ADRENAL HYPERPLASIA, CONGENITAL,

adrenal glands hormones

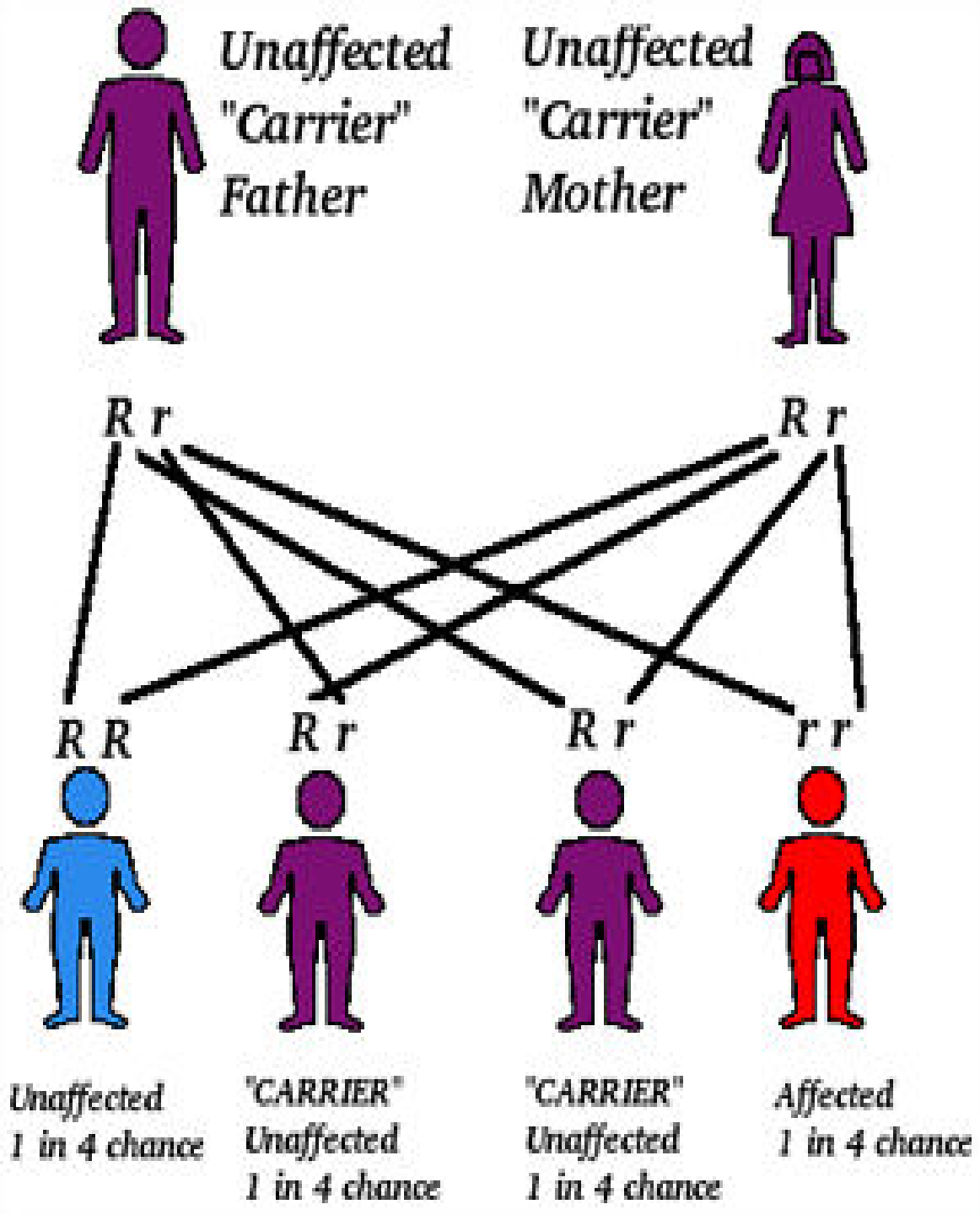
- Cortisol has numerous functions, such as
- **maintaining blood sugar levels**,
- protecting the body from stress, and
- suppressing inflammation.

adrenal glands hormones

- Aldosterone is sometimes called the **salt-retaining hormone** because it
- regulates the amount of salt retained by the kidneys.
- The retention of salt affects fluid levels in the body and blood pressure.
- A lack of aldosterone production contributes to the salt loss in people with the salt-wasting form of this condition.

CAH is an autosomal recessive genetic disorder.

- congenital Adrenal Hyperplasia (CAH) is a family of inherited disorders affecting the adrenal glands.
- CAH is an autosomal recessive genetic disorder. It affects males and females in equal numbers.
- Scientists have pinpointed the location of the group of genes that causes the most common forms of CAH to chromosome 6.

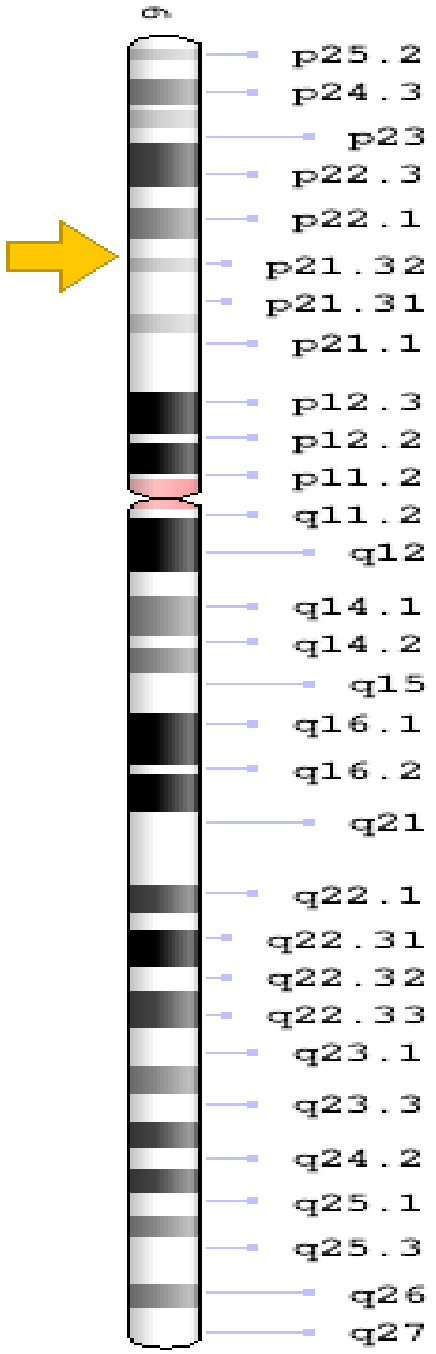


For a child to be born with either form of CAH, both parents must carry a gene for the disorder.

Molecular analysis of CAH

ADRENAL HYPERPLASIA, CONGENITAL, 21-hydroxylase deficiency.

- Molecular Location: on chromosome 6
- Cytogenetic Location: 6p21.3, which is the short (p) arm of chromosome 6 at position 21.3
- More than 100 mutations in the *CYP21A2* gene have been found to cause 21-hydroxylase deficiency.
- mutation in the CYP21A2 gene on chromosome 6p21.3 encoding steroid 21-hydroxylase.



***CYP21A2* gene**

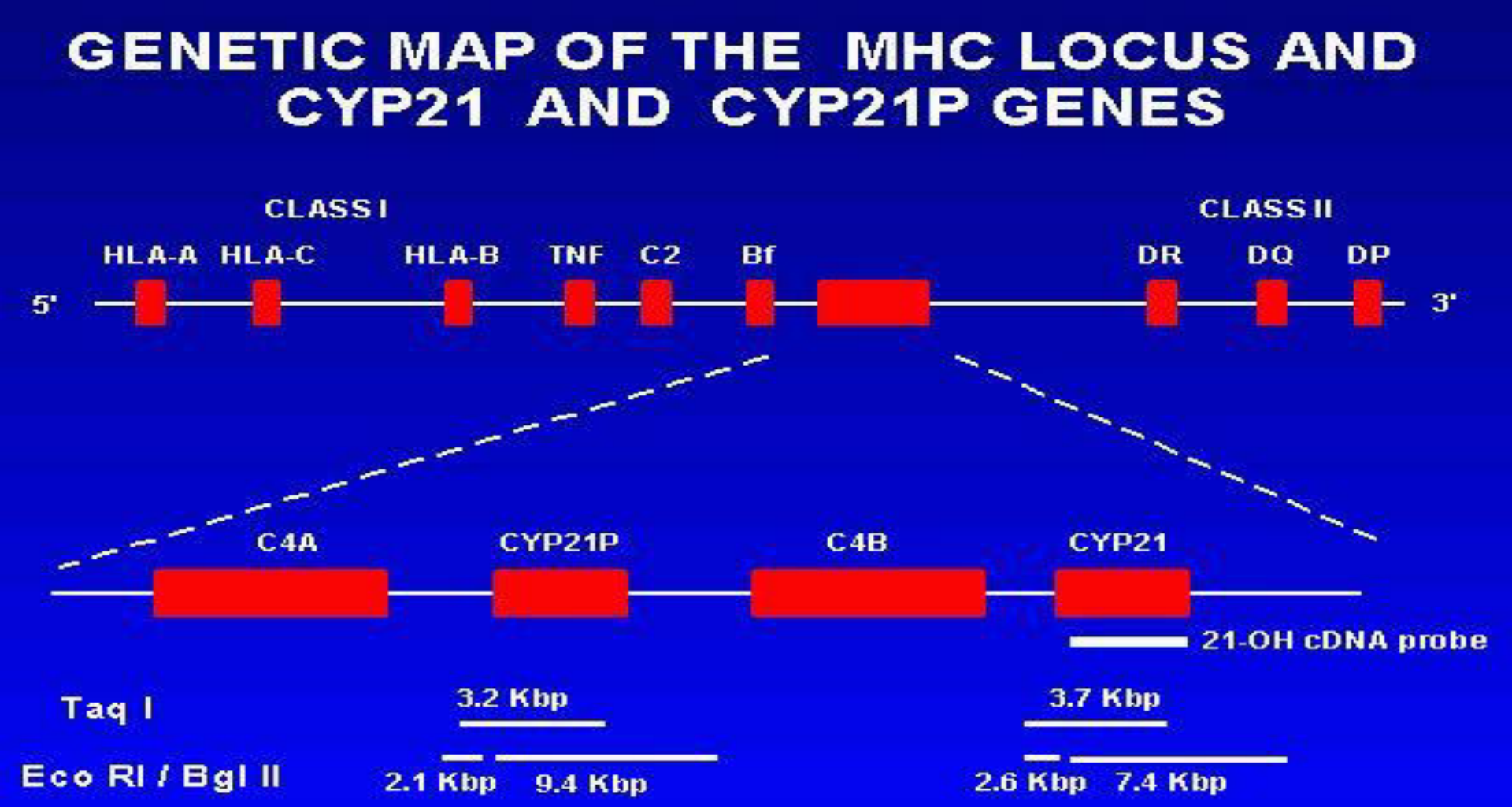
- 21-hydroxylase, is part of **the cytochrome P450 family of enzymes**.
- Cytochrome P450 enzymes are involved in many processes in the body, such as assisting with **reactions that break down drugs and helping to produce cholesterol, certain hormones, and fats (lipids)**

functional 21-OH gene & a non-functional pseudogene, CYP21P

- Most of the pathogenic CYP21 **mutations are found in the pseudogene**, hence, it is assumed that gene conversion is a common mutational mechanism in CAH
- The other significant cause of CAH is gross **deletion of the functional 21-OH gene**.
- Presumably the presence of the tandem homologous CYP21 and CYP21P genes provides the opportunity for unequal crossing over events during meiosis.

Clinical Features

- There are 4 recognized clinical forms of congenital adrenal hyperplasia, the majority of cases being associated with 21-hydroxylase deficiency: salt-wasting (SW), simple virilizing (SV), nonclassic (NC) late-onset (also called attenuated and acquired), and cryptic.
- All 4 forms are closely linked to HLA and represent the effects of various combinations of alleles.



Molecular analysis of CAH is complicated due to the presence of a non-functional pseudogene, CYP21P – also known as P450C21A) adjacent to the functional 21-OH gene.

- The genetic material from the pseudogene contains errors that, when introduced into the *CYP21A2* gene, disrupt the way the gene's instructions are used to make a protein.

gene conversion

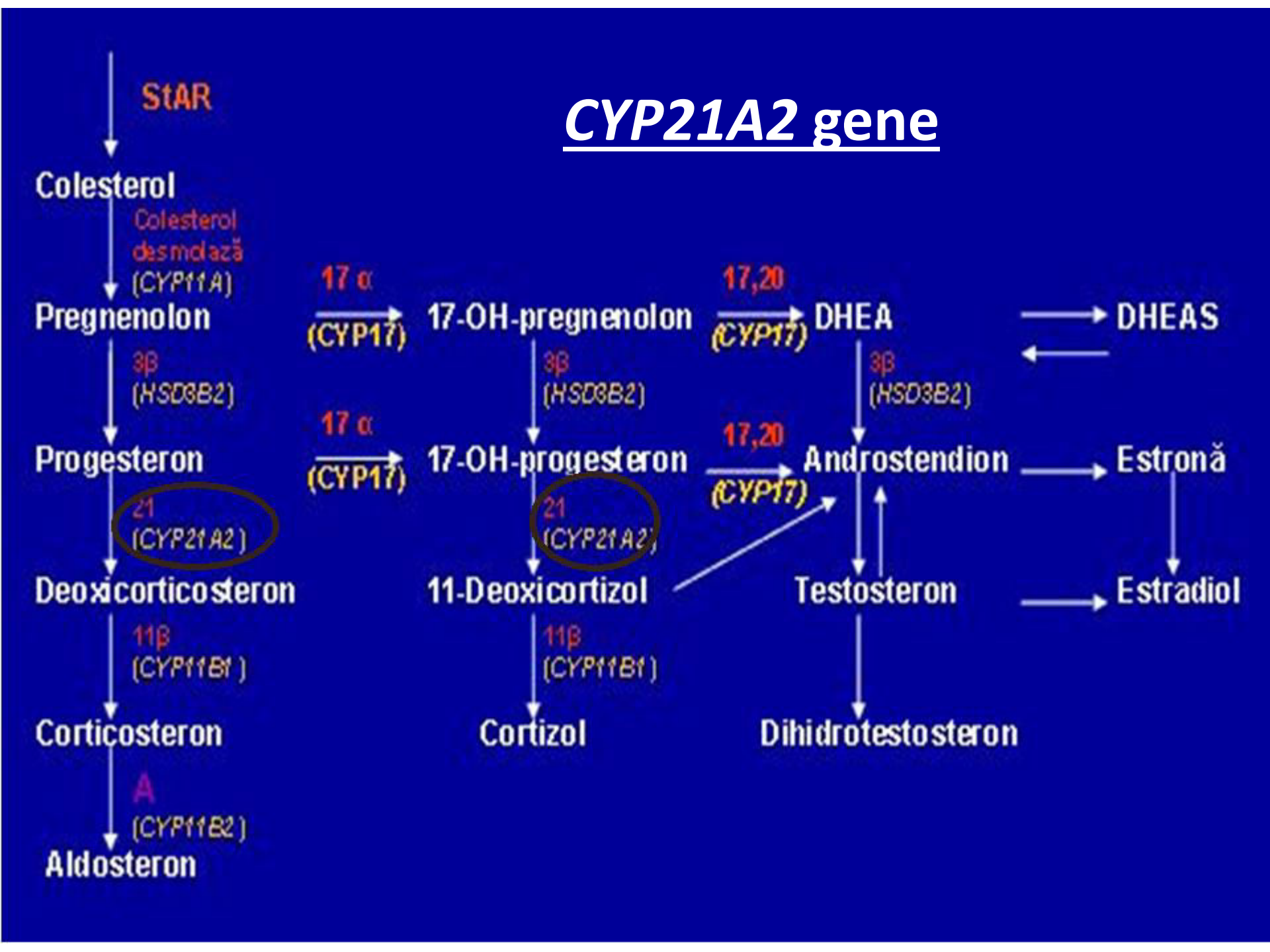
exchange of genetic material between the*CYP21A2* gene & pseudogene

- Some of these mutations result from **an exchange of genetic material between the*CYP21A2* gene and a similar but nonfunctional piece of DNA called a pseudogene, which is located very close to the *CYP21A2* gene on chromosome 6.**
- This type of DNA exchange is called a gene conversion.

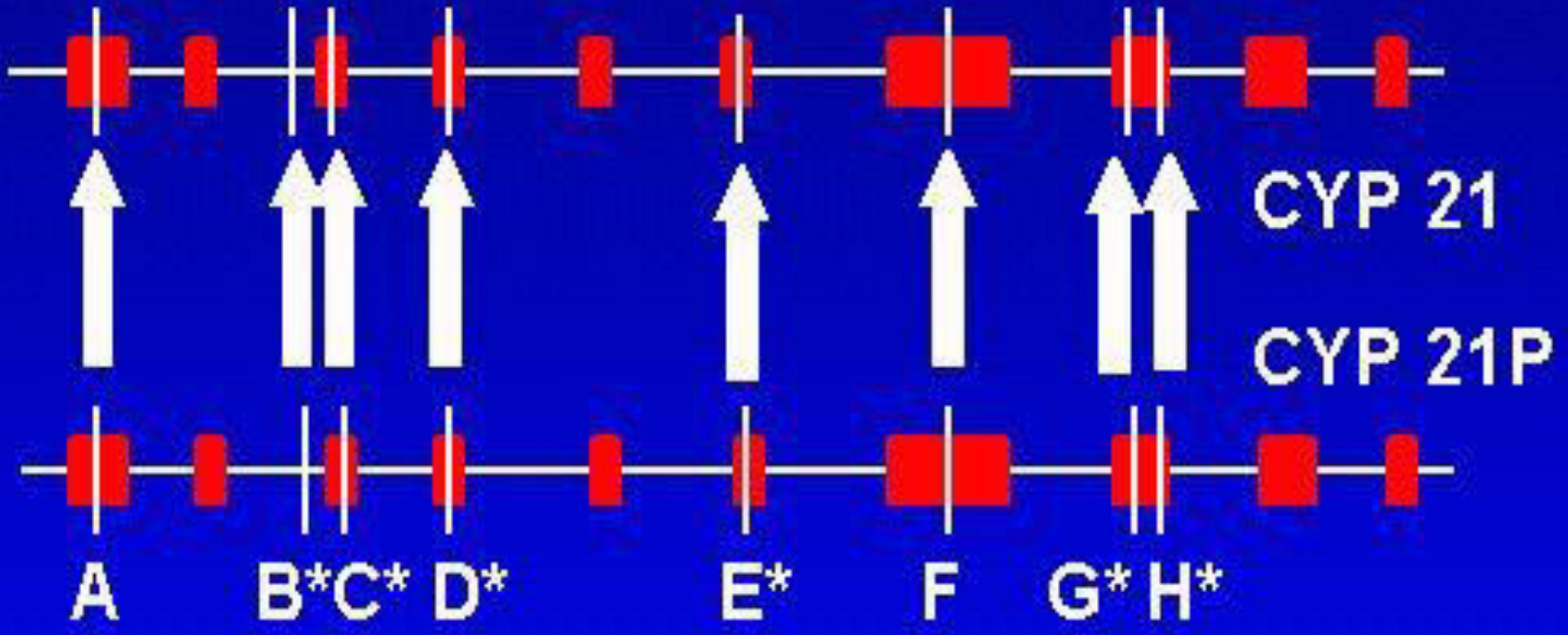
Change in amino acid

- Other mutations that cause 21-hydroxylase deficiency change single protein building blocks (amino acids) in the 21-hydroxylase enzyme
- or **delete or insert pieces of DNA in the *CYP21A2* gene.**

CYP21A2 gene



COMMON MUTATIONS OF CYP21



A : P30L
B*: INTRON 2 SPLICE (A/C656G)
C*: 8 bp DELETION
D*: I172N

E* : exon 6 cluster
F : V281L
G* : Q318X
H* : R356W

* : CYP21 MUTATIONS ASSOCIATED WITH "CLASSIC" PRESENTATION

- These particular groups of genes contain instructions the adrenal glands (located on top of the kidneys) need in order to produce an enzyme called 21-hydroxylase.

- Congenital adrenal hyperplasia (CAH) results from a deficiency in one or another of the enzymes of cortisol biosynthesis
- In about 95% of cases, 21-hydroxylation is impaired in the zona fasciculata of the adrenal cortex so that 17-hydroxyprogesterone (17-OHP) is not converted to 11-deoxycortisol

- Because of defective cortisol synthesis, ACTH levels increase, resulting in overproduction and accumulation of cortisol precursors, particularly 17-OHP, proximal to the block. This causes excessive production of androgens, resulting in virilization.

21-hydroxylase deficiency

- This enzyme is found in the adrenalglands, where it plays a role in producing hormones called cortisol and aldosterone.
- 21-hydroxylase deficiency is an inherited disorder that affects the adrenal glands.
- In people with 21-hydroxylase deficiency, **the adrenal glands produce excess androgens,** which are male sex hormones.

- The adrenal glands are controlled by the pituitary gland.
- The pituitary gland is a small pea-sized gland at the base of the brain. When the pituitary gland senses that there is not enough cortisol present in the bloodstream, it releases a hormone called ACTH (adrenocorticotropic hormone). ACTH stimulates the adrenals to produce more cortisol. However, those with CAH have insufficient amounts of the enzyme 21-hydroxylase, needed to convert a precursor molecule called 17-hydroxyprogesterone (17-OHP) into cortisol.

- As a result, the pituitary gland continues to sense the need for cortisol and pumps out more ACTH. This leads to an overabundance of 17-OHP, which is converted in the adrenals into excess androgens (masculinizing steroid hormones) .
- Lack of adequate cortisol also prevents the body from properly metabolizing sugar and responding to stress. The lack of this stress response can lead to an adrenal crisis.

- In addition, over 75 percent of all individuals with Classical CAH also lack another adrenal hormone called aldosterone, necessary for maintaining normal fluid volume of the body, sodium and potassium, which among other functions, stabilizes the heart.
- When this deficiency occurs it is called “Salt-Wasting CAH” (SW-CAH).
- The remaining 25 percent of those with Classical CAH who produce sufficient aldosterone are referred to as “Simple Virilizers” (SV-CAH).

- When the adrenals cannot make sufficient aldosterone, too much salt and water are lost in the urine, leading to dehydration and salt deficiency. High levels of potassium can cause serious disturbances of heart rhythm and may lead to cardiac arrest. These babies become very ill soon after birth if not diagnosed and treated promptly.

- All types of 21-hydroxylase deficiency interfere with the production of cortisol and aldosterone.
- The substances that are usually used to form these hormones instead build up in the adrenal glands and are converted to **androgens**, which are male sex hormones.
- **The excess production of androgens leads to abnormalities of sexual development in people with 21-hydroxylase deficiency.**

- The amount of functional 21-hydroxylase enzyme determines the severity of the disorder.
- Individuals with the **salt-wasting type** have *CYP21A2* mutations that result in a **completely nonfunctional enzyme.**

three types of 21-hydroxylase deficiency

- There are three types of 21-hydroxylase deficiency.
- **Two types are classic forms**, known as the
- **salt-wasting** (the most severe) and
- **simple virilizing types (** less severe)
- The **third type is called the non-classic type**. non-classic type is the least severe form.

Classical CAH

severe form, called Classical CAH

- The most common form is 21-hydroxylase deficiency (21-OHD), which is inherited in severe or mild forms.
- The **severe form, called Classical CAH**, is usually detected in the newborn period or in early childhood.
- Fortunately, CAH can be managed with medication and, with adequate care, affected individuals go on to live normal lives.

classic forms

- Infant males with CAH appear normal at birth.
- Newborn males show no external signs of the disorder and are sent home unrecognized.
- These babies often present with vomiting or life-threatening shock within the first few weeks of birth where there is no newborn screening.

classic forms

- Males and females with either classic form of 21-hydroxylase deficiency tend to have an early growth spurt, but their **final adult height is usually shorter** than others in their family.
- Additionally, affected individuals may have a decreased fertility.

classic forms

females with ambiguous genitalia

Males with small testes

- genital anomalies resulting from high androgen levels while in the womb when the external genitalia are formed .
- The clitoris is usually enlarged, and may even look like a small penis, and the labial folds may be joined to resemble the scrotum.

classic forms

females with ambiguous genitalia

Males with small testes

- **hirsutism** in females- may also develop excessive **body hair growth** ,male pattern **baldness**, and **irregular menstruation**.
- In **simple virilizing forms** of disorder production of low levels of functional enzyme
- In both the **salt-wasting and simple virilizing forms** of this disorder, females typically have external genitalia that do not look clearly male or female (ambiguous genitalia).
- Individuals with the simple virilizing form do not experience salt loss.

- Sometimes, if the extent of ambiguity is great, the female baby may be misidentified as a male. These anomalies are only external.
- The female reproductive internal organs are not affected and are intact. The child has a uterus and ovaries.
- Some parents may choose reconstructive genital/urological surgery for their daughters.

- Infant females generally come to medical attention at birth because the disorder causes affected females to exhibit recognizable genital anomalies resulting from high androgen levels while in the womb, and therefore receive prompt treatment for adrenal crisis and salt-wasting

classic forms-salt-wasting

- Approximately 75 percent of individuals with classic 21-hydroxylase deficiency have the salt-wasting type, *CYP21A2* mutations in **salt-wasting type** result in a completely nonfunctional enzyme. . Without newborn screening for CAH, the child is at risk for a **life-threatening adrenal crisis**, especially males, who show no outward physical manifestations of the disease.

classic forms-salt-wasting

- Hormone production is extremely low in this form of the disorder.
- Affected individuals **lose large amounts of sodium** in their urine, which can be life-threatening in early infancy.
- Babies with the salt-wasting type can experience **poor feeding, weight loss, dehydration, and vomiting**.

- People with the **simple virilizing type** of this condition have *CYP21A2* gene mutations that allow the production of **low levels of functional enzyme.**

- The remaining 25% of those with classical CAH who produce sufficient aldosterone are called “simple virilizers

Non-classical CAH
late-onset CAH

- Girls born with NCAH have normal genitals. Boys also appear normal.
- Because the symptoms begin later in life, NCAH is sometimes called late-onset CAH, adult-onset CAH, or the attenuated form of CAH.
- Non-classical CAH does not progress to classical CAH in affected individuals

- Individuals with the non-classic type of this disorder have *CYP21A2* mutations that result in the **production of reduced amounts of the enzyme**, but more enzyme than either of the other types.
- NCAH is a much more common disorder than Classical CAH.

- The milder form, called Non-classical CAH (NCAH), may cause symptoms at anytime from infancy through adulthood.
- Some individuals with this type of 21-hydroxylase deficiency have no symptoms of the disorder

- NCAH may be picked up in infants through newborn screening tests, but they do not necessarily need treatment.
- Parents can be aware of the symptoms of the disorder and seek treatment if it becomes necessary.
- Only those children/adults who are symptomatic should be treated.

milder form, called Non-classical CAH

- The nonclassical form of CAH is not life threatening, but can affect puberty and growth in children and can cause infertility in males and females as well as other symptoms affecting quality of life.

non-classic females

- Females with the non-classic type of 21-hydroxylase deficiency have normal female genitalia.
- As affected females get older, they may experience hirsutism, male pattern baldness, irregular menstruation, and decreased fertility.
- Males with the non-classic type may have **early beard growth and small testes**.

3B-HSD , 11B-HD , 17a-HD enzyme deficiency

- Other rare forms of enzyme deficiency that belong to the Congenital Adrenal Hyperplasia family of disorders are: 3Beta-hydroxysteroid dehydrogenase deficiency (3B-HSD), 11-Beta hydroxylase deficiency (11B-HD) and 17-alpha hydroxylase deficiency (17a-HD) which are much less common..