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Androgen Insensitivity Syndrome

Synonym: Testicular Feminization

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Summary

Clinical characteristics

Androgen insensitivity syndrome (AIS) is typically characterized by evidence of feminization (i.e., undermasculinization) of the external genitalia at birth, abnormal secondary sexual development in puberty, and infertility in individuals with a 46,XY karyotype. AIS represents a spectrum of defects in androgen action and can be subdivided into three broad phenotypes:

- Complete androgen insensitivity syndrome (CAIS), with typical female external genitalia
- Partial androgen insensitivity syndrome (PAIS) with predominantly female, predominantly male, or ambiguous external genitalia
- Mild androgen insensitivity syndrome (MAIS) with typical male external genitalia

Diagnosis/testing

The diagnosis of AIS is established in an individual with a 46,XY karyotype who has: undermasculinization of the external genitalia, impaired spermatogenesis with otherwise normal testes, absent or rudimentary müllerian structures, evidence of normal or increased synthesis of testosterone and its normal conversion to dihydrotestosterone, and normal or increased luteinizing hormone (LH) production by the pituitary gland; AND/OR a hemizygous pathogenic variant in *AR* identified by molecular genetic testing.

Management

Treatment of manifestations: To prevent testicular malignancy, treatment of CAIS may include either removal of the testes after puberty when feminization is complete or prepubertal gonadectomy accompanied by estrogen replacement therapy. Because the risk of malignancy is low, however, removal of gonads is increasingly controversial. Additional treatment for CAIS may include vaginal dilation to avoid dyspareunia. Treatment of

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PAIS in individuals with predominantly female genitalia is similar to treatment of CAIS, but is more likely to include prepubertal gonadectomy to help avoid increasing clitoromegaly at the time of puberty. In individuals with PAIS and ambiguous or predominantly male genitalia, the tendency has been for parents and health care professionals to assign sex of rearing after an expert evaluation has been completed. Those individuals with PAIS who are raised as males may undergo urologic surgery such as orchiopexy and hypospadias repair. Those individuals with PAIS who are raised as females and who undergo gonadectomy after puberty may need combined estrogen and androgen replacement therapy. Males with MAIS may require mammoplasty for gynecomastia. A trial of androgen pharmacotherapy may help improve virilization in infancy. It is best if the diagnosis of AIS is explained to the affected individual and family in an empathic environment, with both professional and family support.

Prevention of secondary manifestations: Regular weight-bearing exercises and supplemental calcium and vitamin D are recommended to optimize bone health; bisphosphonate therapy may be indicated for those with evidence of decreased bone mineral density and/or multiple fractures.

Surveillance: Periodic reevaluation for gynecomastia during puberty in individuals assigned a male sex; monitoring of bone mineral density through DXA scanning in adults.

Evaluation of relatives at risk: For an apparently asymptomatic older or younger sib who has normal external female genitalia and who has not yet undergone menarche, a karyotype can be done first. For those phenotypic females who have a 46,XY karyotype, molecular genetic testing for the known *AR* variant in the family can be pursued next. If the *AR* variant in the family is not known, androgen binding assays could be considered.

Genetic counseling

AIS is inherited in an X-linked manner. Affected 46,XY individuals are almost always infertile. Each offspring of a female known to carry an *AR* pathogenic variant (heterozygote) is at a 25% risk for each of the following:

- Having a 46,XY karyotype and being affected
- Having a 46,XY karyotype and being unaffected
- Having a 46,XX karyotype and being a carrier
- Having a 46,XX karyotype and not being a carrier

Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variant in the family is known.

GeneReview Scope

Androgen Insensitivity Syndrome: Included Phenotypes [1]
• Complete androgen insensitivity syndrome (CAIS) • Partial androgen insensitivity syndrome (PAIS) • Mild androgen insensitivity syndrome (MAIS)

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

No formal diagnostic criteria for identifying AIS have as yet been published; large variance is seen at the molecular, biochemical, and morphologic levels due to the extreme variation in these characteristics with the various AIS phenotypes [Gottlieb et al 2012].

Suggestive Findings

Androgen insensitivity syndrome (AIS) **should be suspected** in an individual with the following clinical, family history, radiologic, and supportive laboratory findings.

Clinical features

- Absence of extragenital abnormalities
- Two nondysplastic testes
- Absent or rudimentary müllerian structures (i.e., fallopian tubes, uterus, and cervix) and the presence of a short vagina
- Undermasculinization of the external genitalia at birth
- Impaired spermatogenesis and/or somatic virilization (some degree of impaired virilization at puberty)

Family history of other affected individuals related to each other is in a pattern consistent with X-linked inheritance. "Other affected family members" refers to:

- Affected 46,XY individuals;
- Manifesting heterozygous females (46,XX). About 10% of heterozygous females have asymmetric distribution and sparse or delayed growth of pubic and/or axillary hair.

Note: Absence of a family history of AIS or suggestive features of AIS does not preclude the diagnosis.

Radiology findings in the "predominantly male" phenotype (Table 2) including impaired development of the prostate and of the wolffian duct derivatives demonstrated by ultrasonography or genitourography

Supportive laboratory findings

- Normal 46,XY karyotype
- Evidence of normal or increased synthesis of testosterone (T) by the testes
- Evidence of normal conversion of testosterone to dihydrotestosterone (DHT)
- Evidence of normal or increased luteinizing hormone (LH) production by the pituitary gland
- In CAIS, but not in PAIS: possible reduction in postnatal (0-3 months) surge in serum LH and serum T concentrations [Bouvattier et al 2002]
- In the "predominantly male" phenotype (Table 2):
    - Less than normal decline of sex hormone-binding globulin in response to a standard dose of the anabolic androgen, stanozolol [Sinnecker et al 1997]
    - Higher than normal levels of anti-müllerian hormone during the first year of life or after puberty has begun

Establishing the Diagnosis

The diagnosis of AIS **is established** in a 46,XY proband with:

- Undermasculinization of the external genitalia, impaired spermatogenesis with otherwise normal testes, absent or rudimentary müllerian structures, evidence of normal or increased synthesis of testosterone and its normal conversion to dihydrotestosterone, and normal or increased LH production by the pituitary gland; AND/OR
- A hemizygous pathogenic (or likely pathogenic) variant in *AR* identified by molecular genetic testing (see Table 1).

  Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic

and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a hemizygous *AR* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *AR* is performed first. Gene targeted deletion/duplication analysis to detect multiexon or whole-gene deletions or duplications may be considered if a pathogenic variant in *AR* is not identified by sequence analysis.
- **A multigene panel** that includes *AR* 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 the 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *AR*) fails to confirm a diagnosis in an individual with features of AIS. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Androgen Insensitivity Syndrome

Gene [1]	Method	Proportion of 46,XY Probands w/a Pathogenic Variant [2] Detectable by Method
AR	Sequence analysis [3]	~95%-97% [4]
	Gene-targeted deletion/ duplication analysis [5]	~3%-5% [4]

Table 1. continued from previous page.

Gene [1]	Method	Proportion of 46,XY Probands w/a Pathogenic Variant [2] Detectable by Method
Unknown [6] • CAIS: 65%-95% [4, 7] • PAIS: <50% [4, 7] • MAIS: Unknown	See footnotes 5, 6, and 7.	

CAIS = complete androgen insensitivity syndrome; MAIS = mild androgen insensitivity syndrome; PAIS = partial androgen insensitivity syndrome

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on 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. androgendb.mcgill.ca; www.hgmd.cf.ac.uk

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as 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. AR pathogenic variant detection frequency in individuals with MAIS is more difficult to assess because of the assumption that MAIS diagnoses are often missed: (1) In the presence of deficient or defective androgen binding activity in genital skin fibroblasts in an XY individual with clinical findings of CAIS and PAIS, the likelihood of finding a pathogenic variant in the androgen binding domain of *AR* approached 40% [Weidemann et al 1996]. (2) In the presence of normal androgen binding in genital skin fibroblasts in an XY individual with clinical findings of PAIS, the likelihood of finding an AIS-causing *AR* variant is 10% or less, even when exon 1 is screened and/or sequenced in its entirety [Author, personal observation]. (3) Because the presence of an *AR* pathogenic variant, not abnormal androgen binding, is now the primary diagnostic criterion for AIS, defective androgen binding activity in an XY individual with clinical findings of CAIS, PAIS, or MAIS who does not have an *AR* pathogenic variant may be inappropriately precluded from the above diagnostic categories [Gottlieb et al 2012, Lek et al 2014, Mongan et al 2015]. Indeed, it has now been suggested that a new category of 46,XY disorder of sex development be established, in which no *AR* variant is found, although *AR* binding may be impaired [Lek et al 2014]. However, this would appear to be premature in light of the discovery of a number of cases of somatic mosaicism and intra-tissue genetic heterogeneity [Gottlieb et al 2012].

7. An informal survey of AIS databases in Canada, United States, and Great Britain showed that *AR* pathogenic variant detection frequency ranged from 65% to 95% in individuals with CAIS and from 40% to 45% in those with PAIS. The AIS database at the Lady Davis Institute for Medical Research (Montreal, Canada), which includes 138 individuals with CAIS or PAIS, reflects this variable detection rate [Gottlieb et al 2012]. Indeed, two additional reports have revealed a substantial percentage of individuals with putative PAIS in whom no *AR* variant has been found [Veiga-Junior et al 2012, Lek et al 2014].

Androgen binding assay. If molecular genetic testing fails to identify a pathogenic variant that can explain the affected individual's phenotype, testing of a biopsy of genital skin for defective androgen binding may be considered. As a result of the increasing number of individuals with features of PAIS in whom no pathogenic A*R* variant is able to be identified, there has been an increase in demand for androgen binding assays to confirm the diagnosis of AIS.

Clinical Characteristics

Clinical Description

Androgen insensitivity syndrome (AIS) can be subdivided into three phenotypes: complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS) (Table 2).

Table 2. Classification of AIS Phenotypes

Type	External Genitalia (Synonyms)	Findings
CAIS	Female ("testicular feminization")	• Absent OR rudimentary wolffian duct derivatives • Absence or presence of epididymides &/or vas deferens • Inguinal, labial, or abdominal testes • Short blind-ending vagina • Scant OR absent pubic &/OR axillary hair
PAIS	Predominantly female ("incomplete AIS")	• Inguinal OR labial testes • Clitoromegaly & labial fusion • Distinct urethral & vaginal openings OR aurogenital sinus
	Ambiguous	• Microphallus (<1 cm) with clitoris-like underdeveloped glans; labia majora-like bifid scrotum • Descended OR undescended testes • Perineoscrotal hypospadias OR urogenital sinus • Gynecomastia (development of breasts) in puberty
	Predominantly male	• Simple (glandular or penile) OR severe (perineal) "isolated" hypospadias w/normal-sized penis & descended testes OR severe hypospadias w/micropenis, bifid scrotum, & either descended or undescended testes • Gynecomastia in puberty
MAIS	Male ("undervirilized male syndrome")	• Impaired spermatogenesis &/OR impaired pubertal virilization • Gynecomastia in puberty

Adapted from Sinnecker et al [1997]

Complete androgen insensitivity syndrome (CAIS). Individuals with CAIS have normal female external genitalia with absence of female internal genitalia. They typically present either before puberty with masses in the inguinal canal that are subsequently identified as testes or at puberty with primary amenorrhea and sparse to absent pubic or axillary hair. Breasts and female adiposity develop normally. Sexual identity and orientation are typically female and heterosexual.

CAIS almost always runs true in families; that is, affected XY relatives usually have normal female external genitalia and seldom have any sign of external genital masculinization, such as clitoromegaly or posterior labial fusion [Boehmer et al 2001]. On occasion, wolffian duct development is observed [Hannema et al 2004].

Partial AIS (PAIS) with predominantly female external genitalia presents in a manner similar to CAIS; however, affected individuals have signs of external genital masculinization including clitoromegaly or posterior labial fusion.

Partial AIS with ambiguous genitalia or predominantly male genitalia (PAIS, Reifenstein syndrome). Determining the sex of rearing may be an issue for children with frank genital ambiguity. In families with PAIS, phenotypic disparity may warrant male sex of rearing in one affected sib and female sex of rearing in another affected sib [Boehmer et al 2001, Chen et al 2015]. Individuals wib PAIS and predominantly male genitalia are raised as males. Gynecomastia at puberty and impaired spermatogenesis occur in all individuals with PAIS. Pubic hair is usually moderate; facial, body, and axillary hair are often reduced.

Mild AIS (MAIS, undervirilized male syndrome). The external genitalia of affected individuals are unambiguously male. They usually present with gynecomastia at puberty. They may have undermasculinization that includes sparse facial and body hair and small penis. Impotence may be a complaint. Spermatogenesis may or may not be impaired. In some instances, the only observed abnormality appears to be male infertility [Gottlieb et al 2005]; therefore, MAIS could explain some cases of idiopathic male infertility [Goglia et al 2011].

MAIS almost always runs true in families.

Genotype-Phenotype Correlations

A correlation does exist among certain missense *AR* variants, their functional consequences, and external genital development, particularly in the case of CAIS (see the Androgen Receptor Gene Mutations Database).

The correlation is much less clear in PAIS, in which interfamilial phenotypic variation is observed [Brinkmann & Trapman 2000, Boehmer et al 2001, Deeb et al 2005, Gottlieb et al 2012, Lek et al 2014].

The Androgen Receptor Gene Mutations Database includes 45 instances in which identical *AR* variants produce different AIS phenotypes [Gottlieb et al 2001a, Gottlieb et al 2012].

In some instances, the variable expressivity associated with a number of single-nucleotide variants may be attributed to somatic mosaicism rather than to the modifying influence of "background" genetic factors [Boehmer et al 1997, Holterhus et al 1997, Holterhus et al 2001, Köhler et al 2005]. See Gottlieb et al [2001b] for a detailed discussion of the possible role of somatic mosaicism as a cause of variable expressivity.

It remains to be determined whether specific missense variants can be correlated with normal or impaired spermatogenesis and with absence or presence of localized expressions of undervirilization (e.g., gynecomastia, high-pitched voice, impotence). Although specific variants associated with azoospermia have been reported [Zuccarello et al 2008, Mirfakhraie et al 2011], only a more extensive analysis of more cases of idiopathic male infertility is likely to identify definitive correlations. Melo et al [2010] noted that infertile males who do not produce sperm have a higher number of *AR* variants than do males with impaired sperm production. Idiopathic infertility cases were found in both oligospermic and azoospermic men who had *AR*-CAG repeat lengths that were either significantly shorter (15-18 CAG repeat lengths) or significantly longer (22-28) than normal (i.e., 19-21); see Gottlieb et al [2012] and Giagulli et al [2014].

Penetrance

No definitive data regarding penetrance exist, possibly because of under-ascertainment of affected individuals, particularly phenotypic but infertile males in whom *AR* molecular genetic testing may not be performed [Gottlieb et al 2005]. The problem is compounded by situations where there is a genotype-phenotype disconnect and when individuals with features of AIS are not found to have an identifiable *AR* pathogenic variant.

Nomenclature

The terms "testicular feminization" and androgen resistance syndrome are outdated and thus rarely used now.

Prevalence

Standard references quote a prevalence of 2:100,000 to 5:100,000 for complete AIS (CAIS) based on estimates derived from otherwise healthy phenotypic females found to have histologically normal inguinal or abdominal testes. A survey in the Netherlands over a ten-year period based on reported cases of AIS concluded that the minimal incidence was 1:99,000 [Boehmer et al 2001].

Partial AIS (PAIS) is at least as common as CAIS.

The prevalence of mild AIS (MAIS) has not yet been determined. However, it is much less frequently reported than CAIS and PAIS [Hughes et al 2012].

Genetically Related (Allelic) Disorders

Expansion of the polymorphic CAG trinucleotide repeat within *AR* causes spinal and bulbar muscular atrophy (SBMA; Kennedy disease).

See Molecular Genetics, **Somatic *AR* alterations and cancer** for other disease conditions associated with somatic alterations to AR.

Differential Diagnosis

Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome (OMIM 277000) is diagnosed in phenotypic females who exhibit amenorrhea and have a partial or complete absence of the cervix, uterus, and vagina. Individuals with MRKH can be distinguished from those with CAIS by confirmation of a 46,XX karyotype [Sultan et al 2009].

Hypospadias resulting from an *AR* pathogenic variant (and thus a part of the spectrum of PAIS) cannot be distinguished from hypospadias resulting from other (largely undefined) causes by the examination of the genitalia alone. *AR* variants associated with hypospadias are likely rare.

MAIS caused by single-nucleotide variants of *AR* [Wang et al 1998] may be clinically indistinguishable from MAIS caused by expansion of the polymorphic CAG repeat in *AR* [Tut et al 1997]. Pathogenic expansion of this triplet repeat is the cause of spinal and bulbar muscular atrophy (SBMA), also known as Kennedy disease (see Genetically Related Disorders).

Undermasculinization of the external genitalia and pubertal undervirilization are components of many different syndromes that have no etiologic relation to *AR*. They may or may not have a pathogenic relation to the androgen receptor protein. The one exception is a contiguous gene deletion syndrome that includes the *AR* locus and results in intellectual disability and genital abnormalities [Davies et al 1997].

46,XY infants born small for gestational age may have clinical features of PAIS with no identifiable *AR* pathogenic variant. It has been suggested that this association be termed "XY DSD with fetal growth restriction, as yet unexplained" [Lek et al 2014].

A survey of the Androgen Receptor Gene Mutations Database suggests that AIS may be attributable to factors other than the presence of *AR* variants. Findings that suggest the presence of other identifiable diagnoses in 46,XY individuals with predominantly female, ambiguous, or predominantly male genitalia include the following:

- Elevated levels of testosterone precursors caused by a partial testosterone biosynthetic defect in which compensatory serum LH concentrations stimulate a normal plasma testosterone concentration
- The presence of müllerian duct derivatives as a result of a testicular organogenesis defect with impaired Sertoli cell production of anti-müllerian hormone
- The presence of wolffian duct-derived internal male reproductive structures that differentiate in response to testosterone, suggesting 5-alpha-reductase deficiency, a partial testosterone biosynthetic defect, or PAIS. 5-alpha-reductase deficiency (OMIM 264600) is the result of biallelic pathogenic variants in *SRD5A2*. The enzyme converts testosterone to dihydrotestosterone (DHT), which is primarily responsible for the development of the external genitalia before birth.
- A recent study has reported that some individuals with features of PAIS have been found to have biallelic pathogenic variants in *HSD17B3*, which causes 17-beta hydroxysteroid dehydrogenase III deficiency (OMIM 264300) [Phelan et al 2015].

Issues to consider in individuals with some, but not all, of the clinical features of AIS:

- Normal serum concentrations of T, DHT, and LH after birth do not prove that the concentration was normal during the critical period of fetal genital masculinization.
- Normal responsiveness to androgen after birth does not prove that it was normal before birth. That is, in utero delay in the acquisition of normal androgen biosynthesis or normal androgen sensitivity may lead to features consistent with androgen insensitivity.

- Subnormal sensitivity to androgen after birth may involve components of the overall androgen response system (AR-interacting proteins) beyond the androgen receptor itself.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and the needs of an individual diagnosed with androgen insensitivity syndrome, a complete evaluation by specialists in disorders of sex development (DSDs), which can include specialists in endocrinology, urology, gynecology, clinical genetics, psychology, and psychiatry [Hughes et al 2006, Parisi et al 2007, Douglas et al 2010], is ideal.

Treatment of Manifestations

A number of clinicians have sought to establish a consensus statement on management of DSD including AIS [Hughes & Deeb 2006]. A number of publications have subsequently discussed best management of these disorders. See Diamond & Beh [2008] (full text), Douglas et al [2010] (full text), Pasterski et al [2010] (full text), Wiesemann et al [2010] (full text), and Hughes et al [2012] (full text).

Assignment of sex of rearing. The issue of sex assignment in infancy when the child is being evaluated for ambiguous genitalia is paramount. It requires informed decision making by parents and health care personnel and should be resolved as early as possible, after a multidisciplinary evaluation has been completed.

- Even in CAIS this may not always be easy. Cheikhelard et al [2008] evaluated 29 individuals with CAIS; it was recommended that gonads be retained at least until the completion of spontaneous puberty and the possibility of virilization be evaluated before management decisions are made.
- Psychological counseling and use of support groups can be of benefit [Cull & Simmonds 2010, Hughes et al 2012].
- Gender identity has become a topic of increasing importance due to the possibility of changes in sex assignment over time [Kolesinska et al 2014].
- Issues of sexual orientation regardless of gender phenotype have also become increasingly important to explore and discuss [Brunner et al 2016].

CAIS

A critical consideration of any surgical intervention is the nature and timing of such intervention; thus, surgeons need to be involved with the affected individuals and pediatrician in any such decisions [Purves et al 2008, Munoz & Swan 2010]. Vidal et al [2010] reviewed the evolution of surgical techniques for "feminization" and "masculinization" and their possible outcomes.

A common practice is to remove the testes after puberty when feminization of the affected individual is complete, since feminization occurs partly by testicular estrogen and partly by peripheral conversion of androgen to estrogen.

The rationale for postpubertal gonadectomy is that testicular malignancy, which develops at the usual rate for cryptorchid testes, seldom occurs before puberty [Hannema et al 2006]. Prepubertal gonadectomy is now only considered if inguinal testes are physically or esthetically uncomfortable, and if inguinal herniorrhaphy is necessary. In this event, estrogen replacement therapy is necessary to initiate puberty, maintain feminization, and avoid osteoporosis.

However, the issue of gonadectomy is controversial. Some have argued that the true risk for malignant transformation of the gonads is small and have suggested postpubertal gonad biopsy as opposed to removal

[Hughes et al 2006, Parisi et al 2007, Patel et al 2016], which would allow affected individuals to retain a natural source of androgen production and avoid exogenous hormone replacement.

In one study of 48 individuals diagnosed with either CAIS or PAIS, gonadoblastomas were observed in 9/30 (30%) of individuals with CAIS and 3/18 (16%) of individuals with PAIS, suggesting that the risk of gonadal malignancy may be greater than previously reported; the authors suggest earlier rather than later prophylactic gonadectomy [Liu et al 2014]. Another study found the frequency of gonadal tumor in individuals with CAIS was 13/48 (27%) and in those with PAIS was 2/21 (9%), with similar conclusions regarding the time of gonadectomy [Jiang et al 2016].

Vaginal dilation to augment vaginal length and to avoid dyspareunia is typically the treatment of choice for those with short vaginal length. If this method fails, new treatments of blind vagina have been proposed, including autologous buccal mucosal graft vaginoplasty and enhanced balloon vaginoplasty [Zhao et al 2009, El Saman et al 2011]. Recent studies that examined the long-term outcomes of vaginoplasty with autologous buccal micromucosa indicated a high degree of satisfaction [Li et al 2014]. In addition, a study reported that peritoneal vaginoplasty appeared to be superior to ileal vaginoplasty [Huang et al 2014]. However, surgical reconstruction frequently requires maintenance vaginal dilation to decrease the likelihood of future stricture.

The question of how much and when to disclose the diagnosis of CAIS to an affected individual has not been resolved uniformly; however, it has become obvious that explanation of the diagnosis in an empathic setting is much preferable to systematic concealment or self-discovery of the diagnosis in an environment devoid of support from family, professionals, and other affected individuals [Conn et al 2005].

PAIS with Predominantly Female Genitalia (Incomplete AIS)

The issues are similar to those discussed under CAIS, except prepubertal gonadectomy helps avoid the emotional discomfort of increasing clitoromegaly at the time of puberty.

In instances in which the diagnosis of PAIS is difficult to establish because of the presence of somatic mosaicism, a change of sex assignment can result in concomitant problems [Köhler et al 2005].

PAIS with Ambiguous Genitalia or Predominantly Male Genitalia

The assignment of sex in an infant with ambiguous genitalia is a complex process that requires timely assessment by a multidisciplinary team in consultation with the family and should be resolved as early as possible. Aside from purely anatomic and surgical considerations, the choice of a male sex-of-rearing demands a therapeutic trial with pharmacologic doses of androgen to try to predict potential androgen responsiveness at puberty. Furthermore, appreciable phallic growth in response to administered androgen facilitates reconstructive surgery.

In instances in which maximum information is being gathered on an infant with no family history of AIS before sex is assigned, sequence analysis of *AR* may be considered; however, the lower probability of detecting an *AR* variant in individuals with the PAIS phenotype and the poor positive predictive value of any given variant regarding AIS phenotype need to be considered when making decisions about sex assignment.

It has also been reported that the length of the *AR* exon 1 CAG repeat can influence the efficacy of testosterone treatments: individuals with shorter repeat lengths are more likely to respond to hormonal treatments [Zitzmann 2009]. However, the efficacy of CAG repeat length as a possible marker to assess hormonal treatment must await further studies.

Based on experience with a small number of individuals, the role of long-term androgen pharmacotherapy in individuals with PAIS who are raised as males remains unclear. Response to androgen treatment may be substantial in individuals with certain missense variants in the DNA-binding domain of the androgen receptor [Weidemann et al 1998], and a recent study confirmed the difficulty of accurately predicting the efficacy of

androgen treatment [Becker et al 2016]. Thus, considerable caution should be exercised with regard to androgen treatment [Werner et al 2010], in particular because special hormonal profiles to androgen insensitivity have often not been acknowledged in replacement strategies. It has been proposed that an external masculinization score in neonates could be a reasonable predictor of virilization at puberty in individuals with PAIS who have been assigned a male sex of rearing [Hughes et al 2012].

Gynecomastia that develops in puberty eventually requires reduction mammoplasty. It has been reported that tamoxifen has been used for treating pubertal gynecomastia in two sibs with PAIS [Saito et al 2014].

Those individuals with PAIS who are raised as females and who have gonadectomy after puberty may need combined estrogen and androgen replacement therapy, the latter to maintain libido.

MAIS

Men with MAIS often require reduction mammoplasty for treatment of gynecomastia.

A trial of androgen pharmacotherapy is recommended to attempt to improve virilization [Loy & Yong 2001].

Prevention of Primary Manifestations

The efficacy of androgen therapy in preventing manifestations such as gynecomastia is not clear.

Prevention of Secondary Manifestations

Women with CAIS have decreased bone mineral density, regardless of timing of gonadectomy [Oakes et al 2008]. However, women with PAIS who choose not to undergo gonadectomy do not appear to be at high risk for decreased bone mineral density [Bertelloni et al 2010].

- In addition to estrogen replacement therapy, supplemental calcium and vitamin D are recommended.
- Regular weight-bearing exercises are encouraged to maintain bone health.
- Bisphosphonate therapy may be indicated for those individuals with evidence of decreased bone mineral density and/or multiple fractures.

Surveillance

Appropriate measures include the following:

- Monitoring of postnatal development of genitalia that were ambiguous at birth for changes that could lead to reconsideration of the assigned sex
- For individuals assigned a male sex, evaluation during puberty for signs of gynecomastia
- In adults, monitoring of bone mineral density through DXA (dual-energy x-ray absorptiometry) scanning [Oakes et al 2008]

Evaluation of Relatives at Risk

It is appropriate to evaluate the apparently asymptomatic older and younger sibs of a proband in order to identify as early as possible those who would benefit from institution of treatment and preventive measures.

- Evaluations can include karyotype in sibs who have normal external female genitalia but have not yet undergone menarche.
- Molecular genetic testing can be pursued next if a phenotypic female is found to have a 46,XY karyotype and if the *AR* variant in the family is known.
- Androgen binding assays may be considered if an *AR* variant has not been identified in the family.

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 access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Chen et al [2010] noted that Fkbp52 regulates AR transactivation activity and male urethra morphogenesis, suggesting that *AR* variants may require other genetic factors to produce hypospadias.

Apolipoprotein D (APOD) is a possible biomarker of AR function in AIS [Appari et al 2009].

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

Androgen insensitivity syndrome (AIS) is inherited in an X-linked manner.

Risk to Family Members

Parents of a 46,XY proband

- The father of a proband will not have the disorder nor will he be hemizygous for the *AR* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). If a woman has more than one affected child and the pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism.
- If the proband is the only affected family member (i.e., a simplex case) several possibilities exist regarding the carrier status of the mother:
  - The mother is heterozygous for an *AR* pathogenic variant; in 22 of 30 simplex families with CAIS or PAIS, the mother was proven to be heterozygous for an *AR* pathogenic variant [Hiort et al 1998].
  - The mother has germline mosaicism or somatic and germline mosaicism for an *AR* pathogenic variant [Boehmer et al 1997, Köhler et al 2005].
  - The mother is not a carrier and the pathogenic variant occurred *de novo* in the proband; *de novo* pathogenic variants can be expected to occur approximately 30% of the time [Hughes & Deeb 2006].

Sibs of a 46,XY proband. The risk to the sibs depends on the carrier status of the mother:

- If the mother of the proband has an *AR* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Sibs with a 46,XY karyotype who inherit the *AR* pathogenic variant will be affected.
  - Sibs with a 46,XX karyotype who inherit the *AR* pathogenic variant will be carriers.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *AR* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism [Boehmer et al 1997].

Offspring of a 46,XY proband. Individuals with a 46,XY karyotype who have any of the subtypes of AIS (i.e., CAIS, PAIS, MAIS) are almost always infertile.

Offspring of a heterozygous (carrier) female

- Each offspring of a female known to be a carrier of an *AR* pathogenic variant carrier (heterozygote) has a 25% likelihood of each of the following:
  - Having a 46,XY karyotype and being affected
  - Having a 46,XY karyotype and being unaffected
  - Having a 46,XX karyotype and being a carrier
  - Having a 46,XX karyotype and not being a carrier
- The phenotype of offspring with a 46,XY karyotype and CAIS or MAIS tends to be fairly predictable. The genital phenotype of individuals with PAIS within a family is generally consistent; however, a wide range of phenotypic variability is seen among families who share the same PAIS pathogenic variant, making it difficult to predict the phenotype in a simplex case.

Heterozygote (Carrier) Detection

Female carriers may be identified through one or a combination of the following:

- **Molecular genetic testing.** Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband. If an affected family member is not available for testing, molecular genetic testing can be offered first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

  Note: Inability to detect a pathogenic variant in *AR* in an at-risk female relative when the proband is not available for genetic testing does not preclude carrier status.

- **Family history**

- **Clinical findings.** Ten percent of carriers are manifesting carriers with asymmetric distribution and sparse or delayed growth of pubic or axillary hair, a finding that results from random X-chromosome inactivation. The presence of normal pubic and axillary hair does not rule out the possibility that an individual with a 46,XX karyotype is a carrier.

Related Genetic Counseling Issues

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

Cohen-Kettenis [2010] reviews some similarities in relevant psychosocial and psychosexual issues associated with gender dysphoria in people with disorders of sex development (DSDs) and those with who do not have a DSD. Because few studies focusing on the psychosocial and psychosexual issues in individuals with DSDs have been completed, Cohen-Kettenis [2010] suggests that clinicians working with individuals and families with DSDs consider relying on the literature related to individuals with gender dysphoria who do not have a DSD.

Gender identity. In a long-term outcome study of DSDs that included CAIS, it was noted that while many affected individuals fare well, dissatisfaction with original sex assignment has been underestimated and gender and sexual counseling should be part of the multidisciplinary service available to individuals with DSDs [Warne 2008].

Of particular interest is a case report of an individual with CAIS with male gender identity [Tsjoen et al 2011]. More recently, another individual with CAIS who has a male gender identity was reported; this individual has a sib with CAIS who had female central precocious puberty [Bermúdez de la Vega et al 2015]. Further insight into

issues of gender identity in persons with CAIS is available from analysis of accounts presented by an XY female on the UK AIS Support Group website; see Garrett & Kirkman [2009].

An additional ethical and possibly legal issue is the genetic testing of other family members for AIS. In a 1999 court decision (unrelated to AIS) chromosome findings alone were used to determine an individual's sex. Clinicians should be aware that information provided to individuals with AIS and their families (in the interest of facilitating appropriate medical care) could potentially have legal implications for such individuals/families [Berg et al 2007].

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 affected or at risk.

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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancy. Once the *AR* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Pregnancies not known to be at increased risk for AIS. Prenatal diagnosis of AIS in pregnancies not known to have been at risk have been published. In two cases, diagnosis of AIS was suspected after discordance in sex identified by ultrasonography (female) and karyotype (46,XY) was found [Yalinkaya et al 2007, Bianca et al 2009]. In another report, cell-free fetal DNA obtained using noninvasive prenatal screening found the presence of Y chromosome material in a fetus with female external genitalia by ultrasound. A subsequent amniocentesis revealed the presence of a pathogenic *AR* variant, which resulted in a diagnosis of AIS [Zilberman et al 2015].

Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Androgen Insensitivity Syndrome Support Group Australia (AISSG)**
  PO Box 3239
  South Brisbane Queensland 4101
  Australia
  Email: aissgaustralia@gmail.com
  http://www.aissga.org.au/

- **Androgen Receptor Gene Mutations Database**
  The Lady Davis Institute for Medical Research
  Montreal Quebec

Canada
Email: bruce.gottlieb@mcgill.ca
androgendb.mcgill.ca

- **Intersex Society of North America (ISNA)**
  Rohnert Park CA 94928
  Androgen Insensitivity Syndrome
- **National Library of Medicine Genetics Home Reference**
  Androgen insensitivity syndrome
- **InterConnect**
  https://interconnect.support/

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. Androgen Insensitivity Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AR	Xq12	Androgen receptor	AR @ LOVD alsod/AR genetic mutations The Androgen Receptor Gene Mutations Database	AR	AR

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 Androgen Insensitivity Syndrome (View All in OMIM)

300068	ANDROGEN INSENSITIVITY SYNDROME; AIS
313700	ANDROGEN RECEPTOR; AR

Gene structure. *AR* comprises nine exons. Nucleotide numbering is complicated by the length of the variable polyglutamine and polyglycine repeats (see Kennedy Disease). A reference sequence must be specified when naming variants in *AR*.

For a detailed summary of gene and protein information, see Table A, **Gene**. See also **Normal gene product**.

Coincidentally, two major species of *AR* mRNA (10-11 kb; ~7 kb) result from alternative splicing of a very long 3'-UTR. Two forms of the androgen receptor protein (A and B) exist. Their size difference suggests that the short form (B) represents translation initiation at the internal p.Met190 residue.

Note: The Androgen Receptor Gene Mutations Database has recently changed its nucleotide and amino acid numbering scheme to conform to the HGVS standards, which are based on NCBI cDNA reference sequence NM_000044.2.

Pathogenic variants. More than 550 single-nucleotide variants in *AR* have been found to cause AIS (see Androgen Receptor Gene Mutations Database). The great majority are missense variants that impair DNA or androgen binding and cause CAIS or PAIS; a small number have been proven to cause MAIS.

Single-nucleotide variants in exon 1 are relatively uncommon; the majority of variants are either nonsense or small deletions or insertions that result in a frameshift; thus, they almost always cause CAIS; PAIS is seldom the

result of exon 1 variants [Choong et al 1996]. That said, the number of single-nucleotide variants identified in exon 1 has increased over the past few years; a considerable number are associated with the MAIS phenotype (see Androgen Receptor Gene Mutations Database).

A relatively small number of *AR* deletions/duplications of one or more exons or of the whole gene have been described (see Table A, **Locus-Specific Databases**). In almost all cases when an attempt has been made to test these variant forms of androgen receptor protein, they have been found to be nonfunctional.

Expansion of the trinucleotide repeat tract $(CAG)_nCAA$ that encodes a polyglutamine tract to more than 38 repeats results in Kennedy disease (spinal and bulbar muscular atrophy) with some findings of MAIS, which are likely the result of the reduced transactivation of *AR* with long CAG repeat tracts of androgen receptor proteins that contain expanded polyglutamine tracts.

Normal gene product. Androgen receptor. The entire N-terminal portion of the androgen receptor (~538 amino acids) is encoded by exon 1, the DNA-binding domain (amino acid residues 558-617) by exons 2 and 3, the bipartite nuclear localization signal (amino acid residues 618-637) by exons 3 and 4, and the androgen-binding domain (residues 646-920) by exons 4-8.

Two forms of the androgen receptor protein (A and B) are produced by the alternative splice forms of *AR* (see **Gene structure**). Their size difference suggests that the short form (B) represents translation initiation at the internal p.Met190 residue.

The androgen receptor is a well-defined transcriptional regulatory factor. Once activated by binding to androgen, it collaborates with other co-regulatory proteins (some involve DNA binding, others do not) to achieve control over the rate of transcription of an androgen target gene that is under the influence of a nearby promoter. A large number of AR-associated proteins have now been identified [Heinlein & Chang 2002, Gottlieb et al 2004b, Gottlieb et al 2012]; for latest listing see the Androgen Receptor Gene Mutations Database.

Abnormal gene product. Nearly all single-nucleotide variants in the androgen-binding domain impair androgen binding and impair transactivation by the AR. Some decrease only the apparent equilibrium affinity constant; some increase only the non-equilibrium dissociation rate; others do both, either with all androgens or selectively with certain androgens. Still others are thermolabile or degrade excessively in the presence of androgen. Single-nucleotide variants in the zinc fingers or α-helical portions of the DNA-binding domain impair binding to a sequence of regulatory nucleotides known as an androgen response element. Such binding is essential for the androgen receptor to exert transcriptional regulatory control over most of its target genes.

The effect of specific variants on the functionality of the androgen receptor has been studied using molecular dynamic modeling based on the x-ray crystal structure [Matias et al 2000]. This technique has successfully simulated the effects of particular variants on the ligand-binding properties of mutated androgen receptors [Wu et al 2003, Elhaji et al 2004, Elhaji et al 2006]. It is hoped that this technique may eventually lead to treatments that return to normal the ligand-binding capacity of mutated androgen receptors.

Somatic *AR* alterations and cancer. Some cancers show somatic alterations in *AR*. These, however, appear to result in a gain of function rather than the loss of function seen in AIS. Cancers include the following [Gottlieb et al 2004a, Gottlieb et al 2012]:

- Prostate cancer
- Male breast cancer
- Laryngeal cancer
- Liver cancer
- Testicular cancer
- Bladder cancer [Rahmani et al 2013]

Chapter Notes

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