

# CLINICAL FINDINGS, ENDOCRINE PROFILE AND GENETIC FEATURES OF 5 $\alpha$ -REDUCTASE-2 DEFICIENCY

Gianni Russo <sup>a</sup>, Fulvia Baldinotti <sup>b</sup>, Paolo Ghirri <sup>c</sup>, Silvia Meroni <sup>a</sup>, Ilaria Colombo <sup>a</sup>, Giampiero I Baroncelli <sup>d</sup>, Maria R Sessa <sup>e</sup>, Eleonora Dati <sup>f</sup> and Silvano Bertelloni <sup>d</sup>

<sup>a</sup> Department of Pediatrics and Adolescent Medicine, San Raffaele Hospital, University 'Vita e Salute', Milano, Italy;

<sup>b</sup> Department of Cytogenetic and Molecular Biology, S. Chiara University Hospital, Pisa, Italy;

<sup>c</sup> Department of Neonatology, S. Chiara University Hospital, Pisa, Italy;

<sup>d</sup> Adolescent Medicine, Department of Pediatrics, S. Chiara University Hospital, Pisa, Italy;

<sup>e</sup> Endocrine Laboratory, S. Chiara University Hospital, Pisa, Italy;

<sup>f</sup> Division of Pediatrics, San Giuseppe Hospital, Empoli, Italy.

## Background

5 $\alpha$ -reductase-2 (5 $\alpha$ -R2) deficiency is a rare autosomal recessive form of 46,XY disorder of sex development, which is caused by mutations in the 5 $\alpha$ -R2 gene. 5 $\alpha$ -R2 deficiency impairs the conversion of testosterone (T) to its more active metabolite, dihydrotestosterone (DHT), which is required for the normal development of external genitalia, urethra and prostate in the male fetus, whereas T plays a major role in the virilization of Wolffian ducts. Individuals with 5 $\alpha$ -R2 deficiency have incomplete intrauterine masculinization of external genitalia: phenotype may range from almost complete female to male with penile hypospadias or isolated micropenis. At puberty individuals with intact testes undergo spontaneous virilization. The classic hormonal profile of these patients includes normal T levels contrasting with low DHT levels (increased T/DHT ratio at baseline and/or following hCG stimulation).

## Aims & Methods

Optimal diagnostic and clinical management of 5 $\alpha$ -R2 deficiency is not well defined, as well inferences of genotype on phenotype.

We report the clinical, endocrinological and molecular data on 25 patients with certain 5 $\alpha$ -R2 deficiency (period 2004-14; age at first clinical observation  $0.4 \pm 1.0$  years).

## Results

About 50% of patients had a misdiagnosis before our observation. Mean period from first observation to definitive diagnosis was  $9.1 \pm 10.8$  years (range 0.1 to 47.0 years); in 8 subjects gonadal removal was performed before certain diagnosis. Initial sex assignment was female in 16/25 (64%) and male in 9/25 (36%). After diagnosis of 5 $\alpha$ -R2 sex re-assignment was performed in five babies: four girls to male sex and one boy to female sex. Baseline T/DHT ratio was diagnostic in 6/12 subjects (first months of life, n = 4; puberty, n = 2), while post-hCG T/DHT ratio was diagnostic in all tested patients by setting the cut-off value at 15 or lower; the peak cut-off of 17 and 30 missed 3 (sensitivity 77%) and 7 (sensitivity 54%) individuals, respectively.

18 different mutations in 5 $\alpha$ -R2 gene were identified (homozygous 12/25; compound heterozygous 11/25; monoallelic missense mutation 1/25; homozygous V89L variant associated with high progestin administration during pregnancy 1/25). Five mutations have never been reported (p.G13D, p.P79L, c.281+1G>A, c.331\_332delCT, p.V124D). In some individuals, the same mutations were associated with different phenotypes.

Age at suspicion	Prenatal, n = 2 Birth, n = 15, Postnatal, n = 8
Symptoms for referral	Generic "Ambiguous Genitalia", n = 4; Micropenis/Hypospadias/Cryptorchidism, n = 6 Clitoromegaly/Inguinal Hernia, n = 8 Isolated Clitoromegaly, n = 2 Clitoromegaly/Urogenital Sinus, n = 2 Isolated Micropenis, n = 2 Absence of Uterus, n = 1 (at sonography)
Age at certain diagnosis	$9.5 \pm 10.9$ yrs (range 0.1 – 47 yrs)
Assigned sex at birth	Male, n = 9 Female, n = 16
Final sex assignment	Male, n = 12 Female, n = 13
Sex reassignment	F $\rightarrow$ M, n = 4 M $\rightarrow$ F, n = 1
Gonadectomy	n = 9 (age at surgery 0.3 – 12.0 yrs)

## Conclusions

Consistent time-lag may persist before the diagnosis of 5 $\alpha$ -R2 deficiency is established. Sex assignment and gonadal removal may be done before certain diagnosis. Sex re-assignment is usually to male sex, but the contrary may occur. Accurate endocrine evaluation is recommended, since the use of appropriate cut-off values of T/DHT ratio may permit to select individuals with 5 $\alpha$ -R2 deficiency.

Large genetic variability is present and a clear genotype-phenotype correlation is lacking.

