GnRH-Dependent Precocious Puberty Associated with an *NR0B1* Mutation: First Patient without Adrenal Insufficiency.

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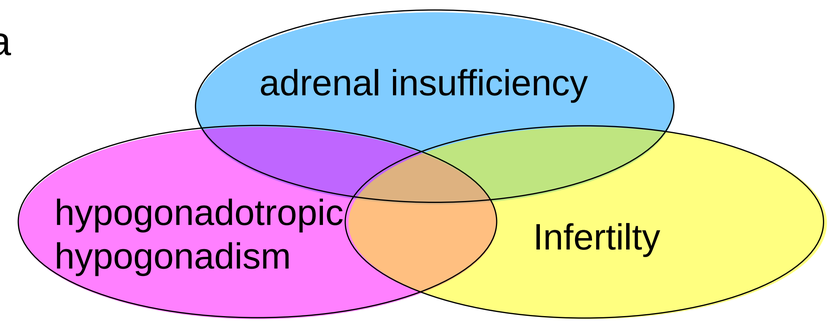
Background

Hemizygous *NR0B1* (*DAX1*) mutations usually lead to X-linked adrenal hypoplasia congenita (AHC), characterized by adrenal insufficiency during infancy or early childhood, hypogonadotropic hypogonadism and infertility at later ages.

Late-onset or latent adrenal insufficiency was reported in patients with p.Gln37*, p.Trp39*[1)] and some other *NR0B1* mutations.

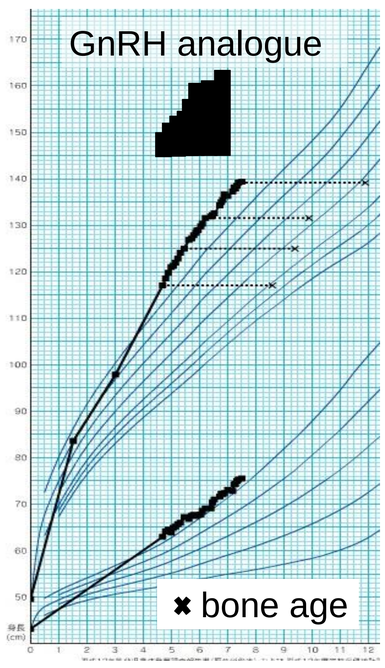
14 boys with *NR0B1* mutations were reported to develop early puberty in addition to adrenal insufficiency. Most of these patients showed elevated gonadotropin levels indicative GnRH-dependent Precocious puberty (PP). In addition, ACTH overproduction was reported to induce GnRH-independent PP by stimulating Leydig cell via human melanocortin 1 receptor [2)].



Typical phenotype of X-linked AHC

Clinical Presentation and Molecular Finding

Growth Curve and Treatment



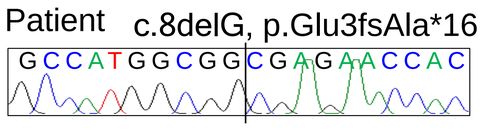
A 4-year-old boy presented with pubic hair (Tanner stage 2),testicular enlargement (6–8 ml), and advanced bone age (8 years and 6 months of age).

Blood examinations revealed increased testosterone levels and hyperresponses of gonadotropins to GnRH stimulation. **The patient was clinically diagnosed with idiopathic central PP. GnRH analogue treatment partially ameliorated the hormonal abnormalities, but did not improve the physical findings.** On his latest visit at 7 years and 6 months of age, the patient showed no clinical signs or laboratory data of adrenal insufficiency.

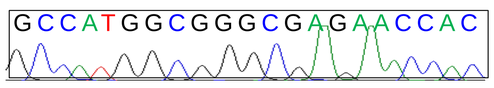
➡ Hormone values above the reference range are boldfaced.
[a]GnRH stimulation test (100 μg/m^2 bolus i.v.; blood sampling at 0, 30, 60, 90, and 120 minutes).
[b]Reference ranges of age-matched prepubertal boys.
☆ 177-497 for boys at 4 yr and 168-339 for boys at 7 yr.

Age at exam.	LH (IU/L)		FSH (IU/L)		Testosterone	ACTH	Cortisol	DHEAS
(yr)	Basal	peak[a]	basal	peak[a]	(nmol/L)	(pmol/L)	(nmol/L)	(nmol/L)
4.7	< 0.2	**12.7**	**3.5**	**11.5**	**4.9**	2.4	210	-
4.8	**0.8**	-	1.9	-	**6.4**	-	-	-
5.8	**0.9**	-	0.8	-	**3.4**	-	-	-
6.7	**0.7**	-	< 0.5	-	**1.2**	-	-	-
7.0	0.3	-	< 0.5	-	**0.4**	-	-	-
7.4	-	-	-	-	**1.0**	6.1	237	1,248
Referance range[b]	< 0.2-0.4	0.4-6.0	0.6-3.0	6.3-15.6	< 0.3	1.9-6.5	☆	54—3,175

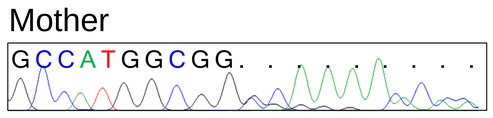
Patient c.8delG, p.Glu3fsAla*16



Father



Mother



We performed whole exome sequencing using the Nextera Rapid Capture Exome Kit (HiSeq SBS Kit v4-HS Illumina, San Diego, CA). and the HiSeq2500 sequencer (Illumina).

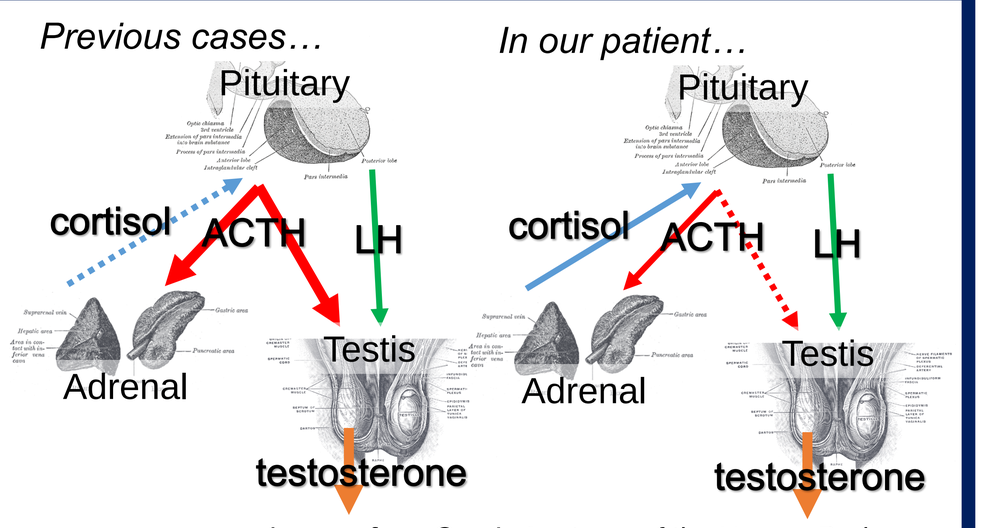
We identified a maternally-inherited hemizygous 1-bp deletion in exon 1 (p.Glu3fsAla*16) of *NR0B1*.

No pathogenic mutations were found in other tested genes including 32 genes known to be involved in the regulation of the HPG axis. (*CHD7, FGF8, FGFR1,FSHB, GNRH1, GNRHR, GNAS1, HESX1, HS6ST1, KAL1, KISS1,KISS1R, LEP, LEPR, LHB, LHCGR, LHX3, LHX4, NELF, NR0B1, MKRN3, OTX2, POU1F1, PROK2, PROKR2, PROP1, SEMA3A, SOX2,SOX3, TAC3, TACR3*, and *WDR11*)

Discussion

Precocious puberty was reported in 14 *NR0B1* mutation-carrying boys. All of these patients had adrenal insufficiency. Most of them had elevated gonadotropin and GnRH analogue was effective in 3 patients indicating GnRH-dependent PP[3-5)]. Testosterone production due to hyperstimulation of Leydig cell by ACTH may cause peripheral PP, because the clinical features of two patients were improved during glucocorticoid supplementation therapy[2&6)].

In our patient, ACTH was within normal range, implying Leydig cells were not stimulated by ACTH. As no other pathogenic mutations were found, ***NR0B1* mutations would cause male PP without adrenal insufficiency**.



Images from Gray's Anatomy of the Human Body.

Conclusion

***NR0B1* mutation analysis should be considered not only for adrenal insufficiency but also for isolated GnRH-dependent PP.**

References & Funding details

1)Ozisik G et al, J Clin Endocrinol Metab 88:417-423 (2003). 2) Domenice S et al, J Clin Endocrinol Metab 86:4068-4071 (2001)
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