Discordance in the Dependence on Kisspeptin Signaling in Mini Puberty vs Adolescent Puberty: Human Genetic Evidence

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Abstract

Context: Hypothalamic kisspeptin signaling plays a critical role in the initiation and maintenance of reproductive function. Biallelic mutations in the coding sequence of KISS1R (GPR54) have been identified in patients with idiopathic hypogonadotropic hypogonadism, but it is unknown whether biallelic variants can also be associated with related reproductive disorders.

Case Description: A missense homozygous variant (c.890> T p. R297L) in KISS1R was identified in a child who presented with microphallus and bilateral cryptorchidism. This variant has been reported to reduce, but not abolish, postreceptor signaling in vitro. Biochemical evaluation during the neonatal period revealed low testosterone levels. By 11 years and 8 months, the boy began demonstrating increases in testicular volume. By 17 years and 3 months, his testicular volume was 20 mL; his penile length was 7.3 cm; and he had adult levels of circulating gonadotropins and testosterone.

Conclusion: This case report associates biallelic loss-of-function mutations in KISS1R with normal timing of adolescent puberty. Because these coding sequence variants occurred in a patient with microphallus and cryptorchidism, they demonstrate different levels of dependence of the hypothalamic-pituitary-gonadal cascade on kisspeptin signaling at distinct times in the reproductive life span. The suppression of the hypothalamic-pituitary-gonadal cascade during early life but not adolescence suggests that the mini puberty of infancy depends more on kisspeptin-induced, gonadotropin-releasing hormone-induced luteinizing hormone secretion than does adolescent puberty.

Palabras clave

KeyWords Plus:PITUITARY-GONADAL AXIS; HYPOGONADOTROPIC HYPOGONADISM; INFANCY; MUTATION; KISS1R; GPR54

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