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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 2 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%). Of the 31 SRD5A2 variants, including 10 previously unreported ones, p.R227Q was the most prevalent (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 homozygous 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.

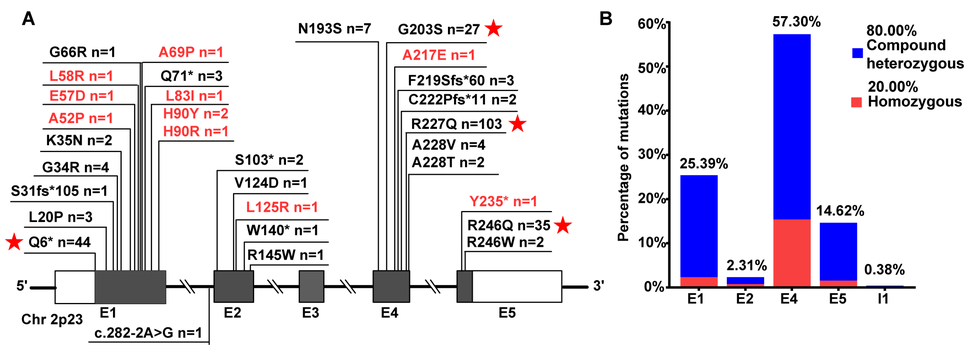

Figure 1. The *SRD5A2* mutational spectrum in 130 Chinese children with 5α-RD
A: Identified *SRD5A2* variants and their frequencies. Red font indicates unreported variants, black font reports variants, and red star indicates common variants.
B: Distribution of variants throughout the *SRD5A2* gene region.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

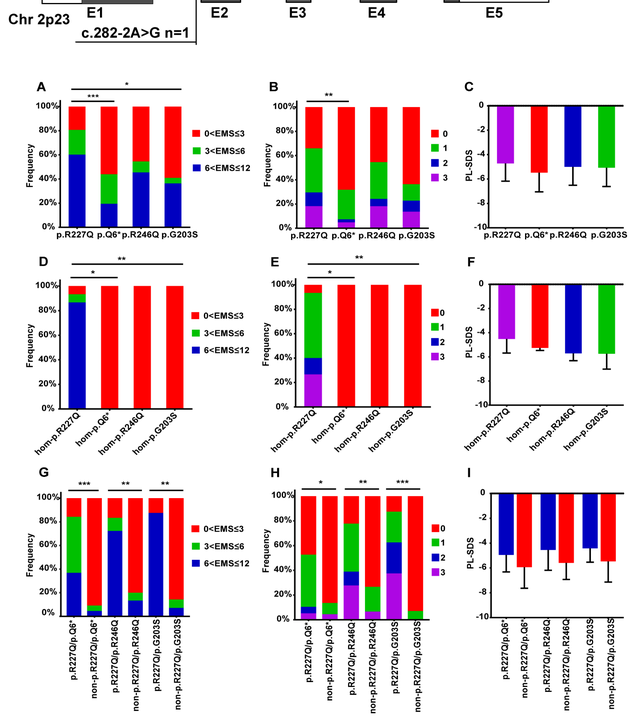

Figure 2. Comparison of phenotypes across *SRD5A2* genotypes
A-C: EMS (A), urethral meatus position (B), and PL-SDS (C) in patients with p.R227Q (n=88), p.Q6* (n=41), p.R246Q (n=33), and p.G203S (n=22). *P* values from left to right: (A), *P*<0.001, *P*=0.024; (B), *P*=0.001.
D-F: EMS (D), urethral meatus position (E), and PL-SDS (F) in patients with different homozygous *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. ***$P<0.001$, **$P<0.01$, *$P\leq0.05$.
Abbreviations: hom, homozygous variants; het, compound heterozygous variants