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Abstract Topic:- Molecular and cytogenetic diagnostics

Abstract Title:- Identification of a rare variant in SRD5A2 gene in siblings with 46,XY Disorder of Sex Development

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Aims:-To investigate the cause of ambiguous genitalia and hormonal imbalance in siblings with apparently normal parents.

Methods:- The biochemical, cytogenetic and molecular testing profiles were studied. The hormonal assays were performed to ascertain the levels of serum testosterone and dihydrotestosterone. The Karyotyping (G-T-G banding technique), Molecular Cytogenetics (FISH) and Whole exome sequencing (WES) by Next generation sequencing (NGS) were performed to understand the genetic insult at the gene level.

Results:- The Testosterone/Dihydrotestosterone ratio in the siblings was 45.4 and 43.2, respectively (biological reference range <10). Chromosomal analysis revealed a 46,XY karyotype and FISH confirmed the presence of SRY gene on the Y chromosome in both siblings. The WES by NGS detected a pathogenic homozygous variant (c.737G>A;p.Arg246Gln) in SRD5A2 gene, and Sanger sequencing confirmed the heterozygous carrier state in the parents.

Conclusions:- The 3-oxo-5-alpha-steroid 4-dehydrogenase 2 enzyme deficiency leads to ambiguous external genitalia with other associated variable phenotype(s). The challenging aspect of managing a patient with DSD diagnosis presented with ambiguous genitalia is the assignment of an appropriate gender. Accurate diagnosis and psychological gender reaffirmation are effective management strategies in managing a case of 46,XY DSD. The present case study emphasis the role of cytogenetics and molecular genetics in individuals with ambiguous genitalia.

Keywords:- 46,XY DSD, Steroid 5α-Reductase type 2 deficiency (SRD5A2), Ambiguous genitalia, Karyotyping, Whole exome sequencing