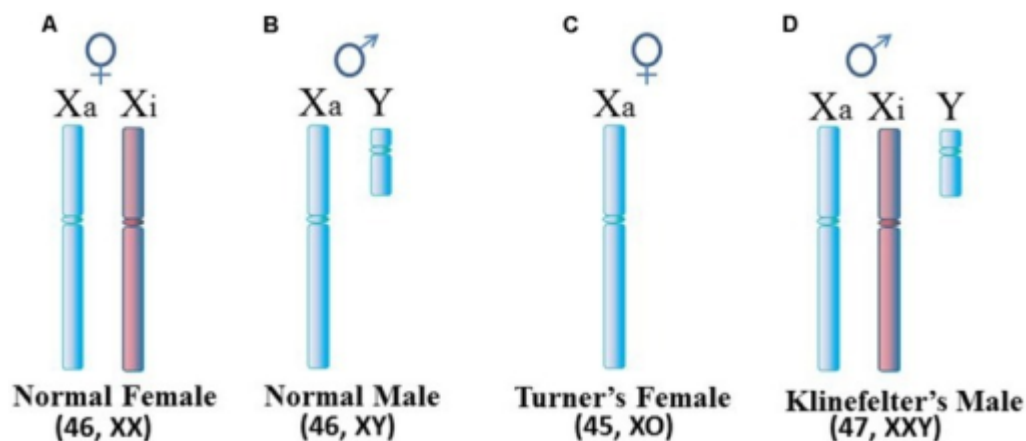


# Disorders of Sexual Differentiation and Sex Development

[See online here](#)

The determination of a baby's sex begins at the chromosomal level with the insemination of the ovum. Further sexual differentiation follows during the subsequent embryogenesis. However, chromosomal anomalies, gene mutations, and other exogenous or endogenous factors can cause disorders of sexual differentiation. These disorders manifest during childhood or at the latest in puberty, making patients consult their doctor. Here, we offer you an overview of the most common syndromes resulting from disorders of sexual differentiation.



## Turner syndrome

An important disorder of **genital development** is **Turner syndrome**, which involves a **chromosomal aberration**. It is based on **monosomy of the sex chromosomes**, i.e. the presence of only 1 chromosome **X** of the 2 **sexual chromosomes**. This manifests as a **45 XO karyotype** with female **phenotype**.

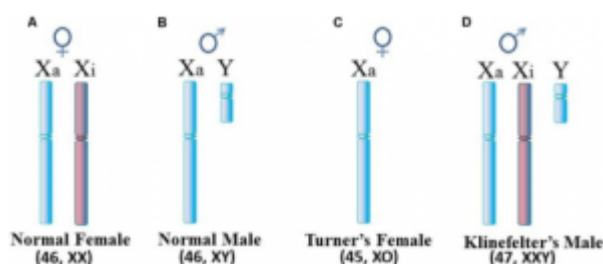
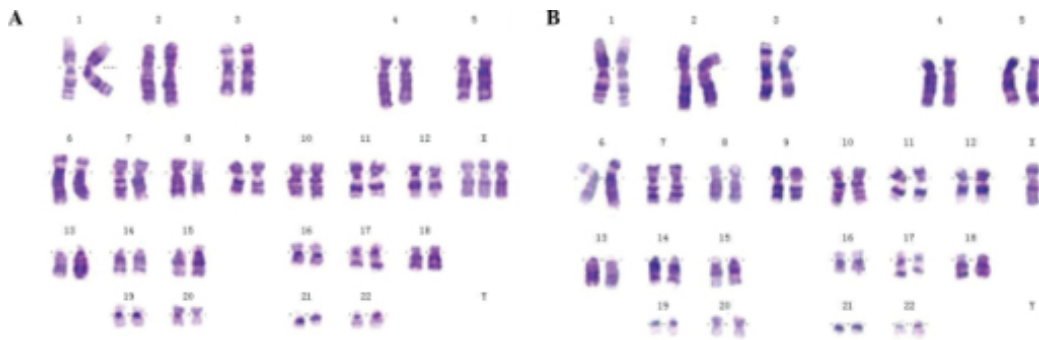


Image: Human sex chromosomes. By Openi, License: [CC BY 4.0](#)

It is the only **monosomy** that is compatible with a relatively normal life. With an incidence of **1:2,500-7,500** (of females born alive), it is the most common **gonadal**

**chromosome anomaly** in women. The syndrome is associated with a **high rate of spontaneous abortion**.

The anomaly is based on the loss of 1 **sex chromosome** during **embryogenesis**, which can happen at different stages of development (**spermatogenesis** or **oogenesis**, **insemination**) and is due to a **nondisjunction** of the **chromosomes** or **chromatids**. In **70%** of the cases, it is the **X chromosome** of the father.



**Image:** Karyotyping of a whole blood sample from a patient with a 45XO/47XXX karyotype, with (A) 68% 47XXX and (B) 32% 45XO. By Openi, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

A structurally altered **X chromosome** can also be the cause. Furthermore, there might be **chromosomal mosaicisms** with inconspicuous or conspicuous cells (e.g., 46, XX/45, X0), but these have a less pronounced clinical manifestation.

While the occurrence of Turner syndrome does not correlate with the age of the mother, the older age of the father possibly plays a role in the development of the disease.

## Symptoms and clinical presentation of Turner syndrome

Individuals with **Turner syndrome** have both a female **phenotype** as well as a female **psychosexual** identity. Cardinal symptoms are **primary amenorrhea** and **short stature** (143–147 cm). Patients are **infertile** and have **sexual infantilism** (**hypoplastic female genitalia** due to the lack of hormonal stimulation). While the **gonads** initially develop normally, they start to **degenerate** and **fibrose** in the 3rd month of pregnancy; from which moment on, the **ovaries** only exist as fibrous tissue, called **streak gonads**.

Other **facultative** symptoms are:

- Short neck
- Ptyergium colli (webbed neck)
- Low hairline
- Lymphedema on the back of hands and feet (in 1st weeks of life)
- Cubitus valgus (X-shaped arms)
- Shield chest with widely spaced nipples and funnel chest
- Multiple (benign) pigment naevi
- Nail and ear dysplasia
- Malformations of the kidneys and urinary tracts
- Malformation of the skeleton (e.g., deformities of the spine) and anomalies of the ligaments
- Primary hypogonadism
- Short stature
- Osteoporosis

- Metabolic disorders (insulin resistance, diabetes mellitus, and dyslipidemia)
- Cardiovascular anomalies (e.g., aortic coarctation, hypertension, vasculopathy, aortic stenosis, aortic isthmus stenosis, and pulmonary vein anomalies)



**Image:** PA plain radiograph Turner syndrome scoliosis. By Openi, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)



**Image:** Puffy feet. By Johannes Nielsen, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)



**Image:** Girl with Turner syndrome before and immediately after her operation for neck-webbing. By Openi, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

These symptoms are not necessarily present all at once and maybe more or less pronounced in different **individuals**. The **intelligence** of affected individuals is normal or can be seen generally reduced partially compromising skills such as mathematics and spatial visualization.

As mentioned above, patients with **mosaicism** show less pronounced physical abnormalities. The degree of **ovary functionality determines the** development of puberty and even the possibility of spontaneous pregnancy, which, however, occurs despite an increase in the rates of abortion and congenital malformations of the child.

## Diagnosis and differential diagnosis of Turner syndrome

**Amenorrhea** and the absence of **puberty** are usually the reasons why patients consult their doctor, in approx. 60–70% of cases, when the diagnosis is not made in prenatal or early postnatal life.

Because of the **insufficiency of the ovaries**, not enough **estrogen** is being produced, which makes the superior centers increase their **hormone production**. In an **endocrinological** examination, this results in increased levels of follicle-stimulating hormone (**FSH**) and **luteinizing hormone (LH)**, and a diminished concentration of **estrogen**. Since this disorder occurs at the level of the gonads, it is also referred to as **hypergonadotropic** or **primary hypogonadism**.

The most suited method for making the diagnosis is a **chromosome analysis** which is performed on **peripheral lymphocytes**. With a **karyogram**, the **karyotype** of the examinee can be determined.

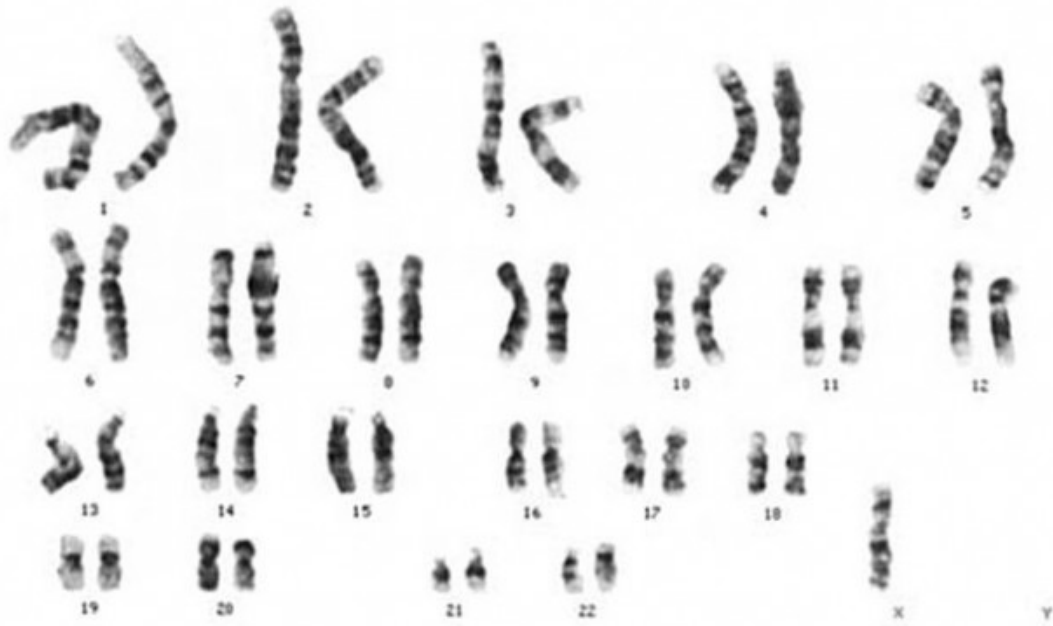


Image: Karyogram 45,X. By The cat--commonswiki, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Regarding **differential diagnoses**, a tumorous condition (e.g., **gonadoblastoma**, **dysgerminoma**) has to be excluded.

## Treatment of Turner syndrome

**Turner syndrome** cannot be cured since the defect is of molecular nature (missing chromosome). Therefore, treatment will always be **symptomatic**, trying to enhance the physical and psychological female traits.

With the onset of puberty (around age 12–13), **hormone replacement therapy** should be commenced. **Estrogen** stimulates the growth of **primary** and **secondary sexual characteristics** (vagina, uterus, breasts, and pubic hair) and serves the **prevention** of **osteoporosis** and **arteriosclerosis**. **Estradiol valerate** (1–2 mg) is often prescribed in this context. **Gestagens** should be taken on at least 10 days of a month to ensure proper **menstruation**. This transforms the **endometrium** instead of continuously stimulating it and thus prevents the development of **endometrial carcinoma**.

An early beginning of **growth hormone therapy (hGH)** can yield **final height increments** of up to 10 cm. For such a result, treatment has to start in early childhood (age 3–4).

The infertility of women affected with Turner's syndrome is not reversible. However, they can be candidates for egg donation for those couples who wish to have children. The **legal status** of egg donation varies by country. While it is completely illegal in some countries (e.g., Germany), it is legal and egg donors can even be compensated in the United States.

The **surgical** removal of bothering stigmata (e.g., webbed neck) is an option. Furthermore, **psychological** counseling can be very important to the affected patients.

# Complications of Turner syndrome

Women who suffer from Turner syndrome have a higher tendency than the normal population to develop **cardiovascular diseases, diabetes mellitus, thyroid disorders, and inflammatory diseases of the intestine.**

The **life expectancy** of the affected individuals can be reduced by 13 years on average.

## Adrenogenital syndrome (AGS)

### Definition, epidemiology, and etiology of AGS

The **adrenogenital syndrome (AGS)** is the most common cause of **feminine pseudohermaphroditism (chromosomal and gonadal female, male habitus)**. It comprises a group of diseases that stem from a **genetic** defect of **enzymes** of the **cortisol synthesis** in the **adrenal cortex**. The result of these enzymatic defects is an increased production of male **sexual hormones (androgens)** with **virilization** of the **outer female genitals**.

The **autosomal recessive** disease has an incidence of 1:5,000–1:15,000.

### Classification of AGS

Generally, every enzyme involved in **cortisol synthesis** can be affected by a defect. The **clinical presentation** varies depending on the affected enzyme. The following enzymes are most frequently affected:

- 21-hydroxylase
- 3-beta-hydroxysteroid-dehydrogenase
- 11-beta-hydroxylase

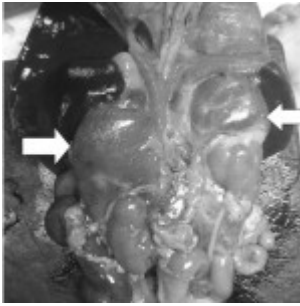
The damage of the enzyme may be **complete** or **incomplete**, which accordingly results in differently pronounced **clinical manifestations** (see below).

Since the **21-hydroxylase deficiency** is the most frequent cause in approx. 95% of cases, it will be the focus of the following discussion.

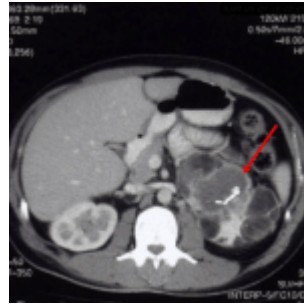
### Pathophysiology of AGS

Because of the **21-hydroxylase deficiency**, **cortisol** is not produced at all or only in a very small amount. Since there is no **negative feedback** in the superior **hormone control centers**, this results in an increased release of adrenocorticotrophic hormone (**ACTH**) from the **hypophysis**. This hormone stimulates the **adrenal cortex** to the point where it becomes hyperplastic (**congenital adrenal hyperplasia, CAH**).

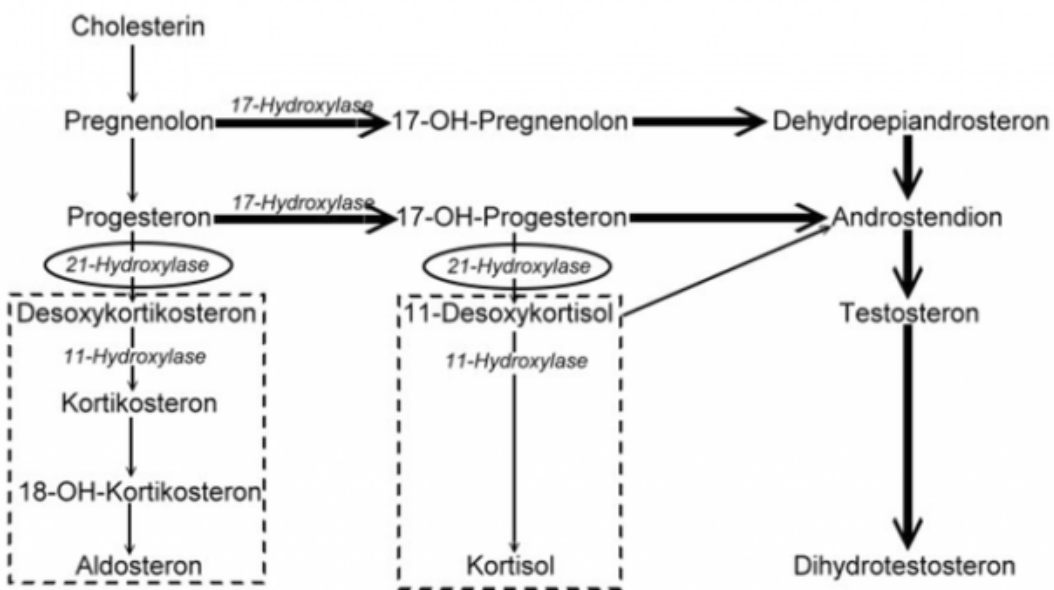
This results in an increased production of **androgens** and an **accumulation of intermediate products**, which can again be utilized in further **androgen synthesis**.



**Image:** Post-mortem examination of a baby showing adrenal hyperplasia. By Patou Tantbiroj, Mana Taweewisit, Suchila Sritippayawan, Boonchai Uerpairojkit, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)



**Image:** Abdominal computed tomography scan before surgery showing the very enlarged and heterogeneous left adrenal gland (arrow) with soft tissue, fat and calcium attenuation. By Openi, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)



**Image:** Congenital adrenal hyperplasia. By StarBuG, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

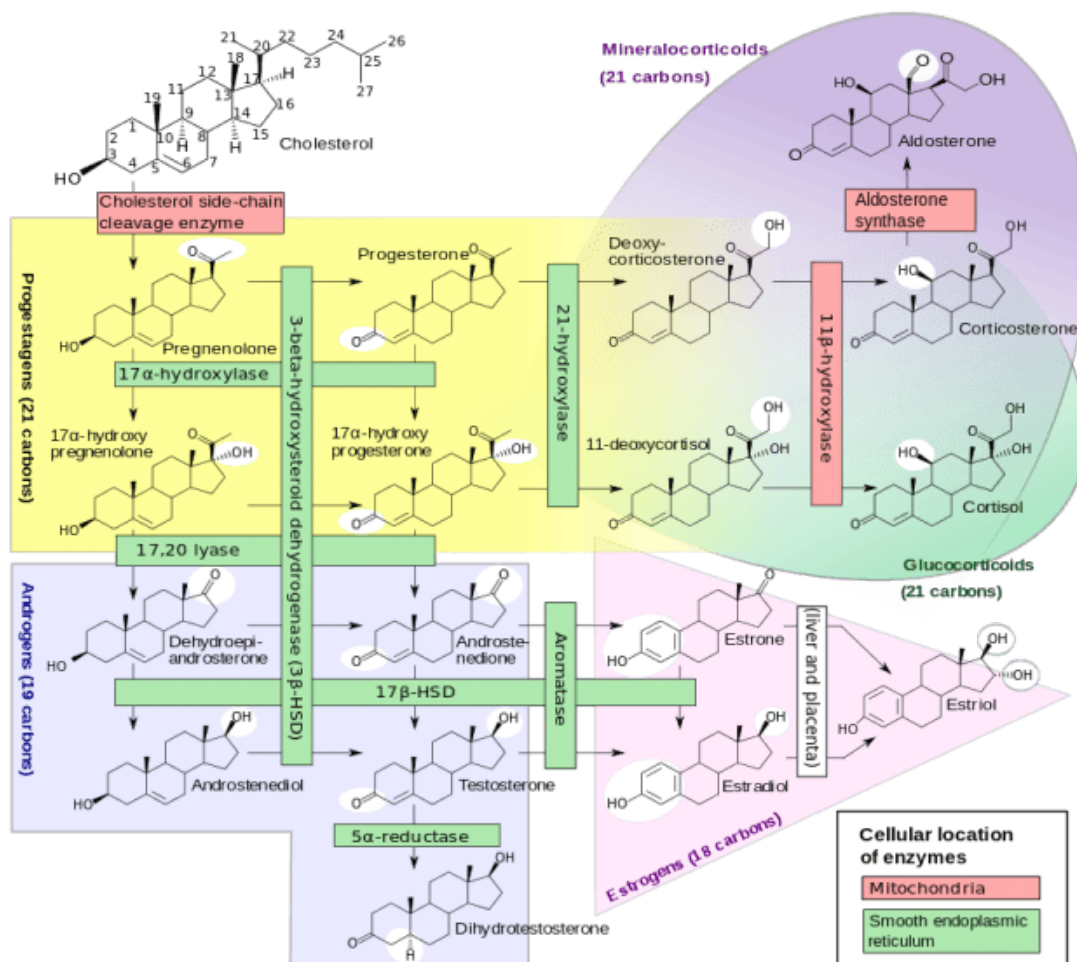


Image: Enzymes, their cellular location, substrates, and products in human steroidogenesis. By David Richfield and Mikael Häggström, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

## Symptoms and clinical presentation of AGS

In the following, the effects of the disease on the female patient will be described.

Patients have **karyotype 46, XX** and normally developed female inner genitals. However, there is **masculinization (virilization)** of the outer genitals, which can be manifested to varying degrees depending on the time and severity of the excess **androgen production**. The manifestations reach from sole **hypertrophy** of the **clitoris** to fusion of the **labioscrotal folds** and the development of male **urethra**.



Image: Clitoral hypertrophy, male hair type.  
By Openi,  
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Image:  
Clitoromegaly



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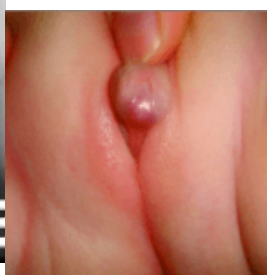


Image:



with normal labia & introitus. By Openi, License: [CC BY 3.0](#)

Ambiguous genitalia of a preterm infant, showing clitoromegaly and hyperpigmentation. There were a number of other abnormalities present, including holoprosencephaly, midline facial defects, polydactyly, etc. Karyotype proved to be 46, XX. By Patou Tantbirojn, Mana Taweewisit, Suchila Sritippayawan, Boonchai Uerpairojkit, License: [CC BY 2.0](#)

Appearance of the external genitalia in the patient (21-hydroxylase deficiency). By Openi, License: [CC BY 2.5](#)

The **time of manifestation** is also variable and can fall into the **fetal period**, **childhood**, or in or after **puberty**.

The classic childhood-onset **simple virilizing 21-hydroxylase deficiency** already manifests in the **prenatal** period as **virilization** of the female **fetuses**; at birth, the **outer genitalia** can be masculinized to varying degrees.



[Image](#): Morphotype masculine. By Openi, License: [CC BY 2.0](#)

If the condition is left untreated, **pubic and axillary hair** will begin to grow already in the 2nd year of life. The affected children are also taller than other children of the same



age. This, however, is reversed in adolescence and adulthood as the **epiphyseal plates** close prematurely and patients will be shorter than other adults. In addition to the body hair (hirsutism) like men, patients can experience a change of voice with more severe tones and because the patients do not present a classic female puberty, therefore, suffer from amenorrhea and infertility.



**Image:** Subject photo before the use of omega-3 poly-nutrient capsules (acne vulgaris). By Openi, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

The **non-classic 21-hydroxylase deficiency (late-onset CAH)** manifests later in life; at birth, the affected girl babies appear inconspicuous. The onset of the disease during **puberty** is characterized by a mild form of **virilization** (possibly **acne**, **hirsutism**, and **seborrhea**). Also, patients may experience **menstrual disorders** with prolonged **menstrual cycles** or **amenorrhea**.



**Image:** Hirsutismus. By Openi, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

In some cases, the synthesis of **aldosterone** may also be impaired, which can result in a **salt-wasting crisis** including **dehydration**, **hyponatremia**, **hypokalemia**, and **acidosis**. The affected infants are **apathetic**, develop severe vomiting, and need immediate treatment—if not, the condition can rapidly cause **death**.

## Diagnosis and differential diagnosis of AGS

A **21-hydroxylase deficiency** can be confirmed by performing an **ACTH stimulation test**: First, the patient must fast for at least 6 hours, and the basal serum levels of **17-hydroxyprogesterone** (17-OHP) and **cortisol** are measured. Then, **ACTH** is injected intravenously (250 mg). One hour after the ACTH injection, 17-OHP and cortisol are measured again. In healthy individuals, the difference between the 1st and the 2nd measuring of 17-OHP should not exceed 2.5 ng/ml. Any increase higher than that is diagnostic of **CAH**.

## Treatment of AGS



[Image](#): Moon facies with hypertrichosis over forehead and lips (Cushing's syndrome). By Openi, License: [CC BY 2.5](#)

Treatment of **CAH** should start as early as possible to prevent any further **virilization** of the patient and to maintain a normalized **ovarian function**. Affected individuals will have to undergo life-long **glucocorticoid replacement** (e.g., with hydrocortisone or dexamethasone). This reduced the ACTH production and thus, the formation of androgens. The treatment has to be adjusted to each patient individually to avoid the occurrence of **Cushing's syndrome** or **growth failure**. With **sufficient** treatment, normal development of the woman can be achieved and even **infertility** can be reversed so that **pregnancy** becomes viable. Healthy offspring will however, be carriers of CAH.

**NOTE:** Excess exposure to glucocorticoids can lead to Cushing's syndrome!

Patients with a salt-wasting form of CAH have to be administered mineralocorticoids (e.g., **fludrocortisone**), and the associated electrolyte imbalances have to be remedied.



[Image](#): Symptoms of Cushing's syndrome. By Mikael Häggström, License: [CC0 1.0](#)

## Prevention of AGS

The disease is of **autosomal recessive** inheritance. This means that if a mother has had 1 child with **AGS**, there is a probability of **25%** for the next child to also have **AGS**. Administration of **dexamethasone** (1-1.5 mg/dL) during pregnancy can prevent the **virilization** of a diseased infant. If male genitalia are detected or **AGS** can be ruled out through **prenatal diagnostics** at a later point of the pregnancy, the administration of **dexamethasone** can be stopped.

## Androgen insensitivity syndrome (AIS)

The androgen insensitivity syndrome (AIS) is a form of **masculine "pseudohermaphroditism"** (**genetic** and **gonadal** male, female **habitus**). Due to a **receptor defect**, the affected individuals are **unresponsive to androgen** which results in the development of **female external genitalia**.

AIS stems from a **mutation** of the **androgen receptor gene**. This gene is located on the **X chromosome**, which gives the disease an **X-linked recessive** mode of inheritance.

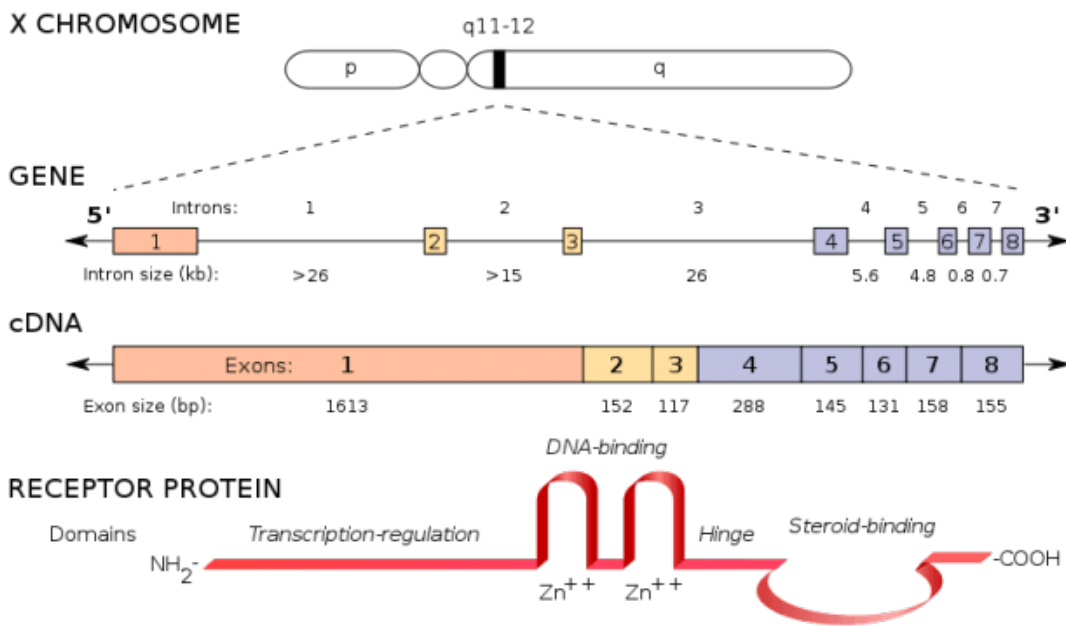


Image: Location and structure of the human androgen receptor. By Jonathan Marcus, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

The incidence of this condition is 1:20,000.

## Classification of AIS

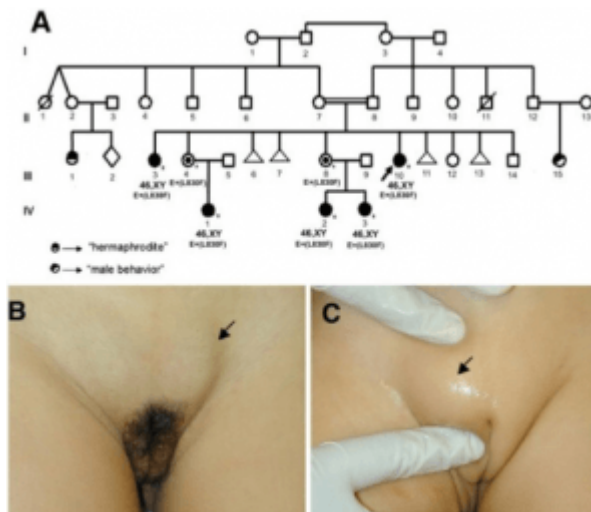


Image: Inheritance of androgen insensitivity syndrome in the family. Family pedigree (A). Female genitalia with palpable gonads in the index case III-10 (B) and her niece IV-1 (C). By Openi, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Based on the phenotype, **AIS** is classified as either **complete androgen insensitivity syndrome (CAIS)** or as **partial androgen insensitivity syndrome (PAIS)**. The latter is indicated when the **androgen resistance** is only incomplete and the development of the external genitalia is highly **variable** (ambiguous, male, or female).

The following sections deal with **complete androgen insensitivity syndrome**.

# Symptoms and clinical presentation of androgen insensitivity syndrome

Affected individuals have **karyotype 46, XY** and male **gonads (testes)**. The testes are located either within the **abdomen**, in the **inguinal rings**, or the **labia majora**.

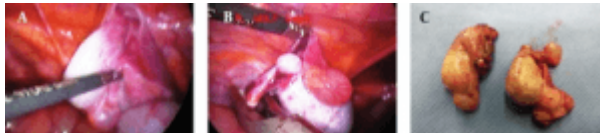
Due to a genetic defect of the **testosterone receptors** in the target tissues, the **testosterone** produced by the testes cannot be effective. This results in female **external genitalia**, which is why the affected individuals are raised as girls. In **puberty**, the condition becomes noticeable since there are no internal female sex organs (**ovaries, fallopian tubes, and uterus**), which consequently leads to **amenorrhea** and **infertility**. The outer appearance of patients is characterized by a tall, slender stature. Breast development is not impaired. A further sign is absent **secondary terminal hair** (axillary and pubic hair). The vagina is often short and blind-ended.

## Diagnosis of AIS

Patients will usually present because of absent **menstruation**. The suitable diagnostic method is a **chromosome analysis**, which can reveal the male **genotype** standing in contrast to the female habitus. Furthermore, **testosterone levels** will be in the normal male range, but **estrogen levels** will be too low for a woman.

## Treatment of AIS

Patients usually **identify** as female. The diagnosis used to be hidden from the affected children, but current practice is the age-appropriate disclosure by the parents and psychological counseling. Patients are capable of **cohabitation** but remain **infertile**.



**Image:** A. Laparoscopic view of the left gonad; B. The right gonad; C. Gross image of the removed gonads. By Openi, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

The standard of care is the post-pubertal surgical removal of the testes (**orchidectomy**) to prevent a **malign degeneration**, followed by hormone replacement therapy with **estrogen** and **gestagen**. Some patients with a short **vagina** or **vaginal aplasia** may also require surgical corrective treatment.

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