REVIEW

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Bone Phenotype is Always Present But Androgen Excess is Less Frequently Seen in PAPSS2 Deficiency

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Abstract

3'-Phosphoadenosine 5'-phosphosulfate synthase 2 (PAPSS2) deficiency is a rare disorder due to biallelic pathogenic variants in the *PAPSS2* gene. This disorder was first described in 1998 by Ahmad et al. and Faiyaz ul Haque et al. To date, 79 patients with PAPSS2 deficiency have been reported. The main reported features of these patients are related to bone abnormalities and clinical/biochemical androgen excess. Disproportionate short stature and symptoms associated with spondylar skeletal dysplasia are the most common clinical features that require clinical attention. Androgen excess has been described much less commonly. This review summarizes the currently published clinical, molecular, and biochemical features of patients with PAPSS2 deficiency.

Keywords: PAPSS2, androgen excess, sulfation, brachyolmia, SEMD, DHEAS

Introduction

An 11.5-year-old Turkish girl was referred to our clinic because of short stature and low back pain. She was born at term with a birth weight of 2950 g [-0.9 standard deviation score (SDS)] after an uncomplicated pregnancy. Her parents were third cousins. At presentation her weight and height were 29.2 kg (-2.01 SDS) and 130.0 cm (-3.03 SDS), respectively. The ratio of upper-to-lower segment was 0.87 (-2.0 SDS). Systemic examinations were normal, except for limited dorsal bending. Her breast and pubic hair stages were Tanner IV. She had no acne or hirsutism. Her bone age was 12 years. Her predicted adult height was 141 cm, while the midparental height was 158 cm (-0.8 SDS). Initial tests for the etiology of her short stature, including routine biochemistry, full blood count, and thyroid function were all normal, and the karyotype was 46, XX. Insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 concentrations were normal. Due to her disproportionate short stature, a skeletal survey was also performed. Radiography of the lateral spine revealed findings suggestive for brachyolmia, including mild lumbar scoliosis, flattened vertebrae (platyspondyly) with rectangular vertebral bodies, irregular endplates and narrowed intervertebral disc spaces. Tubular bones were normal. Hormonal investigations using liquid chromatography-tandem mass spectrometry (LC-MS/MS) demonstrated normal serum 17-hydroxyprogestrone (0.55 ng/mL; N: 0-1 ng/mL), androstenedione (1.07 ng/mL; N: 0.06-1.15 ng/mL), dehydroepiandrosterone (DHEA) (3.34 ng/mL; N: 0-3.4 ng/mL), total testosterone (0.24 ng/mL; N < 0.25 ng/mL), but low dehydroepiandrosterone sulphate (DHEAS) (77 ng/mL; N: 440-3320 ng/mL) concentrations. The plasma DHEAS/DHEA ratio was extremely low (22.6; N: 31-325). Sanger sequencing of the *PAPSS2* gene revealed a homozygous c.337dupG (A113Gfs*18) mutation. Menarche occurred at 12.1 years of age. She did not have clinical or biochemical evidence of androgen excess during two years of follow-up.

PAPSS2 Deficiency

Biosynthesis of 3'-phosphoadenosine 5'-phosphosulfate (PAPS) is essential for various biological processes, particularly in the regulation of sulfate metabolism and sulfation reactions in the body. These reactions are important in the production of substances, such as glycosaminoglycans, steroids and xenobiotics (1). PAPS is produced from ATP and

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inorganic sulfate by the action of PAPS synthetase (PAPSS). PAPSS has 2 domains; the ATP-sulfurylase domain catalyzes the formation of the 5'-adenosine phosphosulfate (APS) intermediate from ATP and inorganic sulfate. The APS kinase domain then further phosphorylates APS by an additional ATP molecule to generate PAPS (Figure 1). This is the rate-limiting step in PAPS biosynthesis. Two different PAPSS isoforms have been identified in human tissues, known as PAPSS1 and PAPSS2 (1). PAPSS1 is the predominant isoform and is found in various human adult tissues. In contrast, PAPSS2 exhibits a more restricted expression pattern and appears to be the major variant in growth plate cartilage (2). The catalytic efficiency of PAPSS2 is 10 to 15 times as great as that of PAPSS1 (2). PAPSS1 deficiency has so far not been shown to be directly linked to the etiology of any human disease. However, the physical interaction between the two enzymes has been shown to influence the cellular localization, and possibly the function, of PAPSS2 (3).

PAPSS2 deficiency was first described by Ahmad et al. (4) in 1998 in a large consanguineous family. The main characteristics of the 16 affected family members (11 males and 5 females) include spondyloepiphyseal metaphyseal dysplasia (SEMD), severe short stature and early-onset joint problems. The authors classified this distinctive autosomal recessive form of SEMD as SEMD Pakistani type. In the same year, Faiyaz ul Haque et al. (5) showed that the molecular defect in this family was a homozygous c.1439C > A; p.Ser480* mutation in the *PAPSS2* gene (Table 1). Ten years later, the second paper on genetically proven PAPSS2 deficiency was published by Noordam et al. (6). They reported a Turkish girl who presented with premature pubarche (early development of pubic hair), advanced bone age, and disproportionate short stature due to skeletal dysplasia affecting the vertebrae with no epiphyseal or metaphyseal changes. The bone phenotype of that patient was more compatible with brachyolmia (*"Brachy" in Greek means "short", and "olmós" means "spine";* osteochondrodysplasia characterized by generalized platyspondyly without significant long bone abnormalities). During follow-up, she developed hirsutism, acne and secondary amenorrhea, meeting the diagnostic criteria for polycystic ovary syndrome (PCOS). In this patient, LC-MS/MS detected high concentrations of androstenedione and testosterone, upper limit of normal DHEA and very low DHEAS. In terms of steroidogenesis, they showed that the etiology of clinical and biochemical androgen excess involved impaired DHEA sulfation, which results in more DHEA available for 3β-hydroxysteroid dehydrogenase activity to produce androstenedione, which in turn is converted to more potent androgens, such as testosterone and dihydrotestosterone by the action of 17β-hydroxysteroid dehydrogenase and 5α-reductase enzymes, respectively (Figure 1) (6).

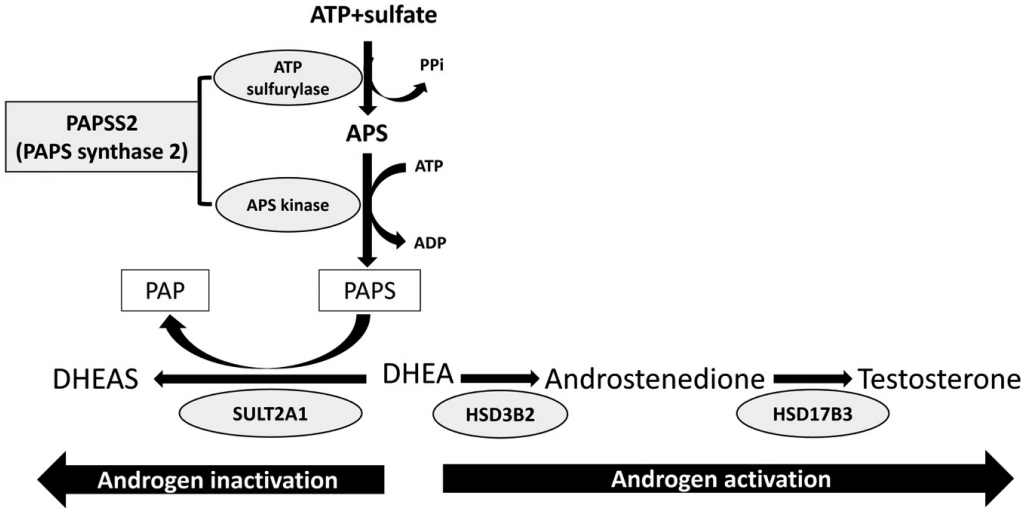

Figure 1. DHEAS production pathway. DHEA is the most abundant weak androgen precursor produced by the adrenal gland. Excess DHEA is sulfated by the enzyme SULT2A1, producing an inactive by-product, DHEAS, in the presence of a sulfate donor, PAPS. PAPS is generated by the PAPSS2 enzyme, which has ATP sulfurylase and APS kinase activities. This safeguarding reaction prevents excess DHEA from being used as a precursor to synthesize more potent androgens, such as androstenedione and testosterone, in adrenal, gonads and peripheral tissues

DHEA: dehydroepiandrosterone, DHEAS: dehydroepiandrosterone sulphate, APS: adenosine 5-phosphosulfate, PAPS: 3-phosphoadenosine 5-phosphosulfate, PAP: 3-phosphoadenosine 5-phosphate, PPi: pyrophosphate, PAPSS2: 3-phosphoadenosine 5-phosphosulfate synthase 2, SULT2A1: DHEA sulfotransferase

The molecular diagnosis of new patients with PAPSS2 deficiency has increased understanding of both the bone and steroid hormone characteristics of this disease. In Table 1, molecular and basic clinical features of patients with genetically confirmed PAPSS2 deficiency are presented in chronological publication order. To date, 79 (41 males, 38 females) patients with PAPSS2 deficiency have been reported, of whom 29 (36.7%) were Turkish patients. In the reported patients, 32 pathogenic *PAPSS2* mutations were identified, 13 (40%) of which led to frameshift and 5 (15.6%) to the formation of truncated proteins. Although the functional consequences of *PAPSS2* variants were rarely studied by *in vitro* assays, more than half of the pathogenic variants (59.3%) detected in the *PAPSS2* gene cause severe, complex alterations in the gene and cause disease. The mutations that diminish the ATP-sulfurylase domain and APS kinase domain are mainly related to 389-611th and 41-196th aminoacid residues of PAPSS2, respectively. The mutations

Table 1. Clinical, molecular and biochemical characteristics of previously reported patients with *PAPSS2* mutations

***PAPSS2* variant (NM_004670.3)**	**Gender**	**BO/SEMD phenotype**	**Androgen excess**	**Ref.**
S480*	11 M, 5 F (Pakistani)	+	No data on hormones	(4)
T48R/R329*	F (Turkish)	+	PP, high androstenedione and testosterone, low DHEAS, upper normal DHEA	(6)
A113Gfs*18, IVS3+2delT, V206Sfs*9/R437Gfs*19, K161Rfs*6/I221Sfs*40	2 M, 4 F (3 Turkish, 2 Japanese and 1 Korean)	+	(-) Clinical androgen excess, low DHEAS	(14)
R329*	3 M, 2 F (Turkish)	+	1 F patient had clinical androgen excess and high testosterone, all had low DHEAS, but normal DHEA	(15)
L76Q, R129Lfs*25,V364Rfs*18, A113Gfs*18, V540N, E183K, Q211Cfs*11, C43Y, c.27+3A>C, F125Sfs*24	5 M, 8 F (12 Turkish, 1 Lebanese)	+	Evaluated in 6/13 pts. 2 patients had hypertrichosis and acnea, 1 had PP. No hormonal w/o	(16)
W462Cfs*3/G270D	2 M (European?)	+	(-) Clinical androgen excess, normal androgens, normal DHEA and testosterone, low DHEAS, p.Trp462Cysfs* heterozygous mother have clinical androgen excess	(10)
H355Ifs*5	M (Kurdish)	+	(-) Clinical androgen excess, high DHEA, no DHEAS data	(9)
R334*, c.639+1G>T	3 M, 4 F (Turkish)	+	All had low DHEAS, 2 had clinical androgen excess, no DHEA data available	(17)
L440Wfs*12	F (Turkish)	+	(+) Clinical androgen excess (PP), high DHEA, low DHEAS, normal testosterone and androstenedione	(18)
G270D, R41*, F283V, G538Afs*4, A493V, R334*, W462Cfs*3, R129P	10 M, 8 F (6 Norwegian, 5 British, 1 Pakistani, 1 Algerian, 1 French, 1 African, 1 Egyptian, 2 Eastern European)	+	Evaluated in 10/18 pts. 2 had clinical androgen excess who had G270D mutation, all patients had low DHEAS, No DHEA measured, 3 had high testosterone or androstenedione	(19)
R238*	F (Chinese)	+	ND	(20)
H496P	1 M, 1 F (Jordanian)	+	No clinical or biochemical androgen excess, high DHEA and low DHEAS	(21)
R346P	3 M, 3 F (Pakistani)	+	ND	(22)

DHEA: dehydroepiandrosterone, DHEAS: dehydroepiandrosterone sulphate, PP: premature pubarche, ND: not defined, M: male, F: female, BO: brachyolmia, SEMD: spondyloepimetaphyseal dysplasia

identified so far appear to be distributed throughout the gene without hotspot regions. There are some founder mutations in Turkish patients (A113Gfs*18, R129Lfs*25, R334*, W462Cfs*3, R238*). High consanguinity and founder mutations may explain the predominance of Turkish patients in the published literature.

The next section of this article will focus on the two main clinical presentations of PAPSS2 deficiency based on published data from patients: skeletal manifestations and steroid metabolome alterations.

Skeletal Manifestations of PAPSS2 Deficiency

Skeletal manifestations are present with variable severity in all patients with PAPSS2 deficiency. The main cause of cartilage and bone disease in PAPSS2 deficiency is the impaired biosynthesis and deposition of sulfated proteoglycans in the cartilage and extracellular bone matrix (7).

Formerly, PAPSS2-related skeletal dysplasia was associated with SEMD Pakistani type, which includes the former "recessive brachyolmia", as well as the older entities "Toledo type" and "Hobaek type" brachyolmia. In the 2023 revision of the Nosology of Genetic Skeletal Disorders, it is now classified as part of the group of sulfation disorders (NOS 04-0050; OMIM 612847) (8).

The most important clinical feature is disproportionately short stature with a short spine associated with variable symptoms, including pain, stiffness and spinal deformity, such as kyphoscoliosis. Short trunk dwarfism becomes apparent in childhood, usually after the age of two years (8). Patients may have a short femur prenatally, but a short spine phenotype develops later in childhood. Genu varum, genu valgum, enlargement in the knee and ankle joints, patella dislocations, limited flexion in the metacarpophalangeal joints and early-onset osteoarthropathic changes in the hand and knee have been described. There are four different bone phenotypes associated with PAPSS2 deficiency:

1. SEMD where both vertebrae and long bones are affected,

2. Symptomatic brachyolmia with dysplastic changes limited to the spine involving minimal epimetaphyseal changes visible only on X-ray,

3. Symptomatic brachyolmia with dysplastic changes limited to the spine,

4. Subclinical brachyolmia with radiologic changes only.

Skeletal surveys may show severe platyspondyly with elongated vertebral bodies, irregular endplates, narrow intervertebral disk spaces, overfacing of the pedicles, and lumbar spinal canal stenosis. Spondylar dysplastic changes may progress with age. The bone age maybe advanced. Short femoral neck, bowed tibia, short and broad ilia, dumbbell deformity of the long and short tubular bones, and irregularities of epiphyseal ossification have been described. Metaphyseal longitudinal striations in the proximal femora are distinctive. Other long bones may show mild epiphyseal flattening and metaphyseal irregularities (9).

Although spondylar dysplasia is a "*sine qua non*" characteristic of the disease, the severity of skeletal manifestations does not correlate with the severity of the *PAPSS2* mutation detected. Thus, there is no clear genotype-phenotype relationship in terms of bone findings. As seen in the patient presented above, the homozygous frameshift mutation led to a brachyolmia phenotype without epiphyseal-metaphyseal changes. *PAPSS2* mutations detected in patients with brachyolmia or SEMD phenotype are shown in Table 2.

Steroid Metabolome Alterations in PAPSS2 Deficiency

Low plasma DHEAS is the most consistent biochemical feature of patients with PAPSS2 deficiency published to date. Low DHEAS concentrations are not associated with the type of the mutation in *PAPSS2*. The DHEAS/DHEA ratio

Table 2. Skeletal phenotypes in patients with *PAPSS2* mutations

***PAPSS2* mutations related to brachyolmia**	***PAPSS2* mutations related to SEMD**
T48R/R239X (6)	S480*/S480* (4)
K161Rfs*6/K161Rfs*6 (14)	R239X/R239X (15)
A113Gfs*18/A113Gfs*18 (14)	G270D/W462fs*3 (10)
V206Sfs*9/R437Gfs*19 (14)	G270D/G270D (19)
c.381 + 2delT/c.381 + 2delT (14)	R239*/R239* (20)
V540D/V540D (16)	
C43Y/C43Y (16)	
V364Rfs*18/V364Rfs*18 (16)	
R129Lfs*25/R129Lfs*25 (16)	
Q211Cfs*11/Q211Cfs*11 (16)	
c.27 + 3A > C/c.27 + 3A > C (16)	
F125Sfs*24/F125Sfs*24 (16)	
H355Ifs*5/H355Ifs*5 (9)	
G270D/R129P (19)	
G270D/G270D (19)	
G270D/W462Cfs*3 (19)	
R41X/R41X (19)	
R334X/R334X (19)	
F283V/F283V (19)	
L440Wfs*12/L440Wfs*12 (18)	
R346P /R346P (22)	
H496P/H496P (21)	

is significantly lower than in the healthy population, but this ratio varies depending on the plasma concentration of DHEA. DHEA can be normal or elevated. In 7 of 17 PAPSS2 deficiency patients with published DHEAS measurement data, DHEAS concentrations were below the measurable limit. In the other 10 patients, the median (range) DHEAS concentration was 10.5 (3.9-48.7) ug/dL. In seven patients with simultaneous DHEA and DHEAS measurements, the median DHEAS/DHEA ratio was 10.5 (4.4-50.6). Concentrations of other adrenal or gonadal androgens, including androstenedione and testosterone, are also variable, and this variability is not associated with the type and location of the *PAPSS2* mutation. Elevated testosterone, androstenedione or DHEA concentrations were reported in nine patients (11.3%). An important point to note is that in some reports the androgen profile of patients was not analyzed in detail (Table 1), but the majority of patients with hormone profile data had normal androgen values, as seen in the case reported at the beginning of this review. Oostdijk et al. (10) reported two brothers with PAPSS2 deficiency who had normal basal androgen concentrations but had higher androgen concentrations after DHEA stimulation testing compared to healthy controls. However, besides normal basal androgens, these patients also had no clinical symptoms of androgen excess.

Clinical signs of androgen excess (acnea, hypertrichosis, premature pubarche, PCOS, and menstrual irregularity) have been reported in 10 (12.6%) of the 79 patients reported so far (Table 1). Premature pubarche was described in three patients (3.7%). As seen in the patient presented at the beginning of this review, the majority of the patients with genetically confirmed PAPSS2 deficiency do not show clinical or biochemical signs of androgen excess.

The prevalence of hirsutism and PCOS in the general population is approximately 5-25% and 6-20% respectively. Premature pubarche is also not uncommon, with a prevalence of 4-7%, and has been reported as 4.3% in Turkey (11,12). Therefore, based on the data of the currently described patients, it seems difficult to speak of an increased frequency of androgen excess in patients with PAPSS2 deficiency compared to the general population. Nevertheless, given that sulfate conjugation is an important mechanism that prevents potent androgen synthesis by inactivating the precursors that can be used in the canonical or backdoor pathway of androgen synthesis, including DHEA, pregnenolone, 17-OH-Pregnenolone, androsterone, and androstenediol, clinical or biochemical androgen excess findings should be suspected and investigated in patients with PAPSS2 deficiency (Figure 2) (13). It is not clear why clinical/biochemical signs of androgen excess are not seen in all patients with PAPSS2 deficiency, although theoretically the pool of androgen precursors that are not sulfated and therefore available for active androgen biosynthesis is larger. One possibility is that, although the catalytic activity of PAPSS1 is 10-15-fold lower than that of PAPSS2, in the absence of PAPSS2 activity, the ubiquitously expressed PAPSS1 can compensate for the missing enzyme and supply tissues with sufficient PAPS. However, this rescue

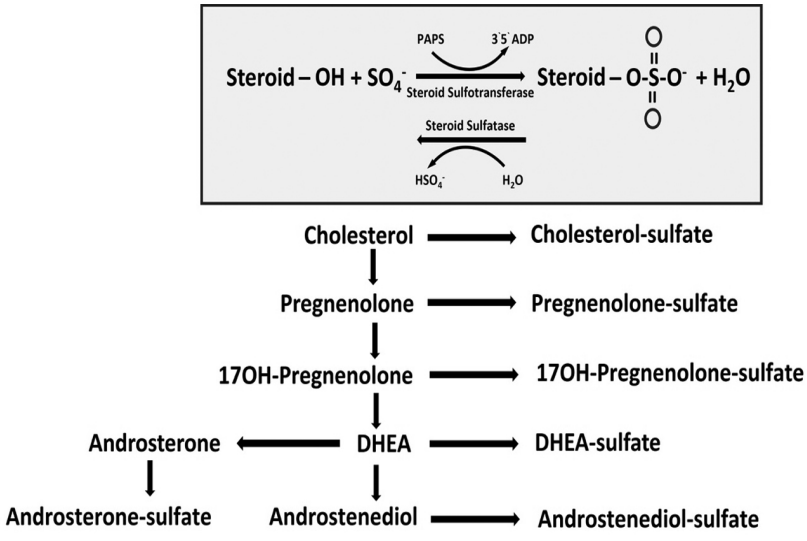

Figure 2. Schematic representation of the implication of steroid sulfatase and steroid sulfotransferase in the regulation of active hydroxylated steroids. The majority of steroid hormone precursors involved in androgen synthesis via canonical or backdoor pathways can be modified by sulfate conjugation

mechanism would also be expected to improve the bone phenotype and would also rescue DHEAS concentrations. Another possibility, at least in some cases with PAPSS2 deficiency, is the existence of at least one currently unknown rescue pathways specific to steroid hormones to prevent androgen excess. Due to the rarity of the disease, multicentre studies are needed to clarify the uncertainties regarding steroid hormone alterations in PAPSS2 deficiency. The research agenda should include comprehensive and integrative plasma and/or urine steroid hormone profile assessment studies, particularly to determine the steroid hormones that are sulfated comparatively in patients with and without androgen excess and the extent to which these steroids are sulfated. Further molecular studies to identify compensatory sulphate donors or sulphate supply pathways may be useful. Additionally, *in vitro/ex vivo* functional studies of identified *PAPSS2* mutations may highlight the impact of given variant on androgen inactivation pattern.

Conclusion

In conclusion, a broad spectrum of bone phenotypes, ranging from brachyolmia to SEMD and severe disproportionate short stature, are the main presenting features of PAPSS2 deficiency. All affected individuals have signs and symptoms related to skeletal dysplasia. The only consistent biochemical markers in affected individuals are low DHEAS and low DHEAS/DHEA ratio. Other adrenal and gonadal androgen concentrations are variable. Most published cases do not have clinical/biochemical hyperandrogenism and the prevalence of the androgen excess phenotype is similar to the general population. Neither the bone phenotype nor the steroid hormone profile correlate with the underlying *PAPSS2* mutation, nor do the skeletal and steroid hormone phenotypes correlate with each other. The reasons for the variability in steroid hormone profiles and androgen excess phenotype warrant further investigation.

Ethics

Authorship Contributions

Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: Didem Helvacıoğlu, Tülay Güran.

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