

Molecular analysis of the *NR0B1* in three Portuguese families with X-linked Adrenal Hypoplasia Congenita

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X-linked Adrenal Hypoplasia Congenita (X-linked AHC) is a rare disorder associated with acute adrenal insufficiency in the newborn age that typically cause vomiting, feeding difficulty, dehydration, and shock due to a salt-wasting episode. Hypoglycemia, frequently presenting with seizures, may be the first symptom. If untreated, adrenal insufficiency is lethal.

Affected males, despite hormonal treatment, typically have delayed puberty (onset after age 14) caused by hypogonadotropic hypogonadism, and most of them are infertile at adult age. Carrier females may occasionally have symptoms of adrenal insufficiency or hypogonadotropic hypogonadism, possibly caused by skewed X-chromosome inactivation.

X-linked AHC is caused by mutations in *NR0B1* gene, a critical gene involved in the development of adrenals and hypothalamic-pituitary-gonadal axis. Since the identification of the *NR0B1* gene, numerous mutations have been discovered including deletions, alterations of splice-sites, missense, nonsense and frameshift mutations.

Here we present the molecular results obtained in three Portuguese families with *NR0B1* mutations. Mutation analysis was performed by PCR followed by SSCP analysis and sequencing of DNA fragments showing abnormal patterns on a second PCR product, or by direct DNA cycle sequencing of PCR products.

Molecular analysis of the *NR0B1* gene in proband A revealed a nonsense mutation, c.1084A>T, p.Lys362*, in exon 1, not previously described. His mother and sister were asymptomatic carriers; in family B a nonsense mutation, c.243C>G; p.Tyr81*, also in exon 1, was identified in two affected males and their mother and sister were also asymptomatic carriers; in family C a frameshift mutation, c.1292delG, p.Ser431Ilefs*6, in exon 2, was detected in a 7 years old affected male and his mother.

The maternal origin of mutations was confirmed in the three families studied.

The identification of a *NR0B1* mutation in a family has important implications: a correct clinical diagnosis can be established, appropriate clinical management of affected members and suitable genetic counselling can be offered, female carriers can be identified and disease can be prevented.