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Genetic Diagnosis of 46,XY Disorders of Sex Development (DSDs): Insights for Personalized Management

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INTRODUCTION & AIM

The 46,XY disorders of sex development (46,XY DSDs) are congenital anomalies in which there is a discordance between chromosomal, gonadal, or phenotypic features of the internal and/or external genitalia. Diagnosis may occur in the neonatal period or during adolescence. The 46,XY DSD spectrum is broad and of variable severity. Patients present with overlapping clinical and biochemical features and exhibit varying degrees of virilization of their external genitalia ranging from a small penis or mild hypospadias to completely female external genitalia. The 46,XY DSD encompasses multiple etiologies such as gonadal dysgenesis, defects in androgen synthesis or action, and disorders of anti-Müllerian hormone (AMH) synthesis or action, all of which impair typical male virilization.
The genetic cause is found in approximately 30% of cases; However, ongoing advances in molecular diagnostics hold the promise of solving a greater proportion of currently unexplained cases. Genetic investigation typically begins with targeted analysis of candidate genes guided by patients' clinical presentation and biochemical findings. Identifying the underlying genetic etiology of these patients is crucial as it provides prognostic information regarding gonadal function, tumor risk, fertility potential, and gender identity development.

This study focused on 14 Tunisian patients diagnosed with 46XY DSD.

METHOD

14 patients with 46,XY DSDs from unrelated families were recruited for this study at the Department of Medical Genetics, Hedi Chaker University Hospital (Sfax, Tunisia), between 2022 and 2024. Informed written consent was obtained from all participants, or from parents/guardians for those under 18 years of age.

Each patient underwent detailed clinical and hormonal assessments, and data were extracted from their medical records.

Clinical presentation and hormonal evaluation led to the following diagnoses within the cohort:

Complete/partial androgen insensitivity syndrome

- **Androgen receptor (*AR*) gene (NM_000044.6)**
- **9 patients (P1 -> P9)**

17β-hydroxysteroid dehydrogenase type 3 deficiency

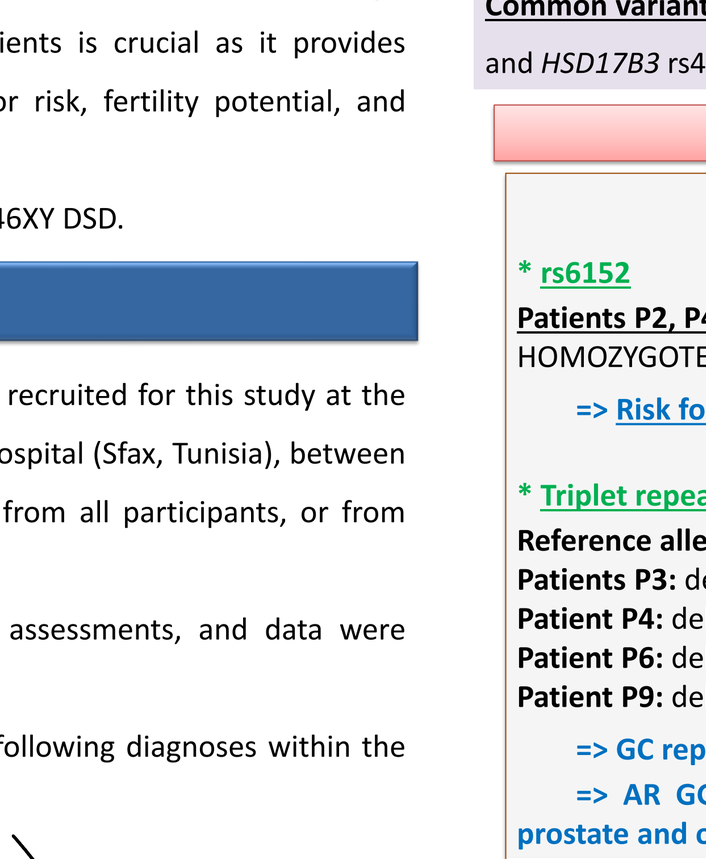
- ***HSD17B3* gene (NM_000197.1)**
- **1 patient (P10)**

Gonadal dysgenesis

- ***SF1/NR5A1* gene (NM_004959.4)**
- **2 patients (P11, P12)**

5α-reductase type 2 deficiency

- ***SRD5A2* gene (NM_000348.4)**
- **2 patients (P13, P14)**



RESULTS & DISCUSSION

Rare variants

AR gene

Patient P2
rs1186031724; HOMOZYGOTE; exon 1; c. 1886G>T; p.Gly454=; MAF: 7.1e-06

Patient P3
rs2060100891; HOMOZYGOTE; exon 7; c.3017T>C; p.Leu831=; MAF: Absent in GnomAD

=> Pathogenic effects on splicing ?

=> Further functional investigation is required to evaluate the role these novel or rare synonymous AR gene variants in the phenotype of carrier patients.

Screening of *HSD17B3*, *SF1* and *SRD5A2* genes

Patients P10 -> P14

=> Absence of mutations

Common variants: *SRD5A2* rs632148 (HETEROZYGOTE), *SRD5A2* rs142200057 (HOMOZYGOTE) and *HSD17B3* rs408876 (HOMOZYGOTE) were found in patients P10, P13, P14

Polymorphisms

AR gene (Exon 1)

* **rs6152**

Patients P2, P4, P6
HOMOZYGOTE; c. 1163G>A; p.E213=; MAF: 0.1640

=> Risk for androgenetic alopecia

* **Triplet repeats GGC**

Reference allele: (GGC)17Gly; AR N-terminal domain
Patients P3: del(GGC)4; 13Gly; HOMOZYGOTE; MAF: 0.03
Patient P4: del(GGC)3; 14Gly; HOMOZYGOTE; MAF: 0
Patient P6: delGGCGGC; 15Gly; HOMOZYGOTE; MAF: 0
Patient P9: delGGC; 16Gly; HOMOZYGOTE; MAF: 0.007

=> GC repeat sizes are directly correlated with cellular AR protein levels [1]

=> AR GGC alleles under 15 repeats are associated with an increased risk of prostate and oesophageal cancer [2, 3, 4]

CONCLUSION

There are a few limitations in the study:
- The impact of VUSs on protein function was predicted only by *in silico* analysis, highlighting the need for *in vitro* functional validation.
- Whole-exome sequencing is essential to elucidate the genetic etiology in patients with undetermined cause.

The management of patients with 46,XY DSD depends on etiology, gender identity, hormonal therapy, and genital surgery, as well as consequent psychosocial implications, all of which necessitate long-term multidisciplinary follow-up.

FUTURE WORK / REFERENCES

Future Work

Epigenetic analysis was not involved in this study; further investigation with larger cohort are needed.

The authors have no conflicts of interest to declare

References: **[1]** Ding et al. 2004; **[2]** Chang et al. 2002; **[3]** Visakorpi 2003; **[4]** Dietzsch et al. 2003