Aetiology of 46,XY DSD in Algeria, putative modifier role of pV89L polymorphism in the SRD5A2 gene in androgen receptor mutation-negative subjects

Asmahane Ladjouze[a], Pascal Philibert[b], Yves Morel[c], Ourida Taleb[a], Lila Kedji[a], Abdeljalil Maoudj[a], Karima Berkouk[a], Nadjet Bouhafs[a], Nabila Dahmane[a], Souhila Melzi[a], Tahar Anane[a], Charles Sultan[b] & Abdenour Laraba[a]

[a]Department of Paediatrics, CHU Bab el Oued, Algiers, Algeria; [b]Laboratoire d'Hormonologie, CHU Montpellier, Montpellier, France, [c] Service d'endocrinologie moléculaire, Hospices civils de Lyon, France

Background

46,XY DSD is a heterogeneous group of pathologies characterized by a wide spectrum of phenotypes and aetiologies. While advances in molecular genetics have permitted discovery of numerous genes implicated in testicular development, the diagnosis still remains uncertain for most patients with 46,XY DSD,

Aim of the study

To identify the aetiologies of 46,XY DSD in Algerian patients.

Methods

We conducted a multicentre prospective study.

All patients referred for DSD (excluding Turner and Klinefelter syndromes) were investigated and classified as 46,XX DSD; sex chromosome DSD and 46,XY DSD.

In this last group, clinical, ultrasonography, MRI, genitography and hormonal analysis were used to sub-classify the patients as having: disorders of androgen synthesis or action; gonadal dysgenesis; Persistent Müllerian Duct Syndrome (PMDS);ovo-testicular DSD; and syndromic DSD.

Mutational analysis was performed for patients with disorders of androgen action (*AR gene* and *SRD5A2*, *MAMLD1*), gonadal dysgenesis (*SRY, NR5A1,WT1)* [Profs Philibert and Sultan, Montpellier]; and androgen synthesis (HSD3B2) [Prof Morel, Lyon].

Results

Of 237 patients in the study: 119 had 46, XX DSD (due to congenital adrenal hyperplasia in 92), 102 had 46,XY DSD and 16 had sex-chromosome DSD. Aetiology among the patients with 46,XY DSD was: disorder of androgen action (52), defective androgen synthesis (7), varying degrees of gonadal dysgenesis (31), PMDS (2), ovo-testicular DSD (1) and syndromic DSD (9).

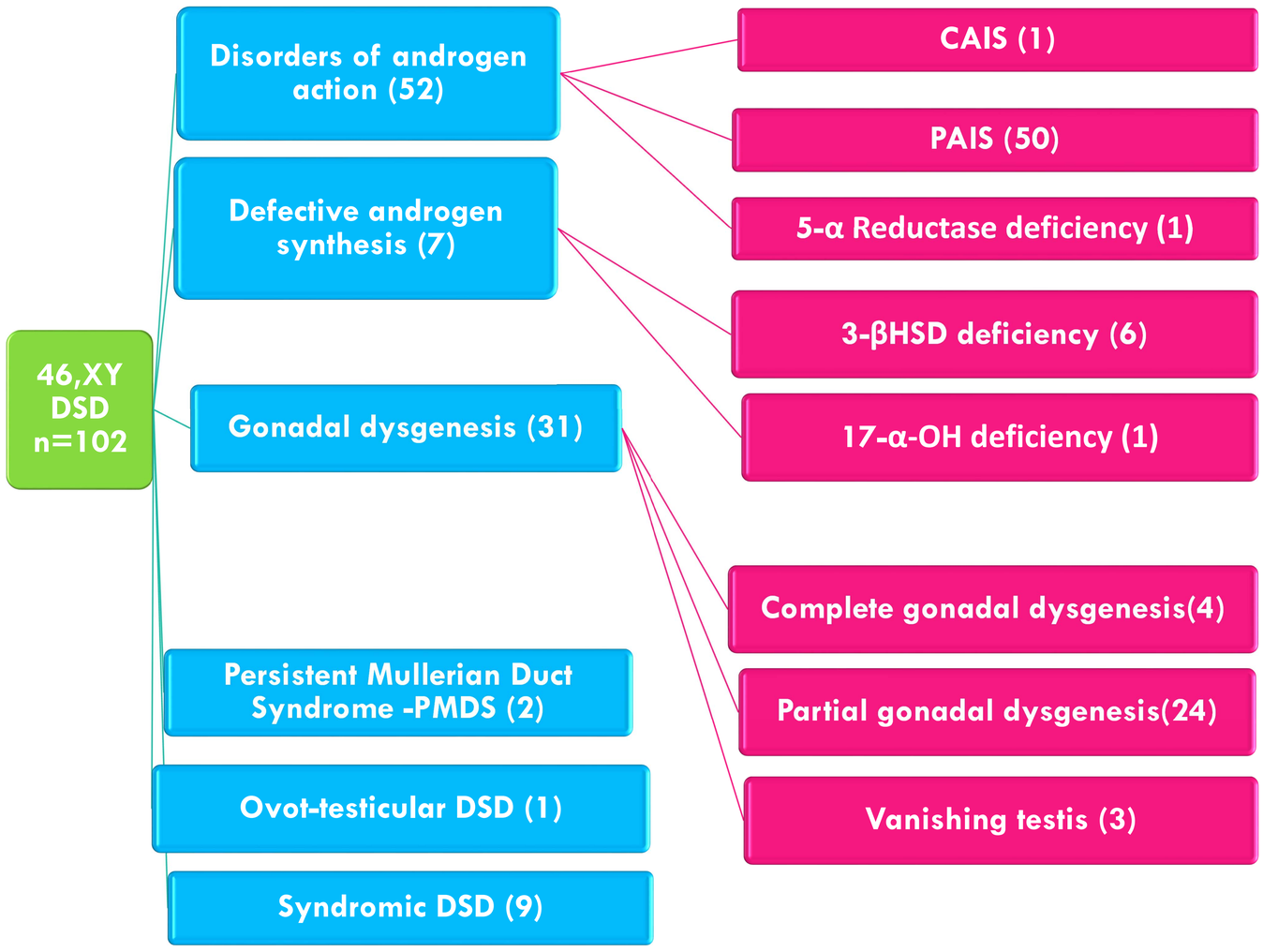

Fig1: Aetiologies of 46,XY DSD

Table 1: Mutational analysis in patients with 46,XY DSD

Gene		Patients
SRD5A2	Homozygous **mutation** c.678_684delCGGAGCT(pGly225Glyfs)*	1 patient
	Polymorphism: Variant c.265G>C heterozygous (p.Val89Leu)	8 patients
Androgen Receptor	**Mosaic mutation** of the AR gene	1 patient
NR5A1	Heterozygous **mutation** c.370delC (P124IfsX171)*	2 patients
	Heterozygous **mutation** c.938G>A(p.Arg313His)	2 patients
	Polymorphism: Variant c.437G>C Heterozygous (p.Gly146Ala)	4 patients
MAMLD1	Heterozygous substitution* c.1868G>A//p.Arg623His(rs145175147)	1 patient
HSD3B2	Homozygous mutation P222Q	3 patients

** New mutation*

Conclusions

Disorders of androgen action were the most frequent cause of 46,XY DSD in this large series, but a mutation of the AR gene itself was rarely found. However, pV89L polymorphism in the SRD5A2 gene is not rare in our patient population. This finding is in keeping with the hypothesis that functional polymorphisms may play an influential role in complex conditions such as DSD, with several factors contributing to the defect. Functional studies are required in order to further explore this area.

Mutational analysis revealed two different mutations in two pairs of siblings in the *NR5A1* gene, one new mutation in the *SRD5A2 gene*, one mutation in the *AR* gene and one new mutation in *MAMLD1*. The p222Q mutation was found in 3 patients with 3 BHSD deficiency. Furthermore, V89L polymorphism in the *SRD5A2* gene was found in 8 patients with androgen resistance, and the p.Gly146Ala polymorphism in the *NR5A1* gene was found in 4 patients. Genetic analysis was negative and cause of DSD unknown in 61/83 patients (73,4%).

55ESPE 401--P2

Gonads & DSD

asmahane ladjouze

DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS

PosterSessionOnline.com