S	A	F	T	K	I	P	E	G	S	F	L	L	T	P	S	L	O	L	L
<i>Xenopus tropicalis</i>	L	S	F	V	R	S	E	F	T	E	I	P	E	G	S	F	L	H	I	P	S	L	O	L	L
<i>Tetraodon nigroviridis</i>	L	S	F	A	N	S	K	F	T	E	I	P	K	E	S	F	I	H	S	P	G	L	H	L	L

- We report three families with novel *LGII* mutations.
- We describe in detail the auras found in individuals with these *LGII* mutations.
- The mutations do not confer specific aura semiology.

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