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Adrenal hypoplasia congenita and hypogonadotropic hypogonadism due to a novel NR0B1 (DAX1) gene mutation associated with common variable immunodeficiency and Hashimoto's thyroiditis

***Jasmina Ćirić*[1], *Ivana Novaković*[2], *Aleksandra Perić-Popadić*[3], *Miloš Žarković*[1], *Biljana Nedeljković Beleslin*[1], *Branka Bonači-Nikolić*[3]**

[1]*Clinic of Endocrinology, Diabetes and Diseases of Metabolism, University Clinical Centre of Serbia, Faculty of Medicine University of Belgrade, Belgrade, Serbia*
[2]*Faculty of Medicine University of Belgrade, Belgrade, Serbia*
[3]*Clinic of Allergy and Immunology, University Clinical Centre of Serbia, Faculty of Medicine University of Belgrade, Belgrade, Serbia*

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Adrenal hypoplasia congenita (AHC) in association with hypogonadotropic hypogonadism (HHG) is an X-linked disorder leading to a deficiency of adrenal and gonadal steroids and infertility. AHC is caused by mutations or deletions of nuclear receptor subfamily 0, group B, member 1 (NR0B1) gene, encoding the transcriptional repressor dosage-sensitive sex-reversal adrenal hypoplasia critical region on the X chromosome protein (DAX-1) [1].

We present long-term course of a 49-year-old man with AHC and HHG due to novel NR0B1 mutation, associated with common variable immunodeficiency (CVID) and Hashimoto's thyroiditis (HT).

The disease presented with adrenal crisis at age 4 years. Treatment with hydrocortisone and fludrocortisone was successfully introduced. At age 16, HHG was confirmed by GnRH test after the lack of expected puberty. On intramuscular testosterone, secondary sex characteristics developed fully.

Apart from numerous infections, the patient was well until age 32, when the frequency of respiratory diseases caused by *Streptococcus pneumonia* and *Haemophilus influenza* increased. Due to fatigue and darkening of the skin, he sought counsel from an adult endocrinologist. At admission his physical findings were normal except splenomegaly (140 mm). Initial therapy was adjusted according to hormonal findings (Tab. 1) and follow-up. Azoospermia was confirmed by semen examination.

The patient is the proband of a family with a history of several unexpected early deaths of male newborns and males diagnosed as AHC at age 4 years (Fig. 1). A novel NR0B1 gene mutation, 14-bp frameshift deletion in the first exon (c.720_733delTGGTGCGCTGCGGC, p.Ala242Glyfs*52) was confirmed in our patient. This variant was not found in the ExAC or 1000G database.

In the further course, on the basis of clinical, immunoserological, and immunophenotyping analyses (Tab. 2), a diagnosis of CVID was established [2]. Regular monthly (400 mg/kg) intravenous immunoglobulin (IVIG) therapy was started. The frequency of respiratory infections was reduced.

At age 42 years, a progressive increase of TSH and thyroid autoantibodies revealed subclinical hypothyroidism caused by HT (Tab. 1) and substitution with L-thyroxine started.

When he was 43 years old, a fifth-generation newborn male of the affected family (Fig. 1) was hospitalised due to adrenal crisis. On the bases of genetic burden, hormonal analyses, and the presence of the same genetic mutation, the appropriate therapy was immediately started.

CVID characterises normal or low number B-cells, low levels of immunoglobulins, and susceptibility to respiratory infections, and autoimmune endocrine disorders [2, 3]. The AHC shows a great inter- and intra-familial variability related to the onset and spectrum

Jasmina Ćirić, Clinic of Endocrinology, Diabetes and Diseases of Metabolism, University Clinical Centre of Serbia, Faculty of Medicine University of Belgrade, Dr Subotića starijeg 13, 11000 Belgrade, Serbia; e-mail: jasminaciric1005@gmail.com

Table 1. *Serum hormone levels*

	Baseline serum level	Normal range
Morning cortisol [nmol/L]	14.9	154–638
Morning ACTH [ng/L]	2400	0–60
Upright aldosterone [ng/L]	33.4	97–626
FSH [IU/L]	2.6	1–10.5
LH [IU/L]	< 0.9	1–8.4
Testosterone [nmol/L]	1.1	8.2–34.6
TSH [mIU/L]	8.9	0.27–4.2
FT4 [pmol/L]	13	12–22
Anti-TPO antibodies [IU/mL]	143	< 34

ACTH — adrenocorticotropic hormone; FSH — follicle-stimulating hormone; LH — luteinizing hormone; TSH — thyroid-stimulating hormone; FT4 — free thyroxine; TPO — thyroid peroxidase. Antibodies are measured before intravenous immunoglobulin application

Table 2. *Immunoserological, immunophenotyping analyses and serum levels of cytokines*

	Results	Normal range
IgG [gr/L]	2.7	6.8–16
IgA [gr/L]	0.17	0.7–4.06
IgM [gr/L]	0.14	0.3–2.5
CD19+B lymphocytes /μL	156	80–490
CD19 + CD27 + IgM-IgD, memory B cells (%)*	6.2	18.4 + 4.9
CD19 + CD21low, activated B cells (%)*	11	3.6 + 1.93
CD45RO/CD4+ T lymphocytes (%)**	92.67	71 +10
CD45RA/CD4+ T lymphocytes (%)**	7.3	25 + 12
B lymphocyte stimulator [pg/mL]	1569.0	751.0–1389.0
IL-10 [pg/mL]	7.2	0.1–2.1
IL-6 [pg/mL]	11.8	1.5–2.3

Ig — immunoglobulin; IL — interleukin; *% of CD19 +B lymphocytes; **% of CD4+ T lymphocytes

of clinical presentation [1]. The predominant lack of mineralocorticoids and/or the exposure to infection influence the presentation and outcome.

We showed that autoimmune disease and infections characteristic for CVID may complicate the course of adrenal insufficiency caused by novel NR0B1 mutation. We demonstrated that molecular testing is useful for carrier detection and genetic counselling. A potential link between *NR0B1* gene mutation and CVID remains to be elucidated.

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Conflict of interests

The authors have nothing to disclose.

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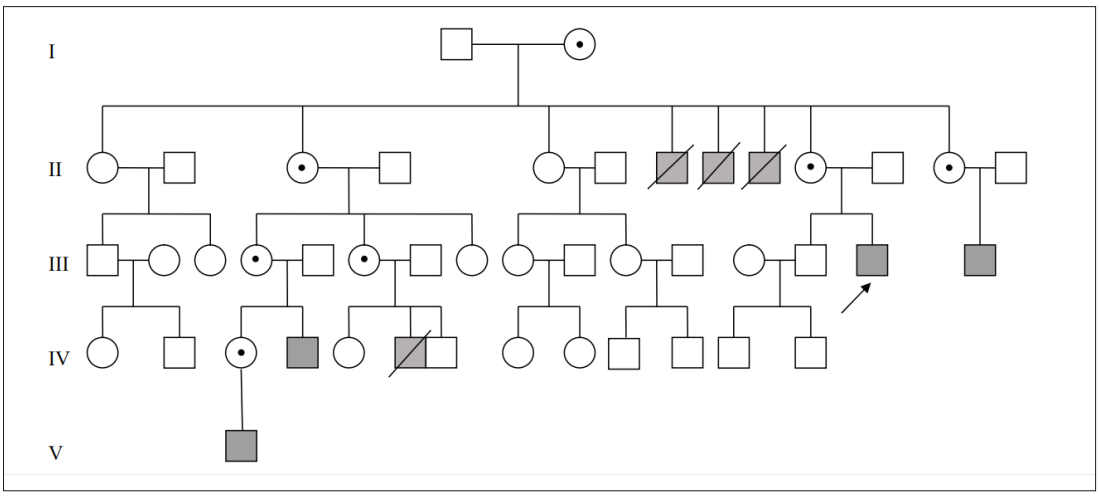

Figure 1. *Genealogical tree of proband family. White squares — healthy males, white circles — healthy females, grey squares — males with adrenal insufficiency, slashed squares-death around the third month of life, dotted circles-healthy female carrier. DNA analysis-proband (arrow) and the male of fifth generation, the only survivor of early disease onset*