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A FAMILY WITH HYPOGONADOTROPIC HYPOGONADISM AND A NOVEL VARIANT OF FGFR1 GENE MUTATION

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INTRODUCTION
FGFR1 gene mutation is a known cause of gonadotropin deficiency such as Kallmann syndrome. We described two related young under-virilized males with a variant of FGFR1 gene mutation. Both were born in a non-consanguineous family. Both have normal senses of smell.

CASES

CASE 1
A 9-month-old male presented with ambiguous genitalia at birth. He had signs of under-virilization at birth including a micropenis with a stretched penile length of 1.7 cm, and bilateral undescended testes. He was planned for work-up but was lost to follow-up until the current presentation. He had a 46,XY karyotype with a positive SRY gene. Beta-hCG stimulation test revealed a poor testosterone rise. LHRH test did not show a response to GnRH. Genetic mutation analysis revealed the FGFR1 mutation variant at position c.1430.

CASE 2
His paternal uncle, a 13-year-6-month-old male was also referred to us for a micropenis. He had no dysmorphic features. He did not have any sign of pubertal development. He had a stretched penile length of 2.5 cm and bilateral prepubertal testicular volumes. He had a 46,XY karyotype and a positive SRY gene. He had low baseline levels of LH, FSH, and testosterone. Both beta-hCG and LHRH tests showed poor pituitary and gonadal responses. His MRI showed a normal pituitary gland and olfactory bulbs. He has the exact mutation variant at the FGFR1 gene as the index case.

CONCLUSION
Both of our patients shared common features of under-virilization and biochemical evidence of hypogonadotropic hypogonadism. Despite there being more than 200 missense mutations of the FGFR1 gene reported in "The Human Gene Mutation Database" and the "ClinVar" database, the genetic mutation variant that our patients shared was not registered in both databases and may suggest a novel mutation associated with hypogonadotropic hypogonadism. Identification of this genetic variant may assist in the proper counseling of the patients and their families.