Genotype-Phenotype Correlation of SRD5A2 Gene Variants in 130 Chinese Children: Based on a Chinese High-Homogeneity Single-Center Cohort

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**Objective** Patients with steroid 5α-reductase deficiency (5α-RD) caused by SRD5A2 variants present variable genotypes and phenotypes. The phenotypic variability has been linked to differences in SRD5A2 gene abnormalities. However, the genotype-phenotype correlations remain unclear.

**Patients** Registry study of a high-homogeneity single-center cohort of 130 46, XY Han Chinese children with SRD5A2 abnormalities diagnosed at the Beijing Children’s Hospital in 2007-2019.

**Method** We analyzed the correlation between phenotype and genotype by comparing external masculinization score (EMS), urethral meatus and gonad position, and penile length-standard deviation score (PL-SDS).

**Results** Of 130 included patients, 113 had hypospadias and 17 had normal urethral meatus position, and the proportion of isolated micropenis was higher than in other countries. The testosterone/dihydrotestosterone ratio (T/DHT) was not significantly associated with phenotypic severity (P=0.539~0.989). The p.R227Q was the most prevalent variants (39.62%), followed by p.Q6* (16.92%), p.R246Q (13.46%), and p.G203S (10.38%). Compared to biallelic missense mutations, biallelic nonsense mutations were associated with lower EMS and urethral meatus scores (P=0.009 and 0.024, respectively). Patients homozygous for p.R227Q exhibited mild and variable phenotypes while those with homozgyous p.Q6*, p.R246Q, and p.G203S showed consistently severe phenotypes. When those mutations were compound heterozygotes for p.227Q, the genotypes were variable and milder. The high-frequency of p.227Q may contribute to the higher proportion of patients with isolated micropenis in our Chinese cohort.

**Conclusions** T/DHT does not predict phenotypic severity. Genotype is consistently severe when variants responsible for complete loss of enzyme activity while phenotype is milder and variable when the enzyme has some residual activity.

**Figure 1. The SRD5A2 mutational spectrum in 130 Chinese children with 5α-RD**
A: Identified SRD5A2 variants and their frequencies. Red font indicates unreported variants, black font reports variants, and red star indicates common variants.
B: Distribution of variants throughout the SRD5A2 gene region.

**Abbreviations:** E, Exon; I, Intron

**Figure 2. Comparison of phenotypes across SRD5A2 genotypes**
A-C: EMS (A), urethral meatus position (B), and PL-SDS (C) in patients with p.R227Q (n=88), p.Q6* (n=41), p.R246Q (n=33), and p.G203S (n=22). P values from left to right: (A), P=0.001, P=0.024; (B), P=0.001.
D-F: EMS (D), urethral meatus position (E), and PL-SDS (F) in patients with different homozgyous SRD5A2 mutations (p.R227Q, n=15; p.Q6*, n=3; p.R246Q, n=2; and p.G203S, n=5). P values from left to right: (D), P=0.027, P=0.003; (E), P=0.045, P=0.006
G-I: EMS (G), urethral meatus position (H), and PL-SDS (I) in patients with vs. without p.R227Q within the subgroup carrying other high-frequency mutations (p.R227Q/p.Q6*, n=19; non-p.R227Q/p.Q6*, n=22; p.R227Q/p.R246Q, n=18; non-p.R227Q/p.R246Q, n=15; p.R227Q/p.G203S, n=8; and non-p.R227Q/p.G203S, n=14). P values from left to right: (G), P=0.001, P=0.001, P=0.001; (H), P=0.011, P=0.006, P=0.001

**Notes:** Data are mean±SD. Statistical tests: Kruskal-Wallis test followed by Dunn-Bonferroni test for EMS and urethral meatus position, one-way ANOVA test followed by Bonferroni's correction for PL-SDS. ***P<0.001, **P<0.01, *P≤0.05.

**Abbreviations:** hom, homozygous variants; het, compound heterozygous variants