Late diagnosis of childhood adrenal insufficiency and hypogonadotropic hypogonadism due to *DAX 1* gene mutation

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Introduction

Dax 1 (dosage – sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1), also known as *NROB1* (nuclear receptor subfamily 0,group B, member 1), encodes a nuclear receptor that is expressed in embryonic stem cells, steroidogenic tissues (adrenals, gonads), the ventromedial hypothalamus and pituitary gonadotropes. Patients with *Dax 1* gene mutations develop adrenal failure and failure to undergo puberty. The adrenal failure reflects a developmental abnormality on the transition of the fetal to adult zone, whereas hypogonadism involves a combined and variable deficiency of hypothalamic GnRH secretion and/or pituitary responsiveness to GnRH.

Case

Patient: Term male newborn born to a G1P1, Esthonian mother.
Birth Weight : 3.600 gr
Pregnancy: Complicated by drug abuse
Family History: Unkown, adopted at 1 year of age
Past Medical History: Diagnosed at 1 moa with congenital adrenal hyperplasia, started on hydrocortisone and fludrocortisone replacement therapy. Genetic testing for *CYP21A2* gene mutations was negative and hydrocortisone was discontinued at the age of 6 months with fludrocortisone continuation with a presumptive diagnosis of hypoaldosteronism. At the age of 2 yrs he underwent unilateral orchiopexy for undescended testis. At 3 yrs he was readmitted secondary to an episode of AGE

Laboratory evaluation:

BG	40 mg/dL
Na	128 mEq/L
K	6.5mEq/L
ACTH	5102 pg/mL
Cortisol	0.6 mcg/dL
Aldosterone	2,4 ng/dL

Physical examination: remarkable for marked hyperpigmentation of skin and mucosal surfaces, unilateral undescended testis, contralateral testis 1cc, soft on palpation
Treatment: Hydrocortisone , fludrocortisone.
Orchiopexy: Unilateral left orchiopexy with right orchiectomy secondary to dysgenetic testis (figures 1, 2).

Figure 1

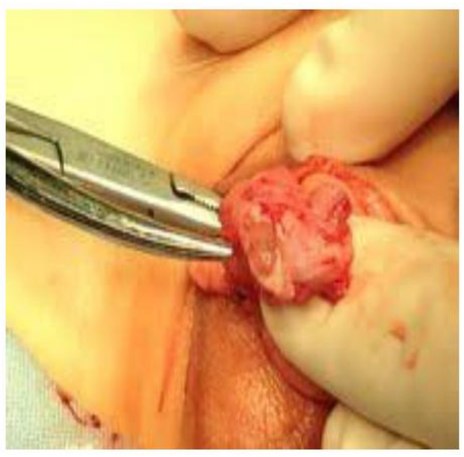
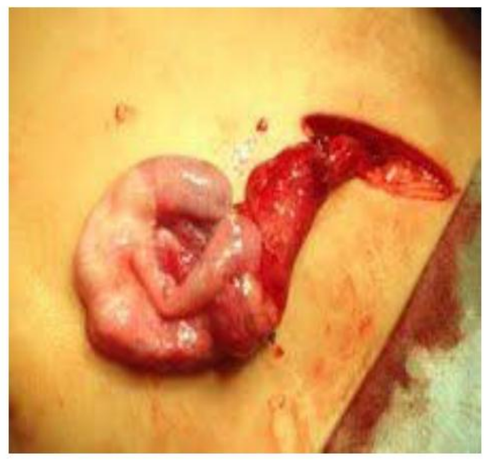


Figure 2



Testicular biopsy: Immature Sertoli cells and spermatogonia. Absence of Leydig cells
Growth and Development: At age 4.5 yrs Ht 25% with Bone age delay at 3.5 yrs, Wt 25%. Normal psychomotor development.

Molecular Genetic Analysis:
The entire coding region of the genes DAX1 and SF1 and their intron/exon junctions, were amplified by PCR and bi-directionally sequenced.
The proband was found to be hemizygote for the insertion c.1289_1290insTTAA, p.S431X in exon 2 of the *DAX1* gene. This insertion mutation creates a premature stop codon resulting to a truncated protein 40 amino acid shorter than the wild type. *The in silico* analysis carried out, employing the algorithm Mutation Taster, predicted that the mutation is a disease causing mutation. (Fig 3.)

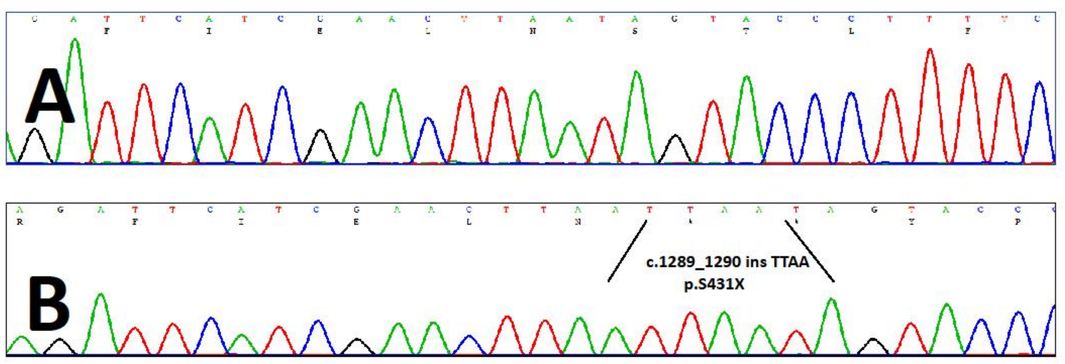


Figure 3. Part of the sequencing chromatogram of exon 2 of the *DAX1-NR0B1* gene (NCBI Reference Sequence: NM_ 000475)
A: wild type sequence B: patient sequence showing the TTAA insertion at nucleotide 1289_1290 creating a stop codon at amino acid 431 and resulting to a truncated protein 40 amino acids shorter than the wild type.

Conclusions

***Dax 1* gene mutation should be entertained in boys with adrenal insufficiency exhibiting signs of hypogonadism. Disease progression might be insidious throughout childhood. This case futher expands the number of *DAX1* gene mutations reported in the literature as well as our clinical knowledge of this rare disease.**

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