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Temporal and Social trends towards sex assignment and gender change in the 5α-reductase type 2 deficiency

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5α-reductase type 2 (5αR2) deficiency is an autosomal recessive inherited condition affecting 46,XY individuals resulting from the inability to convert testosterone into dihydrotestosterone. Affected individuals present a range of external genitalia undervirilization at birth and pronounced masculinization at puberty. Unlike most other 46,XY DSD, the frequency of gender change among 5αR2 deficiency is high.

Objective: to analyze the 451 individuals carrying pathogenic 5αR2 variants in the SRD5A2 gene in both alleles (in

homozygous or compound heterozygous state) in the literature (Pubmed, EMBASE, Medline) and websites (ensemble, HGMD, ClinVar) regarding sex assignment, external genitalia virilization (1-5 Sinnecker score), and gender change accordingly country income

Methods: A total of 357 cases out of 451 had clinical information. All patients included were divided between those born before or after 2006 (the DSD consensus year). Country income was based on the 2018 World Bank classification, classifying income into four categories: low, lower-middle, upper-middle, and high (www.worldbank.org). Categorical variables were analyzed using the Chi-square test followed by the Cramer's V. Continuous variables were analyzed either by Student t-test or ANOVA one way. A binary logistic regression was built using sex assignment and gender change as categorical dependent variables. A $p<.05$ was considered significant.

Results: When we divided the individuals into those diagnosed after and before 2006, the percentage of female sex assignments dropped from 72% to 56% ($p<.0001$), followed by an odds ratio reduction (from 2.52 to 1.65) for female sex assignment. Country income did not impact sex assignment ($p=.21$). However, most cases (86%) were reported from countries with high and upper-middle economies. The absence of reports from low-income countries may be due to several reasons, such as barriers to molecular diagnosis, scientific access, and specialized medical assistance. Most cases were assigned as female (69%). The overall rate of gender change was 25% (89 out 357). All but one changed their gender from female to male. The rate of gender change was significantly different across all countries ($V=0.46$; $p<.001$), but it ranged from 16% to 70%, and gender change was lower among those diagnosed after 2006 ($p=.01$). The association between less external genitalia virilization and female sex assignment was significant ($p<.001$). On the other hand, the virilization score was similar between those who kept or changed gender ($p=.37$). Neither the type of SRD5A2 variant (missense, nonsense, indel) nor zygosity (homo/hetero) impacted sex assignment or gender change.

Conclusion: An apparent temporal trend indicates an increased likelihood of affected 5αR2 deficiency individuals being raised as boys, providing a gender change drop. The external virilization degree influenced sex assignment, but it does not affect gender change. There is no correlation between either both sex assignment and gender development with 5αR2 genetics.

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