Case Report: Identification of Two Variants of ALG13 in Families With or Without Seizure and Binocular Strabismus: Phenotypic Spectrum Analysis

Tao Cai1,2*, Jieting Huang1,3, Xiuwei Ma1, Siqi Hu1,4, Lina Zhu1, Jinwen Zhu5 and Zhichun Feng1,3,4*

1Senior Department of Pediatrics, the Seventh Medical Center of PLA General Hospital, Beijing, China, 2Experimental Medicine Section, National Institutes of Health/National Institute of Dental and Craniofacial Research, Bethesda, MD, United States, 3Beijing Key Laboratory of Pediatric Organ Failure, Beijing, China, 4The National Engineering Laboratory for Birth Defects Prevention and Control of Key Technology, Beijing, China, 5Angen Gene Medicine Technology, Beijing, China

Background: Genetic causes in most affected children with intellectual disability and/or development delay remain unknown.

Methods: To identify potential variants responsible for these disorders, we recruited 161 affected families and performed whole-exome sequencing and associated bioinformatics analysis.

Results: In the present study, we report the identification of variants in the ALG13 gene in two of the families. In family 1, a known pathogenic missense variant (c.23T > C; p.V8A) of ALG13 was identified in a boy and his mother. In family 2, a novel missense variant (c.862C > G; p.L288V) of the same gene was identified in the affected boy and his phenotypically normal mother. Genotype–phenotype correlation analysis by comparing reported 28 different variants (HGMD) showed that three major phenotypes, including various seizures/epilepsy, intellectual disability, and development delay (such as growth, speech, motor, etc.), are present in most affected individuals. However, other phenotypes, such as strabismus and absence of seizure in our second patient, are not reported if any, which may represent a unique case of X-linked recessive nonsyndromic disorder caused by a mutation in ALG13.

Conclusion: We identified two missense variants in ALG13 in a cohort of 161 families with affected individuals diagnosed as intellectual disability and/or development delay. A novel c.862C > G mutation may represent a case of X-linked recessive.

Keywords: ALG13, mutation, whole-exome sequencing, development delay, X-linked
INTRODUCTION

The ALG13 gene encodes a subunit of a bipartite UDP-N-acetylglucosamine transferase that regulates protein folding and stability, which is mapped to Xq23 and widely expressed in human tissues, such as brain, liver, and kidney (MIM: 300776). The first ALG13 mutation with de novo origin was identified in a male infant diagnosed with congenital disorders of glycosylation type I with refractory epilepsy, microcephaly, extrapyramidal, and pyramidal symptoms (Timal, et al., 2012).

Many of the affected individuals were diagnosed with developmental and epileptic encephalopathy 36 (DE36, MIM: 300884), which is caused by heterozygous or hemizygous mutation in ALG13. DE36 is characterized by the onset of seizures at a mean age of 6.5 months. Most patients present with infantile spasms associated with hypsarrhythmia on EEG, consistent with a clinical diagnosis of West syndrome.

To date, a total of 28 different mutations in ALG13 (HGMD) have been identified in affected individuals or families with epileptic encephalopathies (Epi, et al., 2013; Moller, et al., 2016), intellectual disability (Bissar-Tadmouri, et al., 2014), West syndrome (Hino-Fukuyo, et al., 2015) or Lennox–Gastaut syndrome (Zhou, et al., 2018; Stranneheim, et al., 2021), congenital disorder of glycosylation (Alsharhan, et al., 2021), and several rare conditions such as left ventricular obstruction (Jin, et al., 2017) and fetal alcohol syndrome (de la Morena-Barrio, et al., 2018).

In the present study, we report the identification of two variants of ALG13 from two affected males with development delay and seizures or intellectual disability binoocular strabismus, including a novel missense variant (c.862C > G; p.L288V) and a previously reported variant (c.23T > C; p.V8A). For a better understanding of this extremely rare disease, we present a detailed phenotype–genotype correlation analysis and a brief literature review.

MATERIALS AND METHODS

Patients and Standard Protocols

Informed consents were obtained from all participants and in the case of minors, from their parents. This study was approved by the Seventh Medical Center of PLA General Hospital Ethics Committee at Beijing (no. 2022-37). A total of 503 individuals in 161 families, including 175 diagnosed as intellectual disability and/or development delay and 328 unaffected individuals, were recruited for genetic analysis. In the current study, three affected individuals with development defects in two families were presented.

WES Analysis and Sanger Sequencing

Genomic DNAs were isolated from peripheral blood leukocytes. The captured exome by a SureSelect Human All Exon Kit (Agilent, Santa Clara, CA) was sequenced by HiSeq2000 sequencer (Illumina, San Diego, CA) and analyzed as previously described (Yu, et al., 2016; Zhu, et al., 2019; Li, et al., 2021). The reads were aligned to hg19, and the variants were identified through the GATK pipeline. An average sequence depth of coverage was 149× for exome sequences. Potential pathogenic variants were selected for further bioinformatics analysis.

Identifiers for Mutations in the ALG13 Gene by WES

Trio-WES analysis for family 1 identified a known pathogenic missense variant (c.23T > C; p.V8A) in the ALG13 gene (NM_001099922.3) and further confirmed by Sanger sequencing (Figure 2A) from both the affected boy and his mother. The same
mutation as a de novo allele was previously detected in a female patient (Datta, et al., 2021), who showed mild developmental delay and seizures starting from the second year of life (Table 1). The p.V8 residue is located in the Glyco_tran_28_C domain (amino acids 3–133) at the N-terminal region of the encoded protein (Figures 2C,D), which involves monogalactosyldiacylglycerol synthase and UDP-N-acetylglucosamine transferase (Pfam, SmartMotif).

Trio-WES analysis for family 2 identified a previously undescribed potentially pathogenic missense variant (c.862C > G) from the affected boy and his phenotypically normal mother. Sanger sequencing further confirmed this variant (Figure 2B). Bioinformatics analysis revealed that this variant is not present in ExAC or the in-house database and predicted to be disease-causing by MutationTaster and Polyphen2. Smart Motif analysis revealed that the mutation p.L288 is mapped to the OTU domain (amino acids 237–348) in the ALG13 protein (Figures 2C,D), which is OTU-like cysteine protease motif (Makarova, et al., 2000).

**Genotype and Phenotype Profile Related to ALG13 Mutations**

As shown in Table 1, we summarized 28 different mutations that are listed in HGMD and two mutations identified in the present study. Affected individuals and/or families were either in X-linked dominant (XLD) or X-linked recessive (XLR) pattern or with de novo mutation (DNM) origins. Family 1 in our case is in the XLD form, while family 2 is in the XLR pattern. Most of the mutations in Table 1 are missense variants (27/30); three of them are splicing and deletion mutations (3/30). Three major phenotypes, including various seizures/epilepsy, intellectual disability, and development delay (such as growth, speech, motor, etc.), are observed in most of the cases. Less frequently observed phenotypes include strabismus, optic nerve atrophy, left ventricular obstruction, and ataxia.

**DISCUSSION**

In the present study, we identified two variants in the ALG13 gene in patients with either typical phenotypes in family 1 with XLD inheritance form (seizures, intellectual disability, speech, and motor development delay) or atypical phenotypes in family 2 with XLR inheritance pattern (mild intellectual disability, speech and motor development delay, mild ataxia, and binocular strabismus, but no seizures). Previously, only 28 different variants were reported (HGMD). Three of them (c.845G > A; p.G282E,
FIGURE 2 | ALG13 mutations and expression. (A) Sanger sequencing confirmation of the c.23T>C mutation in case 1 and his mother. (B) Sanger sequencing confirmation of the c.862C>G mutation in case 2 and his mother. (C) Schematic representations of functional domains of ALG13. The p.V8A mutation of family 1 is located in the Glyco_tans_28 domain at N-terminus (amino acid 3–133). The p.L288V mutation of family 2 is mapped in the OUT domain (amino acid 237–348). (D) Residue p.V8 and p.L288 positions are indicated in red in the 3-dimensional structure of the ALG13 protein.
such as BioGPS and human brain transcriptome, the human phenotypes as we described earlier.

In contrast, alanine in the p.V8A variant in family 1 is a simple amino acid, which has just a methyl as its side chain. Based on the AlphaFold predicted structure model (Figure 2D), Val8 residue is located in the loop region involving glycosyltransferase activity (amino acids 1–125), thereby causing more severe clinic phenotypes as we described earlier.

Based on several commonly used gene expression databases, such as BioGPS and human brain transcriptome, the human ALG13 gene is widely expressed in many tissues, including neurons in developing and adult brain tissues (Supplementary Figure S1). Brain-associated clinical manifestations, such as seizures and intellectual disability, are apparently correlated with cortical and central nervous dysfunctions in the affected individuals with ALG13 variants. Additional rare phenotypes, such as ataxia, nystagmus, and strabismus, are potentially associated with developmental defects or dysfunctions of the cerebellum and brain stem tissues.

In the Alg13 knockout mouse model, Alg13 deficiency resulted in an increased seizure and susceptibility in the Alg13−/− mice (Gao, et al., 2019). Previous studies also explored the possible mechanisms of Alg13-involved epilepsy by showing hyperactive mTOR signaling pathways in the cortex and hippocampus of Alg13−/− mice (Gao, et al., 2019; Huo, et al., 2020). Further studies using patch-clamp recordings demonstrated that Alg13−/− mice show a marked decrease in the gamma-aminobutyric acid A receptor (GABAAR)–mediated inhibitory synaptic transmission (Huo, et al., 2020). At the human level, a majority of variants are missense, which are linked to either X-linked dominant

Table 1: Genotype–phenotype correlation analyses for affected individuals with ALG13 variants. The bold presents the phenotype in this study or a special phenotype related to this study.

| HGVS | Reported main phenotypes | Brief annotation | References |
|------|--------------------------|-----------------|------------|
| V8A  | Seizures and mild developmental delay (DD) | De novo mutation | Datta et al. (2021) |
| V8A  | Seizures, intellectual disability (ID), speech and motor DD | Affected mother and son | This study |
| I17N | Lennox-Gastaut syndrome | Epileptic encephalopathy | Ji et al. (2019) |
| E30Q | Microcephaly, global DD, hypoxic ischemic encephalopathy, and hypotonia | OMIM: 300776 | Datta et al. (2021) |
| O40H | Epileptic encephalopathy | OMIM: 300884 | Datta et al. (2021) |
| T57P | Epileptic encephalopathy | OMIM: 300884 | Timal et al. (2012) |
| K94E | Congenital disorder of glycosylation 1 | Epileptic encephalopathy | Epi et al. (2013) |
| N107S | Lennox-Gastaut syndrome; strabismus in patient 3 | Omim: 300884 | Paprocka et al. (2021) |
| N107T | Neurodevelopmental disorder | Omim: 300884 | Geisheker et al. (2017) |
| G282E | Epileptic encephalopathy, infantile | Omim: 300884 | Wei et al. (2018) |
| L288V | ID, speech and motor DD; no seizure; finger-nose test (FNT, +); strabismus; MRI: myelination delayed, et al | EEK (+); the variant-carrier mother is normal | This study |
| P294S | West syndrome and optic nerve atrophy | Infantile spasms | Hino-Fukuyo et al. (2015) |
| K411N | Neurological disorder | No detailed info | Jiao et al. (2019) |
| E463G | Seizures, motor, and speech DD | Omim: 300884 | Monies et al. (2019) |
| Q40H | Epileptic encephalopathy | Omim: 300884 | Monies et al. (2019) |
| E30Q | Microcephaly, global DD, hypoxic ischemic encephalopathy, and hypotonia | Omim: 300884 | Monies et al. (2019) |
| I17N | Lennox-Gastaut syndrome | Omim: 300884 | de la Morena-Barrio et al. (2018) |
| P658L | Left ventricular obstruction and neurodevelopmental disorder | Omim: 300884 | Fanwell et al. (2015) |
| R701H | Congenital disorder of glycosylation | Omim: 300884 | Aalsheran et al. (2021) |
| S702R | ID, and gross fine motor DD | Omim: 300884 | Aalsheran et al. (2021) |
| R769W | Epilepsy, motor DD, and learning disability | Omim: 300884 | de la Morena-Barrio et al. (2018) |
| S891F | Fetal alcohol syndrome | Omim: 300884 | Amadori et al. (2020) |
| R701H | Neurodevelopmental disorder | Omim: 300884 | Aalsheran et al. (2021) |
| V8A | Seizures and mild developmental delay (DD) | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| G282E | Epileptic encephalopathy, infantile | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| Q40H | Epileptic encephalopathy, infantile | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| P294S | West syndrome and optic nerve atrophy | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| K411N | Neurological disorder | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| E463G | Seizures, motor, and speech DD | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| Q40H | Epileptic encephalopathy, infantile | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| I17N | Lennox-Gastaut syndrome | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| P658L | Left ventricular obstruction and neurodevelopmental disorder | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| R701H | Congenital disorder of glycosylation | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| S702R | ID, and gross fine motor DD | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| R769W | Epilepsy, motor DD, and learning disability | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |
| S891F | Fetal alcohol syndrome | A triad of seizure, EEG findings, and ID | Zhou et al. (2018) |

*Intellectual disability (ID); development delay (DD).
phenotypes due to stronger pathogenic variants (such as the variant in family 1) or X-linked recessive phenotypes due to mild pathogenic variants (such as the variant in family 2).

CONCLUSION

Taken together, we provided clinical and bioinformatics evidences that two ALG13 variants are pathogenic for the affected individuals with ALG13-associated phenotypes. However, the underlying mechanism remains to be explored in further studies.

DATA AVAILABILITY STATEMENT

The original datasets presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Seventh Medical Center of PLA General Hospital Ethics Committee. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin. Written informed consent was obtained from the individual(s) and minor(s)’ legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

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AUTHOR CONTRIBUTIONS

TC and ZF conceived and designed the experiment and wrote the manuscript. JH, SH, and JZ provided WES and bioinformatics analysis and performed the experiments. XM and LZ provided clinical information.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.892940/full#supplementary-material
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Conflict of Interest: Author JZ was employed by Angen Gene Medicine Technology, Beijing, China.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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