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Normosmic hypogonadotropic hypogonadism associated with a novel TACR3 mutation

Hernan Valdes-Socin, Cécile Libioulle, Marie Christine Lebrethon, Vinciane Corman, François Guillaume Debray, Vinciane Dideberg & Albert Beckers

[Author affiliations](https://www.endocrine-abstracts.org/ea/0063/ea0063p312.htm#authorAffiliates)

Introduction: Neurokinin B (NKB) is a neurotransmitter, regulating GnRH. NKB activates its receptor TACR3. Recessive mutations of TACR3 are associated with a phenotype of normosmic hypogonadism.

Case report: A 17 years old man born in Turkey, present with pubertal delay. He is treated 3 years with testosterone and he is reevaluated without treatment. He is 1.79 m and 1.85 arm span, testicular volume: 3 and 4 ml. He has no olfactory troubles. Testosterone 1.87 nmol/L, Estradiol <17 ng/L, LH 2,3 UI/L, FSH 1,6 UI/L. Pituitary MRI is normal.

Genetic analysis: A set of 16 causatives genes for IHH and KS were investigated by Next Generation Sequencing. We were able to identify a novel heterozygous TACR3 variant (c.530C>A, p.(Thr177Lys)) that is predicted to be deleterious by *in silico* analysis (Polyphen, Mutation Taster, Mutation Assessor). This variant is located in the ‘GPCR, rhodopsin-like’ protein domain and lead to the replacement of Thr177 by a Lysine residue. Functional studies are needed to evaluate the deleterious impact on the NKR3 receptor.

Conclusions: We describe a novel TAC3R mutation associated with normosmic hypogonadotropic hypogonadism. The phenotype is intriguing, because a second pathogen mutation is expected but it was not found with our panel. Further gene investigations will be undertaken.