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Molecular Defects Underlying Genital Ambiguity in Egyptian Patients: A Systematic Review

Authors : Y. Z. Gad

Abstract : Disorders of Sex Development (DSD) are defined as congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical. The DSD are relatively prevalent in Egypt. In spite of that, the relative rarity of the individual disease types or their molecular pathologies frequently resulted in reporting on single or few cases. This augmented the challenging nature of phenotype-genotype correlation in this disease group and its utilization in the management of such medical emergency. Through critical assessment of the published DSD reports, the current review aims at analyzing the clinical characteristics of the various DSD forms in relation to the underlying molecular pathologies. A systematic literature search was done in Pubmed, using relevant keywords (Egypt versus DSD, genital ambiguity or ambiguous genitalia, the old terms of 'intersex, hermaphroditism and pseudohermaphroditism', and a list of the DSD entities and their related genes). The search yielded 24 reports of molecular data in Egyptian patients presenting with ambiguous genitalia. However, only 21 publications fulfilled the criteria of inclusion of detailed clinical descriptions and definitive molecular diagnoses of individual patients. Curation of the data yielded a total of 53 cases that were ascertained from 40 families. Fifty-one patients present with ambiguous genitalia only while 2 had multiple congenital anomalies. Parental consanguinity was noted in 60% of cases. Sex of rearing at initial presentation was female in 75% and 60% in 46,XY and 46,XX DSD cases, respectively. The external genital phenotype in 2/3 of the 46,XY DSD cases showed moderate undermasculinization [Quigley scores 3 & 4] and 1/3 had severe presentations [scores 5 & 6]. For 46,XX subjects, 1 had severe virilization of the external genitalia while 8 had moderate phenotype. Hormonal data were inconclusive or contradictory to final diagnosis in a forth of cases. Collectively, 31 families [31/40, 77.5%] with 46,XY DSD had molecular defects in the genes, 5 alpha reductase 2 (SRD5A2) [12/31], 17 beta-hydroxysteroid dehydrogenase 3 [8/31], androgen receptor [7/31], Steroidogenic factor 1 [2/31], luteinizing hormone receptor [1/31], and fibroblast growth factor receptor 1 [1/31]. In a multiethnic study, 9 families afflicted with 46,XX DSD due to 11 beta hydroxylase (CYP11B1) deficiency were documented. Two recurrent mutations, G34R and N160D, in SRD5A2 were present, respectively, in 42 and 17% of cases. Similarly, 4 recurrent mutations resulted in 89% of the CYP11B1 presentations. In conclusion, this analysis highlights the importance of autosomal recessive inheritance and inbreeding among DSD presentations, the importance of founder effect in at least 2 disorders, the difficulties in relating the genotype with the indeterminate genital phenotype, the under-reporting of some DSD subtypes, and the notion that the reported mutational profiles among Egyptian DSD cases are relatively different from those reported in other ethnic groups.

Keywords : disorders of sex development, genital ambiguity, mutation, molecular diagnosis, Egypt
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