Hyperphosphatasia with Mental Retardation Syndrome Due to a Novel Mutation in *PGAP3*

Sheela Nampoothiri¹ Malavika Hebbar² Arun Grace Roy³ Sheena P. Kochumon¹ Stephanie Bielas⁴
Anju Shukla² Katta M. Girisha²

¹ Department of Pediatric Genetics, Amrita Institute of Medical Sciences and Research Centre, Ponekkara, Cochin, Kerala, India

² Department of Medical Genetics, Kasturba Medical College, Manipal University, Manipal, India

³ Department of Pediatric Neurology, Amrita Institute of Medical Sciences and Research Centre, Ponekkara, Cochin, Kerala, India

⁴ Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, United States

Address for correspondence Katta M. Girisha, MD, DM, Department of Medical Genetics, Kasturba Medical College, Manipal University, Manipal 576104, India (e-mail: girish.katta@manipal.edu).

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Abstract

Keywords

- hyperphosphatasia with mental retardation syndrome
- *PGAP3*
- exome sequencing
- alkaline phosphatase

Hyperphosphatasia with mental retardation syndrome is a heterogeneous genetic condition. Two siblings aged 5 years and 3 years were evaluated for global development delay and facial dysmorphism. A novel missense variant, c.851A>G (p.H284R, NM_033419.3), in *PGAP3* was identified using whole-exome sequencing. Assays for elevated alkaline phosphatase and exome sequencing can be useful for the diagnosis of hyperphosphatasia with mental retardation syndrome.

Introduction

Six subtypes of hyperphosphatasia with mental retardation syndrome or Mabry syndrome (HPMRS; MIM 239300) are reported based on their molecular basis and are caused by the genes including *PIGV*, *PIGY*, *PIGO*, *PGAP2*, *PIGW*, and *PGAP3*.^{1–4} Clinically, it shows variable expressivity ranging from severe syndromic forms to isolated mild intellectual disability. Ten additional pathogenic variants in *PGAP3* causing Mabry syndrome are reported till date. We report an Omani consanguineous family with two siblings bearing a novel missense variant, c.851A>G (p.H284R, NM_033419.3), and delineate additional features of this condition.

Materials and Methods

Patients

Two siblings, born to third-degree consanguineous parents from Oman, were brought for evaluation of global develop-

ment delay and lack of speech (►Fig. 1A). The elder child (IV-1) was a 5-year-old boy. Respiratory distress and feeding difficulty were noted soon after birth (birth weight: 3.2 kg, normal) for which he required mechanical ventilation for 10 days. He was on nasogastric feeding up to 2 months of age. He had not attained any gross motor milestones or speech by 5 years of age. He is presently wheelchair bound. He had febrile seizures at 3 years of age. Cleft palate was noted at birth for which he underwent cleft palate repair at 1 year of age. He also had myringotomy with grommet insertion at 2 years.

On examination, he was 107 cm tall (3–50th centile), weighed 16 kg (3–50th centile), and had an occipitofrontal circumference (OFC) of 50 cm (3–50th centile). Facial dysmorphic features included deep set eyes, narrow and up-slanting palpebral fissures, ptosis, low set large fleshy ear lobes, broad nasal root with a squared nasal tip, long smooth philtrum, exaggerated cupid's bow, thin vermilion of upper lip, and posterior cleft palate. He had generalized hypotonia,

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Fig. 1 (A) Pedigree shows two affected offspring born to a third-degree consanguineous marriage. Facial dysmorphism observed in individual IV-1 (B) and individual IV-2 (C) at the age of 5 and 3 years, respectively, were deep set eyes, narrow upslanting palpebral fissures, ptosis, low set large fleshy ear lobes, broad nasal root with a squared nasal tip, long smooth philtrum, exaggerated cupid's bow, thin vermilion of upper lip, sagging cheeks, small chin, and microdontia. The homozygous missense variant, c.851A>G (p.H284R, NM_033419.3), was confirmed by Sanger sequencing in the siblings. (D) Parents are observed to be carriers.

and sagging cheeks and lower jaw. He also had autistic traits with stereotype movements of the head and hand (►Fig. 1B).

Serum alkaline phosphatase was elevated (644 IU/L; normal range: 10–80 IU/L). Echocardiography showed atrial and ventricular septal defects. Fundus evaluation showed bilateral large discs with tilting of left optic disc. Brainstem auditory evoked response showed severe sensory neural hearing loss.

His younger sister (IV-2) was 3 years old who had a similar postnatal history with a weak cry at birth and required immediate intubation and ventilation. She had a birth weight of 3.5 kg (normal). She too had posterior cleft palate and severe retrognathia for which she underwent cleft palate repair and distraction osteogenesis at 2 months. The cleft palate was repaired at 1 year. At 3 years, she was noted to have global development delay with no speech. She had behavioral problems in the form of self-biting.

She was 93 cm tall (3–50th centile), weighed 10 kg (<3rd centile), and had an OFC of 46.5 cm (at 3rd centile). She had microcephaly, upslanting narrow palpebral fissures, epicanthic folds, broad nasal root with squared nasal tip, low set large fleshy earlobes, long smooth philtrum and exaggerated cupid's bow, sagging cheeks and lower jaw, and microdontia (►Fig. 1C). Serum alkaline phosphatase was elevated (613 IU/L). Echocardiography returned normal findings. Fundus evaluation showed thin temporal crescents.

The routine karyotype analysis and chromosomal microarray were normal for both the siblings.

Mutation Testing

A homozygous novel missense variant in a well-conserved region, c.851A>G (p.H284R, NM_033419.3), was identified

in the exon 7 of *PGAP3* by exome sequencing. This variant was not found in the population databases. Biallelic segregation was confirmed by Sanger sequencing (►Fig. 1D).

Discussion

Both the siblings had distinct facial dysmorphism similar to the previously reported individuals with Mabry syndrome.^{5,6} Ptosis and optic disc changes were novel phenotypic features observed in our patients.

The consistent dysmorphic features of this condition include upslanting narrow palpebral fissures, broad nasal bridge, large fleshy ear lobes, long smooth philtrum, thin vermilion of upper lip, sagging cheeks, small chin, and cleft palate, along with intellectual disability, behavioral problems, seizures, and lack of speech.

PGAP3 encodes a glycosylphosphatidylinositol (GPI)-specific phospholipase A2 expressed in the Golgi complex. Function of the enzyme is important for fatty acid remodeling.⁶ About 27 genes involved in the functioning of GPI anchored proteins have been described. Missense variants are the most common mutations reported till date, supporting the assumption that GPI anchor deficiencies have residual activity of GPI-anchored proteins. It has been observed that all the missense variants in *PGAP3* show a reduced activity of *PGAP3* protein, one of which was observed in the same exon and protein domain. Other truncating frameshift and nonsense variants are reported in compound heterozygous state in association with a missense mutation.^{5,6} This probably makes the condition nonlethal despite being a major hindrance in embryogenesis.

As a preliminary step, serum alkaline phosphatase may be offered to all children with intellectual disability and facial dysmorphism and can be quite handy in diagnosing this group of disorders. The absence of congenital cataract, elevated serum creatinine kinase, and renal involvement distinguishes the condition from the *PIGY* type, reported by two families.⁷ *PIGW* has been implicated in this condition in just one family.¹ Combining the typical phenotype with the elevated alkaline phosphatase level will help to narrow down the molecular analysis to a panel of four genes, *PIGV*, *PIGO*, *PGAP2*, and *PGAP3*. Lack of brachytelephalangy further helps to point toward *PGAP3* rather than allelic variants due to *PIGV*, *PIGO*, and *PGAP2*.

In conclusion, global developmental delay and facial dysmorphism in the presence of elevated alkaline phosphatase is an important clue for HPMRS. This work also highlights the successful application of exome sequencing in genetically heterogeneous conditions often encountered in pediatric practice.

Note

A. S. and M. H. drafted the manuscript and analyzed the exome sequencing data. S. N. and A. G. R. are the clinicians involved in the evaluation of the patient. S. P. K. evaluated the patients and did literature search. S. B. and K. M. G. supervised the entire work. All contributors have read and approved the manuscript.

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Conflict of Interest

None.

Acknowledgment

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