Mutational analysis of *SRD5A2 and AR* genes in Indian children with 46 XY disorders of sex development

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Aim

- To study the mutation spectrum in SRD5A2 and AR genes among Indian children with 46 XY disorders of sex development (DSD).

Subjects and Methods

- This work is part of an ongoing study at Department of Pediatrics, AIIMS, Delhi, approved by the ethics committee of the Institute.

Children with 46 XY DSD in whom endocrine investigations were suggestive of either 5α reductase deficiency or androgen insensitivity syndrome were enrolled after obtaining voluntary informed consent from the parents, and assent from children older than 12 years.

Bidirectional sequencing was undertaken for all 5 exons of steroid 5-alpha reductase 2 (*SRD5A2*) gene in 66 children.

Sequencing for all 8 exons of androgen receptor (*AR*) gene was done in the 42 children without mutation in SRD5A2 gene

Sequence analysis was performed using chromas Pro software

Genotype–Phenotype correlation was studied

Results

- ***SRD5A2* gene**
  - We identified mutations in 24 children (36.4%), the commonest being homozygous missense mutation p.R246Q in exon 5 (in 14 children).
  - There was no genotype-phenotype correlation. For example, of the14 children with mutation p.R246Q, 4 were reared as female and had bilaterally undescended testes, whereas some others had normally descended testes. External masculinization score (EMS) ranged from 2 to 8.5, and T:DHT ratio from 26 to 60.
- ***AR* gene**
  - Mutations were noted in 8 children (22.2%). All were hemizygous, as AR is located on the X chromosome.
  - Two were novel mutations not reported in HGMD, ensembl and 1000 genome data bases

Table 1. Summary of clinical and endocrine parameters of children with mutations

Parameter	SRD5A2[a]	SRD5A2			AR[b]	P value (a vs. b)
		Homozygous (N=19)	Compound heterozygous (N=4)	Heterozygous (N=1)	Hemizygous (N=8)	
Age (years)	5.6 (0.5 to 20)	5.5 (0.5 –18)	8 (3.6–20)	1.6	3 (1.4 – 10.5)	o.22
EMS (range 0-12)	5 (2–9)	6 (2–9)	3 (2–6)	3	4 (0 – 8)	0.53
LH (mIU/ml)	0.2 (0–17.82)	0.14 (0.01–4.9)	0.13 (0.1-17.8)	2.68	0.25 (0.06-7.9)	0.18
FSH (mIU/ml)	1.0 (0.1 – 28.7)	0.95 (0.09 – 3.5)	1.09 (0.2 – 28.8)	3.5	3.4 (0.8-51.4)	0.06
Basal Testosterone (ng/dl)	4.0 (0–846)	2.9 (0 – 149)	10.3 (4– 846)	264	3.5 (1.44 – 25)	0.97
HCG stimulated Testosterone (ng/dl)	398 (3-1388)	354 (71 –974)	900 (142-1388)	971	519 (200 – 758)	0.96
T:DHT ratio	27.6 (18.9-68.8)	26.5 (22.3–68.8)	30 (18.9–42)	32.5	35.5 (25.5-59)	0.67
Gender of rearing	5 F, 19 M				3 F, 5 M	0.51

EMS = External masculinization score, HCG = Human chorionic gonadotropin, T: DHT= testosterone: Dihydrotestosterone

Conclusions

- Mutations were identified in nearly half of the patients (32 of 66) with suspected 5α reductase deficiency or androgen insensitivity syndrome.
- p.R246Q in exon 5 was a hotspot for mutations in *SRD5A2* in Indian patients.
- Clinical and endocrine parameters were similar in those with mutations in either *SRD5A2* or *AR* gene, indicating that genetic analysis is important for correct diagnosis.

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