Steroid 5-a reductase type 2 isoenzyme (SRD5A2) deficiency is a male-limited autosomal recessive disorder that results in decreased conversion of testosterone to dihydrotestosterone with various degree of incomplete virilization in affected 46, XY infants. No clear genotype-phenotype relationship has been reported till date; moreover, the same mutation can result in considerable heterogeneity in clinical manifestations. Of 6 documented cases with Try235Phe homozygous mutation of the SRD5A2 gene, 3 patients had predominantly female external genitalia whereas the other 3 had predominantly male phenotype. We report Try235Phe homozygous mutation of the SRD5A2 gene in a Turkish patient who was initially assigned as a girl because of the predominantly female appearance of the external genitalia.

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teroid 5-a reductase (5aR) type 2 isoenzyme deficiency is a male-limited autosomal recessive disorder causing 46, XY disorders of sex differentiation (DSD). 5aR type 2 enzyme converts testosterone (T) into the more biologically active form of dihydrotestosterone (DHT), which is necessary for the development of the external genitalia, urethra, and prostate in the male fetus. 5aR type 2 gene (SRD5A2) mutations decreased the synthesis of DHT, a key hormone of virilization at the male external genitalia. Various degree of incomplete virilization may be seen in the same homozygotic mutation.1-3

In this paper we report Try235Phe homozygous mutation of the SRD5A2 gene in a Turkish patient with predominantly female appearance of the external genitalia.

CASE

The patient was admitted to the pediatric endocrine department for the evaluation of DSD at the age of 6 days. In the prenatal period, the chromosomal study revealed a karyotype of 46, XY because of abnormal triple test. The patient weighed 2400 g at 38 weeks of gestation, with the normal delivery of a 36-year-old woman. The family history revealed a first-degree relationship between healthy parents, and the patient was the second child in the family.

On clinical examination, the infant showed female phenotype, extremely hypoplastic penis (stretched length 1.5 cm) with a single phallic urethral opening, and palpable right testis in the labio-scrotum (Figure 1).

Pelvic ultrasonography showed no evidence of any mullerian structures. Genitography revealed a urogenital sinus without any vaginal pouch (Figure 2). Laboratory findings included normal serum electrolytes, 28.8 ng/mL 17-hydroxyprogesterone (17-OHP), and 1.19 ng/mL T. The karyotype was 46, XY. Human chorionic gonadotropin (hCG) test was performed at the age of 2 months. The basal plasma T value was 1.46 ng/mL, while T was 5.9 ng/mL and DHT was 0.21 ng/mL after hCG stimulation. A serum T/DHT ratio of 28.1 under hCG stimulation provided evidence for the diagnosis of 5aR deficiency. The SRD5A2 gene analysis revealed Try235Phe homozygous mutation in exon 5. The 17-OHP level decreased to 0.27 ng/mL at
the follow-up period.

The patient’s sex was reared as male because of the parents’ insistent demand. Transdermal 25% DHT gel was administered for 4 months, resulting in an increase in penile length to 3.5 cm (Picture 3).

Genetic analysis

Genomic DNA was extracted from the peripheral blood leukocytes of the patient using standard procedures. The entire SRD5A2 coding region (exons 1–5) was screened for mutations. Polymerase chain reaction (PCR) was performed to amplify all the exons and the exon–intron boundaries of SRD5A2 with the primers reported before. PCR settings, amplicons length, and annealing temperatures for PCR and sequencing analysis were reported elsewhere. After an initial round of PCR amplification, PCR products were visualized by agarose gel electrophoresis to check the quality of PCR products. Subsequently, PCR fragments were purified and subjected to cycle sequence reactions using BigDye Terminators (DNA sequencing kit, Applied Biosystems, Foster City, California, USA). The sequence fragments were precipitated and analyzed using an automated sequencer (ABI3130). Try235Phe (c.A704T) mutation was described with homozygous in the exon 5 SRD5A2 gene (Figure 4).

DISCUSSION

To date, more than 50 SRD5A2 gene mutations have been identified. No clear genotype-phenotype relationship has been reported till date; moreover, the same mutation can result in considerable heterogeneity in clinical manifestations. Six documented cases exist with Try235Phe homozygous mutation of the SRD5A2 gene; 3 patients had predominantly female external genitalia whereas the other 3 had predominantly male phenotype (Table 1). Caucasian patient,1 Egyptian newborn,2 and Italian patient3 were predominantly female phenotypes, which were reared as female. Interestingly, the same homozygous mutation was also found in the Israeli patient with micropenis and hypospadias (Mazen et al, unpublished data, 2003); the two Italian patients of whom one presented only with perineoscrotal hypospadias and undescended testes (Nicoletti et al, 2005) and the other presented with microptenis, perineoscrotal hypospadias, and bilateral cryptorchidism (Baldinotti et al, 2008) were reared as male.1,3,5,6 Try235Phe homozygous mutation was previously known, but it was first reported in a turkish patient.7 The deficiency of 5αR type 2 phenotype shows variation from male to female phenotype with hypospadias or only microphallus. This can thus be explained...
case report

Figure 4. Electropherogram of segment of SRD5A2 pointing the homozygous c.A704T mutation.

Table 1. Main clinical, hormonal, and molecular data of patients having 5αR type 2 deficiency with Try235Phe homozygous mutation.

| Age     | Phenotype                                      | Sex of rearing | Mutation       | Geographical origin |
|---------|-----------------------------------------------|----------------|----------------|--------------------|
| Wigley et al, 1994 | 31 y Female | Female | Y235F in exon 5 | Caucasian, French   |
| Mazen et al, 2003 | 9 mo Female | Female | Y235F in exon 5 | Egyptian           |
| Mazen et al, 2003 | Micropenis, hypospadias in personal data | Male | Y235F in exon 5 | Jewish Israeli     |
| Nicoletti et al, 2005 | 3 y Mild clitoromegaly, blind ending vaginal pouch, testes palpable in the labio-scroton | Female | Y235F | Italian             |
| Nicoletti et al, 2005 | 8 y Perineo-scrotal hypospadias, testes present in the scrotum | Male | Y235F | Italian             |
| Baldinotti et al, 2008 | 1 y Micropenis, hypospadias and bilateral cryptorchidism | Male | Try235Phe in exon 5 | Italian (Sicily)    |

that some factors related to androgen receptor signal transduction, fetal effects of T or steroid 5-a reductase type 1 isoenzyme, or exposure to environmental chemicals may affect clinical expression of the disorder.

In conclusion, this was, to the best of our knowledge, the fourth case of predominantly female phenotype due to 5-a reductase type 2 deficiency and the first case of Try235Phe homozygous mutation published in Turkish patients, which responded positive to the DHT gel treatment.

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