

Prenatal testing for NR0B1 (DAX1) Gene Variants: X-linked Adrenal Hypoplasia Congenita (AHC)

Disorder also known as:

AHC with hypogonadotropic hypogonadism (AHC with HH); Cytomegalic form of AHC.

Clinical Features:

Children and Adults:

Loss-of-function variants in the NR0B1 (DAX1) gene on chromosome Xp21 cause X-linked adrenal hypoplasia congenita (AHC). In males with X-linked AHC, the mature adult zone of the adrenal cortex fails to develop properly, resulting in a cortex that appears disorganized and contains large, cytomegalic cells that resemble cells in the fetal cortex. Typically, males with X-linked AHC develop salt-wasting primary adrenal failure in early infancy (~60%) or childhood (~40%), although later-onset cases presenting in adulthood have been described^{1,2}. Individuals with variants in the NR0B1 gene also develop hypogonadotropic hypogonadism (HH), although the age of onset is variable. HH due to altered hypothalamic-pituitary-gonadal (HPG) activity may be observed in infancy, and greater than 10% of males with X-linked AHC have bilaterally undescended testicles. However, other individuals have normal HPG activity in infancy, and onset of HH is noted at the time of puberty. In rare cases, patients with NR0B1 variants have been reported with spontaneous onset of puberty, although pubertal development is incomplete. Most males have azoospermia and remain infertile even after treatment with gonadotropins², although a male with an NR0B1 variant was reported with preserved fertility³. While variants within the NR0B1 gene result in isolated X-linked AHC, X-linked AHC may also occur as part of a contiguous gene deletion syndrome associated with mental retardation, glycerol kinase deficiency, and/or Duchenne muscular dystrophy, depending on the size of the deletion. Most females who are heterozygous carriers of NR0B1 variants have normal adrenal function and no evidence of HH; however, several have been reported with delayed puberty,⁴ and a female with a contiguous gene deletion including NR0B1 had primary adrenal failure due to skewed X-inactivation⁵. Additionally, one female was reported with a homozygous NR0B1 variant causing HH but apparently normal adrenal and ovarian function³. Duplications of the NR0B1 gene and the surrounding genomic region, referred to as the dosage-sensitive sex reversal (DSS) region, do not cause X-linked AHC but instead result in a 46,XY disorder of sex development. Although most patients reported with duplications of the DSS region have complete gonadal dysgenesis causing XY sex reversal, partial gonadal dysgenesis with ambiguous genitalia has been described¹³. Duplications of DAX1 in 46,XX individuals have no known clinical consequence, but the risk of transmission to 46,XY offspring is a significant consideration.

Prenatal Findings:

Variants in the NR0B1 gene may be suspected in male fetus with normal prenatal ultrasound findings in the presence of low maternal serum estriol (uE3) on prenatal screening¹⁴, especially if the family history is significant for males with adrenal insufficiency, HH, or early death suggestive of an untreated adrenal crisis. Duplications of the NR0B1 gene may be suspected when the fetal karyotype is 46,XY but ultrasound reveals apparently female or ambiguous external genitalia. Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk to inherit a specific known familial pathogenic variant can be offered targeted molecular testing regardless of ultrasound findings, if desired.

Genetics:

X-linked. Germline mosaicism has been reported.⁶

Test Methods:

Using genomic DNA, analysis is performed by bidirectional sequencing of the two coding exons and flanking splice sites of the NR0B1 gene. This method will detect both point variants and large deletions of the NR0B1 gene in fetuses with a 46,XY karyotype. For known familial variants, the relevant portion of the NR0B1 gene will be analyzed in duplicate. When concerned about 46,XY disorder of sex development, prenatal whole genome chromosomal microarray (test code 460) can be performed to evaluate for a duplication of the NR0B1 gene (see MicroarrayDx information sheet for more details). Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed. Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.

Test Sensitivity:

Variants in the NR0B1 gene were identified in 26/31 (84%) males with a clinical diagnosis of AHC, including 14 (45%) with a large deletion and 12 (39%) with an intragenic variant⁹. In a study of males with primary adrenal failure of an unknown etiology, 37/64 (58%) were found to harbor a variant in NR0B1¹⁰. Duplications of NR0B1 are believed to be the cause of dosage-sensitive sex reversal (DSS) in patients with Xp21 duplications (see MicroarrayDx information sheet for more details). The smallest duplication associated with a 46,XY disorder of sex development that has been reported was approximately 800 kb and included the four MAGEB genes adjacent to NR0B1¹³.

REFERENCES:

1. Achermann et al., (2001) *Molec Cell Endocrinol* 185:17-25.
2. Mantovani et al., (2002) *J Clin Endocrinol Metab* 87:44-48.
3. Merke et al., (1999) *NEJM* 340:1248-1252.
4. Seminara et al., (1999) *J Clin Endocrinol Metab* 84:4501-4509.
5. Shaikh et al., (2008) *J Med Genet* 45:e1.
6. Zhang et al., (1998) *Am J Hum Genet* 62:855-864.
7. Ho et al., (2004) *Mol Genet Metab* 83:330-336.
8. McCabe ERB (2007) *Mol Cell Endocrinol* 265-266:179-182.
9. Muscatelli et al., (1994) *Nature* 372:672-676.
10. Lin et al., (2006) *J Clin Endocrinol Metab* 91:3048-3054.
11. Salvi et al., (2002) *J Clin Endocrinol Metab* 87:4094-4100.
12. Bardoni et al., (1994) *Nat Genet* 7:497-501.
13. Barbaro et al., (2008) *Clin Genet* 73:453-464.
14. Peter et al., (1998) *J Clin Endocrinol Metab* 83(8):2666-2674.
15. Morel et al., (January 2010) Studies of a cohort of 46,XY with DSD including steroid biosynthesis deficiencies Presented at Hormonal and Genetic Basis of Sexual Differentiation Disorder and Hot Topics in Endocrinology, Miami, FL.