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SCIENTIFIC LETTER

Maternal Imprinting in Pseudohypoparathyroidism - A Very Rare *GNAS* Gene Mutation Follows the Pattern

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To the Editor: An 11-y-old boy presented with carpopedal spasms for one day with elicitable Trousseau's and Chvostek's signs. Examination revealed round face and brachydactyly suggestive of Albright's hereditary osteodystrophy (AHO). Investigations showed hypocalcemia (5.4 mg/dL), hyperphosphatemia (11.2 mg/dL), elevated alkaline phosphatase (424 U/L) and parathormone (444.7 pg/mL) with normal 25-hydroxy vitamin D, serum magnesium and short metatarsals on X-ray. He was born small for gestational age (SGA) at term (2.25 kg). Levothyroxine was initiated for hypothyroidism in infancy. Computed Tomography of the Brain showed basal ganglia calcifications. Exome sequencing revealed a pathogenic heterozygous 4 base pair deletion in exon 7 of the *GNAS* gene that resulted in a frameshift mutation (chr20:g.58909194_58909197delICTGA) leading to premature truncation of the protein (p.Asp832MetfsTer14), confirming the clinical diagnosis of pseudohypoparathyroidism (PHP). He was treated for hypocalcemia and hyperphosphatemia with calcium, calcitriol and sevelamer carbonate respectively. His asymptomatic mother had phenotypic AHO features similar to the child with normal serum investigations. She was diagnosed with pseudopseudohypoparathyroidism (PPHP) and confirmed to carry the *GNAS* variant reported in her son.

PHP is an autosomal dominant disorder with multiple hormonal resistance [mainly parathyroid hormone (PTH)] and AHO [1]. PHP and PPHP can occur within the same family due to heterozygous *GNAS* mutations on chromosome 20q13.3 by maternal and paternal transmission, respectively (seen in our patient and his mother). AHO is characterized by round face, maxillary hypoplasia, brachydactyly, short stature, obesity, ectopic calcifications. Infants present with SGA and hypothyroidism. PPHP has AHO features without PTH resistance [2]. The *GNAS* variant observed in our case has been reported only once in the literature earlier [3]. Maternal imprinting is present in this family, as described previously [4].

We report a pathogenic frameshift *GNAS* mutation in a mother-son dyad with PPHP and PHP, respectively, confirming maternal imprinting. Our report adds to the phenotypic variability associated with this variant.

Declarations

Informed Consent Written informed consent for publication of clinical details and photographs of child and mother was obtained from the parents.

Conflict of Interest None.

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