Idiopathic Hyperandrogenism in women: Molecular Evaluation of PAPSS2 gene

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Abstract

Hyperandrogenism is characterized by increased androgen production or action. Women with hyperandrogenism may present hirsutism, ovulatory dysfunction, infertility and even virilization and masculinization. The etiology may range from ovarian and adrenal hormonal dysfunction to ovarian and adrenal tumors. However, some female patients may remain with unidentified etiology and are classified as idiopathic hyperandrogenism (IH). Mutations in the steroidogenic genes HSD3B2 and SULT2A1 and also in the cytochrome b5 (CYB5A) are associated with IH. Mutations in PAPSS2 gene were recently published as a genetic cause of IH. Thus, the aim of this study was the molecular investigation of PAPSS2 gene in 9 female with IH.

Key words: Idiopathic hyperandrogenism, mutations, PAPSS2 gene.

Introduction

Hyperandrogenism is one of the most common conditions found among women in reproductive age, affecting approximately 7% of female patients and characterized by increased androgen production or action. Women with hyperandrogenism may present hirsutism, ovulatory dysfunction, infertility and even virilization and masculinization. The etiology, when identified, can range from ovarian and adrenal hormonal dysfunction to ovarian and adrenal tumors. When there is no identifiable cause, the patients are classified as idiopathic hyperandrogenism (IH). Mutations in the genes *HSD3B2*, *SULT2A1* and *CYB5A* are associated with autosomal recessive IH. *SULT2A1* requires 3'-phospho-adenosine-5'-phosphosulfate (PAPS) for catalytic activity and mutations in *PAPSS2* gene were recently published as a genetic cause of IH. The dehydroepiandrosterone (DHEA) sulfation system is shown in Figure 1, where DHEAS is produced from DHEA by *SULT2A1*, a catalytic process in which PAPS (*PAPSS2*) is involved¹.

The aim of this project was to evaluate the molecular integrity of *PAPSS2* gene in 9 female with IH.

(p.Tyr65Cis) and c.1732T>G (p.Phe578Val), in Patient 5 and 9, respectively (Figure 2). Patient 9's mother also presented the p.Phe578Val variant. The p.Tyr65Cis (rs145923739) is registered in ExAC browser with an allelic frequency of 0.0005. None of the variants were found in the human gene mutation database (HGMD-<http://www.hgmd.cf.ac.uk>). The remaining patients presented only common allelic polymorphisms (MAF≥0,01).

Figure 2: Illustration of the 12 exons of *PAPSS2* gene (above) and patients 5 and 9 electropherograms showing (light blue) the c.194A>G in exon 3 (p.Tyr65Cys) and c.1732T>G in exon 12 (p.Phe578Val) substitutions identified (middle), respectively. Below the protein positions affected by the variants found in the APS kinase and ATP sulfurylase domains.

Conclusions

Patients 5 and 9 presented single heterozygous non-synonymous substitutions in *PAPSS2* gene. Since the inheritance of the condition is considered autosomal recessive, a second variant might still to be identified in regions not covered by our oligonucleotides to confirm the compound heterozygosis of the patients.

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Figure 1: Schematic representation of the DHEA sulfation system. *PAPSS2* generates the sulfate donor PAPS through the activities of ATP sulfurylase and APS kinase. DHEA sulfotransferase (*SULT2A1*) requires PAPS for efficient DHEA sulfation. Unconjugated DHEA molecules are ultimately converted to active androgens. Cess Noordam et al. (2009).

Results and Discussion

After PCR and Sanger sequencing of the entire *PAPSS2* gene, two heterozygous missense substitutions were identified in two unrelated female patients: the c.194A>G

¹ Cess Noordam, M.D.; Dhir, V.; McNelis, J.C. et al. *N Engl J Med* 2009;360:2310-18.