WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 11, 2183-2188. Review Article ISSN 2277– 7105

# A REVIEW ON 5-ALPHA-REDUCTASE 2 DEFICIENCY IN NEWBORNS

**Reshma Rajan[1]*, Dhanya Dharman[2] and Shaiju S Dharan[3]**

[1]VIth Year Pharm.D, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkkara, Trivandrum.

[2]Assistant Professor, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkkara, Trivandrum.

[3]Principal, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkkara, Trivandrum.

Article Received on
20 July 2021,

Revised on 10 August 2021,
Accepted on 30 August 2021,

DOI: 10.20959/wjpr202111-21609

***Corresponding Author**
**Reshma Rajan**
VIth Year Pharm.D, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkkara, Trivandrum.

## ABSTRACT

5α-reductase type 2 deficiency (5αRD) is an autosomal recessive hereditary disease of the group of 46, XY disorders of sex development (DSD) characterised by lack of masculinisation in XY individuals due to failure to convert testosterone to dihydrotestosterone, the bioactive androgen. Clinical presentation of these children vary from normal male genitalia to a completely female genitalia. Most of the children with 5AR2D are raised as females and gender conversion to male happens at around puberty due to masculine and voice changes caused by testosterone. Early diagnosis is beneficial in treating this problem. Elevated testosterone: DHT ratio with administration of beta human chorionic Gonadotropin (HCG) is the gold standard test in diagnosis of this defect. Most patients of 5 alpha reductase 2 deficiency are considered infertile, but with recent advancements in assisted reproductive techniques a few 5AR2D have been successful in giving birth to their offsprings.

**KEYWORDS:** 5AR2D, offspring, masculinisation, dihydrotestosterone, atypical genitalia.

## INTRODUCTION

Disorders of sex development (DSD) are a group of pediatric disorders associated with inconformity of gonads, chromosomes and hence external genitalia. DSD can be of two types

based on the chromosomal status as 46, XX DSD and 46, XY DSD. In 46, XY DSD the primary sex organ is most of the affected individuals is testes, but associated with a deficiency in sex hormones or abnormal response of the individuals to the sex hormones. In majority of 46, XY DSD, if the Y chromosome is normal and the primary sex organ is tests, then the major mutations are seen in either androgen receptor or in SRD5A2 (steroid-5-alpha-reductase, alpha polypeptide 2) genes which regulate the production of an important enzyme called as DHT which is involved in conversion of testosterone to Dihydrotestosterone (DHT). DHT plays a very important role during early embryogenesis by its role in development and differentiation of male external genitalia. Deficiency of DHT during first trimester in the developing male fetus will impact the development of external genitalia leading to ambiguous genitalia in new borns.[1]

**Genetics of 5-Alpha-Reductase 2 Deficiency**

The rare 5AR2D was first described in 1974 in patients with pseudovaginal perineoscrotal hypospadias, micro phallus, and cryptorchid testes.[2] The condition is autosomal recessive and often found in males born in consanguineous parents in areas with high rates of inbreeding.[3] The major gene mutations in 5AR2D occur in the androgen receptor (AR) and steroid-5-alphareductase 2, (SRD5A2) genes.[4] Type 1 isoenzyme is encoded by the SRD5A1 gene located on chromosome 5p15, and expressed mainly in the liver and non-genital skin.[2] Type 2 isoenzyme is encoded by the SRD5A2 gene on chromosome 2, band p23, and is expressed at high levels in the prostate, the epididymis, seminal vesicles, genital skin, and its efficiency leads to male pseudohermaphroditism, with incomplete differentiation of male genitalia.[1] SRD5A2 was cloned and shown to contain five exons and four introns, which have over 65 known mutations, including point mutations, deletions, and insertions.[4] The most frequent polymorphism at exon 1, V89L, at the 89th codon, results in valine to leucine substitution, and decreases 5-alphareductase 2 activity by approximately 30%. V89L polymorphism is also more prevalent in patients with micropenis than in normal males.[2,5] Results of one major study of 33 subjects confirm the predominance of homozygous (69.1%) vs. compound heterozygous mutations (30.9%), whereas deletions and disruptive mutations were relatively rare. Mutations was predominantly seen in exons 1 (35.8%) and 4 (21.7%), whereas exons 3 (11.3%) and 5 (9.4%) seemed to be rare.[2,6]

**Epidemiology**

The largest 5AR2D affected kindred known are New Guinean, Dominican and Turkish. The New Guinean kindred's mutation was the first group described, with deletion of the 5α-reductase 2 gene of more than 20 kb resulting in a full loss of enzymatic activity. The Dominican kindred have a missense mutation in exon 5, substituting thymidine for cytosine and resulting in a substitution of tryptophan for arginine, resulting in reduction in binding of 5α-reductase-2 to its critical cofactor NADPH and a great decrease in enzymatic activity. The Turkish kindred have a single base deletion in exon 5, causing a frame shift mutation with complete loss of enzymatic activity.[3] 5AR2D was also identified in populations not considered at risk of inbreeding, such as Europeans or North Americans, particularly in Quebec.[7]

**Clinical Presentation**

5-alpha- reductase 2 deficiency is characterized by external female phenotype at birth, with a shallow vaginal pouch, hypospadias, which is an opening of the urethra on the underside of the penis, and a clitoral-like phallus. Presence of bilateral testes and normally developed internal male genitalia,[3] but an underdeveloped prostate and a bifid scrotum. This is due to the inability to convert testosterone to dihydrotestosterone (DHT). DHT is responsible for the differentiation of genital tubercle and urogenital sinus into the prostate, urethra and external genitalia. Thus, male differentiation fails to occur despite high circulating testosterone levels.[8,9]

**Gender Choice and Fertility**

Most of the patients with 5 alpha reductase 2 deficiency are assigned female gender at birth and are raised as female child. At puberty, the surge in testosterone production prompts virilization, and enlargement of the genitalia with appearance of secondary sexual characteristics like development like muscle growth deepening of voice, pubic and axillary hair.[3,4] Lack of breast development and amenorrhea prompts the suspicion of diagnosis at puberty for most of the subjects with 5 alpha reductase 2 deficiency,[2,10] Fertility is a challenge due to low sperm production, defective transformation of spermatogonia into spermatocytes, and the inability to liquefy semen due to a lack of prostate specific antigen and seminal fluid.[3] Other mutations lead to subtle abnormalities in the enzyme may underlie some forms of commonly encountered urogenital birth defect in males as well as

androgendependent disorders such as male pattern baldness, acne, hirsutism, and benign or cancerous growth of the prostate.[9,11]

**Diagnosis**

Traditionally, the diagnosis relies on DHT measurement, but the results being equivocal can sometimes lead to misdiagnosing the condition. An alternative approach for diagnosis of 5AR2D is urinary steroid profiling (USP), a readily available testing option. In one study, of the 15 patients undergoing USP, all showed low ratios in at least 2 of the 4 pairs of 5-alpha- and 5-beta-reduced steroid metabolites. USP is considered as an ideal test for biochemical phenotyping in 5AR2D 3 months after the birth of the child.[12,8] Mutational analysis of SRD5A2 by PCR and direct DNA sequencing of all 46, XY DSD patients is the key to the diagnosis of 5AR2D, as this is the ultimate tool for diagnosis. Making use of this wonderful technology for identifying the chromosomal abnormalities of DSD will probably help to get a confirmed diagnosis.[10,12] The biological diagnosis of 5AR2D is usually supported by an increase in the T/DHT ratio after human chorionic gonadotropin (HcG) stimulation testing, which is first line of diagnosis in infants and pre-pubertal children.[2,4]

**Treatment**

Early diagnosis of 5AR2D is a key factor in its treatment. Early diagnosis allows the children to be raised as males at an early age and children can avoid embarrassment of gender conversion at a later age. DHT gel treatment for pediatric micropenis was studied with 76 pediatric patients with 46, XY DSD, who were treated with DHT gel (0.1-0.3 mg/kg/day) for three to six months. 22 of these patients had SRD5A2 mutations. The penis length of the patients significantly improved with DHT treatment. The length of the penis increased significantly after long term treatment with DHT resulting in greater improvement. Therefore, the study shows that local application of DHT gel can promote penis growth effectively without systemic adverse reactions.[4] Often these individuals require long-term psychological support to aid in making an informed decision. If the parents chose to raise a female, gonadectomy and surgical correction of the external genitalia are indicated to avoid masculinization, with vaginoplasty for a healthy sexual life. An estrogenonly hormone replacement therapy must be administered these patients throughout life until the 50th year of age.[13]

## CONCLUSION

The multiples studies on 5AR2D underline the wide spectrum of phenotypes and biological profiles in patients with the condition. Physicians must be informed and aware of DSD and 5AR2D in particular, and make informed clinical decisions with the family of the affected individuals, due to the often-sensitive matter in a variety of communities and societies. The decisions made should consider the fact that at puberty, the individuals often become masculine and identify as males. Also, management decisions should aim at preserving functionality, quality of sexual and day-to-day life.

## REFERENCE

1. Narasimha Prasad Vijayashankar, Artem Artemev, Anastasia Pougno, Gopikumar MS. 5Alpha-Reductase 2 Deficiency in Newborns: A Review, International Journal of Physiology, 2020 Jan-Mar; 8(1): 57-63.
2. Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P et al. Phenotypical, Biological, and Molecular Heterogeneity of 5α-Reductase Deficiency: An Extensive International Experience of 55 Patients. The Journal of Clinical Endocrinology & Metabolism, 2011; 96(2): 296-307.
3. Kang H, Imperato-McGinley J, Zhu Y, Rosenwaks Z. The effect of 5α-reductase-2 deficiency on human fertility. Fertility and Sterility, 2014; 101(2): 310316.
4. Fu X, Zhang W, Qu X. Correlation of androgen receptor and SRD5A2 gene mutations with pediatric hypospadias in 46, XY DSD children. Genetics and Molecular Research, 2016; 15(1).
5. Sasaki G, Ogata T, Ishii T, Kosaki K, Sato S, Homma K et al. Micropenis and the 5αReductase-2 (SRD5A2) Gene: Mutation and V89L Polymorphism Analysis in 81 Japanese Patients. The Journal of Clinical Endocrinology & Metabolism, 2003; 88(7): 3431-3436.
6. Maimoun L, Philibert P, Cammas B, Audran F, Pienkowski C, Kurtz F et al. Undervirilization in XY newborns may hide a 5α-reductase deficiency: report of three new SRD5A2 gene mutations. International Journal of Andrology, 2010; 33(6): 841-7.
7. Chan A, But B, Lee C, Lam Y, Ng K, Tung J et al. Diagnosis of 5 -Reductase 2 Deficiency: Is Measurement of Dihydrotestosterone Essential?. Clinical Chemistry, 2013; 59(5): 798-806.
8. Al-Jurayyan N. Ambiguous Genitalia: Two Decades of Experience. Annals of Saudi Medicine, 2011; 31(3): 284-8.

9. Akcay T, Fernandez-Cancio M, Turan S, Güran T, Audi L, Bereket A. ARandSRD5A2gene mutations in a series of 51 Turkish 46,XY DSD children with a clinical diagnosis of androgen insensitivity. Andrology, 2014; 2(4): 572-8.
10. Deeb A, Suwaidi H, Ibukunoluwa F, Attia S. Phenotype, Sex of Rearing, Gender ReAssignment, and Response to Medical Treatment in Extended Family Members with a Novel Mutation in the SRD5A2 Gene. Journal of Clinical Research in Pediatric Endocrinology, 2016; 8(2): 236-40.
11. Thigpen A, Davis D, Milatovich A, Mendonca B, Imperato-McGinley J, Griffin J et al. Molecular genetics of steroid 5 alpha-reductase 2 deficiency. Journal of Clinical Investigation, 1992; 90(3): 799809.
12. Chan A, But B, Lee C, Lam Y, Ng K, Tung J et al. Diagnosis of 5 -Reductase 2 Deficiency: Is Measurement of Dihydrotestosterone Essential?. Clinical Chemistry, 2013; 59(5): 798-806.
13. Markantes G, Deligeoroglou E, Armeni A, Vasileiou V, Damoulari C, Mandrapilia A et al. Callo: The first known case of ambiguous genitalia to be surgically repaired in the history of Medicine, described by Diodorus Siculus. HORMONES, 2015.