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CASE REPORT

PIGN mutation multiple congenital anomalies-hypotonia-seizures syndrome 1: A case report

Fei Hou, Shan Shan, Hua Jin

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Abstract

BACKGROUND

Multiple congenital anomalies-hypotonia-seizures syndrome 1 (MCAHS1) associated with mutations in *PIGN* gene.

CASE SUMMARY

The authors report 1 case of a 16 years old girl who was presented with epilepsy, developmental delay and cerebellar atrophy. She harbors a compound heterozygous variant in the *PIGN* gene, include a nonsense splice site mutation (c.2557A>C) which was inherited from her mother, and a novel site mutation (c.980del) which was inherited from her father.

CONCLUSION

This case report expands the mutation spectrum found in *PIGN* gene, and strengthens the association between *PIGN* mutation and MCAHS1. Mutations in *PIGN* gene may be an underestimated cause of epilepsy. The authors recommend that, for patients with epilepsy or prenatal diagnosis of highly suspicious fetus, gene sequencing should be the preferred detection method.

Key Words: PIGN; Multiple congenital anomalies-hypotonia-seizures Syndrome 1; MCAHS1; Whole-exome sequencing

Core Tip: We report 1 case of a 16-year-old girl who presented with epilepsy, developmental delay, and cerebellar atrophy. She harbors compound heterozygous variants in the *PIGN* gene, including a nonsense splice site mutation (c.2557A>C) that was inherited from her mother and a novel site mutation (c.980del) that was inherited from her father. The maternally inherited variant (c.2557A>C) has not been seen observed in the gnomAD and 1000genomes, which was called variants of unknown significance. The novel mutation c.980del (paternally inherited) that was detected in the prohand was predicted to be "probably damaging".

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INTRODUCTION

Multiple congenital anomalies-hypotonia-seizures syndrome 1 (MCAHS1) associated with mutations in *PIGN* gene, is an autosomal recessive disease featured as epilepsy, stunting, hypotonica, and various congenital disorders. This was initially described in 2011[1]. Mutation in the *PIGN* gene involved in GPI-anchor pathway have been identified cause varied neurological abnormalities[1-4].The authors report on a 16 years old girl who was presented with epilepsy, developmental delay and cerebellar atrophy. She harbors a compound heterozygous variant in the *PIGN* gene, include a nonsense splice site mutation (c.2557A>C) which was inherited from her mother, and a novel site mutation (c.980del) which was inherited from her father.

CASE PRESENTATION

Chief complaints

A female, 16 years old, was presented with epilepsy, developmental delay and cerebellar atrophy.

History of present illness

Weakness of muscles was noticed at age 2 years old. At 1 year of age, she developed clinical seizures. Her seizure types include twitching movements, starting episodes, cluster seizures, and spasms. At a year and a half, there was only partial response to anti-convulsive therapy. Subsequently, global developmental delay was noted by 2 years old of age, there was no speech, and she needed assistance with daily life activities.

History of past illness

She was vigorous in the newborn period and passed her newborn disease screening, began walking around the age of 18 mo.

Personal and family history

The patient was the second child of the family (non-consanguineous), her mother was 33 years old. She was born at full term with normal birth parameters, the pregnancy was normal, there was no known teratogenic exposure.

The parents does not have a personal history of seizures, nor is there a family history seizures.

Physical examination

Clinical examination documented the eyes were deep set with nystagmus, a small nose with nasalbridge (Figure 1).

Laboratory examinations

Whole exome sequencing (WES) was performed commercially at Berrygenomics on the patient and her parents. Sequencing was performed on Illumina Novaseq 6000 (Illumina, San Diego, United States), using the Nano WES Human Exome V1.0 (Berrygenomics, Beijing, China) kit with 200 bp paired-end read, according to the manufacturer's instructions. Annotation of variants was performed using GATK (https://software.broadinstitute.org/gatk/), gnomAD (http://gnomad.broadinstitute.org/), 1000genomes (http://browser.1000genomes.org), SIFT (http://sift.jcvi.org), FATHMM (http://fathmm.biocompute.org.uk), MutationAssessor (http://mutationassessor.org), OMIM (http://www.omim.org), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar), HGMD (http://

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Figure 1 Clinical phenotype characteristics of the proband.

www.hgmd.org).

Sanger sequening

Sequence analysis of exon 28 and 12 of *PIGN,* using genomic DNA from the patient and her parents were performed by amplification of a 438 bp and 239 bp fragment containing the putative mutation identified *via* exome sequencing. The sense primer sequence was 5′-TAAGTCAGTTTCATCAC-CGTTCTAT-3′ and the antisense primer sequence was 5′-ATTTCCTCTAATGACAAGCAACAC-3′ for exon 28. The sense primer sequence was 5′-TCTAGCAAATGACACTTTTAGAGA-3′, and the antisense primer sequence was 5′-TTCCTTACCACTGAGTTAAGAGG-3′ for exon 12.

Imaging examinations

Neuropsychological testing demonstrated moderate intellectual disability. Brain imaging showed the progression of mild global cerebral volume loss and cerebellar atrophy. The parents could not provide the results of previous test, including brain magnetic resonance imaging, various metabolic tests.

FINAL DIAGNOSIS

Whole Exome sequencing was performed commercially at BerryGenomics on the patient and her parents. Compound heterozygous mutations in *PIGN* gene were found, maternally inherited c.2557A>C and paternally inherited c.980del. The mutations were validated by sanger sequencing in the patient and her parents (Figure 2).

The authors also examined several small insertion/deletion variants (Indels), but none of these had an apparent connection to the clinical phenotype.

TREATMENT

The present therapies for patients with *PIGN* gene associated illnesses are mainly supportive, which were aimed to reduce the development of epileptic seizures.

OUTCOME AND FOLLOW-UP

The authors will keep on to follow the patient's disease development. This diagnosis allowed permitted appropriate genetic counseling with related risk evaluation.

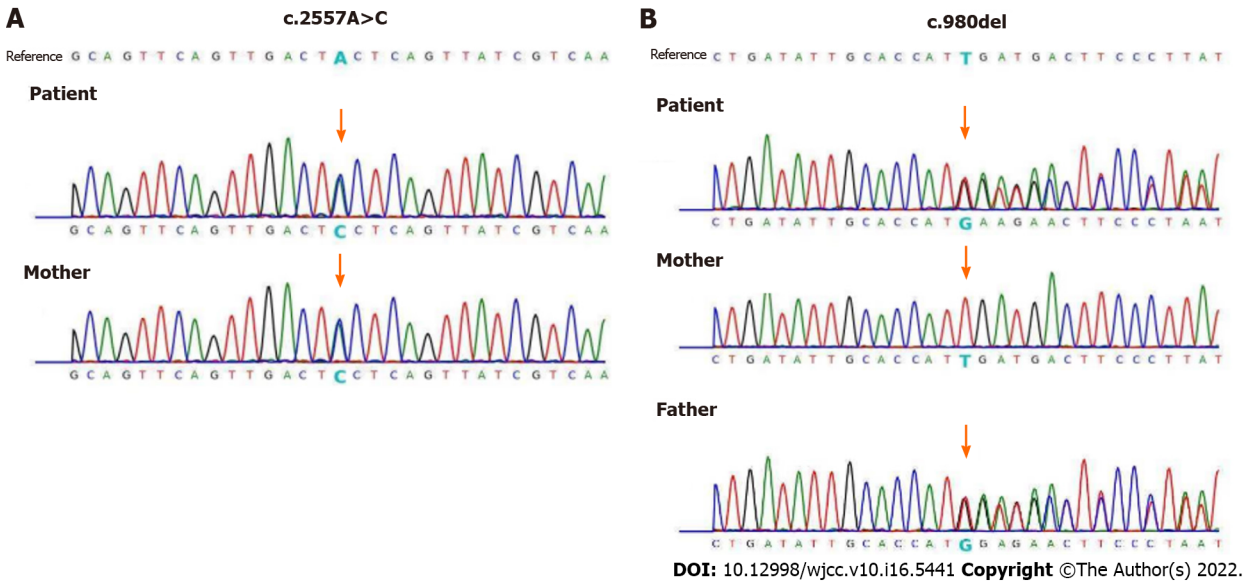

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Figure 2 Sanger sequencing for detection of mutation. A: DNA sequence electropherograms of the c.2557A>C mutation identified in exon 28 of PIGN in the patient and her brother; B: DNA sequence electropherograms of the c.980del mutation identified in exon 12 of PIGN in the patient her parents.

DISCUSSION

There are more than 20 genes that participated in GPI-anchor biosynthesis pathway. *PIGN* is responsible for supplement of phosphoethanolamine to the primary mannose in GPI[2]. Mutations in the *PIGN* gene involved in GPI biosynthesis, have been identified associated with MCAHS1[1,5,6]. The authors report a patient with epilepsy, global delay, cerebellar atrophy with a *PIGN* mutation. The maternally inherited variant (c.2557A>C) has not been seen observed in the gnomAD and 1000genomes, which was called variants of unknown significance. The original mutation c.980del (paternally inherited) discovered in the prohand was estimated as "probably damaging". The novel mutation changes the gene's open reading frameshift, support the conclusion that the novel mutation detected in the patient cause major damage to the GPI-anchored protein, finally leading to the disorder.

Unlike previous reports[1,5,6], the patient did not have other visceral congenital anomalies of urinary, cardiac or gastrointestinal systems. Gastro-esophageal reflux, diaphragmatic hernia, brachycephaly, flat face, hypoplasia of distal parts of all fingers, open mouth, drooling have not been seen in the patient. Evaluation for mutations in *PIGN* causing *PIGN* associated epilepsy or MCAHS1 should be considered in patients of all ethnicities with epilepsy. These phenotypic differences may be explained as allele specific effects.

The clinical severity of the disease seems to correlate with the predicted functional severity of the mutations seen in *PIGN*[6]. Depending upon the severity of mutations, major congenial anomalies may also be present. Other hypotheses of environmental and genetic modification need to be considered. It should also be noted here that for PIGN gene-associated with disability, some tissues are more sensitive than others during body development.

CONCLUSION

This case report expands the mutation spectrum found in *PIGN* gene, and strengthens the association between *PIGN* mutation and MCAHS1. Mutations in *PIGN* gene may be an underestimated cause of epilepsy. The authors recommend that, for patients with epilepsy or prenatal diagnosis of highly suspicious fetus, gene sequencing should be the preferred detection method.

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FOOTNOTES

Author contributions: Hou F performed the research and wrote the manuscript; Shan S analyzed the data; Jin H designed the research study; all authors have read and approve the final manuscript.

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