Whole exome sequencing reveals a new GPR98 mutation in a family with Autosomal dominant lateral temporal epilepsy.

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- Introduction -

Autosomal dominant lateral temporal epilepsy (ADLTE) is a genetic focal epilepsy syndrome characterized by typical auditory auras or ictal aphasia in most affected family members. The molecular basis of ADLTE is still largely unknown because of the multi-factorial and heterogeneous nature of this disorder. Mutations linked to ADLTE have been found in the leucine rich, glioma inactivated 1 (LGI1) gene. More than 30 disease-causing LGI1 mutations have been identified so far, which account for 30–50% of ADLTE families, and in about 2% of sporadic cases with idiopathic partial epilepsy with auditory features. The next-generation sequencing (NGS) is an ideal strategy to identify disease-causing genes, including new mutations (especially in highly heterogeneous disorders such as ADLTE), and provide novel insights into understanding disease mechanisms. Herein, we report on the clinical and genetic characterization of an Italian family with ADLTE.

- Patients-

We investigated an Italian family classified as ADLTE according to the following criteria: two or more affected members with a history of focal epilepsy characterized by auditory, aphasic, or visual symptoms and absence of structural brain abnormalities. The proband (II-2) was born to non consanguineous healty parents and has an affected brother (II-1), and there was family history of the disease. *The family pedigree is shown in Fig. 1.* An informed consent was obtained from each individual (or the parents of minors) before blood samples were collected and genomic DNA was extracted according to standard protocols. This study was approved by the local Ethics Committee.

- Results -

No pathogenic mutations in the known LGI1 gene was found in our family. Exome-sequencing data identified a new heterozygous missense mutation in the G protein-coupled receptor 98 gene (GPR98), which is mutated in the Frings mouse model of audiogenic epilepsy. The mutation c.4330G>A located within exon 20 leading to the amino acid substitution p.Ala1444Thr, and was found in the three family members. This change segregated as heterozygote status in two affect and in one healthy parents, and was confirmed by Sanger sequencing (*Fig.2*). The mutation was found to be inherited from one of parents being absent in the proband's mother. The detected missense variant was excluded in 50 Italian normal controls (100 normal alleles).

- Aim-

We wished to identify the underlying genetic cause in a family with ADLTE, in which no pathogenic mutations in the known LGI1 gene was found.

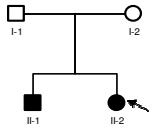

Figure 1. *Familial pedigree. The proband is indicated by an arrow. Affected individuals are indicated in black.*

- Genotyping -

We performed exome sequencing using the Ion AmpliSeq Exome kit on Ion Torrent Proton Sequencer. Possible disease-associated variants were determined by filtering based on minor allele frequency, predicted pathogenicity and segregation analysis in all family members. All members of the family had been previously analyzed by Sanger sequencing for the LGI1 exons without any positive result. We performed exome sequencing in three family members, I-1, II-1, and II-2 (Fig. 1).The entire coding region of the 3 family members was directly enriched and captured by AmpliSeq Exome kit technology and subsequently sequenced by synthesis using Ion Proton system (Life Technologies, CA, USA).

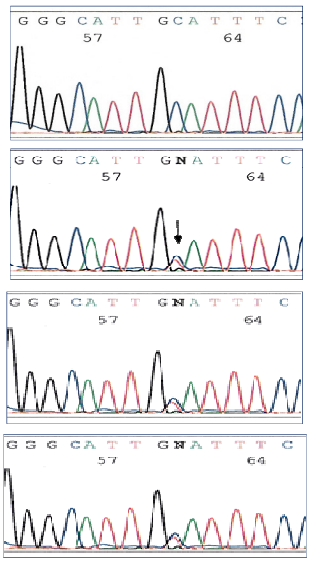

Figure 2: Segregation of mutation with sequencing chromatograms (arrow represent mutation)

- Discussion and conclusions -

This study provided evidence of a pathogenic role of GPR98 for the clinical phenotype observed in our family with ADLTE. In this way, our findings point to this gene as a candidate gene of ADLTE, and additional studies in larger patient populations are needed to better clarify its role in this peculiar type of familial epilepsy. Moreover, the present study well illustrate that next-generation sequencing (NGS) technology is an accurate and effective method for detecting genetic mutations.

- References -

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