



## Neonatal-Onset *PIGT* Encephalopathy: A Rare Korean Case with Hypophosphatasia

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Received: June 27, 2021

Revised: August 10, 2021

Accepted: August 11, 2021

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The phosphatidylinositol glycan anchor biosynthesis class T (*PIGT*) enzyme is a subunit of the glycosylphosphatidylinositol (GPI) transamidase complex, which catalyzes the attachment of GPI anchors to cell membrane proteins [1,2]. Biallelic *PIGT* mutations can lead to GPI deficiencies associated with multiple congenital anomalies-hypotonia-seizures syndrome 3 (MCAHS3, OMIM #615398) [3-6], which is an extremely rare, autosomal recessive disorder. *PIGT* mutations can cause early-onset developmental and epileptic encephalopathy (DEE), dysmorphic features, hypotonia, hypophosphatasia, and various congenital anomalies, including cardiac, skeletal, and genitourinary abnormalities [3,4]. In 2013, Kvarnung et al. [3] first reported four cases of homozygous mutations in the *PIGT* gene. To date, approximately 35 cases of *PIGT* mutations have been reported worldwide, and the first Korean case of *PIGT* mutations was reported in 2021. Here, we describe a Korean boy with several features of MCAHS3 caused by compound heterozygous *PIGT* mutations.

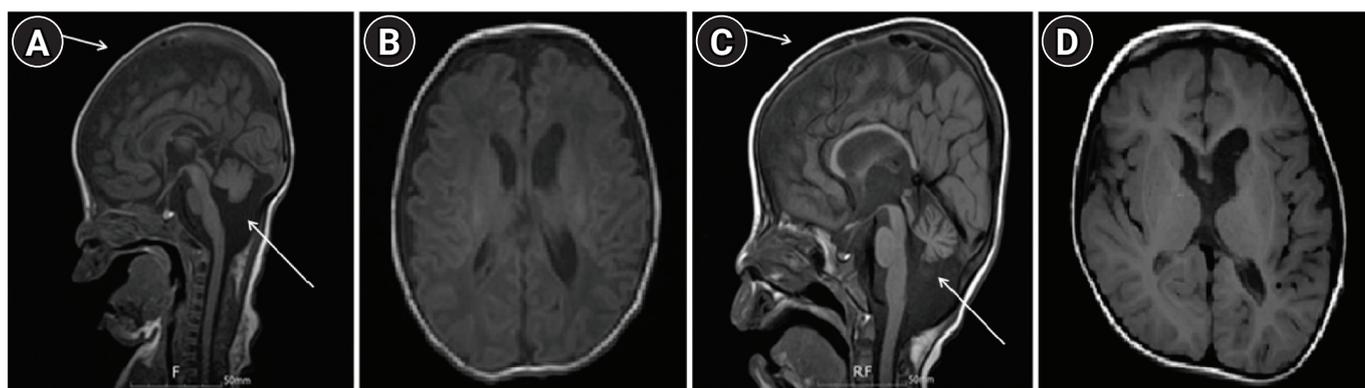
The patient was a 6-year-old boy, who exhibited dysmorphic features including micrognathia,

a depressed nasal bridge, a short anteverted nose, and a long philtrum. He also exhibited abnormal skeletal manifestations, including pectus excavatum, clinodactyly of the fingers, and diffuse osteoporotic changes. He had no cardiovascular or urogenital abnormalities. He was bedridden, in a frog-leg position, and could only move his arms and feet. He showed profound intellectual disability and could not articulate any meaningful words. He had frequent focal and generalized tonic-clonic seizures that first occurred on the 5th postnatal day. At 2 years of age, his electroencephalogram revealed intermittent diffuse high-amplitude delta activity in the background with a few spike discharges from the left frontal and right parieto-temporal areas. His seizures were intractable to multiple anti-epileptic drugs such as levetiracetam and oxcarbazepine, while the frequency of his seizures decreased with a combination of valproic acid, topiramate, and clonazepam. His epileptic seizures disappeared after 6 years of age, but epileptic discharges comprising spike wave complexes were seen on electroencephalography. Ophthalmologic features including strabismus and cerebral visual impairment were observed. A visual evoked potential

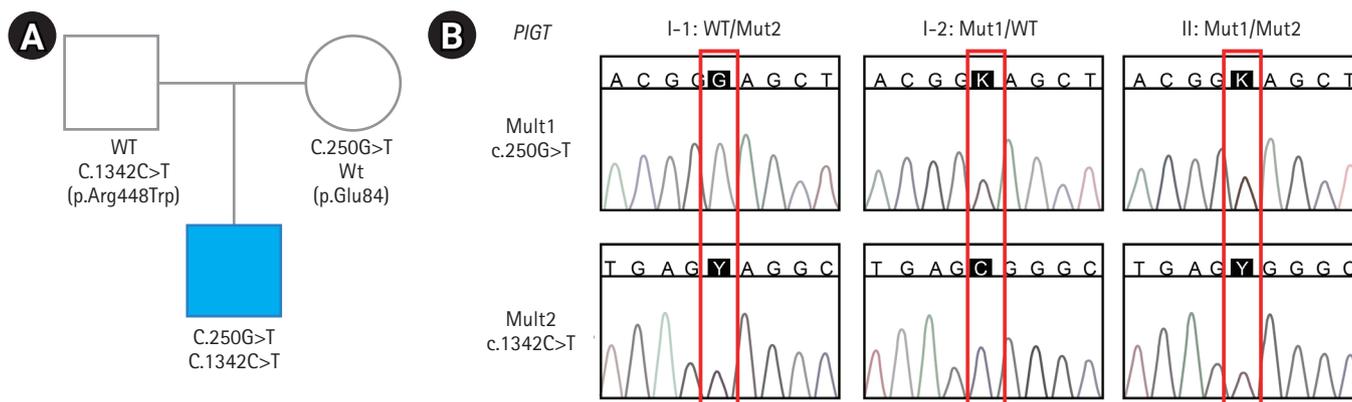
study revealed decreased amplitude and delayed latency. Since infancy, the patient exhibited global delays of psychomotor skills and social development, as well as profound intellectual disability. He also had hypotonia, and could not raise his head at 12 months old or sit up by himself. Biochemical blood analyses repeatedly showed low serum alkaline phosphatase concentrations from 1 year of age (123 IU/L at 1 year and 76 IU/L at 6 years of age). However, serum and urine calcium levels were normal. Brain magnetic resonance imaging at birth (Fig. 1A and B) revealed cerebellar vermis hypoplasia and cisterna magna enlargement. Follow-up magnetic resonance imaging performed at 4 years of age revealed hydrocephalus progression (Fig. 1C and D). Whole-exome sequencing of the proband revealed compound heterozygous *PIGT* mutations: c.250G > T (p.Glu84Ter) and c.1342C > T (p.Arg488Trp). Parental analysis revealed that each parent was a heterozygous *PIGT* mu-

tation carrier (Fig. 2). These *PIGT* mutations have been reported to cause GPI deficiency in functional analyses [4].

We described a case of MCAHS3 due to compound heterozygous *PIGT* mutations. MCAHS3 reportedly has varying clinical features and severity, without obvious genotype-phenotype correlations [6,7]. In a recent report, the missense mutation c.1582G > A in Polish patients was suspected to present a milder phenotype [6]. Conversely, MCAHS3 patients with compound heterozygous mutations—c.250G > T (p.Glu84Ter) and c.1096G > T (p.Gly366Trp)—similar to ours reportedly exhibited more severe clinical features such as epileptic apnea, cortical visual impairment, and hypophosphatasia [4]. Therefore, we recommend that if infants with early-onset DEE have hypotonia and low alkaline phosphatase levels, *PIGT* mutations and *PIGT* encephalopathy should be considered. This case report was approved by



**Fig. 1.** Magnetic resonance imaging of the patient (A, B: at birth; C, D: at the age of 4). Sagittal and axial T1-weighted magnetic resonance images at birth show atrophic changes of the cerebral hemisphere, brainstem, cerebellar vermis, and ventriculomegaly and enlargement of the cisterna magna (white arrows in A, C). Follow-up magnetic resonance imaging at 4 years of age show progression of hydrocephalus (C, D).



**Fig. 2.** The pedigree of family and genetic analysis results of the patient. (A) Compound heterozygous mutations in the phosphatidylinositol glycan anchor biosynthesis class T (*PIGT*) gene appear in proband. Filled symbol indicates the affected individuals and the black arrow indicates the proband. (B) Direct sequencing of the patient's DNA reveals compound heterozygous mutations in the *PIGT* gene (c.250G > T and c.1342C > T) which are inherited from the mother and the father, respectively.

the Institutional Review Board of the Inha University Hospital (IRB No: 2020-12-027) and written informed consent was obtained from the patient's parents.

## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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## Author contribution

Conceptualization: MJC and YSK. Data curation: MJC, YSM, WRJ, and YSK. Formal analysis: MJC and YSK. Project administration: MJC and YSK. Visualization: MJC, YSM, and WRJ. Writing-original draft: MJC. Writing-review and editing: MJC, JHC, and YSK.

## Acknowledgements

We thank the patient's family for participating in this work.

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