



Contents lists available at ScienceDirect

AAACE Clinical Case Reports

journal homepage: www.aaaceclinicalcasereports.com



Case Report

Novel Inactivating Homozygous *PAPSS2* Mutation in Two Siblings With Disproportionate Short Stature

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ARTICLE INFO

Article history:

Received 23 August 2021

Received in revised form

11 November 2021

Accepted 18 November 2021

Available online 24 November 2021

Key words:

disproportionate short stature

idiopathic short stature

PAPSS2

DHEA

DHEA-S

ABSTRACT

Background/Objective: Variants in *PAPSS2* (3'-phosphoadenosine 5'-phosphosulfate synthetase 2) present with varying degrees of brachyolmia (short trunk, platyspondyly, mild long-bone abnormalities). Our objective is to present the phenotype of male and female siblings with the same novel inactivating variant in *PAPSS2*.

Case Report: A Jordanian female (case 1), born to consanguineous parents, was referred at 10 years of age for short stature (SS). She had a normal laboratory workup, including normal growth hormone stimulation testing. Spinal x-rays done for clinical scoliosis revealed platyspondyly. She attained an adult height of 143.5 cm (-3 SD). Years later, her brother (case 2) was referred at 21 months of age for SS. His laboratory workup and bone age were normal. His growth velocity declined at 6 years of age, but normal growth factors did not suggest growth hormone deficiency. When he returned during puberty, disproportionate body measurements were noted. A skeletal survey revealed platyspondyly, increasing suspicion of growth plate pathology. Exome sequencing in the family revealed a homozygous variant, *p.His496Pro (H496P)* in *PAPSS2* (NM_004670.3:c.1487A>C). Both parents carried the same variant.

Discussion: *PAPSS2* assists with the sulfonation of dehydroepiandrosterone (DHEA) to DHEA sulfate and the sulfonation of proteoglycans in the cartilage, necessary for endochondral bone formation. *PAPSS2*-inactivating variants present with skeletal dysplasia and elevated DHEA levels.

Conclusion: This novel variant in *PAPSS2* manifested with mild brachyolmia but disproportionate SS in male and female siblings. Biochemical phenotype with low circulating DHEA sulfate and high DHEA levels reflect a sulfonation defect.

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Introduction

Congenital causes of disproportionate short stature (SS) include a heterogeneous spectrum of skeletal dysplasias. Brachyolmia is characterized by a short trunk, platyspondyly (flattened vertebral bodies), and mild long-bone abnormalities.¹ Three types of brachyolmia are related to variants in the *PAPSS2* gene, coding for *PAPSS2* (3'-phosphoadenosine 5'-phosphosulfate synthetase 2).¹

Abbreviations: DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; *PAPSS2*, 3'-phosphoadenosine 5'-phosphosulfate synthetase 2 gene; *PAPSS2*, 3'-phosphoadenosine 5'-phosphosulfate synthetase 2 protein; SS, short stature.

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<https://doi.org/10.1016/j.aaace.2021.11.003>

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This enzyme converts inorganic sulfate and adenosine triphosphate into 3'-phosphoadenosine sulfate, which serves as a sulfate donor for the sulfonation of dehydroepiandrosterone (DHEA) to dehydroepiandrosterone sulfate (DHEA-S) by sulfotransferase A1 (SULT2A1, [Supplementary Fig. 1](#)) in the adrenal glands.² *PAPSS2* also serves as the sulfate donor for proteoglycans in cartilage, which is necessary for Indian hedgehog signaling in endochondral ossification and bone growth.³ Patients with homozygous *PAPSS2* variants can present with disproportionate SS secondary to skeletal dysplasia. Females may additionally present with premature adrenarche or signs of androgen excess, such as ovulation abnormalities, due to excess unconjugated DHEA that can be diverted into the production of active androgens.⁴ We describe male and female siblings, born to consanguineous parents, who presented with disproportionate SS. Exome sequencing revealed an autosomal recessive homozygous variant in *PAPSS2* (*p.His496Pro*).

Written informed consent was obtained from the patients and parents for the publication of this report and the accompanying images.

Case Presentation

A Jordanian female (case 1) was initially evaluated at 10 years of age for SS. Parents reported normal pubarche around age 9. Her height for age trended between -1 SD and -2 SD from the mean, below her midparental height (176 cm, 50th percentile, 0 SD). Her weight for age was normal at the 50th percentile for age (0 SD). Physical examination was notable for leg length discrepancy and scoliosis, confirmed by radiologic studies, which also identified dysmorphic vertebrae (Fig. 1B). She had an arginine insulin tolerance test that did not suggest growth hormone deficiency, with a peak growth hormone level of 23.7 ng/mL (reference, >10 ng/mL). The patient was lost to follow-up and continued pubertal development, with menarche at 11.5 years of age. She attained an adult height of 143.5 cm (-3 SD).

Her full brother (case 2) was evaluated for SS initially at age 21 months. Laboratory tests were not indicative of underlying organic disease. His height trended below the third percentile (-2.0 SD) for age, significantly below his midparental height (50th percentile, 0 SD). The patient's weight trended normally between the 25th and 50th percentile for age (-0.4 to 0.1 SD). At age 4, bone age was concordant with chronological age. His follow-up at 6 years of age revealed suboptimal growth velocity, but normal insulin growth factor-1 at 78 ng/mL (reference range, 37–192 ng/mL) and normal insulin growth factor binding protein-3 at 2.97 mcg/ml (reference range, 2.04–5.38 mcg/ml). The parents declined growth hormone stimulation testing because of the prior normal result in the affected sister. Of note, 3 other siblings had grown normally. The brother returned to endocrinology at 13 years of age because of

continued concerns for poor growth despite progressing puberty. At that time, the older sister attained her final adult height and was significantly short (143.5 cm, -3 SD). On examination, the boy's height was -2.5 SD from the mean; he had long upper extremities, large hands and feet, and a short torso. Pubic hair and genital stage were Tanner III, but he had few axillary hairs. The skeletal survey revealed platyspondyly (Fig. 1A), which together with the disproportionate SS and family history was suspicious for autosomal recessive growth plate pathology. Exome sequencing was performed on the family, and the 2 affected siblings had the homozygous variant *p.His496Pro (H496P)* in *PAPSS2* (NM_004670.3:c.1487A>C). The variant was not found in the general population database but was predicted to be pathogenic by 3 silico prediction tools (SIFT, MutationTaster, and PolyPhen2). The parents and 2 other siblings were heterozygous carriers of the same mutation (Supplementary Fig. 2). At age 15 (Fig. 2A), the boy's height was 146.1 cm (-2.87 SD), with an abnormally elongated arm span measurement of 160.5 cm. He had progressed normally to the Tanner IV stage of genital development. Laboratory evaluation at 11:45 AM revealed low DHEA-S at <15 ug/dL (reference range, 30–555 ug/dL) and elevated unconjugated DHEA at 572 ng/mL (reference range, 39–481 ng/mL). The androstenedione level was normal at 87 ng/dL (reference range, 21 to 154 ng/dL); the 17-hydroxyprogesterone level was normal for Tanner IV stage at 37 ng/dL (reference range, 29–180 ng/dL); the total testosterone (425.0 ng/dL), serum-free testosterone (51.0 pg/mL), percentage of free testosterone by dialysis (1.2 %), and sex hormone binding globulin (58 nmol/L) were all appropriate for the stage of puberty.

The sister was reevaluated after the genetic results. She reported a necrotic ovarian cyst at 20 years of age that required cystectomy. She had no complaints of hirsutism or acne. On physical examination at age 21, she had a similar disproportionate appearance as the affected brother (Fig. 2B), including a short trunk, short legs,

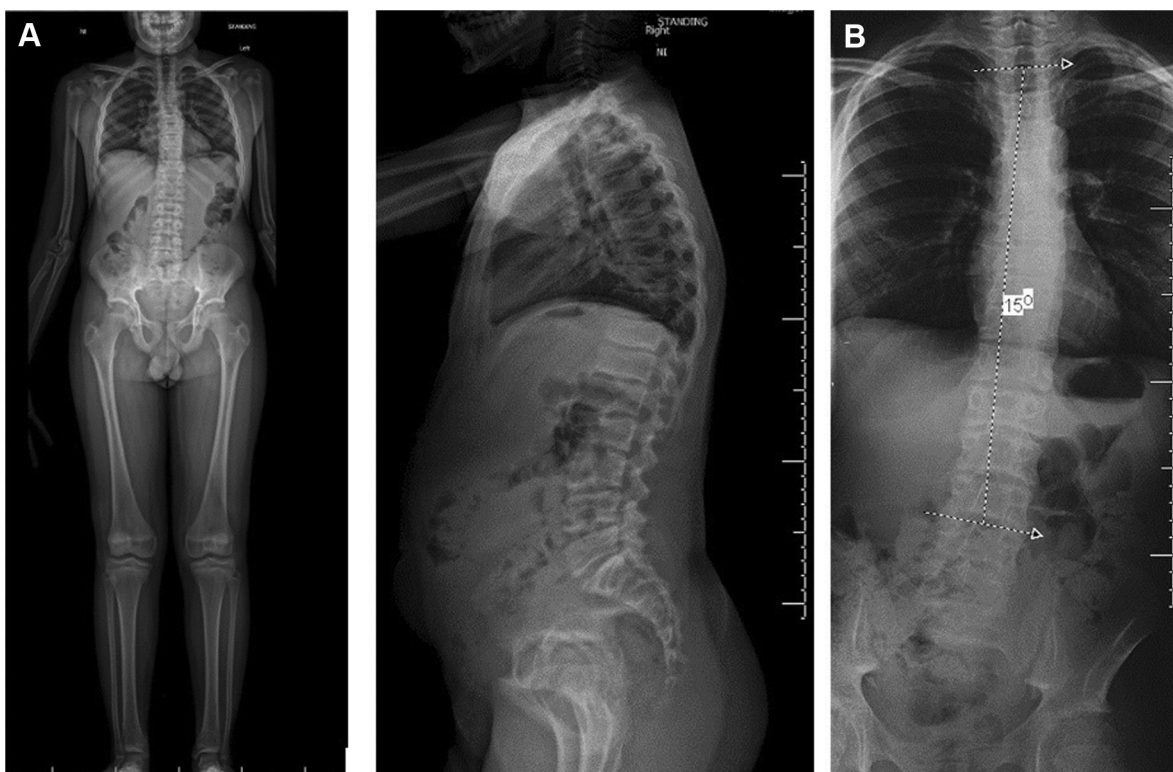


Fig. 1. Skeletal survey of male sibling (case 2) (A) at 13 years, 6 months of age. Note the disproportionate short trunk compared to longer extremities and the flattened appearance of the vertebral bodies (platyspondyly). B, Spinal radiography of the female patient (case 1) revealing thoracolumbar levoscoliosis and pelvic tilt (right side higher than left side).



Fig. 2. A, Case 2: Male sibling at 15 years of age standing beside mother. Notice the large hands and shoe size, as well as short trunk and short legs, compared to longer arms. B, Case 1: Female patient standing beside her father at 21 years of age.

large hands, and abnormal arm span of 155 cm (height was 143.5 cm). Laboratory data at 12:01 PM revealed low DHEA-S at 25 mcg/dL (reference range, 51–321 mcg/dL) and elevated unconjugated DHEA at 1249 ng/dL (reference range, 385–1143 ng/dL); compatible with decreased sulfonation of DHEA, mechanistically expected in *PAPSS2* variants. The other adrenal hormone intermediates were found within the normal range for age: 17-hydroxyprogesterone (89 ng/dL); androstenedione (217 ng/dL); and 17-hydroxypregnenolone (205 ng/dL). The patients and parents were counseled appropriately regarding the genetic variant.

Discussion

We present male and female siblings with disproportionate SS and low DHEA-S due to a novel, inactivating, homozygous variant in *PAPSS2*. Their clinical presentation is consistent with a mild presentation of the previously reported phenotype of patients with pathogenic variants in *PAPSS2*,⁵ including the short trunk, platyspondyly, mild long-bone abnormalities, disproportionate SS, and decreased adrenal sulfonation of DHEA (Table).

Skeletal dysplasias should be considered in children with idiopathic SS and familial SS, especially in patients with abnormal body proportions. Skeletal dysplasias may not be immediately identifiable because of the heterogeneity of these conditions and the gradual development of disproportionate body segments over time. Radiological studies of the spine, pelvis, and extremities may provide helpful hints when findings are not identifiable on physical examination. Family history of consanguinity and disproportionate SS should raise suspicion for genetic causes of SS, including growth plate pathology, such as in the family we are reporting.

Genetic studies may include comparative genomic hybridization or single nucleotide polymorphism arrays to detect copy-number variants or exome sequencing to examine point variants in coding regions of the entire genome.⁶ These patients had a homozygous variant in *PAPSS2*. To our knowledge, this variant (*p.H496P*) has not been previously reported as pathogenic in humans. In-silico analyses, including protein predictors and evolutionary conservation, suggest a deleterious effect. In addition to the brachyolmia, the fact that the affected siblings showed decreased DHEA-S supports impaired sulfonation of DHEA as a result of the identified variant. Previous reports in the literature indicate that the skeletal manifestations in *PAPSS2* defects vary clinically and radiologically, even with the same gene variant.¹

PAPSS2 is abundant in the liver (*PAPSS2b*), cartilage, and adrenal glands (*PAPSS2a*).^{4,7} In the cartilage, absence of *PAPSS2* results in the unavailability of the sulfate donor PAPS, preventing the sulfonation of proteoglycans by chondroitin 6-O-sulfotransferase.⁴ This is thought to be necessary for Indian hedgehog signaling,⁸ critical for proliferation and differentiation of growth plate chondrocytes preceding endochondral bone formation, and one of the main mechanisms of longitudinal bone growth of the axial and appendicular skeleton.⁹ The brachymorphic mouse model is generated with a homozygous variant in *PAPSS2*.⁸ Growth plate analysis in this mutant model elicits decreased sulfonation of chondroitin chains, decreased Indian hedgehog protein content, decreased presence of fibroblast growth factor receptor 3 (FGFR3), and decreased chondrocyte proliferation.⁸

PAPSS2 also provides the sulfate donor for sulfonation of DHEA to DHEA-S, a critical step to regulate the availability of DHEA, which can be converted into androstenedione, in turn convertible into testosterone. Testosterone can act directly on target receptors, or it

Table
Summary of Main Clinical and Paraclinical Findings of the Cases Presented

Feature	Case 1	Case 2
Patient sex of patient and age at measurement	Female, 21 years old	Male, 15 years old
Adult height	143.5 cm (-3.04 SD)	146.1 cm (-2.87 SD)
Calculated midparental height	176 cm ± 9 cm	176 cm ± 10 cm
Arm span	155 cm	160.5 cm
Body appearance	Short trunk, short legs long arms, large hands	
Identified skeletal abnormalities	Pelvic tilt, leg length discrepancy, levoscoliosis, platyspondyly	Platyspondyly
DHEA	1249 ng/dL (reference range, 385–1143)	572 ng/mL (reference range, 39–481)
DHEA-S	25 mcg/dL (reference range, 51–321)	undetectable <15 ug/dL (reference range, 30–555)
Androstenedione	217 ng/dL (reference range, 73–230)	87 ng/dL (reference range, 21–154)
17-hydroxyprogesterone	89 ng/dL (reference range, 23–102)	37 ng/dL (reference range, 51–190)
Testosterone panel	Total testosterone 41 ng/dL (reference range, 2–45), free testosterone 3.7 pg/mL (reference range, 0.1–6.4)	Total testosterone, 425.0 ng/dL (reference range, 350–970), free testosterone 51.0 pg/mL (reference range, 52–280)
Other	Early adrenarche, ovarian cyst as adult	Normal puberty development, no signs of hyperandrogenism

Abbreviations: DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate. Note the SS, long arm span, low DHEA-S, high DHEA levels.

can be transformed into dihydrotestosterone and produce signs of virilization such as hirsutism, acne, or ovulation defects in females. High circulating testosterone levels inhibit luteinizing hormone pulses, critical for cyclic ovulation.

Both patients had a biochemical elevation of DHEA with low DHEA-S levels. The levels of androstenedione and other androgens were not elevated, and there were no clinical signs of androgen excess in the male sibling, as expected in males. However, the female sibling had a necrotic ovarian cyst, which could be the result of an ovulatory defect. Prior literature reports have associated *PAPSS2* variants with premature pubarche,⁴ hyperandrogenism, and polycystic ovary syndrome.¹⁰ The clinical manifestations of hyperandrogenism are variable, despite the more consistent biochemical profile (low DHEA-S and high DHEA).

Conclusion

The reported novel inactivating homozygous variant (*p.H496P*) in *PAPSS2* manifested with SS of undetermined cause, which was further characterized as disproportionate SS in these male and female siblings, born to consanguineous parents. Although their clinical presentation is consistent with the previously reported phenotype of patients with pathogenic variants in *PAPSS2*, their phenotype was characterized by a less severe brachyolmia and no significant clinical hyperandrogenism despite the elevated DHEA and decreased circulating DHEA-S.

Acknowledgment

We thank Youn Hee Jee, MD, and Jeffrey Baron, MD, in the Section on Growth and Development in the National Institute of Child Health and Development at the National Institute of Health (NIH) for the genetic studies provided to the family under the clinical protocol ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02311322) Identifier: NCT02311322). This work was funded by the Intramural Research Program of the National Institute of Child Health and Development, National Institutes of Health. Dr. Perez-Garcia was a pediatric endocrinology fellow in training funded by the philanthropy-supported David-Nicholas fellowship, during the core writing of the manuscript.

Author Contributions

E.M.P.-G. wrote and organized the manuscript and figures; she is also the corresponding author. P.W. performed genetic studies in the family, provided the family pedigree, and reviewed the manuscript. N.G. was the primary clinical provider of the patients; she obtained consent from the parents, contributed to the preparation of the manuscript, and reviewed the manuscript.

Disclosure

The authors have no multiplicity of interest to disclose.

References

- Bownass L, Abbs S, Armstrong R, et al. *PAPSS2*-related brachyolmia: clinical and radiological phenotype in 18 new cases. *Am J Med Genet A*. 2019;179(9):1884–1894.
- Strott CA. Sulfonation and molecular action. *Endocr Rev*. 2002;23(5):703–732.
- Xu ZH, Freimuth RR, Eckloff B, Wieben E, Weinsilboum RM. Human 3'-phosphoadenosine 5'-phosphosulfate synthetase 2 (*PAPSS2*) pharmacogenetics: gene resequencing, genetic polymorphisms and functional characterization of variant allozymes. *Pharmacogenetics*. 2002;12(1):11–21.
- Noordam C, Dhir V, McNelis JC, et al. Inactivating *PAPSS2* mutations in a patient with premature pubarche. *N Engl J Med*. 2009;360(22):2310–2318.
- Tüysüz B, Yılmaz S, Gül E, et al. Spondyloepimetaphyseal dysplasia Pakistani type: expansion of the phenotype. *Am J Med Genet A*. 2013;161A(6):1300–1308.
- Murray PG, Clayton PE, Chernauek SD. A genetic approach to evaluation of short stature of undetermined cause. *Lancet Diabetes Endocrinol*. 2018;6(7):564–574.
- Venkatachalam KV. Human 3'-phosphoadenosine 5'-phosphosulfate (*PAPS*) synthase: biochemistry, molecular biology and genetic deficiency. *IUBMB Life*. 2003;55(1):1–11.
- Cortes M, Baria AT, Schwartz NB. Sulfation of chondroitin sulfate proteoglycans is necessary for proper Indian hedgehog signaling in the developing growth plate. *Development*. 2009;136(10):1697–1706.
- St-Jacques B, Hammerschmidt M, McMahon AP. Indian hedgehog signaling regulates proliferation and differentiation of chondrocytes and is essential for bone formation. *Genes Dev*. 1999;13(16):2072–2086.
- Oostdijk W, Idkowiak J, Mueller JW, et al. *PAPSS2* deficiency causes androgen excess via impaired DHEA sulfation—in vitro and in vivo studies in a family harboring two novel *PAPSS2* mutations. *J Clin Endocrinol Metab*. 2015;100(4):E672–E680.