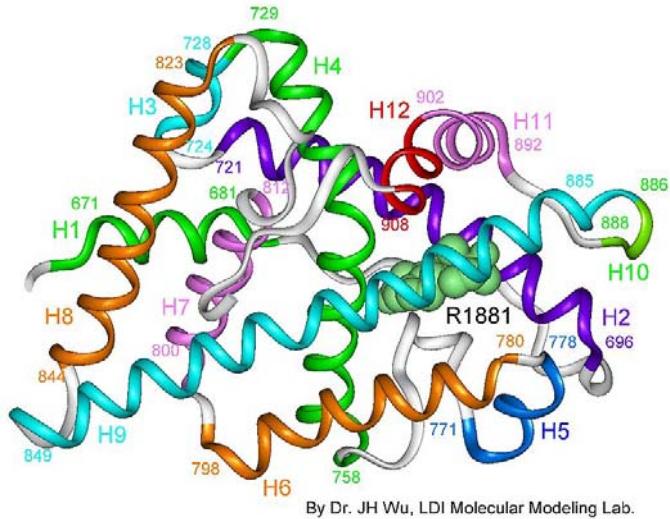


# Androgen insensitivity syndrome

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Androgen Insensitivity Syndrome results when the function of the androgen receptor (AR) is impaired. The AR protein (pictured) mediates the effects of androgens in the human body.

**Androgen insensitivity syndrome (AIS)** is a condition that results in the partial or complete inability of the cell to respond to androgens<sup>[1][2][3]</sup> (androgenic hormones) that stimulate or control the development and maintenance of male physiological characteristics by binding to androgen receptors.<sup>[4]</sup> The unresponsiveness of the cell to the presence of androgenic hormones can impair, or prevent, both the masculinization of male genitalia in the developing fetus, and the development of male secondary sexual characteristics at puberty, though it does not significantly impair the development of female genital or sexual characteristics in females and males with the condition.<sup>[3][5]</sup> As such, androgen insensitivity syndrome is of clinical significance only when it occurs in individuals that are genetically male (that is, persons with a Y-chromosome, or more specifically, an SRY gene).<sup>[1]</sup>

Clinical phenotypes in genetically male individuals with androgen insensitivity syndrome range from a normal external male body plus mild spermatogenic defect in post-pubertal stages, to a full female external body (although internal gonads are male testes instead of female ovaries) including post-pubertal external female characteristic development, despite the presence of a Y-chromosome.<sup>[1][6][7][8][9][10]</sup> Both genetically male and genetically female individuals with AIS show reduced to no secondary terminal hair development.

In genetic males with AIS, the condition is divided into three categories that are differentiated by the degree of genital masculinization: CAIS, or complete androgen

insensitivity syndrome, is indicated when the external genitalia are that of a normal female; PAIS, or partial androgen insensitivity syndrome, is indicated when the external genitalia are partially, but not fully, masculinized; MAIS, or mild androgen insensitivity syndrome, is indicated when the external genitalia are that of a normal male.<sup>[1][2][6][7][8][11][12][13][14]</sup>

Androgen insensitivity syndrome is the largest single entity that leads to 46,XY undermasculinized genitalia in intersex persons.<sup>[15]</sup> As with other intersex conditions, androgen insensitivity syndrome is independent of both sexual orientation and gender identity. The full spectrum of human sexual orientations has been reported among genetically female and genetically male AIS individuals alike, including: androphilia (i.e. sexual attraction to males) reported by most female-identified genetically-male female-bodied CAIS individuals; gynephilia (i.e. sexual attraction to females) reported even among some female-identified genetically-male female-bodied CAIS individuals in "lesbian"<sup>[16]</sup> relationships; ambiphilia (bisexuality).

Similarly, although AIS individuals may report any gender identity, a female gender identity is the gender identity of most, but not all, genetically-male female-bodied individuals with CAIS. Historically, however, the gender identity of CAIS individuals who identify as female has often been the cause of negative social bias and discrimination once their condition is made public. It is a matter of contention for some whether a CAIS individual with a female gender identity and external female body but genetic male sex should be regarded as "transgender". Some might regard such a person as "transgender" for identifying as female despite their genetic sex being male (even though they have an external female body), or they can be regarded as simply identifying as female in harmony to their external female body (despite their genetic male sex). Much social debate and litigation has resulted as a consequence of both arguments.

Male gender identities among a minority of individuals with complete androgen insensitivity syndrome, have also been reported. This has resulted in CAIS individuals who are genetically male with an external female body but a male gender identity<sup>[17]</sup> (irrespective of sexual orientation). A male gender identity among this minority, however, does not eliminate social contentions among some as to whether these individuals are "transgender", as they might be regarded to be identifying as male despite their external female body (even though their genetic sex is male), or they can be regarded as simply identifying as male in harmony to their genetic male sex (despite their external female body). This contention can be seen even in modern medical literature, where in one case study the genetically male CAIS patient with male gender identity was said to "qualif[y] as female-to-male transsexual" after undergoing genital reconstruction surgery.<sup>[18]</sup>

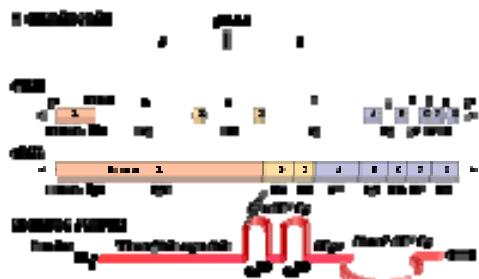
## Signs and symptoms



Women with AIS and related DSD conditions

AIS is broken down into three classes based on phenotype: complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS).<sup>[1][2][6][7][8][11][12][13][14]</sup> A supplemental system of phenotypic grading that uses seven classes instead of the traditional three was proposed by pediatric endocrinologist Charmian A. Quigley et al. in 1995.<sup>[3]</sup> The first six grades of the scale, grades 1 through 6, are differentiated by the degree of genital masculinization; grade 1 is indicated when the external genitalia is fully masculinized, grade 6 is indicated when the external genitalia is fully feminized, and grades 2 through 5 quantify four degrees of decreasingly masculinized genitalia that lie in the interim.<sup>[3]</sup> Grade 7 is indistinguishable from grade 6 until puberty, and is thereafter differentiated by the presence of secondary terminal hair; grade 6 is indicated when secondary terminal hair is present, whereas grade 7 is indicated when it is absent.<sup>[3]</sup> The Quigley scale can be used in conjunction with the traditional three classes of AIS to provide additional information regarding the degree of genital masculinization, and is particularly useful when the diagnosis is PAIS.<sup>[2][19]</sup>

## Genetics



Location and structure of the human androgen receptor. **Top**, The AR gene is located on the proximal long arm of the X chromosome. **Middle**, The eight exons are separated by introns of various lengths. **Bottom**, Illustration of the AR protein, with primary functional domains labeled (not representative of actual 3-D structure).<sup>[3]</sup>

The human androgen receptor (AR) is a protein encoded by a gene located on the proximal long arm of the X chromosome (locus Xq11-Xq12).<sup>[20]</sup> The protein coding region consists of approximately 2,757 nucleotides (919 codons) spanning eight exons,

designated 1-8 or A-H.<sup>[1][3]</sup> Introns vary in size between 0.7 and 26 kb.<sup>[3]</sup> Like other nuclear receptors, the androgen receptor protein consists of several functional domains: the transactivation domain (also called the transcription-regulation domain or the amino / NH<sub>2</sub>-terminal domain), the DNA-binding domain, the hinge region, and the steroid-binding domain (also called the carboxyl-terminal ligand-binding domain).<sup>[1][2][3][14]</sup> The transactivation domain is encoded by exon 1, and makes up more than half of the AR protein.<sup>[3]</sup> Exons 2 and 3 encode the DNA-binding domain, while the 5' portion of exon 4 encodes the hinge region.<sup>[3]</sup> The remainder of exon 4 through exon 8 encodes the ligand binding domain.<sup>[3]</sup>

## Trinucleotide satellite lengths and AR transcriptional activity

The androgen receptor gene contains two polymorphic trinucleotide microsatellites in exon 1.<sup>[2]</sup> The first microsatellite (nearest the 5' end) contains 8<sup>[21]</sup> to 60<sup>[22][23]</sup> repetitions of the glutamine codon "CAG" and is thus known as the polyglutamine tract.<sup>[3]</sup> The second microsatellite contains 4<sup>[24]</sup> to 31<sup>[25]</sup> repetitions of the glycine codon "GGC" and is known as the polyglycine tract.<sup>[26]</sup> The average number of repetitions varies by ethnicity, with Caucasians exhibiting an average of 21 CAG repeats, and Blacks 18.<sup>[27]</sup> In men, disease states are associated with extremes in polyglutamine tract length; prostate cancer,<sup>[28]</sup> hepatocellular carcinoma,<sup>[29]</sup> and intellectual disability<sup>[21]</sup> are associated with too few repetitions, while spinal and bulbar muscular atrophy (SBMA) is associated with a CAG repetition length of 40 or more.<sup>[30]</sup> Some studies indicate that the length of the polyglutamine tract is inversely correlated with transcriptional activity in the AR protein, and that longer polyglutamine tracts may be associated with male infertility<sup>[31][32][33]</sup> and undermasculinized genitalia in men.<sup>[34]</sup> However, other studies have indicated that no such correlation exists.<sup>[35][36][37][38][39][40]</sup> A comprehensive meta-analysis of the subject published in 2007 supports the existence of the correlation, and concluded that these discrepancies could be resolved when sample size and study design are taken into account.<sup>[12]</sup> Some studies suggest that longer polyglycine tract lengths are also associated with genital masculinization defects in men.<sup>[41][42]</sup> Other studies find no such association.<sup>[43]</sup>

## AR mutations

As of 2010, over 400 AR mutations have been reported in the AR mutation database, and the number continues to grow.<sup>[2]</sup> Inheritance is typically maternal and follows an X-linked recessive pattern;<sup>[1][44]</sup> individuals with a 46,XY karyotype will always express the mutant gene since they only have one X chromosome, whereas 46,XX carriers will be minimally affected. 30% of the time, the AR mutation is a spontaneous result, and is not inherited.<sup>[11]</sup> Such de novo mutations are the result of a germ cell mutation or germ cell mosaicism in the gonads of one of the parents, or a mutation in the fertilized egg itself.<sup>[45]</sup> In one study,<sup>[46]</sup> it was found that 3 out of 8 de novo mutations occurred in the post-zygotic stage, leading to the estimate that up to one third of de novo mutations result in somatic mosaicism.<sup>[1]</sup> It is worthwhile to note that not every mutation of the AR gene results in androgen insensitivity; one particular mutation occurs in 8 to 14 percent of

genetic males,<sup>[47][48][49][50]</sup> and is thought to adversely affect only a small number of individuals when other genetic factors are present.<sup>[51]</sup>

## Other causes

Some individuals with CAIS or PAIS do not have any AR mutations despite clinical, hormonal, and histological features sufficient to warrant an AIS diagnosis; up to 5% of women with CAIS do not have an AR mutation,<sup>[2]</sup> as well as between 27%<sup>[7][52]</sup> and 72%<sup>[53]</sup> of individuals with PAIS.

In one patient, it was shown that the underlying cause for presumptive PAIS was a mutant steroidogenic factor-1 (SF-1) protein.<sup>[54]</sup> In another patient, it was shown that CAIS was the result of a deficit in the transmission of a transactivating signal from the N-terminal region of the normal androgen receptor to the basal transcription machinery of the cell.<sup>[55]</sup> It was suggested that a coactivator protein interacting with the activation function 1 (AF-1) transactivation domain of the androgen receptor was deficient in this patient.<sup>[55]</sup> The signal disruption could not be corrected by supplementation with any coactivators known at the time, nor was the absent coactivator protein characterized, which left some in the field unconvinced that a mutant coactivator would explain the mechanism of androgen resistance in CAIS or PAIS patients with a normal AR gene.<sup>[1]</sup>

## XY karyotype

Depending on the mutation, a person with a (46,XY karyotype) and AIS can have either a male (MAIS) or female (CAIS) phenotype,<sup>[56]</sup> or may have genitalia that is only partially masculinized (PAIS).<sup>[57]</sup> The gonads are testes regardless of phenotype due to the influence of the Y-chromosome.<sup>[58][59]</sup> A 46,XY female thus does not have ovaries or a uterus,<sup>[60]</sup> and can neither contribute an egg towards conception nor gestate a child.

Several case studies of fertile 46,XY males with androgen insensitivity have been published,<sup>[5][61][62][63][64]</sup> although this group is thought to be a minority.<sup>[14]</sup> Additionally, some infertile males with MAIS have been able to conceive children after increasing their sperm count through the use of supplementary testosterone.<sup>[1][65]</sup> A genetic male conceived by a man with androgen insensitivity would not receive his father's X chromosome, and thus would neither inherit nor carry the gene for the syndrome. A genetic female conceived in such a way would receive her father's X chromosome, and would thus become a carrier.

## XX karyotype

Genetic females (46,XX karyotype) have two X chromosomes, and thus have two AR genes. A mutation in one (but not both) of the AR genes results in a minimally affected, fertile, female carrier. Some carriers have been noted to have slightly reduced body hair, delayed puberty, and / or tall stature, presumably due to skewed X-inactivation.<sup>[3][5]</sup> A female carrier will pass the affected AR gene to her children 50% of the time. If the

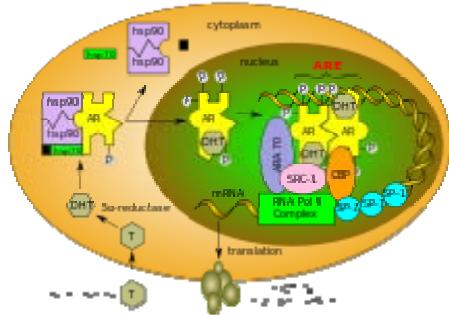
affected child is a genetic female, she too will be a carrier. An affected 46,XY child will have androgen insensitivity syndrome.

A genetic female with mutations in both AR genes could theoretically result from the union of a fertile man with androgen insensitivity and a female carrier of the gene, or from de novo mutation. However, given the scarcity of fertile androgen insensitive men and low incidence of AR mutation, the chances of this occurrence is small. The phenotype of such an individual is a matter of speculation; as of 2010, no such documented case has been published.

## Correlation of genotype and phenotype

Individuals with partial androgen insensitivity, unlike those with the complete or mild forms, present at birth with ambiguous genitalia, and the decision to raise the child as male or female is often not obvious.<sup>[1][45][66]</sup> Unfortunately, it is often the case that little information regarding phenotype can be gleaned from precise knowledge of the AR mutation itself; it is well established that the same AR mutation may cause significant variation in the degree of masculinization in different individuals, even among members of the same family.<sup>[1][44][57][67][68][69][70][71][72][73]</sup> Exactly what causes this variation is not entirely understood, although factors contributing to it could include the lengths of the polyglutamine and polyglycine tracts,<sup>[74]</sup> sensitivity to and variations in the intrauterine endocrine milieu,<sup>[57]</sup> the effect of coregulatory proteins that are active in Sertoli cells,<sup>[26][75]</sup> somatic mosaicism,<sup>[1]</sup> expression of the 5RD2 gene in genital skin fibroblasts,<sup>[67]</sup> reduced AR transcription and translation from factors other than mutations in the AR coding region,<sup>[76]</sup> an unidentified coactivator protein,<sup>[55]</sup> enzyme deficiencies such as 21-hydroxylase deficiency,<sup>[5]</sup> or other genetic variations such as a mutant steroidogenic factor-1 (SF-1) protein.<sup>[54]</sup> The degree of variation, however, does not appear to be constant across all AR mutations, and is much more extreme in some.<sup>[1][5][51][57]</sup> Missense mutations that result in a single amino acid substitution are known to produce the most phenotypic diversity.<sup>[2]</sup>

# Pathophysiology



Normal function of the androgen receptor. Testosterone (T) enters the cell and, if 5-alpha-reductase is present, is converted into dihydrotestosterone (DHT). Upon steroid binding, the androgen receptor (AR) undergoes a conformational change and releases heat shock proteins (hsp60, hsp90). Phosphorylation (P) occurs before or after steroid binding. The AR translocates to the nucleus where dimerization, DNA binding, and the recruitment of coactivators occur. Target genes are transcribed (mRNA) and translated into proteins.<sup>[3][14][23][77]</sup>

## Androgens and the androgen receptor

Main article: [Androgen receptor](#)

The effects that androgens have on the human body --- virilization, masculinization, anabolism, etc. --- are not brought about by androgens themselves, but rather are the result of androgens bound to androgen receptors; the androgen receptor mediates the effects of androgens in the human body.<sup>[78]</sup> Likewise, under normal circumstances, the androgen receptor itself is inactive in the cell until androgen binding occurs.<sup>[3]</sup>

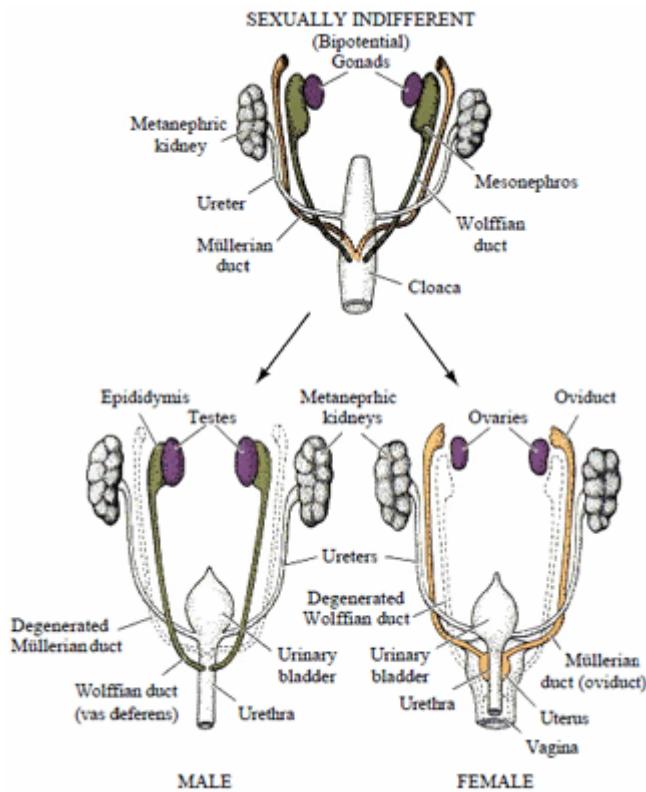
The following series of steps illustrates how androgens and the androgen receptor work together to produce androgenic effects.<sup>[1][2][3][14][23][79][80]</sup>

1. Androgen enters the cell.
  - a. Only certain organs in the body, such as the gonads and the adrenal glands, produce the androgen testosterone.
  - b. Testosterone is converted into dihydrotestosterone, a chemically similar androgen, in cells containing the 5 alpha reductase enzyme.
  - c. Both androgens exert their influence through binding with the androgen receptor.
2. Androgen binds with the androgen receptor.
  - a. The androgen receptor is expressed ubiquitously throughout the tissues of the human body.
  - b. Before it binds with an androgen, the androgen receptor is bound to heat shock proteins.
  - c. These heat shock proteins are released upon androgen binding.

- d. Androgen binding induces a stabilizing, conformational change in the androgen receptor.
- e. The two zinc fingers of the DNA-binding domain are exposed as a result of this new conformation.
- f. AR stability is thought to be aided by type II coregulators, which modulate protein folding and androgen binding, or facilitate NH2/carboxyl-terminal interaction.
- 3. The hormone-activated androgen receptor is phosphorylated.
  - a. Receptor phosphorylation can occur before androgen binding, although the presence of androgen promotes hyperphosphorylation.
  - b. The biological ramifications of receptor phosphorylation are unknown.
- 4. The hormone-activated androgen receptor translocates to the nucleus.
  - a. Nucleocytoplasmic transport is in part facilitated by an amino acid sequence on the AR called the nuclear localization signal.
  - b. The AR's nuclear localization signal is primarily encoded in the hinge region of the AR gene.
- 5. Homodimerization occurs.
  - a. Dimerization is mediated by the second (nearest the 3' end) zinc finger.
- 6. DNA binding to regulatory androgen response elements occurs.
  - a. Target genes contain (or are flanked by) transcriptional enhancer nucleotide sequences that interact with the first zinc finger.
  - b. These areas are called androgen response elements.
- 7. Coactivators are recruited by the AR.
  - a. Type I coactivators (i.e., coregulators) are thought to influence AR transcriptional activity by facilitating DNA occupancy, chromatin remodeling, or the recruitment of general transcription factors associated with RNA polymerase II holocomplex.
- 8. Target gene transcription ensues.

In this way, androgens bound to androgen receptors regulate the expression of target genes, and thus produce androgenic effects.

It is theoretically possible for certain mutant androgen receptors to function without androgens; in vitro studies have demonstrated that a mutant androgen receptor protein can induce transcription in the absence of androgen if its steroid binding domain is deleted.<sup>[81][82]</sup> Conversely, the steroid-binding domain may act to repress the AR transactivation domain, perhaps due to the AR's unliganded conformation.<sup>[3]</sup>



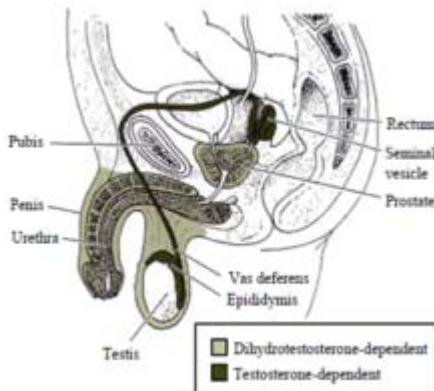
Sexual differentiation. The human embryo has indifferent sex accessory ducts until the seventh week of development.<sup>[83]</sup>

## Androgens in fetal development

Human embryos develop similarly for the first six weeks, regardless of genetic sex (46,XX or 46,XY karyotype); the only way to tell the difference between 46,XX or 46,XY embryos during this time period is to look for Barr bodies or a Y-chromosome.<sup>[84]</sup> The gonads begin as bulges of tissue called the genital ridges at the back of the abdominal cavity, near the midline. By the fifth week, the genital ridges differentiate into an outer cortex and an inner medulla, and are called indifferent gonads.<sup>[84]</sup> By the sixth week, the indifferent gonads begin to differentiate according to genetic sex. If the karyotype is 46,XY, testes develop due to the influence of the Y chromosome's SRY gene.<sup>[58][59]</sup> This process does not require the presence of androgen, nor a functional androgen receptor.<sup>[58][59]</sup>

Until approximately the seventh week of development, the embryo has indifferent sex accessory ducts, which consist of two pairs of ducts: the Müllerian ducts and the Wolffian ducts.<sup>[84]</sup> Sertoli cells within the testes secrete anti-Müllerian hormone around this time to suppress the development of the Müllerian ducts, and cause their degeneration.<sup>[84]</sup> Without this anti-Müllerian hormone, the Müllerian ducts develop into the female internal genitalia (uterus, cervix, fallopian tubes, and upper vaginal barrel).<sup>[84]</sup> Unlike the Müllerian ducts, the Wolffian ducts will not continue to develop by default.<sup>[85]</sup> In the presence of testosterone and functional androgen receptors, the Wolffian ducts develop into the epididymides, vasa deferentia, and seminal vesicles.<sup>[84]</sup> If the testes fail

to secrete testosterone, or the androgen receptors do not function properly, the Wolffian ducts degenerate.<sup>[86]</sup>



Masculinization of the male genitalia is dependent on both testosterone and dihydrotestosterone.<sup>[83]</sup>

Masculinization of the external genitalia (the penis, penile urethra, and scrotum), as well as the prostate, are dependent on the androgen dihydrotestosterone.<sup>[87][88][89][90]</sup> Testosterone is converted into dihydrotestosterone by the 5-alpha reductase enzyme.<sup>[91]</sup> If this enzyme is absent or deficient, then dihydrotestosterone will not be created, and the external male genitalia will not develop properly.<sup>[87][88][89][90][91]</sup> As is the case with the internal male genitalia, a functional androgen receptor is needed in order for dihydrotestosterone to regulate the transcription of target genes involved in development.<sup>[78]</sup>

## Pathogenesis of Androgen Insensitivity Syndrome

Mutations in the androgen receptor gene can cause problems with any of the steps involved in androgenization, from the synthesis of the androgen receptor protein itself, through the transcriptional ability of the dimerized, androgen-AR complex.<sup>[3]</sup> AIS can result if even one of these steps is significantly disrupted, as each step is required in order for androgens to successfully activate the AR and regulate gene expression.<sup>[3]</sup> Exactly which steps a particular mutation will impair can be predicted, to some extent, by identifying the area of the AR in which the mutation resides. This predictive ability is primarily retrospective in origin; the different functional domains of the AR gene have been elucidated by analyzing the effects of specific mutations in different regions of the AR.<sup>[3]</sup> For example, mutations in the steroid binding domain have been known to affect androgen binding affinity or retention, mutations in the hinge region have been known to affect nuclear translocation, mutations in the DNA-binding domain have been known to affect dimerization and binding to target DNA, and mutations in the transactivation domain have been known to affect target gene transcription regulation.<sup>[3][85]</sup> Unfortunately, even when the affected functional domain is known, it is difficult to predict the phenotypical consequences of a particular mutation (see Correlation of genotype and phenotype).

Some mutations can adversely impact more than one functional domain. For example, a mutation in one functional domain can have deleterious effects on another by altering the way in which the domains interact.<sup>[85]</sup> A single mutation can affect all downstream functional domains if a premature stop codon or framing error results; such a mutation can result in a completely unusable (or unsynthesizable) androgen receptor protein.<sup>[3]</sup> The steroid binding domain is particularly vulnerable to the effects of a premature stop codon or framing error, since it occurs at the end of the gene, and its information is thus more likely to be truncated or misinterpreted than other functional domains.<sup>[3]</sup>

Other, more complex relationships have been observed as a consequence of mutated AR; some mutations associated with male phenotypes have been linked to male breast cancer, prostate cancer, or in the case of spinal and bulbar muscular atrophy, disease of the central nervous system.<sup>[10][28][92][93][94]</sup> The form of breast cancer that is seen in some men with partial androgen insensitivity syndrome is caused by a mutation in the AR's DNA-binding domain.<sup>[92][94]</sup> It has been hypothesized that this mutation causes a disturbance of the AR's target gene interaction that allows it to act at certain additional targets, possibly in conjunction with the estrogen receptor protein, to cause cancerous growth.<sup>[3]</sup> The etiology of spinal and bulbar muscular atrophy (SBMA) demonstrates that even the mutant AR protein itself can result in pathology. The trinucleotide repeat expansion of the polyglutamine tract of the AR gene that is associated with SBMA results in the synthesis of a misfolded AR protein that the cell fails to properly proteolyze and disperse.<sup>[95]</sup> These misfolded AR proteins form aggregates in the cell cytoplasm and nucleus.<sup>[95]</sup> Over the course of 30 to 50 years, these aggregates accumulate and have a cytotoxic effect, eventually resulting in the neurodegenerative symptoms associated with SBMA.<sup>[95]</sup>

## Diagnosis

The phenotypes that result from the insensitivity to androgens are not unique to AIS, and thus the diagnosis of AIS requires thorough exclusion of other causes.<sup>[15][69]</sup> Clinical findings indicative of AIS include the presence of a short vagina<sup>[96]</sup> or undermasculinized genitalia,<sup>[1][68][87]</sup> partial or complete regression of Müllerian structures,<sup>[97]</sup> bilateral nondysplastic testes,<sup>[98]</sup> and impaired spermatogenesis and / or virilization.<sup>[1][6][7][10]</sup> Laboratory findings include a 46,XY karyotype<sup>[2]</sup> and normal or elevated postpubertal testosterone, luteinizing hormone, and estradiol levels.<sup>[2][15]</sup> The androgen binding activity of genital skin fibroblasts is typically diminished,<sup>[3][99]</sup> although exceptions have been reported.<sup>[100]</sup> Conversion of testosterone to dihydrotestosterone may be impaired.<sup>[3]</sup> The diagnosis of AIS is confirmed if androgen receptor gene sequencing reveals a mutation, although not all individuals with AIS (particularly PAIS) will have an AR mutation (see Other Causes).<sup>[2][7][52][53]</sup>

Each of the three types of AIS --- complete, partial, and mild --- has a different list of differential diagnoses to consider.<sup>[1]</sup> Depending on the form of AIS that is suspected, the list of differentials can include:<sup>[58][59][101][102][103]</sup>

- Chromosomal anomalies:
  - Klinefelter syndrome (47,XXY karyotype)
  - Turner syndrome (45,XO karyotype)
  - Mixed gonadal dysgenesis (45,XO/46,XY karyotype)
  - Tetragametic chimerism (46,XX/46,XY karyotype)
- Androgen biosynthetic dysfunction in 46,XY individuals:
  - Luteinizing hormone (LH) receptor mutations
  - Smith-Lemli-Opitz syndrome (associated with intellectual disability)
  - Lipoid congenital adrenal hyperplasia
  - 3 $\beta$ -hydroxysteroid dehydrogenase 2 deficiency
  - 17 $\alpha$ -hydroxylase deficiency
  - 17,20 lyase deficiency
  - 17 $\beta$ -hydroxysteroid dehydrogenase deficiency
  - 5 $\alpha$ -reductase deficiency
- Androgen excess in 46,XX individuals:
  - 21-hydroxylase deficiency
  - 3 $\beta$ -hydroxysteroid dehydrogenase 2 deficiency
  - Cytochrome P450 oxidoreductase deficiency (disorder in mother causes 46,XX fetal virilization)
  - 11 $\beta$ -hydroxylase deficiency
  - Aromatase deficiency
  - Glucocorticoid receptor mutations
  - Maternal virilizing tumor (e.g. luteoma)
  - Increased androgen exposure in utero, not otherwise specified (e.g. androgenic drugs)
- Developmental
  - Mayer-Rokitansky-Küster-Hauser syndrome (46,XX karyotype)
  - Swyer syndrome (46,XY karyotype)
  - XX gonadal dysgenesis (46,XX karyotype)
  - Leydig cell agenesis or hypoplasia, not otherwise specified (46,XY karyotype)
  - Absent (vanishing) testes syndrome
  - Ovotesticular DSD
  - Testicular DSD (i.e. 46,XX sex reversal)
- Teratogenic causes (e.g. estrogens, antiestrogens)
- Other causes:
  - Frasier syndrome (associated with progressive glomerulopathy)
  - Denys-Drash syndrome (associated with nephropathy and Wilms tumor)
  - WAGR syndrome (associated with Wilms tumor and aniridia)
  - McKusick-Kaufman syndrome (associated with postaxial polydactyly)
  - Robinow syndrome (associated with dwarfism)
  - Aarskog-Scott syndrome (associated with facial anomalies)
  - Hand-foot-genital syndrome (associated with limb malformations)
  - Popliteal pterygium syndrome (associated with extensive webbing behind knees)
  - Kallmann syndrome (often associated with anosmia)

- Hypospadias not otherwise specified
- Cryptorchidism not otherwise specified
- vaginal atresia not otherwise specified

## **CAIS**

Main article: [Diagnosis of Complete Androgen Insensitivity Syndrome](#)

## **PAIS**

Main article: [Diagnosis of Partial Androgen Insensitivity Syndrome](#)

## **MAIS**

Main article: [Diagnosis of Mild Androgen Insensitivity Syndrome](#)

## **Management**

Management of AIS is currently limited to symptomatic management; no method is currently available to correct the malfunctioning androgen receptor proteins produced by AR gene mutations. Areas of management include sex assignment, genitoplasty, gonadectomy in relation to tumor risk, hormone replacement therapy, genetic counseling, and psychological counseling.

## **CAIS**

Main article: [Management of Complete Androgen Insensitivity Syndrome](#)

## **PAIS**

Main article: [Management of Partial Androgen Insensitivity Syndrome](#)

## **MAIS**

Main article: [Management of Mild Androgen Insensitivity Syndrome](#)

## **Epidemiology**

Estimates for the incidence of androgen insensitivity syndrome are based on a relatively small population size, and thus are known to be imprecise.<sup>[1]</sup> CAIS is estimated to occur in 1 out of every 20,400 46,XY births.<sup>[104]</sup> A nationwide survey in The Netherlands based on patients with genetic confirmation of the diagnosis estimates that the minimal incidence of CAIS is 1 in 99,000.<sup>[67]</sup> The incidence of PAIS is estimated to be 1 in

130,000.<sup>[105]</sup> Due to its subtle presentation, MAIS is not typically investigated except in the case of male infertility,<sup>[87]</sup> and thus its true prevalence is unknown.<sup>[2]</sup>

## Controversy

### Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD or PIGD) refers to genetic profiling of embryos prior to implantation (as a form of embryo profiling), and sometimes even of oocytes prior to fertilization. When used to screen for a specific genetic sequence, its main advantage is that it avoids selective pregnancy termination as the method makes it highly likely that a selected embryo will be free of the condition under consideration.

In the UK, AIS appears on a list of serious genetic diseases that may be screened for via PGD.<sup>[106]</sup> Some ethicists, clinicians and intersex advocates have argued that screening embryos to specifically exclude intersex traits are based on social and cultural norms as opposed to medical necessity.<sup>[107][108][109][110][111]</sup>

## History

Recorded descriptions of the effects of androgen insensitivity syndrome date back for hundreds of years, although significant understanding of its underlying histopathology would not occur until the 1950s.<sup>[1]</sup> The taxonomy and nomenclature associated with androgen insensitivity went through a significant evolution that paralleled this understanding.

### Timeline of major milestones

- 1950: Lawson Wilkins administers daily methyltestosterone to a 46,XY female patient, who shows no signs of virilization. His experiment is the first documented demonstration of the pathophysiology of androgen insensitivity syndrome.<sup>[69][112]</sup>
- 1970: Mary F. Lyon and Susan Hawkes report that a gene on the X chromosome caused complete insensitivity to androgens in mice.<sup>[113][114]</sup>
- 1981: Barbara Migeon et al. narrow down the locus of the human androgen receptor gene (or a factor controlling the androgen receptor gene) to somewhere between Xq11 and Xq13.<sup>[115][116]</sup>
- 1988: The human androgen receptor gene is first cloned and partially analyzed by multiple parties.<sup>[117][118]</sup> Terry Brown et al. report the first mutations proven to cause AIS.<sup>[2][116]</sup>
- 1989: Terry Brown et al. report the exact locus of the AR gene (Xq11-Xq12),<sup>[20]</sup> and Dennis Lubahn et al. publishes its intron-exon boundaries.<sup>[119]</sup>
- 1994: The androgen receptor gene mutations database is created to provide a comprehensive listing of mutations published in medical journals and conference proceedings.<sup>[120]</sup>

## Early terminology

The first descriptions of the effects of androgen insensitivity appeared in the medical literature as individual case reports or as part of a comprehensive description of intersex physicalities. In 1839, Scottish obstetrician Sir James Young Simpson published one such description<sup>[121]</sup> in an exhaustive study of intersexuality that has been credited with advancing the medical community's understanding of the subject.<sup>[122]</sup> Simpson's system of taxonomy, however, was far from the first; taxonomies / descriptions for the classification of intersexuality were developed by Italian physician and physicist Fortuné Affaitati in 1549,<sup>[123][124]</sup> French surgeon Ambroise Paré in 1573,<sup>[122][125]</sup> French physician and sexology pioneer Nicolas Venette in 1687 (under the pseudonym Vénitien Salocini),<sup>[126][127]</sup> and French zoologist Isidore Geoffroy Saint-Hilaire in 1832.<sup>[128]</sup> All five of the aforementioned authors used the colloquial term "hermaphrodite" as the foundation of their taxonomies, although Simpson himself questioned the propriety of the word in his publication.<sup>[121]</sup> Use of the word "hermaphrodite" in the medical literature has persisted to this day,<sup>[129][130]</sup> although its propriety is still in question. An alternative system of nomenclature has been recently suggested,<sup>[131]</sup> but the subject of exactly which word or words should be used in its place still one of much debate.<sup>[102][132][133][134][135]</sup>



"Pudenda pseudo-hermaphroditii ovi." Illustration of ambiguous genitalia from Frederik Ruysch's *Thesaurus Anatomicus Octavius*, 1709.<sup>[136]</sup>

## Pseudohermaphroditism

"Pseudohermaphroditism" has, until very recently,<sup>[131]</sup> been the term used in the medical literature to describe the condition of an individual whose gonads and karyotype do not match the external genitalia in the gender binary sense. For example, 46,XY individuals who have a female phenotype, but also have testes instead of ovaries --- a group that includes all individuals with complete androgen insensitivity (CAIS), as well as some individuals with partial androgen insensitivity (PAIS) --- are classified as having "male pseudohermaphroditism," while individuals with both an ovary and a testis (or at least one ovotestis) are classified as having "true hermaphroditism".<sup>[130][131]</sup> Usage of the word in the medical literature predates the discovery of the chromosome, and thus its definition has not always taken karyotype into account when determining an individual's sex. Previous definitions of "pseudohermaphroditism" relied on perceived inconsistencies between the internal and external organs; the "true" sex of an individual was determined by the internal organs, and the external organs determined the "perceived" sex of an individual.<sup>[121][128]</sup>

German-Swiss pathologist Edwin Klebs is sometimes noted for using the word "pseudohermaphroditism" in his taxonomy of intersexuality in 1876,<sup>[137]</sup> although the word is clearly not his invention as is sometimes reported; the history of the word "pseudohermaphrodite," and the corresponding desire to separate "true" hermaphrodites

from "false," "spurious," or "pseudo" hermaphrodites, dates back to at least 1709, when Dutch anatomist Frederik Ruysch used it in a publication describing a subject with testes and a mostly female phenotype.<sup>[136]</sup> "Pseudohermaphrodite" also appeared in the Acta Eruditorum later that same year, in a review of Ruysch's work.<sup>[138]</sup> There is also evidence that the word was already being used by the German and French medical community long before Klebs used it; German physiologist Johannes Peter Müller equated "pseudohermaphroditism" with a sub-class of hermaphroditism from Saint-Hilaire's taxonomy in a publication dated 1834,<sup>[139]</sup> and by the 1840s "pseudo-hermaphroditism" was appearing in several French and German publications, including <sup>[140][141][142][143]</sup> dictionaries.

## Testicular feminization

In 1953, American gynecologist John Morris provided the first full description of what he called "testicular feminization syndrome" based on 82 cases compiled from the medical literature, including 2 of his own patients.<sup>[1][3][144]</sup> The term "testicular feminization" was coined to reflect Morris' observation that the testicles in these patients produced a hormone that had a feminizing effect on the body, a phenomenon that is now understood to be due to the inaction of androgens, and subsequent aromatization of testosterone into estrogen.<sup>[1]</sup> A few years before Morris published his landmark paper, Lawson Wilkins had shown through his own experiments that unresponsiveness of the target cell to the action of androgenic hormones was a cause of "male pseudohermaphroditism".<sup>[69][112]</sup> Wilkins' work, which clearly demonstrated the lack of a therapeutic effect when 46,XY women were treated with androgens, caused a gradual shift in nomenclature from "testicular feminization" to "androgen resistance".<sup>[87]</sup>

## Other names

A distinct name has been given to many of the various presentations of androgen insensitivity syndrome, such as Reifenstein syndrome (1947),<sup>[145]</sup> Goldberg-Maxwell syndrome (1948),<sup>[146]</sup> Morris' syndrome (1953),<sup>[144]</sup> Gilbert-Dreyfus syndrome (1957),<sup>[147]</sup> Lub's syndrome (1959),<sup>[148]</sup> "incomplete testicular feminization" (1963),<sup>[149]</sup> Rosewater syndrome (1965),<sup>[150]</sup> and Aiman's syndrome (1979).<sup>[151]</sup> Since it was not understood that these different presentations were all caused by the same set of mutations in the androgen receptor gene, a unique name was given to each new combination of symptoms, resulting in a complicated stratification of seemingly disparate disorders.<sup>[69][152]</sup>

Over the last 60 years, as reports of strikingly different phenotypes were reported to occur even among members of the same family, and as steady progress was made towards the understanding of the underlying molecular pathogenesis of AIS, it has been demonstrated that these disorders are different phenotypic expressions of one syndrome caused by molecular defects in the androgen receptor gene.<sup>[1][14][69][152]</sup>

Androgen insensitivity syndrome (AIS) is now the accepted terminology for the syndromes resulting from unresponsiveness of the target cell to the action of androgenic hormones.<sup>[1]</sup> AIS is broken down into three classes based on phenotype: complete

androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS).<sup>[1][2][6][7][8][11][12][13][14]</sup> CAIS

encompasses the phenotypes previously described by "testicular feminization," Morris' syndrome, and Goldberg-Maxwell syndrome.<sup>[1][153]</sup> PAIS includes Reifenstein syndrome, Gilbert-Dreyfus syndrome, Lub's syndrome, "incomplete testicular feminization," and Rosewater syndrome;<sup>[152][154][155]</sup> and MAIS includes Aiman's syndrome.<sup>[156]</sup>

The more virilized phenotypes of AIS have sometimes been described as "undervirilized male syndrome," "infertile male syndrome," "undervirilized fertile male syndrome," etc., before evidence was reported that these conditions were caused by mutations in the androgen receptor gene.<sup>[63]</sup> These diagnoses were used to describe a variety of mild defects in virilization; as a result, the phenotypes of some men that have been diagnosed as such are better described by PAIS (e.g. micropenis, hypospadias and undescended testes), while others are better described by MAIS (e.g. isolated infertility or gynecomastia).<sup>[1][63][64][155][157][158]</sup>

## Popular culture

In the 1991 Japanese horror novel *Ring*, by Koji Suzuki (later adapted into Japanese, Korean, and American films), the central antagonist Sadako has this syndrome.

In Season 2 Episode 13 ("Skin Deep") of the TV series *House*, the main patient's cancerous testicle is mistaken for an ovary due to the patient's undiscovered AIS.

In Season 2 of the MTV series *Faking It*, it is revealed that a character has androgen insensitivity syndrome.

In the film *Orchids, My Intersex Adventure*, Phoebe Hart and her sister Bonnie Hart, both women with CAIS, documented their exploration of AIS and other intersex issues.