U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Achermann JC, Vilain EJ. *NR0B1*-Related Adrenal Hypoplasia Congenita. 2001 Nov 20 [Updated 2018 Jan 25]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

NR0B1-Related Adrenal Hypoplasia Congenita

John C Achermann, MB, MD, PhD, FRCPCH[1] and Eric J Vilain, MD, PhD, FACMG[2]

Created: November 20, 2001; Updated: January 25, 2018.

Summary

Clinical characteristics

NR0B1-related adrenal hypoplasia congenita includes both X-linked adrenal hypoplasia congenita (X-linked AHC) and Xp21 deletion (previously called complex glycerol kinase deficiency). X-linked AHC is characterized by primary adrenal insufficiency and/or hypogonadotropic hypogonadism (HH). Adrenal insufficiency is acute infantile onset (average age 3 weeks) in approximately 60% of affected males and childhood onset (ages 1-9 years) in approximately 40%. HH typically manifests in a male with adrenal insufficiency as delayed puberty (i.e., onset age >14 years) and less commonly as arrested puberty at about Tanner Stage 3. Rarely, X-linked AHC manifests initially in early adulthood as delayed-onset adrenal insufficiency, partial HH, and/or infertility. Heterozygous females very occasionally have manifestations of adrenal insufficiency or hypogonadotropic hypogonadism.

Xp21 deletion includes deletion of *NR0B1* (causing X-linked AHC) and *GK* (causing glycerol kinase deficiency), and in some cases deletion of *DMD* (causing Duchenne muscular dystrophy). Developmental delay has been reported in males with Xp21 deletion when the deletion extends proximally to include *DMD* or when larger deletions extend distally to include *IL1RAPL1* and *DMD*.

Diagnosis/testing

The diagnosis of *NR0B1*-related adrenal hypoplasia congenita is established in a male proband by detection of either a hemizygous pathogenic variant in *NR0B1* or a non-recurrent Xp21 deletion that includes *NR0B1*.

Management

Treatment of manifestations: Episodes of acute adrenal insufficiency are usually treated in an intensive care unit with close monitoring of blood pressure, hydration, clinical status, and serum concentration of glucose and electrolytes. Once the initial acute episode has been treated, affected individuals are started on replacement doses of glucocorticoids and mineralocorticoids and – in younger children – oral supplements of sodium

Author Affiliations: 1 Genetics and Genomic Medicine UCL Great Ormond Street Institute of Child Health University College London London, United Kingdom; Email: j.achermann@ucl.ac.uk. 2 Center for Genetic Medicine Research Children's National Medical Center Washington, DC; Email: evilain@childrensnational.org.

chloride. Steroid dosage must be increased during periods of stress (e.g., intercurrent illness, surgery, trauma); glucose and sodium may be needed. HH may be treated with increasing doses of testosterone to induce age-appropriate puberty and should be monitored by a pediatric endocrinologist. Treatment is usually initiated at around or just after the time puberty would be expected (age 12 years in boys).

Surveillance: If mineralocorticoid production is sufficient at the time of initial diagnosis, long-term follow up of adrenal mineralocorticoid function is necessary. If glucocorticoid production is sufficient at the time of initial diagnosis, long-term follow up of adrenal glucocorticoid function is necessary.

If puberty has not started by age 14 years, monitoring of serum concentrations of LH, FSH, testosterone, and inhibin B to evaluate for the possibility of HH is necessary. If puberty has started spontaneously, it is likely to arrest; thus, yearly routine monitoring of levels of LH, FSH, and testosterone is necessary.

Evaluation of relatives at risk: At birth: If the genetic status of an at-risk male relative has not been established prior to birth by prenatal molecular genetic testing, it is appropriate to monitor him with biochemical testing for evidence of adrenal insufficiency in the first few days of life in order to determine if he would benefit from prompt initiation of glucocorticoid and mineralocorticoid hormone replacement therapy to avoid a salt-losing adrenal crisis. Later in childhood: When the *NR0B1* pathogenic variant in the family is known, it is reasonable to clarify the genetic status of at-risk asymptomatic maternal male relatives by molecular genetic testing as approximately 40% of affected males will not manifest adrenal insufficiency until childhood or later.

Genetic counseling

NR0B1-related adrenal hypoplasia congenita is inherited in an X-linked manner.

X-linked AHC: The risk to sibs depends on the genetic status of the mother: if the mother is heterozygous for an *NR0B1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will typically not be affected but will be carriers. Most males with AHC are infertile.

Xp21 deletion: Although most mothers of an individual diagnosed with an Xp21 deletion are carriers, a proband may have the disorder as the result of a *de novo* contiguous gene deletion. The risk to the sibs of the proband depends on the genetic status of the mother: if the mother is heterozygous for the Xp21 deletion, the chance of transmitting the deletion in each pregnancy is 50%. Males who inherit the deletion will be affected; females who inherit the deletion will typically not be affected.

Once the *NR0B1* pathogenic variant or Xp21 deletion has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

NR0B1-Related Adrenal Hypoplasia Congenita: Included Phenotypes
• X-linked adrenal hypoplasia congenita • Xp21 deletion (complex glycerol kinase deficiency)

For synonyms and outdated names see Nomenclature.

Diagnosis

NR0B1-related adrenal hypoplasia congenita includes both X-linked adrenal hypoplasia congenita (X-linked AHC) and Xp21 deletion (previously called complex glycerol kinase deficiency), which includes deletion of *NR0B1* (causing X-linked AHC) and *GK* (causing glycerol kinase deficiency), and in some cases deletion of *DMD* (causing Duchenne muscular dystrophy).

Suggestive Findings

NR0B1-related adrenal hypoplasia congenita **should be suspected** in males with the clinical findings of X-linked adrenal hypoplasia congenita (X-linked AHC) or Xp21 deletion and supportive laboratory and imaging findings.

Clinical Findings

X-linked AHC and Xp21 deletion

- Acute primary adrenal insufficiency in the first (or second) month of life
- Primary adrenal insufficiency later in childhood
- Primary adrenal insufficiency and/or hypogonadotropic hypogonadism in young adulthood

Xp21 deletion only. Clinical findings of:

- Xp21 deletion. Developmental delay and seizures, strabismus
- Glycerol kinase deficiency. Metabolic acidosis, hypoglycemia
- Duchenne muscular dystrophy. See Dystrophinopathies.

Laboratory Findings

X-linked AHC and Xp21 deletion

- Primary adrenal insufficiency
  - A high serum ACTH concentration in the presence of a low or normal serum concentration of cortisol is diagnostic of primary adrenal insufficiency. Note: An impaired cortisol response is usually seen after an ACTH (cosyntropin) stimulation test.

    Note: Basal plasma concentration of cortisol is not reliable by itself in the evaluation of an individual with suspected adrenal insufficiency, as it may be within normal limits (which is – in a sick child – inappropriately low).
  - In some individuals salt loss may be the presenting feature of adrenal insufficiency, and cortisol insufficiency may develop with time.
  - Rarely, boys may have a predominant cortisol insufficiency and normal salt balance.
- Hypogonadotropic hypogonadism
  - Low or normal basal gonadotropins (luteinizing hormone (LH), follicle-stimulating hormone (FSH), and low testosterone in the context of absent or arrested puberty (primary hypogonadism)
  - Impaired LH and FSH response in an LHRH (LH-releasing hormone) stimulation test
  - Low inhibin B

Xp21 deletion only

- Glycerol kinase deficiency, diagnosed by either of the following:
  - Elevated serum concentrations of glycerol (hyperglycerolemia) and triglycerides (pseudohypertriglyceridemia)
  - Increased urine glycerol (measured in a urinary organic acids test prepared by solvent extraction method)
- Duchenne muscular dystrophy (See Dystrophinopathies.)

Imaging Studies

X-linked AHC and Xp21 deletion. Abdominal CT, MRI, or ultrasound examination may reveal small adrenal glands.

Note: (1) While ultrasound imaging is less specific than CT or MRI, it avoids the radiation exposure of CT and the need for sedation for MRI in a potentially sick child. (2) The apparent absence of the adrenal glands on imaging studies may also rarely be due to ectopia of normal-sized adrenal glands.

Establishing the Diagnosis

The diagnosis of *NR0B1*-related adrenal hypoplasia congenita **is established** in a male proband by detection of either a hemizygous pathogenic variant in *NR0B1* or a non-recurrent Xp21 deletion that includes *NR0B1* (see Table 1).

Molecular testing approaches can include **single-gene testing**, **chromosomal microarray analysis (CMA)**, and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *NR0B1* is performed first if findings suggest X-linked AHC, followed by gene-targeted deletion/duplication analysis or CMA if no pathogenic variant is found on sequence analysis.
- **CMA** is performed first if the clinical presentation suggests Xp21 deletion.
- **A multigene panel** that includes *NR0B1* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of a condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in *NR0B1*-Related Adrenal Hypoplasia Congenita

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
NR0B1	Sequence analysis [3]	~75% [4]
	Gene-targeted deletion/duplication analysis [5, 6]	~25% [7]
	CMA [8, 9]	<25% [7, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lin et al [2006], Suntharalingham et al [2015], Bizzarri et al [2016], Guran et al [2016]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Gene-targeted deletion/duplication analysis may not detect deletion of adjacent genes (see Footnote 7).
7. Note that, although gene-targeted deletion/duplication assays may detect smaller events than genomic deletion/duplication assays, gene-targeted deletion/duplication assays will detect larger events but may not be able to determine the size. The majority of reported intragenic deletions and duplications, as well as Xp21 deletions, are detectable by CMA. It is possible that additional smaller deletions and duplications could be detected by these methods.
8. Deletion/duplication analysis (genomic approach) detects deletion of *NR0B1* and other contiguous genes using a chromosomal microarray (CMA) that specifically includes this gene/chromosome segment.
9. Xp21 deletion includes X-linked AHC (caused by deletion of *NR0B1*) and glycerol kinase deficiency (caused by deletion of *GK*) with or without Duchenne muscular dystrophy (caused by deletion of *DMD*).

Clinical Characteristics

Clinical Description

NR0B1-related adrenal hypoplasia congenita includes both X-linked adrenal hypoplasia congenita (X-linked AHC) and the phenotypes resulting from deletion of some of the genes in the Xp21 region: *NR0B1* (causing X-linked AHC) and *GK* (glycerol kinase deficiency), and in some cases *DMD* (Duchenne muscular dystrophy).

X-linked Adrenal Hypoplasia Congenita

X-linked adrenal hypoplasia congenita (X-linked AHC) is characterized by primary adrenal insufficiency and/or hypogonadotropic hypogonadism (HH).

Adrenal insufficiency has acute infantile onset (average age 3 weeks) in approximately 60% of affected males and childhood onset (ages 1-9 years) in approximately 40% [Peter et al 1998, Reutens et al 1999, Guran et al 2016].

HH typically manifests in a male with adrenal insufficiency as delayed puberty (i.e., onset age >14 years) and less commonly as arrested puberty at about Tanner Stage 3. Rarely, the initial manifestation of X-linked AHC occurs in early adulthood with a primarily reproductive phenotype (e.g., infertility) [Tabarin et al 2000, Mantovani et al 2002].

Intrafamilial variability in age of onset occurs [Wiltshire et al 2001]; however, in families in which two brothers are affected, the younger one is usually diagnosed earlier as clinical suspicion is greater [Achermann et al 2001].

Adrenal insufficiency. The initial clinical presentation is typically acute, especially in infants, with vomiting, feeding difficulty, dehydration, and shock caused by a salt-wasting episode. In some instances hypoglycemia, frequently presenting with seizures or mineralocorticoid deficiency, may be the presenting manifestation of adrenal insufficiency [Wiltshire et al 2001, Verrijn Stuart et al 2007].

In older children, adrenal insufficiency may be precipitated by intercurrent illness or stress.

If untreated with glucocorticoids and mineralocorticoids, adrenal insufficiency is rapidly lethal as a result of hyperkalemia, acidosis, hypoglycemia, and shock. If not recognized and treated in children, acute adrenal insufficiency and its complications of hypoglycemia and shock may result in neurologic abnormalities and developmental delay.

In rare instances delayed-onset adrenal insufficiency becomes evident in early adulthood [Mantovani et al 2002, Ozisik et al 2003, Guclu et al 2010, Kyriakakis et al 2017]. In these individuals residual glucocorticoid and mineralocorticoid activity in the hypoplastic adrenal cortex may explain the late onset. These individuals may not have overt adrenal insufficiency, but rather biochemical evidence of compensated adrenal insufficiency (e.g., high serum ACTH concentration). In some instances progressive adrenal insufficiency occurs, resulting in clinically significant adrenal insufficiency in early adulthood.

Adrenal insufficiency is usually accompanied by varying degrees of hyperpigmentation caused by increased pituitary production of POMC (proopiomelanocortin); the original report of X-linked AHC described an affected newborn with "coal-black hyperpigmentation" of the skin sparing the palms and soles [Sikl 1948]. Hyperpigmentation present at the time of diagnosis typically regresses over time with appropriate steroid therapy.

Hypogonadotropic hypogonadism (HH) is of mixed hypothalamic and pituitary origin. The "mini puberty" of infancy is normal in boys with X-linked AHC, suggesting that the loss of function of the hypothalamic-pituitary-gonadal axis occurs after early infancy. Although reported in several instances, cryptorchidism has not emerged as a common feature of X-linked AHC. Indeed, macrophallia (large penis) at birth and signs of early puberty in childhood are now increasingly reported in some boys with X-linked AHC [Domenice et al 2001, Landau et al 2010, Durmaz et al 2013]. Of note, one boy with central precocious puberty and normal adrenal function has recently been shown to have a pathogenic variant in *NR0B1* [Shima et al 2016].

Typically, HH is manifest in affected males as delayed puberty (onset age >14 years). In addition, a proportion of males may experience pubertal arrest, i.e., they enter puberty normally and progress to about Tanner Stage 3 (or testicular volume of 6-8 cc) after which pubertal development ceases. Without testosterone treatment, full attainment of secondary sexual characteristics is unlikely.

Males with classic X-linked AHC typically have azoospermia and are infertile despite treatment with exogenous gonadotropin therapy or pulsatile gonadotropin-releasing hormone (GnRH) [Seminara et al 1999, Mantovani et al 2006]. Although some men with X-linked AHC have oligospermia, progressive decline in spermatogenesis may occur with time [Tabarin et al 2000, Raffin-Sanson et al 2013].

Other. In one male with a pathogenic variant in *NR0B1*, tall stature and renal ectopy were associated with adrenal insufficiency [Franzese et al 2005].

Progressive high-frequency sensorineural hearing loss starting at about age 14 years was described in two individuals with X-linked AHC whose *NR0B1* status is unknown [Zachmann et al 1992, Liotta et al 1995]. To the authors' knowledge no other individuals with hearing loss and classic X-linked AHC have been reported; thus, it is increasingly unlikely that hearing loss is an associated feature.

Heterozygous females may very occasionally have manifestations of adrenal insufficiency or hypogonadotropic hypogonadism, potentially caused by skewed X-chromosome inactivation.

A heterozygous female with extreme pubertal delay has been described [Seminara et al 1999].

In one family with affected males, a female homozygous for an *NR0B1* pathogenic variant had isolated hypogonadotropic hypogonadism [Merke et al 1999].

Xp21 Deletion

The phenotypes resulting from deletion of some of the genes in the Xp21 region are X-linked AHC (deletion of *NR0B1*), glycerol kinase deficiency (deletion of *GK*), and Duchenne muscular dystrophy (deletion of *DMD*).

The clinical findings in glycerol kinase deficiency vary and can include metabolic crisis during starvation, hypoglycemia, seizures, growth restriction, and developmental delay.

Developmental delay has been reported in males with Xp21 deletion when the deletion extends proximally to include *DMD* or when larger deletions extend distally to include *IL1RAPL1* and *DMD* [Zhang et al 2004].

IL1RAPL1 deletions are associated with global developmental delay / intellectual disability and, sometimes, autistic spectrum disorder.

Heterozygous females. A female with mild adrenal failure and Duchenne muscular dystrophy was reported [Shaikh et al 2008]. Molecular studies confirmed extremely skewed X-chromosome inactivation in the region of Xp21 that resulted in preferential expression of the abnormal allele.

Two girls reported with developmental delay and myopathy due to an Xp21 deletion involving *DMD*, *GK*, *NR0B1*, and *IL1RAPL1* did not have adrenal dysfunction [Heide et al 2015].

Genotype-Phenotype Correlations

In X-linked AHC caused by a single-nucleotide variant in *NR0B1* no clear correlation exists between the location or type of variant and the clinical phenotype, except as outlined below:

- Late-onset X-linked AHC can result from variants in the ligand-like binding region of *NR0B1* around the hydrophobic core (e.g., p.Tyr380Asp, p.Ile439Ser) [Tabarin et al 2000, Achermann et al 2001, Mantovani et al 2002]. Changes close to the repression helix domain can also present with late-onset X-linked AHC (e.g., p.Ser259Pro, p.Pro279Leu) [Kyriakakis et al 2017].
- Late-onset X-linked AHC may also occur as a result of nonsense variants at the amino-terminal region of *NR0B1* (e.g., stop codons at position 37 or 39) [Ozisik et al 2003, Guclu et al 2010, Raffin-Sanson et al 2013]. It has been proposed that translation reinitiation from a methionine at codon 83 produces an amino-terminally truncated protein with partially conserved function [Ozisik et al 2003].

Nomenclature

The term "congenital adrenal hypoplasia" is used less and less because it is easily confused with the much more common disorder, congenital adrenal hyperplasia. Both terms can be abbreviated as "CAH," adding to potential confusion. Thus, adrenal hypoplasia congenita (AHC) is the preferred term.

Xp21 deletion is also referred to as Xp21 contiguous gene deletion or complex glycerol kinase deficiency.

Prevalence

The incidence of *NR0B1*-related X-linked AHC is unknown. Current estimates are fewer than 1:70,000 males [Lin et al 2006, Guran et al 2016].

No specific populations are known to be at increased or decreased risk for this disorder.

Genetically Related Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be caused by pathogenic variants or deletions in *NR0B1*.

Duplication of *NR0B1* is associated with 46,XY gonadal dysgenesis (OMIM 300018) [Barbaro et al 2007, Barbaro et al 2012].

Differential Diagnosis

In males with salt-losing primary adrenal insufficiency and either a family history of X-linked adrenal insufficiency or other features of *NR0B1*-related X-linked AHC (e.g., hypogonadotropic hypogonadism), the likelihood of identifying a pathogenic *NR0B1* variant is increased [Lin et al 2006]. In contrast, in males with salt-losing primary adrenal insufficiency with no family history of adrenal insufficiency and no other features of *NR0B1*-related X-linked AHC in whom other causes of primary adrenal insufficiency have been excluded (e.g., congenital adrenal hyperplasia), the likelihood of identifying a pathogenic *NR0B1* variant is about 20%-40% [Lin et al 2006, Suntharalingham et al 2015, Bizzarri et al 2016, Guran et al 2016].

The differential diagnosis of *NR0B1*-related adrenal hypoplasia congenita (X-linked AHC) includes congenital adrenal hyperplasia (CAH) caused by the following:

- The salt-losing form of 21-hydroxylase deficiency (21-OHD), the most common disorder to consider in the differential diagnosis of X-linked AHC. 21-OHD also typically presents with an acute, salt-wasting episode of adrenal insufficiency in the neonatal period. Serum concentration of cortisol precursors (e.g., 17-OH progesterone) are elevated in 21-OHD, but normal or low in X-linked AHC. 21-OHD is inherited in an autosomal recessive manner.
- Deficiency in 11-hydroxylase (OMIM 202010), in which affected individuals may experience a transient salt-losing phase before salt retention occurs

The following disorders may present with findings similar to those seen in *NR0B1*-related X-linked AHC:

- ACTH deficiency presents with glucocorticoid (but not mineralocorticoid) insufficiency and low or unmeasurable serum concentration of ACTH (with and without corticotropin-releasing hormone stimulation). Isolated ACTH deficiency can result from alterations in *TBX19* (OMIM 604614), *POMC* (OMIM 176830), or *PCSK1* (OMIM 162150). ACTH deficiency can also occur as part of multiple pituitary hormone deficiency (see *PROP1*-Related Combined Pituitary Hormone Deficiency).
- Congenital adrenal lipoid hyperplasia may present with salt-losing adrenal failure in a manner similar to X-linked AHC. Congenital adrenal lipoid hyperplasia is caused either by biallelic pathogenic variants in *STAR* (encoding steroidogenic acute regulatory protein) (OMIM 201710) or by CYP11A1 deficiency (OMIM 613743). Individuals with *STAR* or *CYP11A1* pathogenic variants and a 46,XY karyotype classically have atypical genitalia or female external genitalia. Adrenal imaging usually reveals enlarged and fatty adrenal glands. However, milder pathogenic variants in *STAR* or *CYP11A1* (or in *HSD3B2*; OMIM 201810) can be found in males with hypospadias or "normal" male genitalia and delayed-onset adrenal insufficiency in childhood (often around ages 2-9 years) [Guran et al 2016]. Usually, the salt loss is not severe in these cases.
- Adrenal hypoplasia congenita, autosomal recessive form (OMIM 240200), is the "miniature adult" type of adrenal hypoplasia; the adrenal cortex is composed of a small amount of permanent adult cortex. The molecular basis of this condition is currently unknown.
- Familial glucocorticoid deficiency and ACTH resistance (OMIM PS202200) is caused by biallelic pathogenic variants in *MC2R* (encoding the ACTH receptor), *MRAP* (encoding the MC2R accessory protein), or *NNT* (encoding NAD(P) transhydrogenase) [Meimaridou et al 2012]. This form of adrenal hypoplasia usually has normal mineralocorticoid secretion, although transient hyponatremia can be seen in severe cases [Guran et al 2016].

Syndromes with AHC or AHC-like manifestations as a feature include the following:

- Pena-Shokeir syndrome, type 1 (fetal akinesia deformation sequence) (OMIM 208150)

- Holoprosencephaly, alobar type
- Meckel syndrome (OMIM 249000)
- SeRKAL (46,XX *se*x *r*eversal with dysgenesis of *k*idneys, *a*drenals, and *l*ungs) caused by biallelic pathogenic variants in *WNT4* (OMIM 611812)
- IMAGe syndrome (*i*ntrauterine growth retardation, *m*etaphyseal dysplasia, *A*HC, *ge*nital abnormalities) caused by pathogenic variants in *CDKN1C*. Growth restriction is a key component of this condition.
- MIRAGE syndrome (*m*yelodysplasia, *i*nfection, *r*estriction of growth, *a*drenal hypoplasia, *g*enital phenotypes, *e*nteropathy) caused by pathogenic variants in *SAMD9*. Monosomy 7 can occur and is associated with the development of myelodysplastic syndrome.
- Triple A (*a*chalasia, *a*ddisonianism, *a*lachrima) or Allgrove syndrome caused by biallelic pathogenic variants in *AAAS* (OMIM 231550)
- Natural killer cell and glucocorticoid deficiency with DNA repair defect (NKGCD) caused by biallelic pathogenic variants in *MCM4* (encoding DNA replication licensing factor MCM4) (OMIM 609981)
- Primary adrenal insufficiency and steroid-resistant nephrotic syndrome caused by biallelic pathogenic variants in *SGPL1* (see Sphingosine Phosphate Lyase Insufficiency Syndrome). Ichthyosis and neurologic symptoms can also occur. Sometimes adrenal insufficiency can precede the nephropathy [Prasad et al 2017].

Chromosomal abnormalities with AHC or AHC-like manifestations as a feature:

- Tetraploidy
- Triploidy
- Trisomy 19
- Trisomy 21
- 5p duplication
- 11q- syndrome (OMIM 147791)

Other forms of primary adrenal failure may need to be considered in boys presenting with primary adrenal failure:

- X-linked adrenoleukodystrophy (X-ALD) affects the nervous system white matter and the adrenal cortex. Three main phenotypes are seen in affected males:
  - The childhood cerebral form manifests most commonly between ages four and eight years. It initially resembles attention deficit disorder or hyperactivity; progressive impairment of cognition, behavior, vision, hearing, and motor function follow the initial symptoms and often lead to total disability within two years.
  - Adrenomyeloneuropathy (AMN) manifests most commonly in the late 20s as progressive paraparesis, sphincter disturbances, sexual dysfunction, and often, impaired adrenocortical function; all symptoms are progressive over decades.
  - "Addison disease only" presents with primary adrenocortical insufficiency between age two years and adulthood and most commonly by age 7.5 years, without evidence of neurologic abnormality; however, some degree of neurologic disability (most commonly AMN) usually develops later.

  Approximately 20% of females who are carriers develop neurologic manifestations that resemble AMN but have later onset (age ≥35 years) and milder disease than do affected males. *ABCD1* is the only gene known to be associated with X-ALD.

- Other metabolic causes; for example, Wolman disease (see Lysosomal Acid Lipase Deficiency), mitochondrial disease (see Mitochondrial Disorders Overview and a recent review by Chow et al [2017]), and Smith-Lemli-Opitz syndrome)

- Autoimmune syndromes (e.g., polyglandular endocrine disease caused by mutation of *AIRE*; OMIM 240300)
- Extrinsic (e.g., mechanical, infective, or drug-related) causes

Management

Evaluations Following Initial Diagnosis

To assess the extent of disease and needs in an individual diagnosed with *NR0B1*-related adrenal hypoplasia congenita, the following evaluations are recommended under the care of an experienced pediatric endocrinologist.

All Individuals with *NR0B1*-Related Adrenal Hypoplasia Congenita (X-linked AHC or Xp21 Deletion)

Assessment of adrenal function:

- If the presentation is predominantly mineralocorticoid insufficiency (salt loss), assess adrenal glucocorticoid function (basal ACTH, cortisol, cosyntropin test). If function is reduced, appropriate glucocorticoid replacement is needed (see Treatment of Manifestations). If it is adequate, long-term follow up is necessary (see Surveillance).
- If the presentation is predominantly glucocorticoid insufficiency, assess adrenal mineralocorticoid function (sodium, potassium, aldosterone, plasma renin activity). If function is reduced, fludrocortisone replacement is required as well as adequate salt supplementation in young children (age <1 year) (see Treatment of Manifestations). If it is adequate, long-term follow up is necessary (see Surveillance).

Assessment for early puberty or hypogonadotropic hypogonadism:

- When the initial diagnosis is in infancy or childhood, assess for signs of **early** puberty such as pubic hair development or penile enlargement between ages two and nine years. Monitor for the onset of puberty in adolescence (12-13 years). Even if puberty starts it is likely to arrest; thus, close monitoring is needed.
- When the initial diagnosis is after the usual time of puberty and if testosterone production has been adequate, consider discussion of the options of semen analysis for sperm count and sperm banking.

Other:

- Consultation with a clinical geneticist and/or genetic counselor for the affected person and family are advised.
- Psychological support should be offered.

Xp21 Deletion

In addition to the evaluations for adrenal function and hypogonadotropic hypogonadism discussed above, the following evaluations are warranted for those with Xp21 deletion:

- Serum creatine kinase to evaluate for Duchenne muscular dystrophy
- Plasma glycerol, triglycerides, and urinary glycerol to evaluate for glycerol kinase deficiency
- Developmental assessment regarding possible global developmental delays

Treatment of Manifestations

Adrenal Insufficiency

Some guidance on the treatment of adrenal insufficiency in children and adults is provided by recent Endocrine Society clinical practice guidelines [Bornstein et al 2016].

Acute episodes. Episodes of acute adrenal insufficiency are usually treated in an intensive care unit with close monitoring of blood pressure, hydration, clinical status, and serum concentration of glucose and electrolytes. Correction of hyperkalemia may be needed. Individuals are treated by the IV administration of saline, glucose, and hydrocortisone (e.g., Solu-Cortef®). If the serum concentration of electrolytes does not improve, a mineralocorticoid (fludrocortisone) is added or the dose of Solu-Cortef® is increased. Adequate sodium must be provided as well as monitoring for hypoglycemia.

Chronic treatment. Once the initial acute episode has been treated, affected individuals are started on replacement doses of glucocorticoids and mineralocorticoids and – in younger children – oral supplements of sodium chloride (NaCl).

- Steroid doses need to be adjusted to allow normal linear growth without risking an adrenal crisis.
- Maintenance hormone treatment is best managed in growing children by a pediatric endocrinologist.

Treatment during stress. Steroid dosage must be increased during periods of stress (e.g., intercurrent illness, surgery, trauma); glucose and sodium may be needed.

- Local hospitals should provide parents with a plan for emergency treatment and instruction regarding when extra oral or injected hydrocortisone is needed. Correction of hypoglycemia may also be needed. Parents should have access to rapid medical advice; guidelines for hospital admission should be clear.
- Children should carry appropriate documentation indicating that they are steroid deficient. Death from acute adrenal insufficiency in individuals known to have *NR0B1*-related adrenal hypoplasia congenita may still occur if steroid replacement therapy is not adequate, particularly during times of stress or fluid imbalance (e.g., severe gastroenteritis).

Other. Steroid replacement therapy is monitored clinically and hormonally by an endocrinologist. ACTH levels should normalize when replacement therapy is adequate. A sudden rise in ACTH despite steroid treatment has revealed the presence of a pituitary adenoma in one case [De Menis et al 2005].

The wearing of a Medic Alert® bracelet is strongly recommended.

Ongoing education and support, as well as access to appropriate resources, is important for families and young people.

Hypogonadotropic Hypogonadism

Hormone replacement therapy. If there is evidence of HH, treatment with increasing doses of testosterone to induce age-appropriate puberty may be necessary and should be monitored by a pediatric endocrinologist. Treatment is usually initiated at around or just after the time puberty would be expected (age 12 years in boys). Testosterone doses are increased gradually over a two- to three-year period until adult replacement doses are reached. Lifelong hormone replacement is needed.

Testosterone supplementation is also needed to support growth and bone mineralization.

Fertility has been achieved in a man with classic early-onset X-linked AHC using testicular sperm extraction-intracytoplasmic sperm injection following fairly extensive prior gonadotropin treatment [Frapsauce et al 2011]. It is not yet known whether this success will be possible in general or whether this represents an isolated case.

Psychological counseling is indicated as needed for families and young people to discuss the issues related to hormone replacement therapy and future issues with fertility.

Other. Developmental delay is evaluated and managed in the routine manner.

Surveillance

Primary Adrenal Insufficiency

If mineralocorticoid production is sufficient at the time of initial diagnosis, long-term follow up of adrenal mineralocorticoid function (sodium, potassium, aldosterone, plasma renin activity) is necessary. Monitoring should be fairly intense in the first two years of life (e.g., every 4 months) or at times of clinical concern. With age, mineralocorticoid sensitivity improves, but annual reviews would be appropriate and care needed during times of limited salt intake, fluid restriction, fluid loss (e.g., vomiting, diarrhea), or extreme heat. Clinical concern in the older child (e.g., postural hypotension or dizziness) needs investigation.

If glucocorticoid production is sufficient at the time of initial diagnosis, long-term follow up of adrenal glucocorticoid function (basal ACTH, cortisol, cosyntropin test) is necessary. Basal ACTH is a useful marker of impaired glucocorticoid function and should be measured together with cortisol during the first two years of life. If there are any concerns, a cosyntropin stimulation test should be performed, looking for an impaired cortisol response, not just an inadequate basal cortisol level. Annual reviews of basal ACTH/cortisol and possibly cosyntropin stimulation should be considered in a boy with a genuine X-linked AHC if glucocorticoid insufficiency has not yet developed. Any clinical concerns (e.g., tiredness, symptoms of hypoglycemia, poor weight gain, hyperpigmentation) need urgent investigation with measurement of ACTH concentration and a cosyntropin stimulation test.

Hypogonadotropic Hypogonadism

If puberty has not started by age 14 years, serum concentrations of LH and FSH (basal concentration and GnRH-stimulated concentration), testosterone, and inhibin B are monitored to evaluate for the possibility of HH. If the results of this laboratory testing indicate that HH is likely to occur, the young person may want to start puberty induction earlier in keeping with his peer group.

If puberty has started spontaneously, it is likely to arrest; thus, yearly routine monitoring of levels of testosterone, LH, and FSH is needed.

Evaluation of Relatives at Risk

At birth. If the genetic status of an at-risk male relative has not been established prior to birth by prenatal molecular genetic testing, it is appropriate to monitor him for evidence of adrenal insufficiency in the first few days of life with biochemical testing in order to determine if he would benefit from prompt initiation of glucocorticoid and mineralocorticoid hormone replacement therapy to avoid a salt-losing adrenal crisis. Note that although levels of electrolytes and basal cortisol may initially be within normal ranges, they can gradually change. Basal ACTH is a useful adjuvant test if available with a rapid turnaround time. A cosyntropin stimulation test usually shows an impaired cortisol response in affected children.

Later in childhood. When the *NR0B1* pathogenic variant in the family is known, it is reasonable to clarify the genetic status of at-risk asymptomatic maternal male relatives by molecular genetic testing, as approximately 40% of affected males do not present until childhood or later. Presymptomatic diagnosis allows prompt initiation of glucocorticoid and mineralocorticoid hormone replacement therapy to avoid a salt-losing adrenal crisis [Achermann et al 2000].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

NR0B1-related adrenal hypoplasia congenita includes X-linked adrenal hypoplasia congenita (X-linked AHC) and Xp21 deletion.

X-Linked Adrenal Hypoplasia — Risk to Family Members

Parents of a male proband

- The father of an affected male will not have *NR0B1*-related AHC nor will he be hemizygous for the *NR0B1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected male, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one son and no other affected relatives and if the *NR0B1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* pathogenic variant, in which case the mother is not a carrier. The percent of male probands with a negative family history in whom the pathogenic variant occurred *de novo* is unknown but probably low.

Sibs of a male proband

- The risk to sibs depends on the genetic status of the mother.
- If the mother of the proband is heterozygous for an *NR0B1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes (carriers) and, in rare cases, have manifestations of adrenal insufficiency and/or hypogonadotropic hypogonadism (see Clinical Description, X-Linked Adrenal Hypoplasia Congenita, **Heterozygous females**).
- Germline mosaicism is possible but uncommon. If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *NR0B1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a male proband

- Most males with AHC are infertile.
- If an affected male conceives through assisted reproductive technologies:
  - All daughters will be heterozygotes and may, in rare instances, have manifestations of adrenal insufficiency and/or hypogonadotropic hypogonadism (see Clinical Description, X-Linked Adrenal Hypoplasia Congenita, **Heterozygous females**).
  - No son will inherit the *NR0B1* pathogenic variant.

Other family members. The proband's maternal aunts and their offspring may be at risk of being carriers or of being affected (depending on their sex and family relationship and the genetic status of the proband's mother).

Xp21 Deletion – Risk to Family Members

The specific Xp21 deletion in a family generally affects all members similarly. Some families have a deletion that includes *NR0B1*, *GK*, and *DMD* (resulting in *NR0B1*-related adrenal hypoplasia congenita, glycerol kinase deficiency, and Duchenne muscular dystrophy, respectively), while other families have a deletion that includes *NR0B1* and *GK* only.

Parents of a male proband

- Most mothers of individuals diagnosed with an Xp21 deletion are carriers; however, a proband may have the disorder as the result of a *de novo* contiguous gene deletion.
- The proportion of cases caused by a *de novo* Xp21 deletion is unknown.
- Evaluation of the mother of a child with an Xp21 deletion and no known family history of an Xp21 deletion should include chromosomal microarray analysis (CMA) (see Table 1).

Sibs of a male proband

- The risk to the sibs of the proband depends on the genetic status of the mother.
- If the mother is heterozygous for the Xp21 deletion, the chance of transmitting the deletion in each pregnancy is 50%. Males who inherit the deletion will be affected; females who inherit the deletion will be heterozygotes and, in rare instances, have clinical manifestations (see Clinical Description, Xp21 Deletion, **Heterozygous females**).
- If the mother does not have the Xp21 deletion, the risk to sibs is presumed to be low (<1%) but greater than that of the general population because of the theoretic possibility of maternal germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Males with an Xp21 deletion do not reproduce as they typically die in adolescence or young adulthood of complications from DMD, or are severely ill.

Other family members. The proband's maternal aunts and their offspring may be at risk of being heterozygous or of being affected (depending on their sex and family relationship and the genetic status of the proband's mother).

Heterozygote Detection

Genetic testing of at-risk female relatives to determine their genetic status is most informative if the *NR0B1* pathogenic variant or an Xp21 deletion has been identified in an affected family member.

Note: (1) In rare instances, heterozygotes for this X-linked disorder may develop clinical findings related to the disorder, for example as a result of skewed X-chromosome inactivation [Shaikh et al 2008]. (2) Identification of heterozygous females requires either (a) prior identification of the *NR0B1* pathogenic variant or Xp21 deletion in the family or (b) if an affected male is not available for testing, molecular genetic testing first by *NR0B1* sequence analysis, and then, if no pathogenic variant is identified, by CMA to detect an Xp21 deletion.

Related Genetic Counseling Issues

See Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Pedigree analysis. An in-depth family history may identify as-yet-untested male relatives possibly at risk of developing adrenal insufficiency.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers, are at risk of being carriers, or are affected.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *NR0B1* pathogenic variant or Xp21 deletion has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Usually fetal sex is determined first and genetic testing is performed if the karyotype is 46,XY.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  X-linked adrenal hypoplasia congenita
- **National Adrenal Diseases Foundation (NADF)**
  505 Northern Boulevard
  Great Neck NY 11021
  Phone: 516-487-4992
  Email: nadfmail@aol.com
  www.nadf.us

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. NR0B1-Related Adrenal Hypoplasia Congenita: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DMD	Xp21.2-p21.1	Dystrophin	DMD homepage - Leiden Muscular Dystrophy pages	DMD	DMD
GK	Xp21.2	Glycerol kinase	GK homepage - Leiden Muscular Dystrophy pages	GK	GK
IL1RAPL1	Xp21.3-p21.2	Interleukin-1 receptor accessory protein-like 1	IL1RAPL1 @ LOVD	IL1RAPL1	IL1RAPL1

Table A. continued from previous page.

NR0B1	Xp21.2	Nuclear receptor subfamily 0 group B member 1	NR0B1 @ LOVD	NR0B1	NR0B1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for NR0B1-Related Adrenal Hypoplasia Congenita (View All in OMIM)

300143	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED 21; XLID21
300200	ADRENAL HYPOPLASIA, CONGENITAL; AHC
300206	INTERLEUKIN 1 RECEPTOR ACCESSORY PROTEIN-LIKE 1; IL1RAPL1
300377	DYSTROPHIN; DMD
300473	NUCLEAR RECEPTOR SUBFAMILY 0, GROUP B, MEMBER 1; NR0B1
300474	GLYCEROL KINASE; GK
307030	GLYCEROL KINASE DEFICIENCY; GKD
310200	MUSCULAR DYSTROPHY, DUCHENNE TYPE; DMD

Gene structure. The *NR0B1* reference sequence NM_000475.4 has two exons and contains one open reading frame that starts at the ATG codon (nucleotide 1) and ends at the TAA stop codon (nucleotide 1410). A single intron of 3 kb is inserted between nucleotides 1167 and 1168.

NR0B1 is the standard name for the gene, but it has historically been known as *DAX1* (and sometimes *Ahch*). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 200 instances of single-nucleotide variants and deletions of *NR0B1* in individuals with *NR0B1*-related adrenal hypoplasia congenita have been reported.

In the late 1980s and early 1990s these reports focused on individuals and families with an Xp21 deletion [Muscatelli et al 1994, Zanaria et al 1994]. Later studies sequenced *NR0B1* and reported sequence variants. Lin et al [2006] combined these data and estimated that approximately 25% of boys with *NR0B1*-related adrenal hypoplasia congenita have a deletion of *NR0B1* and, in approximately 33% of them, this may extend into a contiguous gene deletion.

Sequence analysis detects a pathogenic variant in the remaining approximately 75% of probands [Lin et al 2006, Suntharalingham et al 2015]. Missense variants tend to cluster in key regions of the ligand-like binding domain [Achermann et al 2001, Suntharalingham et al 2015]. Some of these may be associated with partial loss of function and late-onset condition (e.g., p.Ile439Ser, p.Tyr380Asp).

Two missense variants in the amino-terminal repeat region of *NR0B1* have been associated with a clinical phenotype. The p.Trp105Cys variant was associated with mineralocorticoid insufficiency [Verrijn Stuart et al 2007], and Cys200Trp was identified in a female age eight years with late-onset AHC. Her father, who was hemizygous for the variant, had no overt adrenal phenotype, yet the p.Cys200Trp variant impaired subcellular localization of *NR0B1*, shifting it toward the cytoplasm [Bernard et al 2006]. This variant is present in the ExAC database at low allele frequency (rs143141578, 8/19356 European).

Late-onset X-linked AHC is associated with nonsense variants in the amino-terminal region of *NR0B1*. Several individuals or families with stop codons at position p.37 or p.39 have been reported [Ozisik et al 2003, Guclu et al 2010, Raffin-Sanson et al 2013]. It has been proposed that translation reinitiation from a methionine at codon p.83 produces an amino-terminally truncated protein with partially conserved function [Ozisik et al 2003].

Table 2. *NR0B1* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.315G>C	p.Trp105Cys	NM_000475.4 NP_000466.2
c.600C>G	p.Cys200Trp	
c.775T>C	p.Ser259Pro	
c.836C>T	p.Pro279Leu	
c.1138T>G	p.Tyr380Asp	
c.1316T>G	p.Ile439Ser	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The predicted size of the protein product NP_000466.2 is 470 amino acids. The protein encoded by *NR0B1* (NM_000475.4) has the structure of a transcription factor and is classified as an orphan nuclear receptor.

The carboxyl-terminal region of NR0B1 has a structure similar to the ligand-binding domains of nuclear receptors. The amino-terminal region of NR0B1 contains repeat motifs and lacks a typical DNA-binding domain found in other nuclear receptors. Crystal studies have shown that NR0B1 can bind to NR5A2 directly as part of a complex involving two NR0B1 transcripts [Sablin et al 2008].

NR0B1 plays an important role in the normal development of the adrenal glands, the hypothalamus, the pituitary, and the ovary and testis and is expressed in these tissues during development and into postnatal life. The exact biologic role of NR0B1 is unknown. Most studies have shown that NR0B1 acts as a negative regulator of other nuclear receptor-signaling pathways including transactivation mediated by steroidogenic factor 1 (SF1) [Iyer & McCabe 2004]. Other studies have shown that NR0B1 can activate gene transcription [Verrijn Stuart et al 2007, Ferraz-de-Souza et al 2009, Xu et al 2009]. One hypothesis is that NR0B1 functions as a repressor that controls the rate of stem cell differentiation during organ development [Lalli & Sassone-Corsi 2003]. Premature differentiation of these pluripotent stem cells into mature cells without prior expansion of cell numbers could lead to transient overactivity and then to subsequent hypoplasia of the organ due to depletion of the pluripotent cell pool. Some evidence for this hypothesis comes from a mouse model of *Nr0b1* (exon 2) deletion [Scheys et al 2011].

In addition to its role in the pathogenesis of X-linked AHC, *NR0B1* plays a major role in sex determination. *NR0B1* is located in the DSS locus, a 160-kb region in Xp21 responsible, when duplicated, for dosage-sensitive sex reversal. NR0B1 has been hypothesized to act as an antagonist of SRY, the main male sex-determining gene.

Abnormal gene product. Inactivating pathogenic variants (deletion, nonsense, frameshift) in *NR0B1* result in absent or truncated NR0B1. Missense variants in *NR0B1* are predicted to have a deleterious effect on the normal conformation and function of NR0B1 or to affect nuclear localization of the protein.

References

Literature Cited

Achermann JC, Ito M, Silverman BL, Habiby RL, Pang S, Rosler A, Jameson JL. Missense mutations cluster within the carboxyl-terminal region of DAX-1 and impair transcriptional repression. J Clin Endocrinol Metab. 2001;86:3171–5. PubMed PMID: 11443184.

Achermann JC, Silverman BL, Habiby RL, Jameson JL. Presymptomatic diagnosis of X-linked adrenal hypoplasia congenita by analysis of DAX1. J Pediatr. 2000;137:878–81. PubMed PMID: 11113848.

Barbaro M, Cook J, Lagerstedt-Robinson K, Wedell A. Multigeneration inheritance through fertile XX carriers of an NR0B1 (DAX1) locus duplication in a kindred of females with isolated XY gonadal dysgenesis. Int J Endocrinol. 2012;2012:504904. PubMed PMID: 22518125.

Barbaro M, Oscarson M, Schoumans J, Staaf J, Ivarsson SA, Wedell A. Isolated 46,XY gonadal dysgenesis in two sisters caused by a Xp21.2 interstitial duplication containing the DAX1 gene. J Clin Endocrinol Metab. 2007;92:3305–13. PubMed PMID: 17504899.

Bernard P, Ludbrook L, Queipo G, Dinulos MB, Kletter GB, Zhang YH, Phelan JK, McCabe ER, Harley VR, Vilain E. A familial missense mutation in the hinge region of DAX1 associated with late-onset AHC in a prepubertal female. Mol Genet Metab. 2006;88:272–9. PubMed PMID: 16459121.

Bizzarri C, Olivini N, Pedicelli S, Marini R, Giannone G, Cambiaso P, Cappa M. Congenital primary adrenal insufficiency and selective aldosterone defects presenting as salt-wasting in infancy: a single center 10-year experience. Ital J Pediatr. 2016;42:73. PubMed PMID: 27485500.

Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101:364–89. PubMed PMID: 26760044.

Chow J, Rahman J, Achermann JC, Dattani MT, Rahman S. Mitochondrial disease and endocrine dysfunction. Nat Rev Endocrinol. 2017;13:92–104. PubMed PMID: 27716753.

De Menis E, Roncaroli F, Calvari V, Chiarini V, Pauletto P, Camerino G, Cremonini N. Corticotroph adenoma of the pituitary in a patient with X-linked adrenal hypoplasia congenita due to a novel mutation of the DAX-1 gene. Eur J Endocrinol. 2005;153:211–5. PubMed PMID: 16061826.

Domenice S, Latronico AC, Brito VN, Arnhold IJ, Kok F, Mendonca BB. Adrenocorticotropin-dependent precocious puberty of testicular origin in a boy with X-linked adrenal hypoplasia congenita due to a novel mutation in the DAX1 gene. J Clin Endocrinol Metab. 2001;86:4068–71. PubMed PMID: 11549627.

Durmaz E, Turkkahraman D, Berdeli A, Atan M, Karaguzel G, Akcurin S, Bircan I. A novel DAX-1 mutation presented with precocious puberty and hypogonadotropic hypogonadism in different members of a large pedigree. J Pediatr Endocrinol Metab. 2013;26:551–5. PubMed PMID: 23585174.

Ferraz-de-Souza B, Martin F, Mallet D, Hudson-Davies RE, Cogram P, Lin L, Gerrelli D, Beuschlein F, Morel Y, Huebner A, Achermann JC. CBP/p300-interacting transactivator, with Glu/Asp-rich C-terminal domain, 2, and pre-B-cell leukemia transcription factor 1 in human adrenal development and disease. J Clin Endocrinol Metab. 2009;94:678–83. PubMed PMID: 18984668.

Franzese A, Brunetti-Pierri N, Spagnuolo MI, Spadaro R, Giugliano M, Mukai T, Valerio G. Inappropriate tall stature and renal ectopy in a male patient with X-linked congenital adrenal hypoplasia due to a novel missense mutation in the DAX-1 gene. Am J Med Genet A. 2005;135:72–4. PubMed PMID: 15800903.

Frapsauce C, Ravel C, Legendre M, Sibony M, Mandelbaum J, Donadille B, Achermann JC, Siffroi JP, Christin-Maitre S. Birth after TESE-ICSI in a man with hypogonadotropic hypogonadism and congenital adrenal hypoplasia linked to a DAX-1 (NR0B1) mutation. Hum Reprod. 2011;26:724–8. PubMed PMID: 21227944.

Guclu M, Lin L, Erturk E, Achermann JC, Cangul H. Puberty, stress and sudden death. Lancet. 2010;376:1512. PubMed PMID: 21036276.

Guran T, Buonocore F, Saka N, Ozbek MN, Aycan Z, Bereket A, Bas F, Darcan S, Bideci A, Guven A, Demir K, Akinci A, Buyukinan M, Aydin BK, Turan S, Agladioglu SY, Atay Z, Abali ZY, Tarim O, Catli G, Yuksel B, Akcay T, Yildiz M, Ozen S, Doger E, Demirbilek H, Ucar A, Isik E, Ozhan B, Bolu S, Ozgen IT, Suntharalingham JP, Achermann JC. Rare causes of primary adrenal insufficiency: genetic and clinical

characterization of a large nationwide cohort. J Clin Endocrinol Metab. 2016;101:284–92. PubMed PMID: 26523528.

Heide S, Afenjar A, Edery P, Sanlaville D, Keren B, Rouen A, Lavillaureix A, Hyon C, Doummar D, Siffroi JP, Chantot-Bastaraud S. Xp21 deletion in female patients with intellectual disability: Two new cases and a review of the literature. Eur J Med Genet. 2015;58:341–5. PubMed PMID: 25917374.

Iyer AK, McCabe ER. Molecular mechanisms of DAX1 action. Mol Genet Metab. 2004;83:60–73. PubMed PMID: 15464421.

Kyriakakis N, Shonibare T, Kyaw-Tun J, Lynch J, Lagos CF, Achermann JC, Murray RD. Late-onset X-linked adrenal hypoplasia (DAX-1, NR0B1): two new adult-onset cases from a single center. Pituitary. 2017;20:585–93. PubMed PMID: 28741070.

Lalli E, Sassone-Corsi P. DAX-1, an unusual orphan receptor at the crossroads of steroidogenic function and sexual differentiation. Mol Endocrinol. 2003;17:1445–53. PubMed PMID: 12775766.

Landau Z, Hanukoglu A, Sack J, Goldstein N, Weintrob N, Eliakim A, Gillis D, Sagi M, Shomrat R, Kosinovsky EB, Anikster Y. Clinical and genetic heterogeneity of congenital adrenal hypoplasia due to NR0B1 gene mutations. Clin Endocrinol (Oxf). 2010;72:448–54. PubMed PMID: 19508677.

Lin L, Gu WX, Ozisik G, To WS, Owen CJ, Jameson JL, Achermann JC. Analysis of DAX1 (NR0B1) and steroidogenic factor-1 (NR5A1) in children and adults with primary adrenal failure: ten years' experience. J Clin Endocrinol Metab. 2006;91:3048–54. PubMed PMID: 16684822.

Liotta A, Maggio C, Casimiro L, Giuffre M, La Grutta S. Congenital adrenal hypoplasia and hearing loss. A case report. Minerva Pediatr. 1995;47:471–6. PubMed PMID: 8684342.

Mantovani G, De Menis E, Borretta G, Radetti G, Bondioni S, Spada A, Persani L, Beck-Peccoz P. DAX1 and X-linked adrenal hypoplasia congenita: clinical and molecular analysis in five patients. Eur J Endocrinol. 2006;154:685–9. PubMed PMID: 16645015.

Mantovani G, Ozisik G, Achermann JC, Romoli R, Borretta G, Persani L, Spada A, Jameson JL, Beck-Peccoz P. Hypogonadotropic hypogonadism as a presenting feature of late-onset X-linked adrenal hypoplasia congenita. J Clin Endocrinol Metab. 2002;87:44–8. PubMed PMID: 11788621.

Meimaridou E, Kowalczyk J, Guasti L, Hughes CR, Wagner F, Frommolt P, Nürnberg P, Mann NP, Banerjee R, Saka HN, Chapple JP, King PJ, Clark AJ, Metherell LA. Mutations in NNT encoding nicotinamide nucleotide transhydrogenase cause familial glucocorticoid deficiency. Nat Genet. 2012;44:740–2. PubMed PMID: 22634753.

Merke DP, Tajima T, Baron J, Cutler GB Jr. Hypogonadotropic hypogonadism in a female caused by an X-linked recessive mutation in the DAX1 gene. N Engl J Med. 1999;340:1248–52. PubMed PMID: 10210708.

Muscatelli F, Strom TM, Walker AP, Zanaria E, Récan D, Meindl A, Bardoni B, Guioli S, Zehetner G, Rabl W, et al. Mutations in the DAX-1 gene give rise to both X-linked adrenal hypoplasia congenita and hypogonadotropic hypogonadism. Nature. 1994;372:672–6. PubMed PMID: 7990958.

Ozisik G, Mantovani G, Achermann JC, Persani L, Spada A, Weiss J, Beck-Peccoz P, Jameson JL. An alternate translation initiation site circumvents an amino-terminal DAX1 nonsense mutation leading to a mild form of X-linked adrenal hypoplasia congenita. J Clin Endocrinol Metab. 2003;88:417–23. PubMed PMID: 12519885.

Peter M, Viemann M, Partsch CJ, Sippell WG. Congenital adrenal hypoplasia: clinical spectrum, experience with hormonal diagnosis, and report on new point mutations of the DAX-1 gene. J Clin Endocrinol Metab. 1998;83:2666–74. PubMed PMID: 9709929.

Prasad R, Hadjidemetriou I, Maharaj A, Meimaridou E, Buonocore F, Saleem M, Hurcombe J, Bierzynska A, Barbagelata E, Bergadá I, Cassinelli H, Das U, Krone R, Hacihamdioglu B, Sari E, Yesilkaya E, Storr HL, Clemente M, Fernandez-Cancio M, Camats N, Ram N, Achermann JC, Van Veldhoven PP, Guasti L,

Braslavsky D, Guran T, Metherell LA. Sphingosine-1-phosphate lyase mutations cause primary adrenal insufficiency and steroid-resistant nephrotic syndrome. J Clin Invest. 2017;127:942–53. PubMed PMID: 28165343.

Raffin-Sanson ML, Oudet B, Salenave S, Brailly-Tabard S, Pehuet M, Christin-Maitre S, Morel Y, Young J. A man with a DAX1/NR0B1 mutation, normal puberty, and an intact hypothalamic-pituitary-gonadal axis but deteriorating oligospermia during long-term follow up. Eur J Endocrinol. 2013;168:K45–50. PubMed PMID: 23384712.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR. UK10K Consortium, Hurles ME. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Reutens AT, Achermann JC, Ito M, Ito M, Gu WX, Habiby RL, Donohoue PA, Pang S, Hindmarsh PC, Jameson JL. Clinical and functional effects of mutations in the DAX-1 gene in patients with adrenal hypoplasia congenita. J Clin Endocrinol Metab. 1999;84:504–11. PubMed PMID: 10022408.

Sablin EP, Woods A, Krylova IN, Hwang P, Ingraham HA, Fletterick RJ. The structure of corepressor Dax-1 bound to its target nuclear receptor LRH-1. Proc Natl Acad Sci U S A. 2008;105:18390–5. PubMed PMID: 19015525.

Scheys JO, Heaton JH, Hammer GD. Evidence of adrenal failure in aging Dax1-deficient mice. Endocrinology. 2011;152:3430–9. PubMed PMID: 21733829.

Seminara SB, Achermann JC, Genel M, Jameson JL, Crowley WF Jr. X-linked adrenal hypoplasia congenita: a mutation in DAX1 expands the phenotypic spectrum in males and females. J Clin Endocrinol Metab. 1999;84:4501–9. PubMed PMID: 10599709.

Shaikh MG, Boyes L, Kingston H, Collins R, Besley GT, Padmakumar B, Ismayl O, Hughes I, Hall CM, Hellerud C, Achermann JC, Clayton PE. Skewed X inactivation is associated with phenotype in a female with adrenal hypoplasia congenita. J Med Genet. 2008;45:e1. PubMed PMID: 18762570.

Shima H, Yatsuga S, Nakamura A, Sano S, Sasaki T, Katsumata N, Suzuki E, Hata K, Nakabayashi K, Momozawa Y, Kubo M, Okamura K, Kure S, Matsubara Y, Ogata T, Narumi S, Fukami M. NR0B1 Frameshift mutation in a boy with idiopathic central precocious puberty. Sex Dev. 2016;10:205–9. PubMed PMID: 27648561.

Sikl H. Addison's disease due to congential adrenal hypoplasia of the adrenals in an infant aged 33 days. J Pathol Bacteriol. 1948;60:323–6. PubMed PMID: 18099667.

Suntharalingham JP, Buonocore F, Duncan AJ, Achermann JC. DAX-1 (NR0B1) and steroidogenic factor-1 (SF-1, NR5A1) in human disease. Best Pract Res Clin Endocrinol Metab. 2015; 2015;29:607–19. PubMed PMID: 26303087.

Tabarin A, Achermann JC, Recan D, Bex V, Bertagna X, Christin-Maitre S, Ito M, Jameson JL, Bouchard P. A novel mutation in DAX1 causes delayed-onset adrenal insufficiency and incomplete hypogonadotropic hypogonadism. J Clin Invest. 2000;105:321–8. PubMed PMID: 10675358.

Verrijn Stuart AA, Ozisik G, de Vroede MA, Giltay JC, Sinke RJ, Peterson TJ, Harris RM, Weiss J, Jameson JL. An amino-terminal DAX1 (NR0B1) missense mutation associated with isolated mineralocorticoid deficiency. J Clin Endocrinol Metab. 2007;92:755–61. PubMed PMID: 17164309.

Wiltshire E, Couper J, Rodda C, Jameson JL, Achermann JC. Variable presentation of X-linked adrenal hypoplasia congenita. J Pediatr Endocrinol Metab. 2001;14:1093–6. PubMed PMID: 11592565.

Xu B, Yang WH, Gerin I, Hu CD, Hammer GD, Koenig RJ. Dax-1 and steroid receptor RNA activator (SRA) function as transcriptional coactivators for steroidogenic factor 1 in steroidogenesis. Mol Cell Biol. 2009;29:1719–34. PubMed PMID: 19188450.

Zachmann M, Fuchs E, Prader A. Progressive high frequency hearing loss: an additional feature in the syndrome of congenital adrenal hypoplasia and gonadotrophin deficiency. Eur J Pediatr. 1992;151:167–9. PubMed PMID: 1601004.

Zanaria E, Muscatelli F, Bardoni B, Strom TM, Guioli S, Guo W, Lalli E, Moser C, Walker AP, McCabe ER, et al. An unusual member of the nuclear hormone receptor superfamily responsible for X-linked adrenal hypoplasia congenita. Nature. 1994;372:635–41. PubMed PMID: 7990953.

Zhang YH, Huang BL, Niakan KK, McCabe LL, McCabe ER, Dipple KM. IL1RAPL1 is associated with mental retardation in patients with complex glycerol kinase deficiency who have deletions extending telomeric of DAX1. Hum Mutat. 2004;24:273. PubMed PMID: 15300857.

Chapter Notes

Acknowledgments

JCA is a Wellcome Trust Senior Research Fellow in Clinical Science (grant 098513/Z/12/Z) with support from the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust, UCL, and Great Ormond Street Hospital Children's Charity.

Revision History

- 25 January 2018 (bp) Comprehensive update posted live
- 17 October 2013 (me) Comprehensive update posted live
- 7 May 2009 (cd) Revision: deletion/duplication analysis available clinically
- 1 August 2006 (me) Comprehensive update posted live
- 10 December 2003 (me) Comprehensive update posted live
- 20 November 2001 (me) Review posted live
- March 2001 (ev) Original submission

License