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A Novel Nonsense Mutation in Leucine-Rich, Glioma-Inactivated-1 Gene as the Underlying Cause of Familial Temporal Lobe Epilepsy

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Dear Editor,

Epilepsy constitutes a group of chronic neurological disorders that can be diagnosed at all ages and is characterized by recurrent seizures in which abnormal electrical activity causes altered perception or behavior. The prevalence of epilepsy varies between countries and ethnic groups, and generally ranges from 0.1% to 0.5%, but this increases to more than 1% in underdeveloped countries. Multiple factors such as genetic and environmental factors are associated with the etiology of epilepsy. Epilepsy is genetically highly heterogeneous and shows a weak genotype-phenotype correlation.[1] More than 100 genes have been reported to be implicated in the seizure phenotype. As the environmental factors, infection, brain tumor, cerebrovascular disease, degenerative brain disease, trauma, and impairment of the cerebral cortex are suggested to be associated.

Autosomal dominant lateral temporal lobe epilepsy (ADLTE or ETL1; MIM 600512) is a specific form of temporal lobe epilepsy characterized by partial seizures. ADLTE is caused by dominant mutations in the leucine-rich, glioma-inactivated-1 (*LGI1*) gene on chromosome 10q22-q24.[2,3] Many *LGI1* mutations have been reported as causes of ADLTE and sporadic epilepsy.[4] LGI1 protein is strongly expressed in the lateral temporal lobe, and it is known to form the LGI1-ADAM22 epilepsy-related ligand-receptor complex that plays important roles in synaptic transmission and brain excitability.[5]

More than two million people in Pakistan suffer from epilepsy, which constitutes around 5% of the epilepsy patients worldwide. However, genetic tests for epilepsy have rarely been performed in Pakistan. This study examined a large Pakistani autosomal dominant epilepsy family (family ID: EF-23) comprising seven siblings: five affected and two unaffected individuals (Fig. 1A). The five affected family members had a history of complex partial seizures. All of them had experienced auditory auras or ictal aphasia followed by secondarily generalized tonic-clonic seizures (SGTCs), and one individual (II-1) additionally had visual symptoms followed by SGTCs. The ages at seizure onset ranged from 5 to 15 years (10.8±3.7 years, mean±SD). Both the seizure semiology and the neuropsychological findings pointed to lateral temporal lobe dysfunction in this ADLTE family. This study was approved by the IRB of Kongju National University (IRB No. KNU-IRB-2015-67-2) and Samsung Medical Center (IRB No. SMC 2015-08-057-002).

Exome sequencing of the proband (II-6) revealed a novel c.988C>T (p.R330X) nonsense mutation in *LGI1*. Sanger sequencing showed complete cosegregation of the mutation, with the five affected individuals in the EF-23 pedigree (Fig. 1A and B). The *LGI1* mutation was located in the highly conserved third leucine-rich glioma-inactivated epitempin protein repeat domain (Fig. 1C and D). The p.R330X mutation was not reported in several global human genome databases, including the 1,000 Genomes Project (http://www.1000genomes.org/),

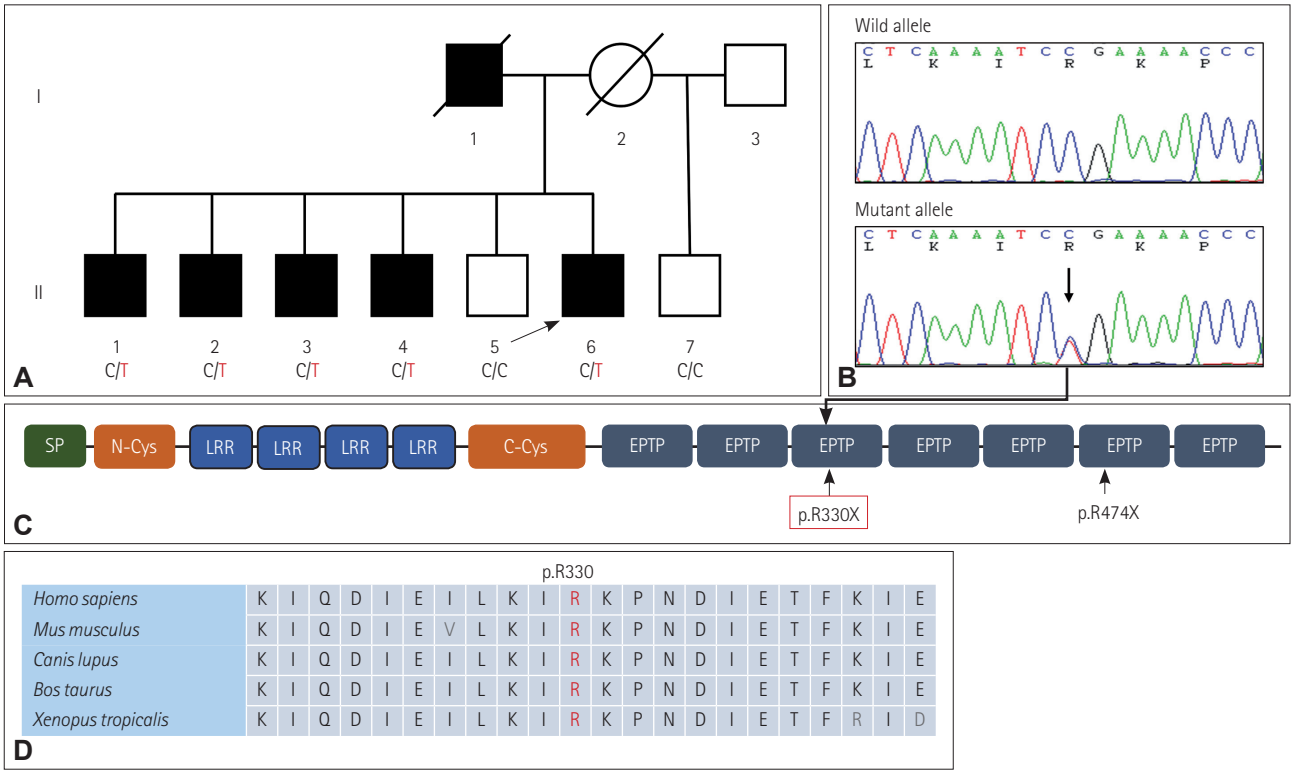

Fig. 1. *LGI1* mutation in an ADLTE family. A: Pedigree of an ADLTE (EF-23) Pakistani family. The pedigree shows six affected individuals: A deceased father and five siblings. The genotype of the c.988C>T mutation in *LGI1* is indicated underneath each examined individual. The proband (II-6) is indicated by an arrow. Open and filled symbols indicate unaffected and affected members, respectively. B: Sequencing chromatograms of the c.988C>T mutation in *LGI1*. The mutation site is indicated by the vertical arrow. C: Schematic of the domain structure of the IGI1 protein and the location of the p.R330X mutation (red box), which is located in the third EPTP domain. The p.R474X mutation was reported by Morante-Redolat et al.[3] D: Conservation of the amino acids at the mutation site among several vertebrate species. ADLTE: autosomal dominant temporal lobe epilepsy, C-Cys: cysteine-rich region from the C-terminal to the leucine-rich repeat region, EPTP: epitempin protein, LGI1: leucine-rich, glioma-inactivated-1, LRR: leucine-rich repeat region, N-Cys: cysteine-rich region from the N-terminal to the leucine-rich repeat region, SP: signal peptide.

Exome Sequencing Project (http://evs.gs.washington.edu/EVS/), the Exome Aggregation Consortium (http://exac.broadinstitute.org/), or the Korean Reference Genome Database (http://152.99.75.168/KRGDB/menuPages/introKor.jsp). Another nonsense mutation (p.R474X) in *LGI1* has been reported in an ADLTE family.[3] In addition to the *LGI1* p.R330X mutation, several rare or private nonsynonymous variants were identified in the epilepsy-related genes from the exome of the proband (Supplementary Table 1 in the online-only Data Supplement). However, they were not considered to be the underlying cause of the epilepsy phenotype due to the presence of nonsegregation within the family. Examination of mitochondrial DNA revealed no causative variants including long deletions or depletions.

This study has identified a novel *LGI1* stop-gain mutation in a large autosomal dominant family with lateral temporal lobe epilepsy, which represents the first case of an *LGI1* mutation in Pakistan. These findings will be helpful when setting up the molecular diagnosis of epilepsy in Pakistan.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2018.14.4.591.

Conflicts of Interest

The authors have no financial conflicts of interest.

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