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PAPSS2 gene molecular analysis in 46,XX patients with Idiopathic Hyperandrogenism.

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Abstract

Androgen excess is the most common endocrine disorder of adult women. Polycystic ovary syndrome and idiopathic hyperandrogenism (IH) are the first and the second most common androgen disorder, respectively. Women with IH may present with hirsutism, ovulatory dysfunction, infertility and even virilization and masculinization. Mutations in PAPSS2 gene were recently published as a genetic cause of IH. Therefore, the aim of this study was to analyse the PAPSS2 gene sequence in 10 patients with diagnosis of IH.

Key words: Idiopathic hyperandrogenism, PAPSS2 gene, single nucleotide variants

Introduction

Idiopathic hyperandrogenism (IH) is one of the most common endocrine disorders among women in reproductive age. It is characterized by increased androgen production or action. Women with IH may present with hirsutism, ovulatory dysfunction, infertility and even virilization and masculinization¹. Mutations in *PAPSS2* gene were published as a genetic cause of IH². *PAPSS2* encodes human PAPS synthase 2, which provides the sulfate donor PAPS (3'-phospho-adenosine-5'-phosphosulfate) to all human sulfotransferases including SULT2A1. Dehydroepiandrosterone (DHEA) can be converted to its inactive sulfate ester, DHEA sulfate (DHEAS), by SULT2A1, a catalytic process in which PAPS (*PAPSS2*) is involved (Figure 1).

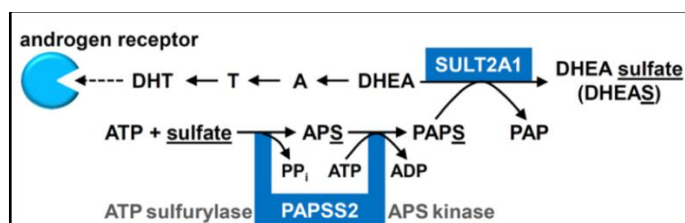


Figure 1: DHEA may be converted to T and DHT, activating the androgen receptor, or DHEA may be sulfated by DHEA sulfotransferase (SULT2A1), which requires an active universal sulfate donor PAPS, generated by successive ATP sulfurylase and APS kinase activities of *PAPSS2*. A = androstenedione; APS = adenosine 5'-phosphosulfate; PAPS = 3-phosphoadenosine-5'-phosphosulfate; PAP, 3'-phosphoadenosine-5'-phosphate; PPi = pyrophosphate. Adapted from Oostdijk et al. (2015)³.

PAPSS2 gene comprises 12 exons and is located in chromosome 10. The aim of this study was to evaluate *PAPSS2* gene sequence in patients with diagnosis of IH.

Results and Discussion

The 12 exons, approximately 700 pb from 5'UTR, 3'UTR and exon-intron boundaries from *PAPSS2* gene (MIM* 603005, NM004670) were direct sequenced in ten female patients diagnosed with IH. No pathogenic variants were identified. However, we identified the following rare heterozygous single nucleotide variants (SNV) (MAF < 0.01, 1000 genomes, TOPMED) in two non-related patients: c.753+101C>T in intron 6 (rs557350619), c.881-

159A>T in intron 8 (rs968001089) (Figure 2). We also identified two heterozygous variants, both with MAF < 0.05, in one patient: c.27+293A>G (rs143716379) and c.382-41G>A (rs17125089), in intron 1 and 4, respectively (Figure 2). Besides these rare variants, we also identified other frequent variants in the remaining patients.

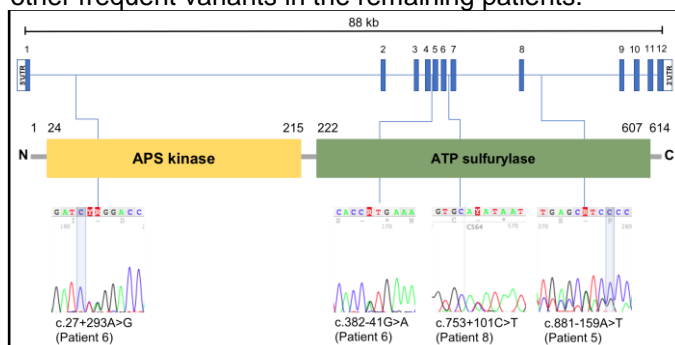


Figure 2: Illustration of the 12 exons of *PAPSS2* gene (above) and the corresponding protein domains APS kinase and ATP sulfurylase (middle). Below, electropherograms from patients 6, 8 and 5, showing the rarer heterozygous variants identified.

Although we identified rare heterozygous SNVs in the IH patients analyzed in this study in *PAPSS2* gene, there are no reports in the literature associating them to androgen excess. Further studies would be necessary to evaluate their deleterious effect on the protein function. *PAPSS2* is important in DHEA sulfation, but other enzymes, such as SULT2A1, can also be involved in the IH condition.

Conclusions

After *PAPSS2* gene Sanger sequencing in ten IH patients, no pathogenic variants were identified. We identified rare heterozygous SNVs in three patients, however they are present in databases with no correlation with androgen excess.

Acknowledgement

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¹Carmina, E. *Ann NY Acad Sci.* (2006);1092:130-7.

²Noordam, C; Dhir, V; McNelis, JC, et al. *N Engl J Med* (2009);360:2310-18.

³Oostdijk, W; Idkowiak, J; Mueller, JW, et al. *J Clin Endocrinol Metab* (2015); 100(4):E672-E680.