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A novel rare case of normosmic congenital hypogonadotropic hypogonadism associating a GnRHR and a KISS1R variants

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**Case report:** We describe a 28 years old male patient born in IRAK, beeing referred to us because of suspicion of congenital hypogonadism. The patient was 1.86 m tall and 1.97 spam arm and he was no anosmic. He had a 2.5 cm micropenis, and a bilateral reduced testicular volume (3.6 and 3.9 ml). LH 1.7 U/l (2–10), FSH 3.1 U/l (1–8), testosterone 0.7 mmol/l, estradiol <12 ng/l, inhibine B 54 ng/l (105–439) Pituitary MRI was normal.

**Genetic studies:** A set of 16 causatives genes for IHH and KS were investigated by Next Generation Sequencing (KAL1, FGFR1, PROKR2, PROK2, CHD7, FGF8, KISS1, KISS1R, TAC3, TACR3, GNRHR, GNRH1, NELF, WDR11, HS6ST1, SEMA3A). We were able to identify two variants at the heterozygous state: one is a novel **KISS1R variant: c.389G>T, p.Cys130Phe**, that is predicted to be deleterious by *in silico* analysis (SIFT, Polyphen, Mutation Taster). This variant is localized in GPCR and rhodopsin-like protein domains, but it is difficult to predict the importance of the pathogenic impact without functional studies. The second one is a pathogenic variant described in several patients presenting GnRH deficiency and affect the gonadotrophin-releasing hormone receptor (**GNRHR: c.317A>G, p.Gln106Arg**).

**Discussion:** The kisspeptin receptor (KISS1R) is a G-protein–coupled receptor expressed in GnRH neurons and encoded by *KISS1R.* Relatively few inactivating *KISS1R* variants have been reported to date in patients with nCHH. Patients with KISSR and GnRHR mutations carry them in the biallelic state, in keeping with autosomal recessive transmission. Our findings expand the GnRHR and KISSR mutation spectrum and phenotype-genotype correlation in CHH.