



Short communication

Screening *LG11* in a cohort of 26 lateral temporal lobe epilepsy patients with auditory aura from Turkey detects a novel *de novo* mutation



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SUMMARY

Autosomal dominant lateral temporal lobe epilepsy (ADLTE) is an autosomal dominant epileptic syndrome characterized by focal seizures with auditory or aphasic symptoms. The same phenotype is also observed in a sporadic form of lateral temporal lobe epilepsy (LTLE), namely idiopathic partial epilepsy with auditory features (IPEAF). Heterozygous mutations in *LG11* account for up to 50% of ADLTE families and only rarely observed in IPEAF cases. In this study, we analysed a cohort of 26 individuals with LTLE diagnosed according to the following criteria: focal epilepsy with auditory aura and absence of cerebral lesions on brain MRI. All patients underwent clinical, neuroradiological and electroencephalography examinations and afterwards they were screened for mutations in *LG11* gene. The single *LG11* mutation identified in this study is a novel missense variant (NM.005097.2: c.1013T > C; p.Phe338Ser) observed *de novo* in a sporadic patient. This is the first study involving clinical analysis of a LTLE cohort from Turkey and genetic contribution of *LG11* to ADLTE phenotype. Identification of rare *LG11* gene mutations in sporadic cases supports diagnosis as ADLTE and draws attention to potential familial clustering of ADLTE in suggestive generations, which is especially important for genetic counselling.

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Introduction

Lateral temporal lobe epilepsy (LTLE) is a group of conditions with specific seizure characteristics including auditory aura or aphasic symptoms with a high tendency to generalize. Non-lesional LTLE characterized by negative magnetic resonance imaging (MRI) findings has been described for a number of familial and sporadic cases. Familial non-lesional LTLE, namely Autosomal Dominant Lateral Temporal Lobe Epilepsy (ADLTE; OMIM 600512) is inherited in an autosomal dominant fashion presenting reduced penetrance with an overall estimate of 66% (Ho et al., 2012). Sporadic non-lesional LTLE, on the other hand, is known as idiopathic partial epilepsy with auditory features (IPEAF). Both ADLTE and IPEAF are

clinically characterized by focal seizures with typical involvement of auditory symptoms and mostly benign outcomes (Michelucci et al., 2009). Both conditions are reported to have homogenous clinical courses regarding frequency of seizures, response to treatment and disease onset with a mean age of 18–19 years (Bisulli et al., 2004a).

Heterozygous variations in leucine-rich, glioma-inactivated 1 (*LG11*) gene have been implicated both in ADLTE and IPEAF (Dazzo et al., 2015a). Substantial proportion of ADLTE families (up to 50%) and only very rare IPEAF cases carry inherited or *de novo* point mutations in *LG11*, respectively (Michelucci et al., 2003; Bisulli et al., 2004b; Dazzo et al., 2015a). Small *LG11* micro-rearrangements have also been spotted in ADLTE (Fanciulli et al., 2012; Dazzo et al., 2015a). *LG11* encodes a secreted protein that is expressed predominantly in hippocampal and cortical neurons (Senechal et al., 2005). The *LG11* protein contains four leucine-rich repeat (LRR) motifs in its N-terminal domain responsible for protein-protein interactions (Kobe and Kajava, 2001) and a epitempin (EPTP) domain containing seven EPTP repeats in its C-terminal domain, which has prominent role in the development of epileptic disorders (Staub et al., 2002). Herein, we report clinical and genetic analyses of a cohort of 26 patients from Turkey exhibiting focal epilepsy with auditory features leading to identification of a novel *de novo* *LG11* mutation.

Abbreviations: ADLTE, Autosomal Dominant Lateral Temporal Lobe Epilepsy; AED, Antiepileptic drugs; EEG, Electroencephalography; EPTP, Epitempin; IPEAF, Idiopathic Partial Epilepsy with Auditory Features; *LG11*, Leucine-rich Glioma-Inactivated 1; LoC, Loss of Consciousness; LRR, Leucine-Rich Repeat; LTLE, Lateral Temporal Lobe Epilepsy; MRI, Magnetic Resonance Imaging.

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Materials and Methods

Subjects and Clinical Investigations

A cohort of 26 unrelated patients with focal epilepsy and clear-cut recurring auditory auras were enrolled to this study. This cohort had been followed up between the years 1996–2013 at Istanbul University Epilepsy Center (EPIMER). All patients underwent full clinical, neuroradiological and electroencephalography (EEG) examinations. Informed consents were obtained from all patients and their recruited family members in accordance with ethics approval obtained for the study from Ethics Committee of Istanbul Medical Faculty (2012/740-1058).

Clinical data from each patient was collected including details of seizure types and frequency, nature of auditory aura, response to treatment, antiepileptic drugs (AED) used, ictal and interictal EEG recordings, and neuroradiological findings.

Genetic Analysis

All exons and exon-intron boundaries of *LGII* gene were analysed for sequence variants from genomic DNA extracted from whole blood for all patients. All sequence variants presented herein are named according to *LGII* gene transcript variant NM.005097.2. Upon identification of a *de novo* variant in *LGII*, the relevant trio was analysed for relationship specification using the application Graphical Representation of Relationships (Abecasis et al., 2001) after whole genome genotyping with the GeneChip Mapping 250 K Nsp Array (Affymetrix Inc., Santa Clara, Calif., USA).

Results

All 26 patients admitted to our clinic over the course of 17 years were non-lesional, i.e. their MRI findings were unremarkable and/or unrelated to their seizures. The breakdown of familial origin of LTLE in the cohort is as follows: ADTLE (5); LTLE with positive family history of epilepsy (5); sporadic LTLE (16) (Table 1).

Sequence analysis of *LGII* in the cohort revealed a novel heterozygous variant only in a single case with a negative family history of epilepsy. This transition, c.1013T>C resides in exon 8 and at the protein level results in substitution of the amino acid phenylalanine at position 338 with a serine (p.Phe338Ser) in the 3rd EPTP repeat. Upon detection of this novel variant in *LGII*, the unaffected family members (parents and two siblings) were recruited to the study. Their genetic screenings were accordingly negative for c.1013T>C suggesting a *de novo* mechanism (Fig. 1a). The *de novo* nature of the variant has prompted us to confirm parent offspring relationship via whole genome SNP genotyping.

LGII c.1013T>C; p.Phe338Ser variant was not detected neither in Ensembl Genome Browser (Human release 81), which retrieves human variation information from a variety of sources including Database of Short Genetic Variations (dbSNP), the National Heart Lung and Blood Institute Exome Sequencing Project (ESP) and The Human Gene Mutation Database (HGMD-Public) or in The Exome Aggregation Consortium (ExAC) Browser. The variant was also found to be absent in 300 unrelated individuals from Turkey. The amino acid p.Phe338 is found to be evolutionary conserved from human to zebrafish (Fig. 1b) and the substitution is predicted to be damaging by *in silico* prediction tools, including Mutation Taster, SIFT and Polyphen. Substitution of hydrophobic and aromatic phenylalanine at position 338 with the uncharged serine may alter the structure of the EPTP repeat domain and result in a misfolded protein. This variant has been submitted to the freely accessible NCBI ClinVar Database. 42 different *LGII* gene mutations

Table 1

The characteristics of the cohort and associated phenotypes.

Patient Characteristics	Patients (Total: 26) N(%)
Gender: Female/Male	13/13; (50%)/(50%)
Mean age (\pm standard deviation)	34.8 \pm 11.24
Follow-up duration (years)	6.8 \pm 5.5
Age at onset of epilepsy (years)	16.83 \pm 11.12
Consanguinity of the parents	6 (23.1%)
Family history of epilepsy	10 (38.5%)
Family history of ADLTE	5 (19.2%)
Comorbid diseases	Hypertension (n = 1); diabetes mellitus (n = 1); Hashimoto's thyroiditis (n = 1); Hodgkin lymphoma (n = 1)
Seizure Characteristics*	
History of febrile seizures	6 (23.1%)
Focal and bilateral convulsive seizures	10 (38.5%)
Focal seizures with LOC ^a only	5 (19.2%)
Bilateral convulsive seizures and focal seizures with LOC	11 (42.3%)
Seizure precipitation by noises	2 (7.7%)
Seizure relapse after AED withdrawal	11 (42.3%)
Elementary auditory aura	9 (34.6%)
Complex auditory aura	13 (50%)
Negative auditory aura (decrease of sound etc.	4 (15.4%)
Bilateral perception of auditory aura	18 (69.2%)
Lateralized auditory aura	8 (30.8%) (4 left -4 right-sided)
Other coexisting aura symptoms	<i>Déjà vu</i> (n = 3), vertigo (n = 4), paresthesia (n = 3), nausea (n = 1), blurred vision (n = 1).
Good prognosis (drug-responsive)	18 (69.2%)
EEG Findings	
Normal/nonspecific	8 (30.8%)
Focal interictal epileptic discharges	18 (69.2%)

^a LOC, Loss of consciousness;

* The seizure types were diagnosed according to the ILAE classification in 2010 (Berg et al., 2010)

identified to date are presented in Table 2 along with the novel *de novo* mutation in this study.

The 38-year-old male patient (E5 in Fig. 1a) with the novel variant is the youngest among three siblings of non-consanguineous parents. He had a normal developmental period and had no history of febrile seizures. He had started experiencing elementary auras (buzzing and ringing) and bilateral convulsive seizures at the age of 12 years. He had mild hypertension, which was under control with antihypertensive drugs. Neurological examination was unremarkable and his three Tesla MRI was normal. He had four EEG investigations and one of them showed nonspecific abnormalities of theta range. He was seizure-free for 7 years under carbamazepine treatment with a history of seizure recurrence upon medication withdrawal. He has been currently using carbamazepine (800 mg/day) and has 2–3 short elementary auras per month, not disturbing his quality of life.

Discussion

The present study describes *LGII* mutation screening in a cohort of 26 patients selected on the basis of focal epilepsy with auditory auras and absence of a symptomatic etiology. Our inclusion criterion was solely based on phenotypic distinction, rather than having a positive or negative family history. Reduced penetrance and variable expressivity of a potential *LGII* variant in the preceding generations as well as emergence of a *de novo* variant for the first time in the family can bias familial clustering of the condition at the time of the study. Sporadic cases arising due to such mechanisms may eventually result in dominant transmission of the condition in suggestive generations, which in turn will lead to reclassification of the condition as ADTLE. The two *LGII* mutations p.Arg136Trp and p.Arg474X (Table 2) each reported for both

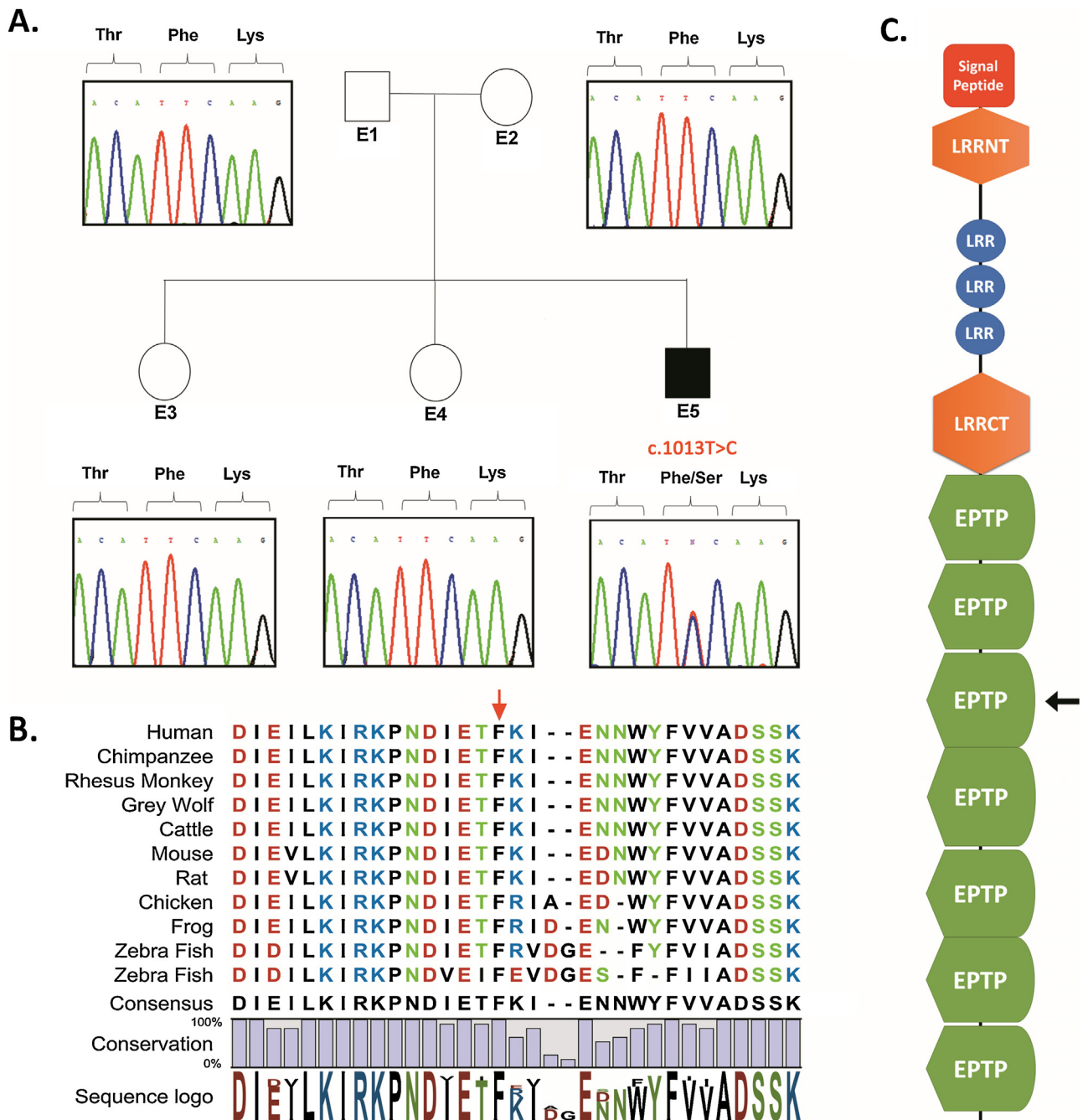


Fig. 1. A novel *de novo* mutation in *LGI1*. (A) DNA sequence analysis of c.1013T>C variant in the relevant family. (B) The evolutionary conservation of phenylalanine at position 338 (marked with an arrow) is shown with multiple sequence alignments among human (*H.sapiens*; NP.005088.1), chimpanzee (*P.troglodytes*; NP.001065246.1), Rhesus monkey (*M.mulatta*; XP.001093284.1), grey wolf (*C.lupus*; XP.534971.2), cattle (*B.taurus*; NP.001040056.2), mouse (*M.musculus*; NP.064674.1), rat (*R. norvegicus*; NP.665712.1), chicken (*G.gallus*; NP.001038120.1), frog (*X.tropicalis*; NP.001072366.1) and zebrafish (*D.rerio*; NP.001122241.1 and NP.955921.1). (C) Schematic representation of the domain structure of *LGI1* protein. LRR: leucine-rich repeat; LRRNT and LRRCT: Cysteine-rich domains residing N- and C-terminal to LRRs, respectively; EPTP: epitempin (domains are plotted to scale).

sporadic and familial cases serve as good examples for this phenomenon. The single *LGI1* mutation identified in this study is a novel missense change (c.1013T>C; p.Phe338Ser) observed *de novo* in a sporadic patient. Having identified the causative mutation, the patient is now informed about the possible transmission of the ADTLE phenotype in his future children.

It is interesting to note that in families with *LGI1* mutations, the most commonly reported type of auditory seizure symptoms was simple, unformed sounds (Ottman et al., 2004), similar to our patient positive for *LGI1* mutation. Additionally, this patient

is responsive to therapy with recurrence after drug withdrawal, which is a typical feature of reported patients with *LGI1* mutations (Berkovic et al., 2004).

None of the 10 LTLE patients from our cohort with a positive family history of epilepsy had *LGI1* mutations, even though *LGI1* mutations account for almost 50% of ADLTE families. Nevertheless, copy number variations (CNVs) have not been tested for this cohort, which are not a frequent cause of ADLTE. Dazzo et al., 2015a reported identification of only one family with a novel microdeletion spanning *LGI1* exon 2 in a group of 24 ADLTE families and 140

Table 2
Current catalogue of *LG11* mutations (NM.005097.2) in ADLTE and IPEAF arranged according to mutation location. The variant descriptions are checked with the 'Name Checker' or 'Position Converter' options from the Mutalyzer website (<https://mutalyzer.nl/>) and corrected accordingly, whenever required.

Region	Variation	Protein Change	F/S*	Reference
Exon 1	c.77T>C	p.Leu26Ser	F	Pizzuti et al., 2003
Exon 1	c.124T>C	p.Cys42Arg	F	Ottman et al., 2004
Exon 1	c.124T>G	p.Cys42Gly	F	Berkovic et al., 2004
Exon 1	c.136T>C	p.Cys46Arg	F	Gu et al., 2002
Exon 1	c.137G>T	p.Cys46Phe	F	Lee et al., 2014
Exon 2	c.245T>C	p.Ile82Thr	F	Sadleir et al., 2013
Exon 3	c.329C>A	p.Ala110Asp	F	Ottman et al., 2004
Exon 3	c.329del	p.Ala110ValfsX8	F	Hedera et al., 2004
Intron 3–4	c.360–3C>A	Truncation	F	Kalachikov et al., 2002
Exon 4	c.365T>A	p.Ile122Lys	F	Striano et al., 2008
Exon 4	c.365T>C	p.Ile122Thr	F	Di Bonaventura et al., 2011
Exon 4	c.367G>A	p.Glu123Lys	F	Di Bonaventura et al., 2009
Exon 4	c.377–379del	p.Asn126del	F	De Bellescize et al., 2009
Exon 4	c.406C>T	p.Arg136Trp	S, F	Michelucci et al., 2007; Di Bonaventura et al., 2011
Intron 4–5	c.431+1G>A	Truncation	F	Chabrol et al., 2007
Intron 4–5 & Exon5	c.432–2.436del	Truncation	F	Sadleir et al., 2013
Exon 5	c.435C>G	p.Ser145Arg	F	Hedera et al., 2004
Exon 5	c.461T>C	p.Leu154Pro	F	Pisano et al., 2005
Exon 6	c.535T>C	p.Cys179Arg	F	Di Bonaventura et al., 2011
Exon 6	c.598T>C	p.Cys200Arg	F	Michelucci et al., 2003
Exon 6	c.598del	p.Cys200AlafsX40	F	Heiman et al., 2010
Exon 6	c.611del	p.Pro204GlnfsX36	F	Kalachikov et al., 2002
Exon 6	c.673G>T	p.Glu225X	F	Sadleir et al., 2013
Exon 7	c.695T>C	p.Leu232Pro	F	Chabrol et al., 2007
Exon 7	c.758del	p.Ala253ValfsX32	F	Morante-Redolat et al., 2002
Intron 7–8	c.839–2A>G	Truncation	F	Kobayashi et al., 2003
Exon 8	c.856T>C	p.Cys286Arg	S	Dazzo et al., 2015a
Exon 8	c.893T>C	p.Ile298Thr	F	Ottman et al., 2004
Exon 8	c.953T>G	p.Phe318Cys	F	Fertig et al., 2003
Exon 8	c.1013T>C	p.Phe338Ser	S	Current study
Exon 8	c.1050–1051del	p.Asp350GlnfsX31	F	Kalachikov et al., 2002
Exon 8	c.1075A>G	p.Ile359Val	F	Di Bonaventura et al., 2011
Exon 8	c.1118T>C	p.Leu373Ser	F	Dazzo et al., 2015a
Exon 8	c.1148A>C	p.Glu383Ala	F	Kalachikov et al., 2002
Exon 8	c.1219C>T	p.Arg407Cys	F	Striano et al., 2011
Exon 8	c.1295T>A	p.Val432Glu	F	Michelucci et al., 2003
Exon 8	c.1418C>T	p.Ser473Leu	F	Berkovic et al., 2004; Kawamata et al., 2010
Exon 8	c.1420C>T	p.Arg474X	F, S	Morante-Redolat et al., 2002; Bisulli et al., 2004b
Exon 8	c.1421G>A	p.Arg474Gln	F	Kawamata et al., 2010
Exon 8	c.1477G>A	p.Gly493Arg	F	Heiman et al., 2010
Exon 8	c.1636–1637del	p.Gln546AspfsX8	F	Heiman et al., 2010
Exon 8	c.1639dup	p.Ile547AsnfsX8	F	Kalachikov et al., 2002

sporadic cases with no evidence of point mutations in *LG11*. Nevertheless, the clinical utility of diagnostic screening of CNVs in *LG11* are still debatable (Magini et al., 2014) (Dazzo et al., 2015a).

LG11, unlike most of the other epilepsy related genes, encodes a neuronal secreted protein instead of an ion channel subunit (Senechal et al., 2005). Secreted *LG11* presumably acts as an antiepileptogenic ligand that modulates AMPA-type glutamate receptor mediated synaptic transmission (Fukata et al., 2010). *In vitro* mutagenesis assays and *in vivo* studies with homozygous and heterozygous null mice (*Lgi1*^{-/-} and *Lgi1*^{+/-}) collectively suggest that heterozygous loss-of-function alleles contribute to disease pathogenesis by haploinsufficiency (Senechal et al., 2005) (Fukata et al., 2010). It is proposed that *LG11* protein secretion and stability are altered by *LG11* mutations (Senechal et al., 2005). A rat model carrying a missense mutation (L385R) in *Lgi1* has recently been generated (Baulac et al., 2012), which probably serves as a suitable model for *LG11*-related epilepsies, where the majority of human *LG11* mutations (66%) are missense (Ho et al., 2012). In this model, the depletion of *LG11* protein in neurons has not been attributed only to a failure of *Lgi1* secretion, but also to rapid degradation of *Lgi1*-L385R (Baulac et al., 2012). Interestingly, heterozygous *Lgi1*^{+/-}L385R rats are shown to be more susceptible to sound-induced seizures, which may be controlled by AEDs such as carbamazepine, phenytoin and levetiracetam (Fumoto et al., 2014). However, in contrast to the findings in the pertinent

rat model, two sporadic patients from our cohort describing sound-induced seizures were detected negative for *LG11* mutations. In addition to haploinsufficiency, *LG11* mutations may have pathogenic effects through dominant-negative mechanisms (Zhou et al., 2009).

Analysis of genes related to dominant epilepsy syndromes should both focus on familial and sporadic forms in order to get a better picture of the mutation frequency, molecular diagnosis and genetic counselling. For ADLTE, the distinctive features including auditory aura and non-lesional brain MRI findings are shared among familial and sporadic cases pointing involvement of common genes and pathways. Recently, heterozygous mutations in reelin (*RELN*) have been shown to be segregating in ADLTE-affected families (Dazzo et al., 2015b). Secreted *RELN* and *LG11* co-localize in rat brain, which support involvement of overlapping mechanisms in ADLTE pathogenesis. Nevertheless, *RELN* like *LG11* and further ADLTE genes yet to be identified need to be screened in large and well-defined cohorts for extensive analysis of the genotype–phenotype correlations.

Conclusion

In conclusion, we report identification of a novel *de novo* *LG11* mutation in a patient from Turkey, which both aids the

diagnosis of the condition as ADLTE and brings up more solid genetic counselling options for the patient.

Conflict of Interest

None of the authors has any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Further reading

ClinVar: <http://www.ncbi.nlm.nih.gov/clinvar/>(last accession: 12 August 2015)

Ensembl Genome Browser: <http://www.ensembl.org/index.html> (last accession: 12 August 2015)

The Exome Aggregation Consortium (ExAC) Browser: <http://exac.broadinstitute.org/>(last accession: 12 August 2015)

Mutation Taster: <http://www.mutationtaster.org/>(last accession: 12 August 2015)

Polyphen: <http://genetics.bwh.harvard.edu/pph2/>(last accession: 12 August 2015)

SIFT: <http://sift.jcvi.org/>(last accession: 12 August 2015)