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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.1Trp39+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 NR0H-dependent Precocious puberty (PP). In addition, ACTH overproduction was reported to induce GnRH-independent PP by stimulating Leydig cell via human melanocortin 1 receptor.1

**Clinical Presentation and Molecular Finding**

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 hyperresponsiveness 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.

<table>
<thead>
<tr>
<th>Age at exam.</th>
<th>LH (IU/L)</th>
<th>FSH (IU/L)</th>
<th>Testosterone (nmol/L)</th>
<th>ACTH (pmol/L)</th>
<th>Cortisol (nmol/L)</th>
<th>DHEAS (nmol/L)</th>
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<tbody>
<tr>
<td>(yr)</td>
<td>basal</td>
<td>peak*</td>
<td>basal</td>
<td>peak*</td>
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<td>2.4</td>
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<td>-</td>
<td>1.9</td>
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<tr>
<td>6.7</td>
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<tr>
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<td>6.1</td>
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</table>

**Reference range**< 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

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.Glu3fsA16) 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, FGF1, FSHB, GNRH1, GNRHR, GNAS1, HESX1, H66ST1, KAL1, KISS1, KISS1R, LEP, LEPR, LHB, LHCGR, LHX3, LHX4, NELF, NR0B1, MKNR3, 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.

**Conclusion**

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

References & Funding details


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