Mutations

Clinical Syndromes &
Laboratory Investigations

Overview

It has been known since biblical times that certain disorders are inherited or related to disturbances in intrauterine development.

The earliest sanitary codices contain guidelines on how to choose a healthy spouse, how to conceive healthy children and what to do or not do during pregnancy.

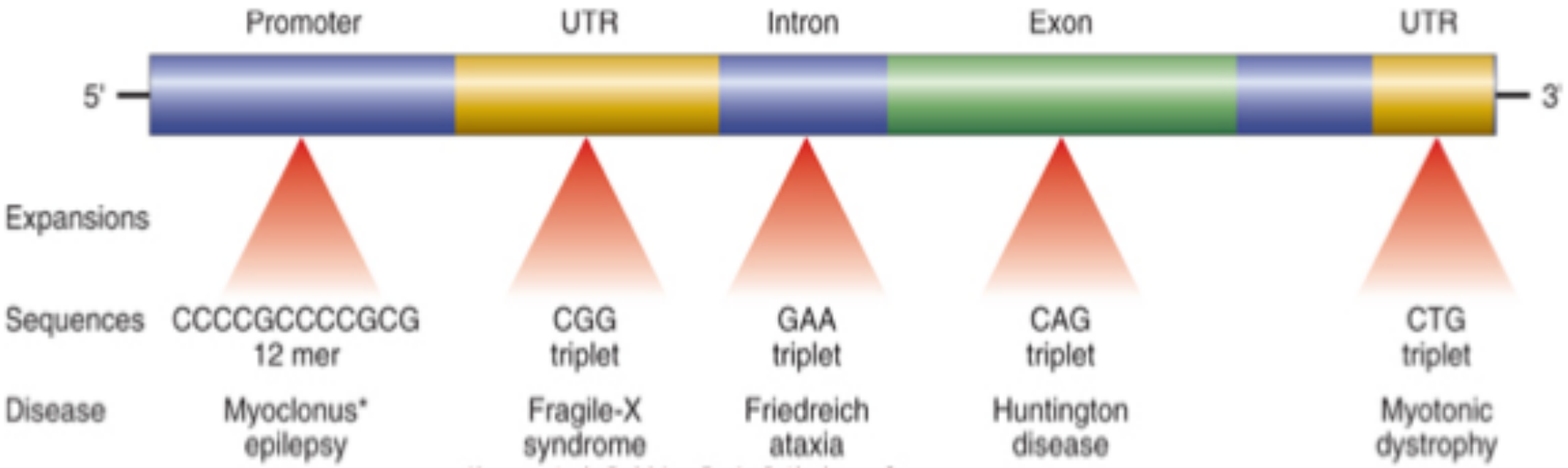
Nevertheless, most of our scientific understanding and genetic disorders comes from only the past three decades.

Overview

At least 1 in 50 newborns has a major congenital anomaly, 1 in 100 has a single-gene abnormality and 1 in 200 has a major chromosomal abnormality.

Here, we will examine the causes of human genetic diseases that result from defects in single genes and chromosomal anomalies.

Because the list of genetic syndromes is inexhaustible, we shall discussion only a few example.



Some Neurodegenerative Diseases with TNRE

1. Fragile X Syndrome

Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment.

Its an X-linked dominant disorder.

Usually, males are more severely affected by this disorder than females and children have anxiety and hyperactive behavior, autism disorders and intellectual disorders.

FXS Mutation

Mutations in the *FMR1 gene* cause fragile X syndrome.

The *FMR1 gene* provides instructions for making a protein called fragile X mental retardation 1 protein, or FMRP.

This protein helps regulate the production of other proteins and plays a role in the development of synapses.

FXS Mutation

Nearly all cases of FXS are caused by a mutation in which a DNA segment, known as the CGG triplet repeat, is expanded within the *FMR1* gene.

Normally, this DNA segment is repeated from 5 to about 40 times.

In people with fragile X syndrome, however, the CGG segment is repeated more than 200 times.

FXS Mutation

The abnormally expanded CGG segment turns off (silences) the *FMR1* gene, which prevents the gene from producing FMRP.

Deficiency of this protein disrupts nervous system functions and leads to the signs and symptoms of fragile X syndrome.

FXS Mutation

Males and females with 55 to 200 repeats of the CGG segment are said to have an *FMR1* gene premutation.

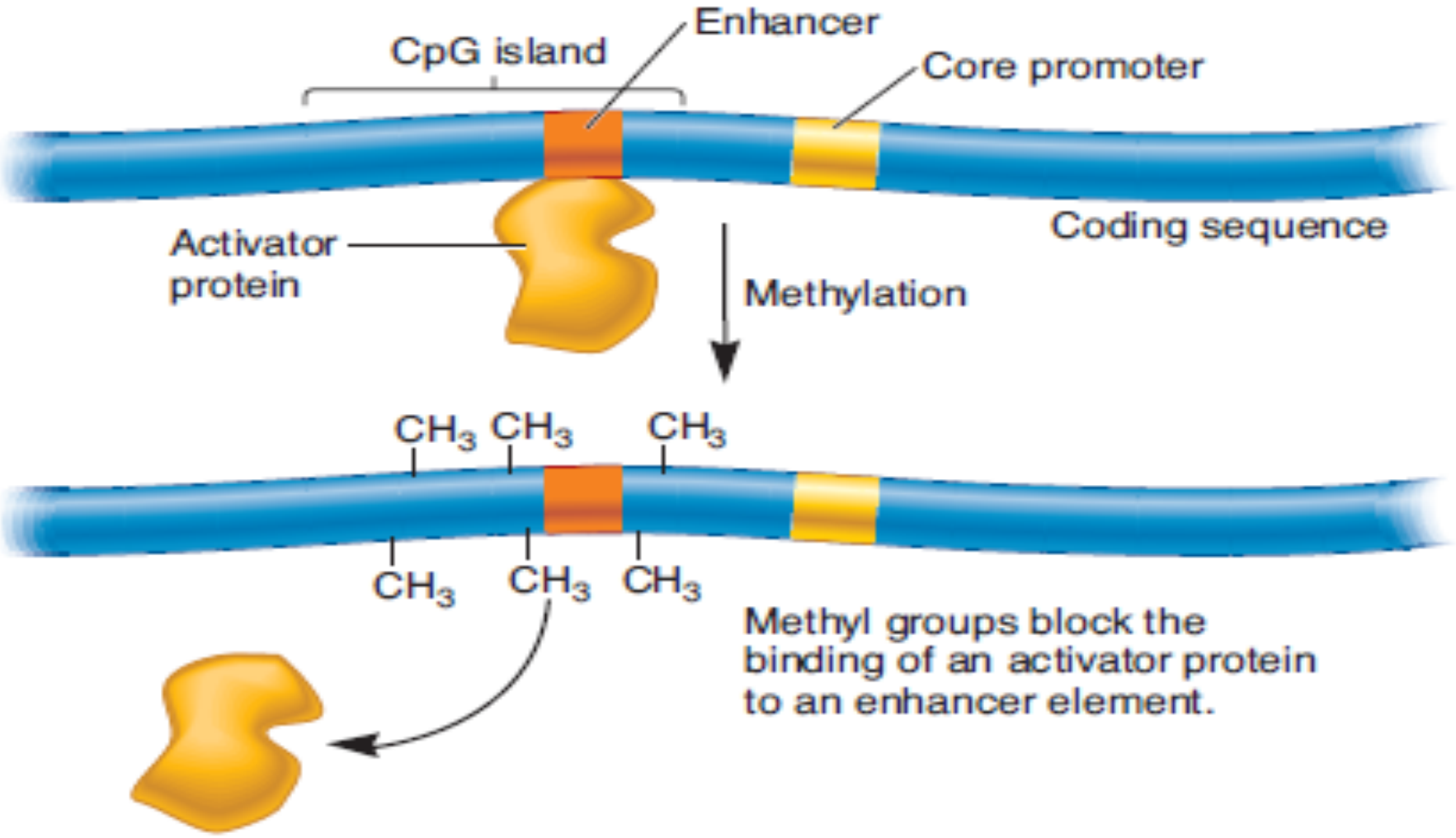
Most people with a premutation are intellectually normal.

However some may have mild versions of the physical features seen in fragile X syndrome

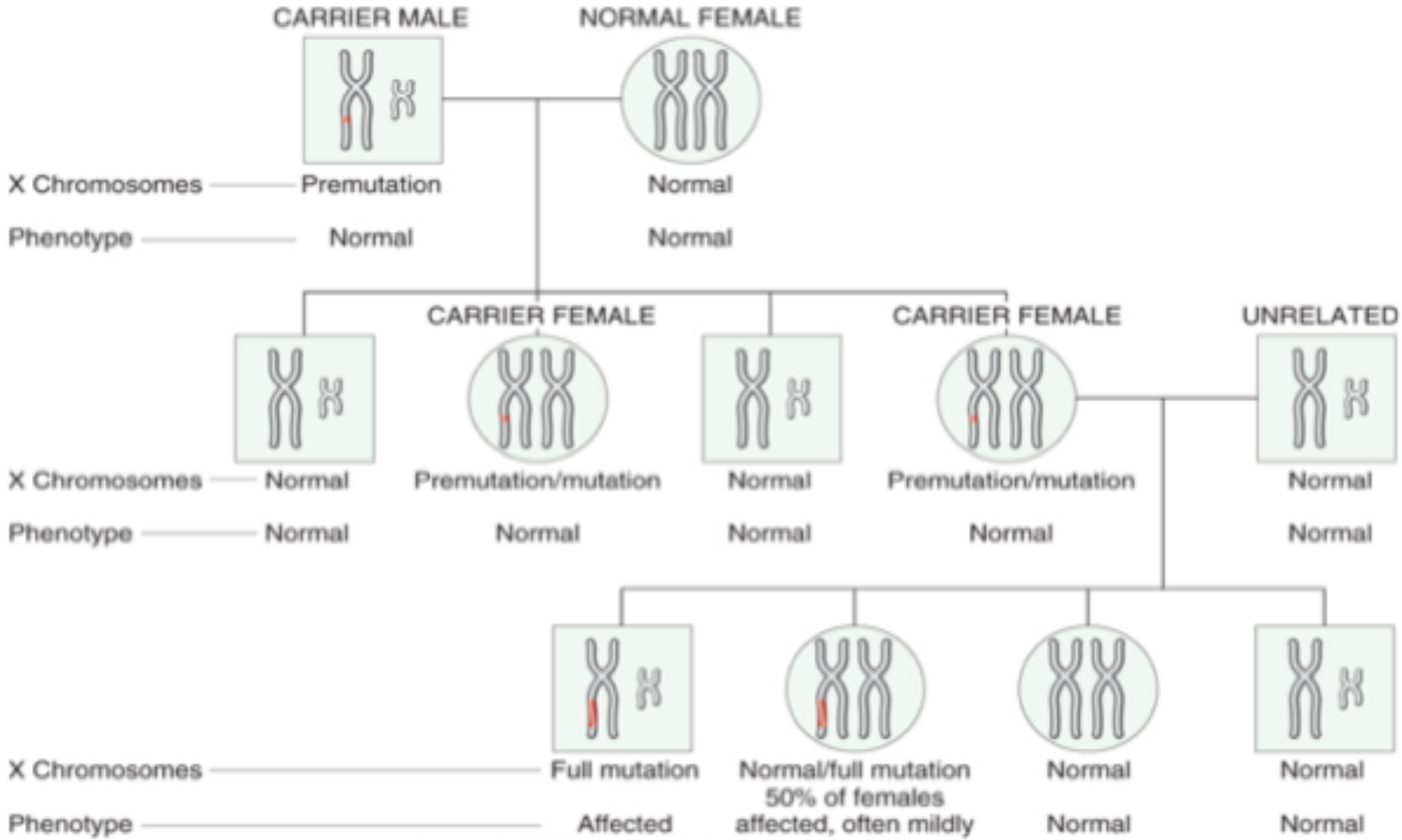
FXS Mutation

In women, the *FMR1* gene premutation on the X chromosome can expand to more than 200 CGG repeats in cells that develop into eggs.

This means that women with the premutation have an increased risk of having a child with fragile X syndrome.



Major Mechanism by which FXS gene is Silenced



Inheritance of FXS

Diagnosis of FXS

Identification of a loss-of-function mutation in the *FMR1* gene is sufficient to diagnose fragile X syndrome in an individual exhibiting developmental delay or intellectual disability.

This targets mutation analysis to the trinucleotide repeat region of *FMR1*.

2. Huntington disease

Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability.

Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties.

Mutations in the *HTT* gene cause Huntington disease.

Huntington disease Mutations

The *HTT* gene provides instructions for making a protein called huntingtin.

Although the function of this protein is unknown, it appears to play an important role in nerve cells in the brain.

The *HTT* mutation that causes Huntington disease involves a DNA segment known as a CAG trinucleotide repeat.

Huntington disease Mutations

Normally, the CAG segment is repeated 10 to 35 times within the gene.

In people with Huntington disease, the CAG segment is repeated 36 to more than 120 times.

People with 36 to 39 CAG repeats may or may not develop the signs and symptoms of Huntington disease, while people with 40 or more repeats almost always develop the disorder.

Huntington disease Mutations

An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein.

The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells.

The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of Huntington disease.

Inheritance of HD

An affected person usually inherits the altered gene from one affected parent.

This condition is inherited in an autosomal dominant pattern.

In rare cases, an individual with Huntington disease does not have a parent with the disorder.

Inheritance of HD

As the altered *HTT* gene is passed from one generation to the next, the size of the CAG trinucleotide repeat often increases in size.

A larger number of repeats is usually associated with an earlier onset of signs and symptoms.

This phenomenon is called anticipation.

Diagnosis of HD

Targeted mutation analysis - PCR-based methods detect alleles up to about 115 CAG repeats

Southern blot protocols are occasionally useful for the following: Identification of large expansions (which may fail to amplify well by PCR analysis) associated with juvenile-onset HD.

Confirmation of apparent homozygous genotypes obtained by PCR analysis.

3. Down syndrome

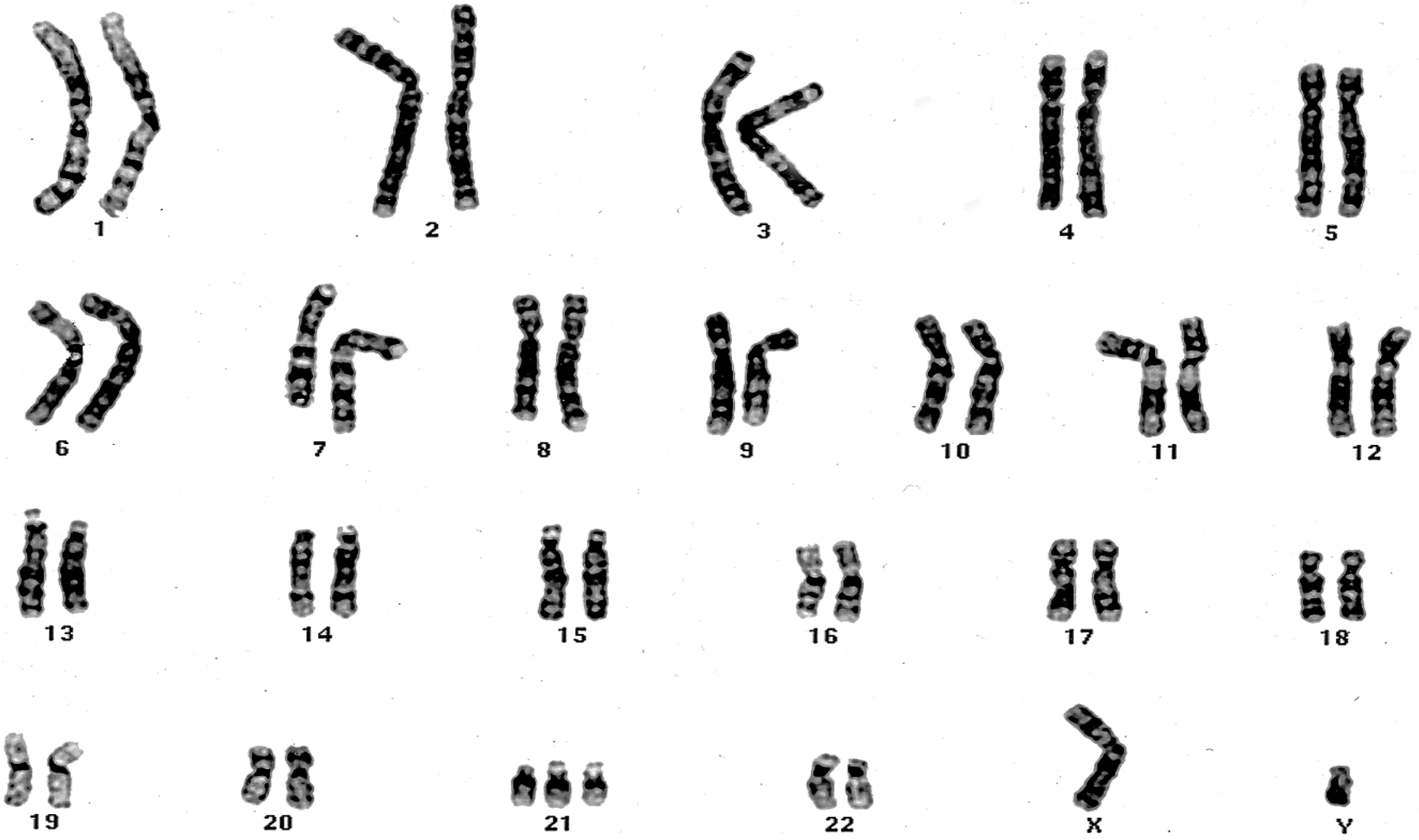
Down syndrome is a chromosomal condition that is associated with intellectual disability, a characteristic facial appearance, and weak muscle tone in infancy.

All affected individuals experience cognitive delays, but the intellectual disability is usually mild to moderate.

Down syndrome

Individuals with Down syndrome have an increased risk of developing several medical conditions.

These include gastroesophageal reflux, hypothyroidism hearing, vision problems, leukemia and developing Alzheimer disease



Down Syndrome Karyotype

Genetic Changes of DS

Most cases of Down syndrome result from trisomy 21.

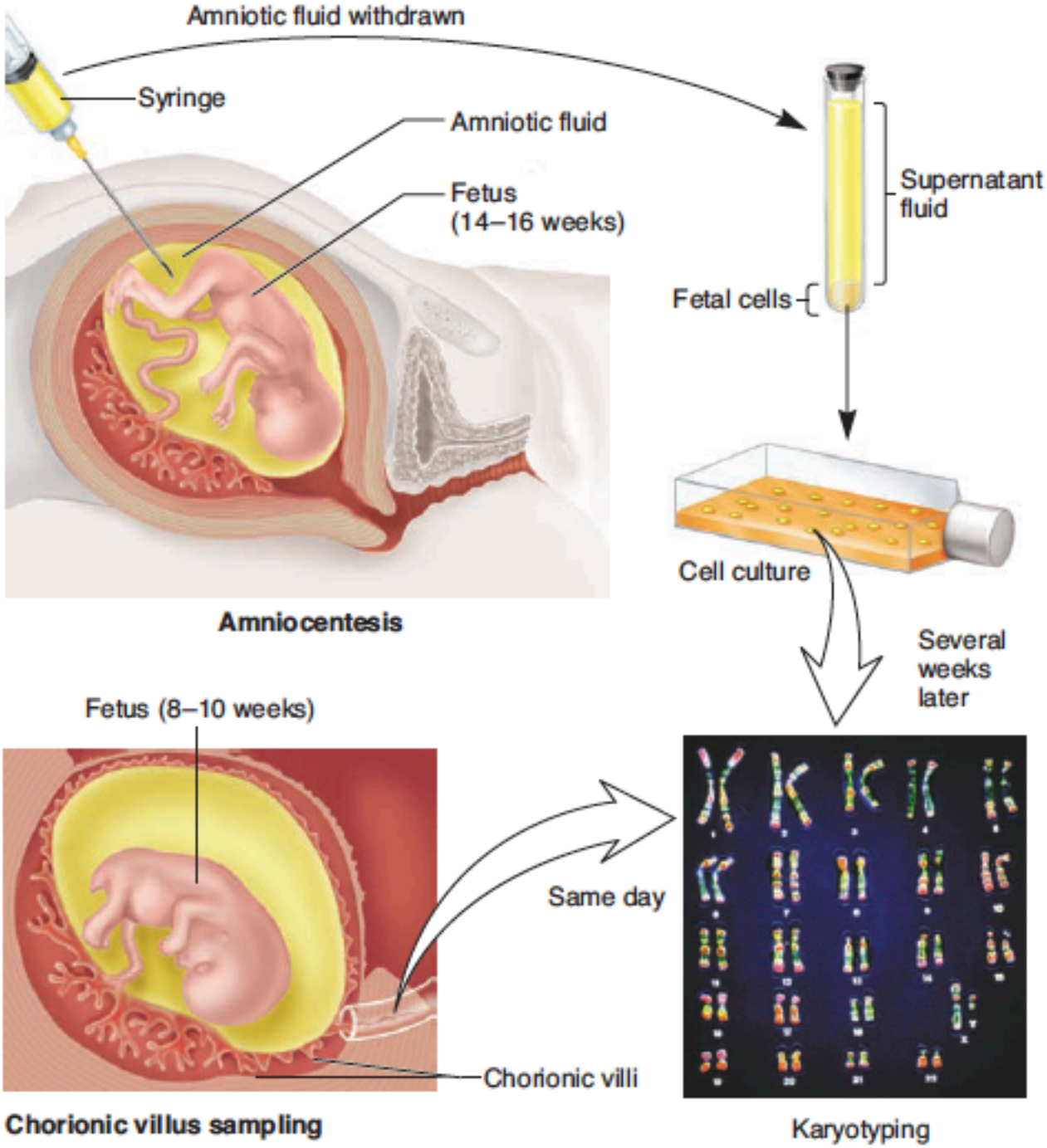
Less commonly, Down syndrome occurs when part of chromosome 21 becomes attached (translocated) to another chromosome during the formation of reproductive cells in a parent or very early in fetal development.

Diagnosis of DS

A complete or partial extra copy of chromosome 21 confirms the diagnosis.

A blood sample is usually obtained for karyotyping.

Amniocentesis or umbilical cord blood sampling for karyotype


Amniotic fluid withdrawn
Syringe
Amniotic fluid
Fetus
(14–16 weeks)
Supernatant
fluid
Fetal cells
Cell culture
Several
weeks
later
Fetus (8–10 weeks)
Same day
Chorionic villi
Amniocentesis
Chorionic villus sampling
Karyotyping

4. Dubin-Johnson Syndrome

Dubin-Johnson syndrome is a condition characterized by jaundice.

In most affected people jaundice appears during adolescence or early adulthood, although a few individuals have been diagnosed soon after birth.

Jaundice is typically the only symptom of Dubin-Johnson syndrome, but some people also experience weakness, mild upper abdominal pain, nausea, and/or vomiting.

Mutations of D-J Syndrome

Dubin-Johnson syndrome is caused by mutations in the ATP-binding cassette sub-family C member 2 (*ABCC2)* gene.

The *ABCC2* gene codes for a protein called multidrug resistance protein 2 (MRP2).

This protein acts as a pump to transport substances out of the liver, kidneys, intestine, or placenta so they can be excreted from the body.

Mutations of D-J Syndrome

For example, MRP2 transports bilirubin out of liver cells and into the bile canaliculi.

ABCC2 gene mutations lead to a version of MRP2 that cannot effectively pump substances out of cells, affecting the transport of bilirubin into bile.

As a result, bilirubin accumulates in the body, causing a chronic hyperbilirubinaemia.

D-J Syndrome

The buildup of bilirubin in the body causes the yellowing of the skin and whites of the eyes seen in people with Dubin-Johnson syndrome.

This condition is inherited in an autosomal recessive pattern.

Laboratory Analysis

DNA Sequence analysis of the entire coding region

Deletion/duplication analysis.

Biochemical test : Conjugated Hyperbilirubinemia, AST and ALT levels are usually normal.

Use of Genetic Test

Genetic tests are utilized to study and diagnose genetic syndromes.

The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder.

More than 1,000 genetic tests are currently in use, and more are being developed.

Use of Genetic Test

Several methods can be used for genetic testing:

Molecular genetic tests study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.

Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.

Use of Genetic Test

Biochemical genetic tests study the amount or activity level of proteins as a result in a genetic disorder.

It is important for people considering genetic testing to know whether the test is available on a clinical or research basis.

Key Points Review

Both FXS & HD are non-classical inheritance neurodegenerative disorders that involved CGG and CAG TNRE respectively, - a trinucleotide repeat that have increased above a certain critical size.

Down Syndrome involves a chromosomal mutation that may occur due to chromosomal nondisjunction, translocation or mosaicism.

Key Points Review

D-J syndrome involves a mutation in a gene coding for a bilirubin transport protein leading to hyperbilirubinaemia.

Genetic clinical syndromes maybe tested or diagnosed by molecular genetic tests, chromosomal genetic tests, which maybe supported by specific biochemical test.

End