

Central precocious puberty in a boy with pseudohypoparathyroidism type Ia due to a novel *GNAS* mutation

Ryosuke Kagami^{1,2}, Takeshi Sato², Tomohiro Ishii², Eriko Araki¹, Yukio Yamashita¹, Hironori Shibata², Jun Ishihara¹, and Tomonobu Hasegawa²

¹Department of Pediatrics, Yokohama Municipal Citizen's Hospital, Kanagawa, Japan

²Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan

Introduction

Pseudohypoparathyroidism (PHP) is characterized by hypocalcemia, hyperphosphatemia, and elevated PTH levels owing to the resistance of target tissue to PTH. PHP Ia is associated with the phenotype of Albright hereditary osteodystrophy, including short stature, obesity, round face, and brachydactyly. PHP Ia is caused by an inactivating mutation in the *GNAS* gene on the maternal allele, which encodes the α -subunit of the stimulatory guanine nucleotide-binding protein (1).

Pubertal development in male patients with PHP Ia has not been fully elucidated. Among female patients with PHP Ia, some have been observed to show delayed puberty due to resistance to LH and FSH (2). Although two boys with PHP Ia and peripheral precocious puberty have been reported (3), no reports have described PHP Ia with central precocious puberty.

Here, we report a boy with central precocious puberty and PHP Ia due to a novel *GNAS* mutation.

Case Report

The proband was an 11-yr-old boy, who was the first child of healthy Japanese parents. He was born after an uneventful pregnancy and delivery. Neither significant hypocalcemia nor precocious puberty were reported in first-degree relatives.

At 10 yr of age, he had afebrile convulsions for 5 min due to hypocalcemia (5.3 mg/dL, reference: 8.2–10.2 mg/dL). Hyperphosphatemia (11.1 mg/dL, reference:

2.5–4.6 mg/dL) and elevated serum intact PTH levels (363 pg/mL, reference: 10–65 pg/mL) were also detected. The serum 25-hydroxyvitamin D level was 16.2 ng/mL (reference: ≥ 20.0 ng/mL). His height was 138 cm (+ 0.2 SD), weight was 38.5 kg (+ 0.7 SD), face was rounded, and the fourth and fifth metacarpals were shortened. The Wechsler Intelligence Scale for Children-IV showed a Full Scale Intelligence Quotient of 61, indicating intellectual disability. We clinically diagnosed the patient as having PHP Ia.

On admission, at 10 yr and 1 mo of age, voice breaking was noticed. The right and left testicular volumes were 8 and 6 mL, respectively. The stretched penile length was 9.5 cm, and his genital hair development was characterized as Tanner stage II. A growth spurt occurred at 9 yr of age, and his bone age was assessed to be 13 yr, indicating accelerated growth and maturation. Testosterone (2.5 ng/mL, reference for adults: 1.42–9.23 ng/mL) and stimulated gonadotropin levels (LH: 18.0 mIU/mL; FSH: 7.0 mIU/mL) after administration of GnRH were consistent with central precocious puberty. No abnormal findings, except calcifications in the basal ganglia, were detected using magnetic resonance imaging of the head.

We started treatment with sc injection of leuporelin to suppress pubertal progression. Leuporelin treatment suppressed testosterone (0.074 ng/mL) and gonadotropin (LH: 0.6 mIU/mL; FSH: 0.4 mIU/mL) levels close to a prepubertal range.

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Co-corresponding authors: Tomonobu Hasegawa, MD, PhD, Department of Pediatrics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

E-mail: thaseg@keio.jp

Tomohiro Ishii, MD, PhD, Department of Pediatrics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

E-mail: tishii@1992.jukuin.keio.ac.jp



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Mutation Analysis

After receiving approval from the institutional review board of Yokohama Municipal Citizen's Hospital and obtaining informed consent from the proband's mother, we extracted genomic DNA from the peripheral blood samples of the proband. We amplified exons 2–13 and their splice sites in the *GNAS* gene and performed direct sequencing. A heterozygous frameshift variant, c.568dupT, p.Tyr190Leufs*20, in the *GNAS* gene (NM_000516; **Fig. 1**) was identified. This variant was not found in the Human Genetic Variation Database or the Exome Aggregation Consortium Database.

Discussion

We identified a novel *GNAS* frameshift mutation in a boy clinically diagnosed as having PHP Ia with central precocious puberty. To the best of our knowledge, this is the first report of PHP Ia with central precocious puberty.

The association between inactive *GNAS* mutation and central precocious puberty is unclear. *GNAS* is expressed in many cell types but has not been reported to be involved in the gonadotropin inhibitory system. Signal transduction of the gonadotropin inhibitory hormone receptor was not regulated by the stimulatory G protein, but by the inhibitory G protein (4). Precocious puberty has not been reported in cases of nearby frameshift mutations, such as c.565_568delGACT (5). It is unlikely that such truncated *GNAS* proteins preserving approximately 190 amino acids in the amino terminus are constitutively active even in a tissue-specific manner. This case showed that central precocious puberty could occur in patients with PHP Ia, who show less resistance to gonadotropin when gonadotropin secretion is accelerated early. However, the specific cause for this occurrence in these patients is still unclear.

In this case, central precocious puberty secondary to peripheral precocious puberty is highly improbable for the following two reasons. First, the testosterone

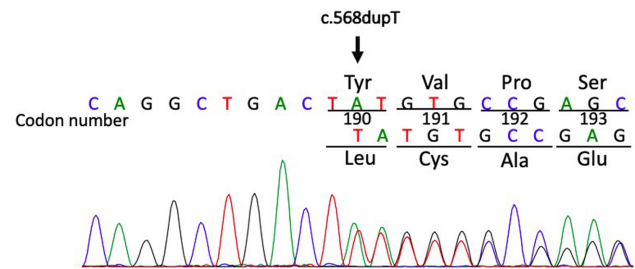


Fig. 1. Partial sequence of exon 7 in the *GNAS* gene. This figure shows a chromatogram of the proband who had a heterozygous mutation, c.568dupT, p.Tyr190Leufs*20, denoted by an arrow.

and gonadotropin levels were suppressed following leuporelin treatment. Second, it is unlikely that the function of the truncated *GNAS* protein in our patient would depend on temperature. Peripheral precocious puberty was only reported in a case of PHP Ia with the mutant *GNAS* protein, p.Ala366Ser, that showed both gain and loss of functions in a temperature-dependent manner (3). Thus, patients with PHP Ia can develop not only peripheral precocious puberty with a mutation-specific cause but also central precocious puberty with other causes.

In summary, we report a boy with central precocious puberty who had PHP Ia due to a novel *GNAS* mutation.

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