A nonvirilized form of classical 3β-hydroxysteroid dehydrogenase deficiency due to a homozygous S218P mutation in the HSD3B2 gene in a girl with classical phenylketonuria

Ayfer Alikasifoglu[1], Gonul Buyukyılmaz[1], E. Nazli Gonc[1], Z. Alev Ozon[1], N Kandemir[1], Munis Dundar[2] , Seher Polat[2], Emine Pektas[3], Ali Dursun[3], Serap Sivri[3], Aysegul Tokatli[3] and Turgay Coskun[3]

[1] Hacettepe University, Division of Pediatric Endocrinology, Ankara, Turkey
[2] Erciyes University, Department of Medical Genetics, Kayseri, Turkey
[3] Hacettepe University, Division of Metabolic Diseases, Ankara, Turkey

BACKGRAUND

3β-hydroxysteroid dehydrogenase (3βHSD) deficiency is a rare form of congenital adrenal hyperplasia (CAH). It is caused by loss of function mutations in the HSD3B2 gene. In classical form, affected patients have salt wasting early in infancy and may have ambiguous genitalia in both sexes. Herein we report a non virilized female with classical form of 3βHSD deficiency due to homozygous S218P mutation in the HSD3B2 gene and classical phenylketonuria.

CASE REPORT

35 days old female
- ❖Diagnosed with classical phenylketonuria in newborn screening
- ❖On phenylalanine restricted diet

At one month of age
- ❖Lethargic
- ❖Failed to gain weight

Family history
- ❖Parents are first degree cousins

Physical examination
- ❖ Height: 50 cm (3-10p)
- ❖ Weight:3.4 kg (10p)
- ❖ Head circumference: 36cm (25 p)
- ❖Dehydrated
- ❖Normal female external genitalia

Laboratory

Na	**119 mEq/L**
K	**7** mEq/L
Cl	90 mEq/L
BUN	25.1 mg/dL
Creatinine	0.45 mg/dL
Glucose	80 mg/dL
Urinary Na	75.4 mEq/L
Urinary K	25.5 mEq/L
Blood pH	7.38

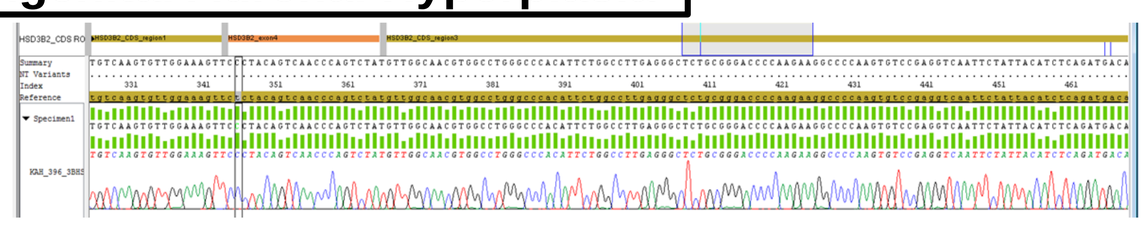
Hormones

ACTH	**926pg/mL**
Cortisol	**7.3 µg/dL**
Renin	**1205 pg/mL**
Testosterone	**216 ng/dL**
Androstenedione	**>10 ng/mL**
17OHP	**105 ng/mL**
11-deoxycortisol	**132 ng/mL**
DHEAS	**1387 µg/dL**

Standard ACTH Stimulation Test

	Cortisol µg/dL	17OHP ng/mL	11-deoxycortisol ng/mL	Androstenedione ng/mL	DHEA ng/mL
0.min	7.3	16.5	20	>10	29.8
60.min	9.3	41.7	32.7	>10	

Congenital Adrenal Hyperplasia



HSD3B2 gene, S218P, homozygote missense mutation

- ❖**Karyotype** 46,XX
- ❖**Pelvic ultrasonography:** Normal female internal genitalia
- ❖ Mineralocorticoid and glucocorticoid replacement was started.

3β-hydroxysteroid dehydrogenase deficiency

DISCUSSION

Our patient was a 46,XX phenotypic female infant with salt wasting 3βHSD deficiency. A paradoxical elevation in the concentration of serum 17OHP and other Δ4 steroids are common in 3βHSD deficiency, because a second isozyme (HSD3B1) which is 93.5% homologous to HSD3B2 is expressed in peripheral tissues, and mediates peripheral conversion of the inactive adrenal precursors that accumulate into active androgens. However further conversion of androstenedione into testosterone may not be effective enough to virilize female patients since circulating concentration of androstenedione would be much below the Km of 17 β- hydroxysteroid dehydrogenase type 5. This could explain the lack of virilization in some affected females. Homozygous missense (S218P) mutation in the HSD3B2 gene did not lead to virilization of external genitalia in our patient. Previously the same mutation in monoallelic form in a patient with compound heterozygous (Y190C and S218P) HSD3B2 mutations has been reported to cause moderate virilization. These findings suggest complex relationship between genotype and phenotype.

CONCLUSION

3βHSD deficiency is associated with a wide spectrum of clinical presentations with or without salt-wasting. The hormonal phenotype can be complicated in this disorder. This report expands the genotype-phenotype relationship in HSD3B2 deficiency. Also this is the first case in the literature with the co-existence of 3βHSD deficiency and classical phenylketonuria. The high rate of consanguineous marriages in Turkey might increase the possibility of co-existence of autosomal recessive disorders.

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