X-linked Adrenal Hypoplasia Congenita: report of two families and a new *NR0B1* mutation

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Background:

X-linked Adrenal Hypoplasia Congenita (X-linked AHC) tipically manifests as adrenal insufficiency in a bimodal clinical presentation (5–60 days and 2–13 years) and, at pubertal age, hypogonadotropic hypogonadism (HH) in males. It is caused by mutations in *NR0B1 (*present in Xp21.2), a gene with a critical role in the development of adrenals and hypothalamic-pituitary-gonadal (HPG) axis. It represents ~1% of all causes of primary adrenal insufficiency under age 18. We present two kindreds with NR0B1 mutations, one with a previously unreported mutation.

Clinical case - family A:

The proband presented with adrenal crisis at day 18 of life. Family history was relevant for an uncle death as a newborn. Hormonal assays revealed elevated ACTH (34,5 pmol/L, reference: <11), normal cortisol (220.8 nmol/L, reference: 56-665) and androgens (17-OHP: 9.9 nmol/L, reference: 7.5-24.6; 11-deoxycortisol: 83.52 nmol/L, reference: 47.9-260.9;), which showed no response to ACTH stimulation test and progressed to undectetable levels on serial measurements. From 6,8 years-old (yo) to 14 yo his height curve crossed from -0,1SD to -1,86SD, and at 14,1 yo testicular volume was 3mL. His gonadotropins (FSH 0.95 UI/L; LH <0.1 UI/L), total testosterone (TT, <0.35 nmol/L; reference: 0.5-17.5) and GnRH test (LH - basal: <0.1 UI/L; peak: 0.8 UI/L; FSH - basal: 0.67 UI/L; peak: 1.9 UI/L) confirming HH. Molecular analysis of the *NR0B1* gene revealed the mutation c.1084A>T, leading to a premature stop codon, p.Lys362*, in exon 1. His mother and sister were both asymptomatic carriers for this

mutation. This mutation, not described previously, leads probably to a non-functional truncated protein.

Clinical case - family B:

Kindred B had two males who presented with adrenal crisis at the newborn age (proband: 14 days; brother: 16 days). At 6 months of age, the proband had elevated ACTH (193.2 pmol/L, reference: <11) and elevated levels of cortisol (634 nmol/L, reference: 107-405) and 17-OHP (15.2 nmol/L; reference: 1.55-5.03), with no increase at Synacthen® test (peak cortisol: 635 nmol/L; peak 17-OHP: 11.5 nmol/L). His affected brother had also elevated 17-OHP at presentation (48.5 nmol/L, reference: 7.5-24.6), but beyond the 1st year poor compliance with replacement therapy revealed persistently elevated ACTH (249.3 pmol/L) and undectectable androgens (17-OHP: <0,3 nmol/L; androstenedione <1 nmol/L; DHEA-S <0,27 nmol/L). Both cases had delayed bone age at 9 months (proband: 6 months of chronologic age) and 2 years (brother: 2,6 years of chronologic age). At 14 yo they had pubertal Tanner stage 1. Basal gonadotropin and TT levels were also prebubertal (proband: FSH 2.61 UI/L; LH <0.1 UI/L; TT <0.35, reference: 0.5-17.5; brother: FSH 0.4 UI/L; LH <0.1 UI/L; TT <0.35 nmol/L). *NR0B1* molecular analysis allowed the identification of the nonsense mutation, c.234C>G; p.Tyr81*, in exon 1, present in the two affected males. His mother and one sister were also asymptomatic carriers.

Conclusion: Our kindreds highlights the clinical aspects of the rare X-linked AHC and its challenging differential diagnosis. The diagnosis was based on …. Completar … and an apparently X-linked mode of inheritance. Molecular analysis of the *NR0B1* gene allowed the identification of the molecular defect in both families. Two different nonsense mutation in exon 1 were identified, giving rise most probably to truncated non-functional proteins, confirming the disease severity or the clinical phenotype of the affected boys. Mutation identification was relevant for genetic counseling of the parents, as well as for the patient's sisters.

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Case	rp	mc
Age	19 days	6 months
17-hydroxyprogesterone	9,9 (ref. 7,5-24,6)	15,2 (1,55-5,03)
11-deoxycortisol	83,52 (ref. 47,9-260,9)	11,5 (4,11-22,6)
Androstenedione	25,12 (ref. 0,63-5,9)	4,2 (0,21-1,05)
Cortisol	220,8 (ref. 55,5-664,7)	634,5 (107,4-404,9
ACTH		193,2