Idiopathic Hypogonadotrophic Hypogonadism Caused by Inactivating Mutations in *SRA1*

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Objective: What initiates pubertal process in humans and other mammals has remained elusive. We hypothesized that gene(s) taking roles in triggering human puberty may be identified by studying a cohort of idiopathic hypogonadotropic hypogonadism (IHH) cases via autozygosity mapping coupled with whole exome sequencing.

Case: Our studies revealed three independent families in which IHH/delayed puberty was associated with inactivating *SRA1* variants. *SRA1* was the first gene to be identified to function through its protein as well as noncoding functional ribonucleic acid products. These products act as co-regulators of nuclear receptors including sex steroid receptors as well as SF-1 and LRH-1, the master regulators of steroidogenesis. Functional studies with a mutant *SRA1* construct showed a reduced co-activation of ligand-dependent activity of the estrogen receptor alpha, as assessed by luciferase reporter assay in HeLa cells.

Conclusion: Our findings strongly suggest that *SRA1* gene function is required for initiation of puberty in humans. Furthermore, *SRA1* with its alternative products and functionality may provide a potential explanation for versatility and complexity of puberty.

A Novel Missense Mutation in *HSD17B3* Gene in Two 46,XY Siblings with Female External Gelitalia

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Objective: Deficiency of 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3), which catalyzes the synthesis of testosterone from Δ4-androstenedione and is encoded by *HSD17B3*, is a rare cause of 46,XY disorders of sex development (DSD). Up to now, over 30 mutations in HSD17B3 have been reported. To report two siblings with a novel mutation in *HSD17B3* gene leading to 17β-HSD3 deficiency.

Case: A 15-year-old female patient was referred because of primary amenorrhea and signs of virilization. The chromosome analysis showed a 46,XY karyotype. Hormonal evaluation revealed a high Δ4-androstenedione level with a low serum testosterone/androstenedione (T/A) ratio. A homozygous missense mutation in *HSD17B3* resulting in a premature stop codon (p.Y287) was found. Gonadectomy was performed after the molecular diagnosis and estrogen replacement therapy was initiated. Screening of relevant mutation was performed in remaining family members. The father, mother, and a sibling were heterozygous, while a 12-year-old sibling who was raised as a female was homozygous for the same mutation. Her karyotype was 46,XY as well. Hormonal evaluation revealed a high Δ4-androstenedione level with a low serum T/A ratio. Gonadectomy was performed and estrogen replacement therapy was initiated consequently.

Conclusion: We emphasize that 17β-HSD3 deficiency should be considered in virilized female patients at puberty if the T/A ratio is less than 0.8 and the molecular analysis should be performed in both index case and the family members for precise diagnosis and genetic counselling.