Pubertal induction with hCG in a patient with Kallmann syndrome secondary to novel variant in *PROK2* gene

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Background

- Kallmann syndrome (KS) is caused by an impairment of olfactory and gonadotropin-releasing hormone (GnRH) neuron migration in utero resulting in anosmia and hypogonadotropic hypogonadism (HH).

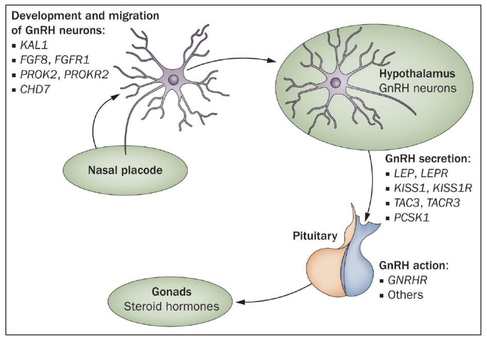

Figure 1. *The genetic basis of idiopathic hypogonadotropic hypogonadism. PROK2 helps regulate GnRH neuronal migration. (Bianco SD, Kaiser UB. Nat Rev Endocrinology, 2009)*

- Knockout mouse models of the *PROK2* gene have shown olfactory bulb hypoplasia, absent hypothalamic GnRH cells, and hypogonadism.
- *PROK2* mutations cause KS in humans through aberrant production of prokineticin-2, a chemoattractant protein needed for normal migration of neuronal progenitor cells.
- The standard of care for pubertal induction in children with KS is testosterone replacement therapy (TRT), but it does not induce testicular growth, spermatogenesis, or fertility.
- An emerging treatment approach utilizes human chorionic gonadotropin (hCG) to induce puberty with improved testicular growth and spermatogenesis compared with TRT.
- hCG is structurally similar to LH, thus inducing puberty.
- Precocious puberty has been reported in the literature due to hCG-secreting tumors.

Presentation & Work-Up

- 15 yo male presented with delayed puberty, micropenis, and hyposmia.
- Micropenis treated with testosterone injections as an infant.
- Prior evaluation showed ACTH, cortisol, thyroid profiles, growth factors, and CAH panel all within the reference ranges.
- Family hx of delayed puberty in patient's father (growth spurt at age 18, started shaving at age 19).
- Physical exam was notable for absent axillary hair, Tanner II pubic hair, stretched penile length 5.5 cm, testes volume 2.5 mL bilaterally.
- No synkinesia noted, but not specifically tested.
- 46,XY karyotype without Y chromosome microdeletion
- Bone age delayed by 2 years
- MRI brain normal
- Initial gonadotropin levels were all in the pre-pubertal range (see Table 1, below).

Genetic Testing Results & Treatment Regimen

- Genetic testing revealed a previously unreported, potentially damaging, sequence variant of the *PROK2* gene (c.215C>T), consistent with the diagnosis of Kallmann syndrome.
- To induce puberty, subcutaneous hCG injections (1000 IU three times per week) were initiated under the guidance of a urologist with expertise in male infertility and reproductive medicine.
- After 8 weeks, hCG injections were increased to 1500 IU every other day.

MOLECULAR GENETICS REPORT:
Hypogonadotropic Hypogonadism/Kallmann Syndrome
Sequencing Panel with CNV Detection

SUMMARY OF RESULTS **INDETERMINATE**

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variations, Predicted Effects, Zygosity	dbSNP ID Number	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
PROK2, NM_001126128.1	AD, 607002	c.215C>T, p.Thr72Ile, Heterozygous	rs765020287	0.023%, Latino	Damaging	UNCERTAIN

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive=AR, X-Linked=XL
Allele Frequency registered in a large population database (http://gnomad.broadinstitute.org/). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v2.0 (The "Other" population is excluded).
Missense Predictions via PolyPhen-2, SIFT, MutationTaster, and FATHMM (PMID: 26555599). Output summarized as Damaging, Conflicting, or Tolerated

Figure 2. *Prevention Genetics molecular genetics report showing the patient is heterozygous in the PROK2 gene for a sequence variant c.215C>T, which likely results in the amino acid substitution p.Thr72Ile. Nearby missense variants are known to cause HH and KS.*

	Baseline	After 8 Weeks of hCG*	After 6 Months of hCG
Total Testosterone (ng/dL)	<7	127	288
LH (mIU/mL)	1.44	--	1.4
FSH (mIU/mL)	2.34	--	1.3
Inhibin B (pg/mL)	19	49	49
Hemoglobin (g/dL)	12.5	--	14.3
Hematocrit (%)	36.3	--	41.6

***At this time point the hCG injection was increased to 1500 IU every other day.**

Table 1. *Response to hCG treatment from pre-pubertal baseline gonadotropin levels to pubertal levels within 6 months of therapy.*

Response to Treatment

- After 6 months of treatment, physical exam showed:
  - Growth acceleration
  - More mature behavior
  - Increased body hair
  - Tanner stage IV pubic hair
  - Penile growth
  - Testes volume 8 mL bilaterally
- The patient will continue on hCG therapy through the pubertal years.
- Once pubertal maturation is achieved, we will test for any recovery in pituitary function. If not, will proceed with semen cryopreservation and TRT/hCG therapy into adulthood (until achieving fertility goals).

Conclusions & Discussion

- Here we report a novel sequence variant in *PROK2,* which may be associated with Kallmann syndrome.
- Treating hypogonadotropic hypogonadism in patients with Kallmann syndrome poses significant challenges, especially with testosterone replacement therapy (TRT), the current standard of care.
- hCG therapy in this patient has resulted in successful pubertal induction as well as testicular growth. We are hopeful he will have an improved fertility outcome compared with TRT.
- Long-term studies are needed to determine potential benefits of hCG therapy on future fertility in young populations with HH.

Acknowledgements

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