Molecular analysis of *AR*, *SRD5A2*, *NR5A1* and *HSD17B3* genes in a Brazilian 46,XY DSD cohort

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Topic: Late Breaking category

Introduction and objectives

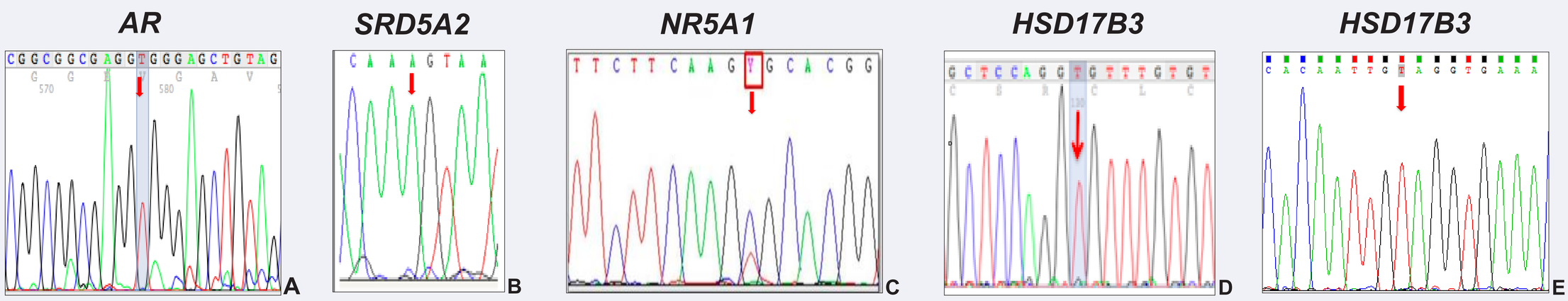
Disorders of Sex Development (DSD) comprise several phenotypes due to dysfunction in genes involved in human sexual determination and differentiation. The most frequent aetiologies among 46,XY DSD are androgen insensitivity syndrome and 5-alpha-reductase type 2 deficiency due mutations in *AR* and *SRD5A2* genes, respectively. The purpose of this study was to investigate mutations in *AR* and *SRD5A2* genes in 21 paediatric patients classified as 46,XY DSD. For cases without mutation in these genes, complementary analysis of *NR5A1* or *HSD17B3* genes was performed, according to clinical and hormonal characteristics.

Methods

Genomic DNA was obtained from blood samples. Molecular alterations were investigated by sequencing exons and exon-intron junctions. Each fragment was amplified by polymerase chain reaction and used for direct sequencing. The sequences obtained were analysed and compared with the reference sequence for each gene.

Results

Six alterations were identified: p.Ala475Val and p.Leu57Gln in *AR*; p.Gly183Ser in *SRD5A2*; p.Arg39Cys in *NR5A1*; and p.Ala203Val and p.Gly262Val in *HSD17B3*.



GCG>GTG
p.Ala475Val

GGT>AGT
p.Gly183Ser

CGC>TGC
p.Arg39Cys

GCG>GTG
p.Ala203Val

GGA>GTA
p.Gly262Val

Parts of the eletropherograms obtained for *AR*, *NR5A1* and *HSD17B3* sequencing: In A: GCG>GTG *AR* nucleotide change within exon 1; B: GGT>AGT *SRD5A2* nucleotide change within exon 3; C: CGC>TGC *NR5A1* nucleotide change within exon 3; D and E: GCG>GTG nucleotide change within exon 9 and GGA>GTA within exon 10, both in *HSD17B3* gene.

The p.Leu57Gln alteration found in exon 1 of *AR* remain in analysis for genotype X phenotype correlation.

Conclusion

Individuals with 46,XY DSD show significant overlap of clinical and hormonal features, which make it difficult to reach diagnosis, to indicate treatment and to perform genetic counselling. In the casuistic here analysed, six patients revealed sequence variations in *AR, SRD5A2, NR5A1* and *HSD17B3*. However, 15 patients did not show any abnormality indicating that other genes may be involved in the aetiology. The p.Gly262Val alteration identified in *HSD17B3* is firstly described here. Although this finding is relevant to diagnostic elucidation, investigation of *in vitro* functional effects of novel mutation is crucial.

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