

BACKGROUND AND METHODS

- **Idiopathic hypogonadotropic hypogonadism (IHH)** is due to the failure of gonadotrofin releasing hormone (GnRH) secretion which impairs the physiological initiation of puberty
- About 30 to 50% of IHH is associated to **hereditary causes** and about 50 mutated genes have been identified
- We present three intra-familial cases of normosmic IHH (nIHH) related to a **new association of two heterozygotic TARC3 mutations**

CASE REPORT

- 16-year-old male (III-1)
- Referred due to **no pubertal development:**

- **Small** intrascrotal testes (2-3 ml)
- **Spair** pubic hair (P1-P2)
- **Small** phallus (4 cm)
- **Height:** 161,5 cm (Z-score -1,57) and **weight:** 61,9 kg (z-score 0,08)
- Bone age 12.5 years
- **Normal** body proportions
- **Normal** sense of smell, **no** renal or craniofacial abnormalities.

- **Two** of his three **sisters** also presented **complete hypogonadism** at 14 and 13 years old (III-3 and III-4), both had a **normal sense of smell**
- Onset of their mother's (II-1) menarche was at 15 years-old. Their father (II-2) had a normal pubertal development in adolescence

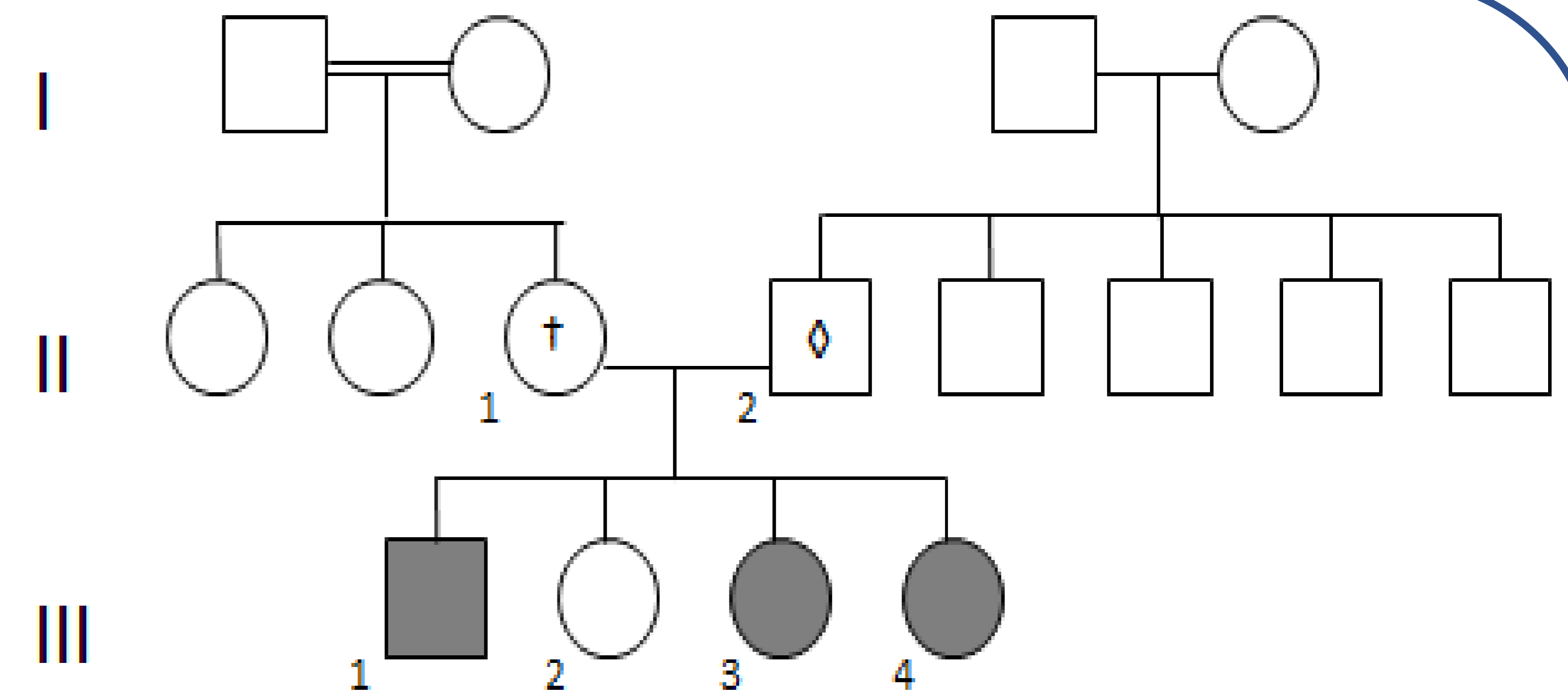


Figure 1. Family Pedigree

Solid symbols indicate affected subjects (III-1, III-3, III-4), open symbols indicate subjects with no mutations. The inside symbols ◇ and † indicate unaffected heterozygotes - ◇ - mutation c.824G>A (p.Trp275*) inherited from the subject II-2 and † mutation c.689G>A (p.Arg230His) from subject II-1.

Investigation

Subject	III-1	III-3	III-4
LH (mIU/ml)	0,2	<0,1	<0,09
FSH (mIU/ml)	0,6	0,7	0,29
Ratio FSH/LH	3	7	3,2
Estradiol (pg/ml)	ND	<10	<10
Testosterone (ng/mL)	0,14	0,15	ND
Prolactin (ng/ml)	3,42	4,3	ND
IGF-1 (ng/mL)	272	144	144
Bone age (years)	12,6	12,5	10
LH pulsatility	Apulsatile		

- **Low sex steroid and gonadotropin levels**
- **No evidence** of a mass lesion in the cerebral MRI
- **Normal** Karyotypes
- **Normal** function of the anterior pituitary, thyroid, and adrenal glands

Genetic testing in all subjects:

- Two heterozygous mutations on TACR3 gene:
 - c.824G>A (p.Trp275*) - from the father
 - c. 689G>A (p. Arg230His) - from the mother

The father's mutation was previously described as **pathogenic**, but the mother's mutation was classified as of **uncertain significance at date**

These findings support **nIHH diagnosis** and this family cluster supports the **evidence of the pathogenicity of the second variant**

Follow-up

- **Hormonal replacement** was started in **III-1 and III-3** with success (III-4 is awaiting)
- All of them maintain their follow-up at paediatric endocrinology outpatient clinic

CONCLUSION

Congenital IHH is a very rare genetic disorder that if undiagnosed or untreated may lead to infertility associated to complete or partial absence of GnRH. TAC3/TACR3 mutations have a critical importance on sexual maturation and are an important genetic cause of nIHH that should be particularly searched in patients with high serum FSH/LH ratio. The treatment of nIHH is based on sex steroids replacement, therefore promoting the pubertal development.

REFERENCES

1. Topaloglu AK. Update on the Genetics of Idiopathic Hypogonadotropic Hypogonadism. J Clin Res Pediatr Endocrinol 2017;9(Suppl 1):113-122. doi: 10.4274/jcrpe.2017.S010.
2. Topaloglu AK et al. TAC3 and TACR3 mutations in familial hypogonadotropic hypogonadism reveal a key role for Neurokinin B in the central control of reproduction. Nature Genetics 2009; 41;3: 354-358.
3. Topaloglu AK, Kotan LD. Genetics of Hypogonadotropic Hypogonadism. Endocr Dev. Basel, 2016;29:36-49. doi: 10.1159/000438841.

4. Shekhar S. Familial normosmic idiopathic hypogonadotropic hypogonadism: is there a phenotypic marker for each genetic mutation? Report of three cases and review of literature. BMJ Case Reports 2012. doi:10.1136/bcr-2012-007537.
5. Aoyama K et al. Molecular genetic and clinical delineation of 22 patients with congenital hypogonadotropic hypogonadism. J Pediatr Endocrinol Metab 2017;30:10.doi: https://doi.org/10.1515/jpem-2017-0035.
6. Francou B et al. Normosmic Congenital Hypogonadotropic Hypogonadism Due to TAC3/TACR3 Mutations: Phenotypes and Novel Mutations. PLoS ONE 2011;6:1-11.