The Evaluation of *AR* and *SRD5A2* Gene Mutations in 87 Patients with 46, XY DSD Children in Turkey

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Nese AKCAN[1] , Güven TOKSOY[3], Z. Oya UYGUNER[3], Nurcin SAKA[2], Umut ALTUNOĞLU[3], Zehra YAVAŞ ABALI[2] Mikayir GENENS[2], Sukran POYRAZOGLU[2], Firdevs BAS[2], Rüveyde BUNDAK[2], Hulya KAYSERILI[3], Feyza DARENDELILER[2]

[1]Near East University, Faculty of Medicine, Department of Paediatrics, Paediatric Endocrinology, Nicosia , Cyprus
[2]Istanbul University, Istanbul Faculty of Medicine, Department of Pediatrics, Pediatric Endocrinology
[3] Istanbul University, Istanbul Faculty of Medicine, Department of Medical Genetics, Istanbul, Turkey

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Background: AIS (Androgen insensivity syndrome) or 5α-reductase deficiency present indistinguishable phenotypes that necessitate the molecular analyses for the definitive diagnosis in prepubertal period .

Objective and hypotheses: Clinical, hormonal and genetic investigation of 46, XY DSD patients who were considered as AIS or 5α-RD and to understand the causes underlining the phenotype for suitable follow up, prognosis and management

Method: Ninety patients diagnosed as AIS or 5α-RD according to clinical and hormonal evaluations, were investigated. Basal LH, FSH ,T, dihydrotestosterone (DHT) levels were determined. Short hCG test was done and T/DHT ratios were calculated. *SRD5A2* mutations were analyzed in cases with T/DHT ratio > 20, whereas *AR* mutations were investigated when the ratio was below 20. Sanger DNA sequencing was used for molecular analysis.

Results: The mean age of cases at presentation was 1.9 years (3.5). At admission, 43 patients were at minipuberty (0-6 months), 41 were in prepubertal period, and 5 were in pubertal stage. Parental consanguinity was present in 5/9 patients with SRD5A2 mutations (55.5%), 1/12 (13.3%) in AR(+) patients, 1/12 (8%) in patients with homozygous polymophisms at 5α-reductase genes and 23/57 (40.3%) in mutation(–) patients. The main complaints at presentation in DSD patients were ambiguous genitalia 80% (n=72). Mutations that can lead to disease were detected in 21 (24.1%) patients out of 90 patients (n= 12 for *AR*, n=9 for *SRD5A2*). Eight of the patients were found to have homozygous and one was found to have compound heterozygous mutations in *SRD5A2* gene. 13 of the patients had homozygous functional polymorphism in *SRD5A2* that was previously reported to reduce the gene expression by 30 %. One novel *SRD5A2* mutation in homozygous form were detected in one patient (c.269A>C; p.H90P). Furthermore, three novel mutations were detected in three patients with *AR* mutations (c.330G>C; p.Leu110=, c.2585delAGCTCCTG; p.K862Rfs*16, c.2084C>T; p.695S).Three patients were found to have Klinefelter Syndrome (n=1 with *SRD5A2* mutation, n=1 with *AR* mutation, n=1 undetermined genetic cause). One patient had 47, XYY karyotype with *AR* mutation. Except two, all the other cases with *AR* mutations had T/DHT ratio under 20. This ratio was below 20 in three of the *SRD5A2* cases. The total of 11 patient raised as female (5 with *AR* mutation, 4 with *SRD5A2* mutation, 2 undiagnosed) and 2 patients were first raised as females than after the diagnosis of 5α-reductase deficiency, their identities were changed.

Table 1. Hormonal and Molecular Results of Patient with ARK mutation

Patient	Age at presentation/ Moleculer diagnosis	At presentation			Hormonal Results					Genetic Analysis			Parental consanguinity	Sex of Rearing
		Pubertal Stage (Tanner Stage)	Testes Volumes (ml)	Quigley Scale	Basal LH mIU/ml	Basal FSH mIU/ml	Induced T(ng/ml)	Induced DHT (ng/ml)	T/DHT	Karyotype	AR gene Mutation	Described/ Novel		
1(AKF)	0.1 / 3.0	mini-puberty	1/1	3	7.0	2.0	2.9	0.5	6.3	46, XY	p.L110.L	*Novel*	No	Male
2(AAA)	0.01 / 7.7	mini-puberty	2/1	4	4.3	1.2	2.4	0.5	4.6	46, XY9qh+	p.R608Q	Described	No	Male
3(BS)	3.3 / 10	1	3/3	6	0.7	1.5	9.0	2.9	3.0	47, XYY	p.F828V	Described	No	Female
4(BB)	0.02 / 10.5	mini-puberty	1/1	3	4.3	4.1	2.0	0.4	5.6	46, XY	p.P392S	Described	No	Male
5(CK)*	1.3 / 6.0	1	orchiectomy	6	0.3	0.9	6.0	ND	ND	46, XY	p.P892L *	Described*	No	Female
6(DK)*	0.2 / 4.8	mini-puberty	0.5/nonpalpable	5	0.3	0.4	1.6	0.3	6.4	47, XXY	p.P892L*	Described*	No	Male
7(EK)	1.2 / 5.4	1	1/1	6	2.7	1.7	8.0	497	0.02	46, XY9qh+	p.R841S	Described	Yes	Female
8(HK)	/22.3	ND	ND	ND	ND	ND	ND	ND	ND	ND	p.P286G / p.L862fx	*Novel*	ND	Female
9(MAA)	1.0 / 1.6	1	2/2	3	0.2	0.7	3.0	0.04	*74.4*	46, XY	p.P392S	Described	No	Male
10(MFS)	0.4 / 3.6	mini-puberty	1/1	3	4.8	1.2	6.3	1.5	4.3	46, XY	p.P392S	Described	No	Male
11(NNS)	7.2 / 13.0	1	orchiectomy	6	25.0	8.7	8.5	0.07	*115.0*	46, XY	p.V890M	Described	No	Female
12(SK)	11.0 / 11.6	3	10/nonpalpable	7	2.4	2.0	4.3	0.5	9.5	46, XY	p.P695L	*Novel*	No	Male
Mean SD	2.3 3.6 / 7.0 3.8				5.3 6.9	2.2 2.4	4.9 2.6		22.9 39.1					

*Siblings
ND: Non determined

Table 2. Hormonal and Molecular Results of Patient with SRD5A2 mutation

Patient	Age at presentation / Moleculer diagnosis	At presentation			Hormonal Results					Genetic Analysis				Parental consanguinity	Sex of Rearing
		Pubertal Stage (Tanner Stage)	Testes Volumes (ml)	Quigley Scale	Basal LH mIU/ml	Basal FSH mIU/ml	Induced T(ng/ml)	Induced DHT (ng/ml)	T/DHT	Karyotype	SRD5A2 Gene Mutation Allel 1 / Allel 2		Described/ Novel		
1(AK)	ND/39.6	1	2/2	4	10.7	22.7	2.6	0.01	260	46,XY	p.P252S	p.P252S	Described	ND	Male
2(BD)	7.5/13.3	1	orchiectomy	6	ND	ND	1.1	0.05	23.2	47,XXY	p.G196S	p.G196S	Described	No	Female
3(DA)	0.02/4.4	mini-puberty	1/1	6	3.5	1.1	7.8	0.2	37.4	46,XY	p.R246W	p.R246W	Described	Yes	Male
4(EK)	1.3/1.5	1	3/2	6	0.9	1.6	2.0	0.05	37.9	46,XY	p.L55Q	p.H90P	*Novel*	No	Male (after diagnosis)
5(KB)*	0.9/1.8	1	1/1	3	0.08	0.6	2.7	0.03	90.1	46,XY	p.P151fx*	p.P151fx*	Described	Yes	Male
6(NE)	14.9/20.9	3	10/10	5	5.9	7.2	5.4	1.5	*3.4*	46,XY	p.A65P	p.A65P	Described	Yes	Female
7(NB)*	4.8/14.5	1	1/1	6	0.1	0.2	0.8	0.06	*14.5*	46,XY	p.P151fx*	p.P151fx*	Described	No	Female
8(ZA)	16.5/16.7	3	10/10	3	12.2	17.5	9.2	0.1	74.7	46,XY	p.A65P	p.A65P	Described	Yes	Male (after puberty and then diagnosis)
9(AS)	14.4/33.3	2	4/4	5	2.2	5.2	7.5	0.4	*17.4*	46,XY	p.G156Gfx	p.G156Gfx	Described	Yes	Female (consider as male after puberty)
Mean ±SD	7.5±6.9 / 16.2±13.4	3			3.6±4.3	4.8±6.1	3.6±3.2	0.1±0.1	60.9±76.4						

*From the same family
ND: Non determined

CONCLUSION

Novel *SRD5A2* and *AR* mutations were identified in our study. T/DHT ratio in diagnosis of AIS and 5α-RD is an important hormonal criterion, but in some cases, T /DHT ratio may lead to diagnostic confusion. Molecular diagnosis is important for the robust diagnosis of 46,XY DSD patients correctly.

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