

COMMON TYPES OF CHROMOSOME ABNORMALITIES

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- A. Trisomy:** instead of having the normal two copies of each chromosome, an individual has three of a particular chromosome. Which chromosome is trisomic determines the type and severity of the disorder.

Down syndrome or Trisomy 21, is the most common trisomy, occurring in 1 per 800 births (about 3,400) a year in the United States. It is one of the most common genetic birth defects. According to the National Down Syndrome Society, there are more than 400,000 individuals with Down syndrome in the United States.

Patients with Down syndrome have three copies of their 21 chromosomes instead of the normal two. The major clinical features of Down syndrome patients include low muscle tone, small stature, an upward slant to the eyes, a single deep crease across the center of the palm, mental retardation, and physical abnormalities, including heart and intestinal defects, and increased risk of leukemia. Every person with Down syndrome is a unique individual and may possess these characteristics to different degrees.



Karyotype of a male patient with trisomy 21



Down syndrome patients

What are the causes of Down syndrome?

- 95% of all Down syndrome patients have a trisomy due to **nondisjunction** before fertilization
- 1-2% have a **mosaic** karyotype due to nondisjunction after fertilization

- 3-4% are due to a **translocation**

1. Nondisjunction refers to the failure of chromosomes to separate during cell division in the formation of the egg, sperm, or the fetus, causing an abnormal number of chromosomes. As a result, the baby may have an extra chromosome (trisomy). If the trisomic chromosome is number 21, then the fetus will have Down syndrome. Trisomies for other chromosomes often result in miscarriage.

Nondisjunction in cell division of the sperm or egg before fertilization causes about 95 percent of the cases of Down syndrome.

Down Syndrome Occurrence and Mother's Age

There is an increased risk of nondisjunction in women with advanced age. The chance of having a child with a trisomy 21 becomes greater as women grow older.

At age 25, the risk of having a baby with Down syndrome is 1 in 1,250.

At age 30, the risk is 1 in 1,000.

At age 35, the risk is 1 in 400.

At age 40, the risk is 1 in 100.

At age 45, the risk is 1 in 30.

At age 50, the risk is 1 in 10.

Prenatal tests such as chorionic villus sampling or amniocentesis can help rule out the presence of a trisomy with a high degree of certainty in pregnancy.

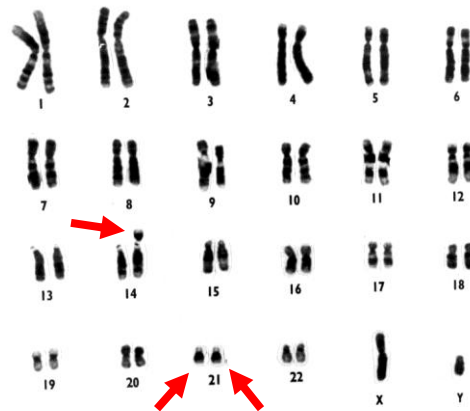
Parents of a baby with Down syndrome usually have a 1 percent risk of having another affected baby. However, there is an additional risk based on the mother's age.

2. Mosaic Down syndrome

About 1 to 2 percent of individuals with Down syndrome have mosaicism. In mosaic Down syndrome, the error in cell division (nondisjunction) occurs after fertilization of the egg by the sperm, in the fetus. These individuals have some cells with an extra chromosome 21 and others with the normal number. Because not all their cells have the trisomy 21, patients with the mosaic type of Down syndrome may have milder symptoms of the disease.

3. Translocation Down syndrome

Occasionally, chromosome 21 can attach to another chromosome.. The resulting fetus may have what is called translocation Down syndrome. Affected individuals have two normal copies of chromosome 21, plus extra chromosome 21 attached to another chromosome.



Translocation Down syndrome karyotype with two normal 21 chromosomes and an extra 21 translocated to chromosome 14.

This type of error in cell division causes about 3 to 4 percent of the cases of Down syndrome.

In about half of all translocation Down cases, one of the parents is carrying the rearrangement of chromosome 21, called a **balanced translocation**. The parent may be unaware that he or she is a carrier of this balanced translocation, since it does not affect his or her health. However, this parent can pass the **unbalanced translocation** to his or her child. Routine chromosome analysis and fluorescence in situ hybridization (FISH) is often done on the patient and the parents to determine if one of the parents is carrying the balanced translocation.

Translocation Down syndrome is the only form of the disorder that can be passed from parent to child. The chance of passing on the unbalanced translocation depends on the sex of the parent who carries the rearranged chromosome 21:

- If the father is the carrier, the risk is about 3-5 percent.
- If the mother is the carrier, the risk is about 12-15 percent.

Other common trisomies include:

- Trisomy 16
- Trisomy 18 (Edwards syndrome)
- Trisomy 13 (Patau syndrome)

All of these often result in miscarriage. In rare cases, a fetus with one of these trisomies can survive, but the clinical features include severe and multiple birth defects, mental retardation, and shortened life expectancy.

B. Monosomy X or Turner syndrome affects approximately 1 out of every 2,500 female live births worldwide. These patients have only one X chromosome and a total of 45 chromosomes.



Karyotype of a patient with Turner syndrome demonstrating only one X chromosome (monosomy X).

Almost all people with Turner syndrome have short stature and loss of ovarian function, but the severity of these problems varies considerably among individuals. Some patients with Turner syndrome have a short neck with a webbed appearance, a low hairline at the back of the neck, and low-set ears. It is standard medical practice to treat girls with Turner syndrome with estrogen to induce breast development and other features of puberty. A woman with Turner syndrome has a low probability of being fertile, since the ovaries are negatively impacted in this disorder.

Causes of Turner syndrome:

1. **Monosomy X.** During the process in which eggs or sperm are formed, one of the sex chromosomes (the X or Y) is sometimes "lost". About half of all Turner syndrome patients have this type of chromosome abnormality.
2. **Mosaic Turner syndrome.** A sex chromosome may also be lost during early stages of embryonic development. As a result, some cells receive a single X chromosome and some have the normal number of chromosomes. These patients have milder clinical features and may possibly become pregnant.
3. **X chromosome abnormalities.** This involves one of the X chromosome having a defect rather than complete loss. For example, one X-chromosome may be broken, have portions deleted or other structural problems such as ring formation. The clinical consequences of having one normal and one structurally defective X-chromosome vary widely.

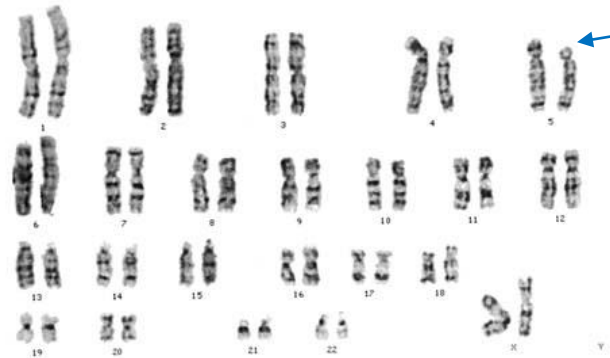
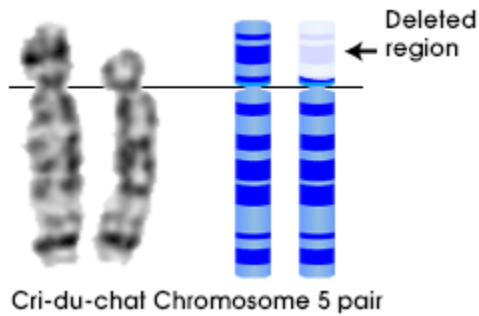
C. **Microdeletions** are caused by a loss of a piece of chromosome that is often too small to be seen under a microscope using routine chromosome analysis. They cause a variety of **contiguous gene**

syndromes (syndromes caused by a loss of many genes). Incidence rates are not available for all of these syndromes, since they are rare and may be sometimes undiagnosed.

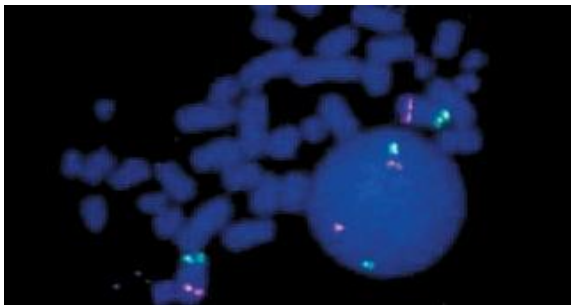
Some **contiguous gene syndromes** caused by microdeletions are listed in the table below.

Chromosome microdeletion region	Contiguous gene syndrome	Clinical features
4p16.3	Wolf-Hirshhorn syndrome	Typical facial appearance, mental retardation, growth delay, and seizures
5p15.2	Cri-du-chat syndrome	High-pitched cat-like cry, mental retardation, delayed development, distinctive facial features, small head size (microcephaly), widely-spaced eyes (hypertelorism), low birth weight and weak muscle tone (hypotonia) in infancy
7q11.23	Williams Syndrome	Mild to moderate intellectual disability or learning problems, unique personality characteristics, distinctive facial features, and heart and blood vessel (cardiovascular) problems
15q11-q13	Angelman Syndrome	Severe mental retardation and functional impairment, usually absent speech, hyperactivity, easily excitable, frequent smiling and/or laughing, difficulty walking, and seizures.
15q11-q13	Prader-Willi Syndrome	The newborn has trouble growing and gaining weight (failure to thrive) and has weak muscles (hypotonia). The older child has obesity, mental retardation, small testicles, and small hands and feet
17p13.3	Miller Dieker Syndrome	Abnormally smooth brain with fewer folds and grooves. These brain malformations cause severe intellectual disability, developmental delay, seizures, abnormal muscle stiffness (spasticity), weak muscle tone (hypotonia), and feeding difficulties.
17p11.2	Smith Magenis Syndrome	Mental retardation, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems.
22q11.2	DiGeorge / Velocardiofacial Syndrome	Cleft palate, heart abnormalities, learning disabilities, hypocalcemia, absent thymus

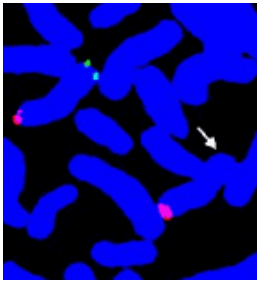
If the physician suspects any of the above syndromes, prometaphase chromosomes and *fluorescence in situ* hybridization (FISH) should be ordered to detect the microdeletion. Specific DNA probes are used to analyze the presence or absence of the specific gene regions.



Karyotype of a patient with cri-du-chat syndrome missing a piece of chromosome 5 (5p-).



Fluorescence *in situ* hybridization (FISH) of normal metaphase and interphase cells showing two copies of the cri-du-chat gene region (green) and a control (red).



Fluorescence *in situ* hybridization (FISH) of a patient with cri-du-chat syndrome missing the 5p15 region (green) on one of the 5 chromosomes. The red signal is the control probe.

Other types of chromosome abnormalities exist which are not included in this review. The table below is a list of abbreviations used by the chromosome laboratories to describe their observations. These can be explained by a geneticist and a certified genetic counselor.

When any chromosome abnormality is discovered, follow up by a geneticist and genetic counselor is highly recommended. It is important for geneticists to explain what results of genetic and chromosome testing mean for an individual, his or her family, and future family members.

Abbreviations used in describing chromosomes and karyotypes

Abbreviation	meaning	example	description
cen	centromere		
del	deletion	46, XX, del(5)(p15.3)	Cri du chat syndrome deletion of band 5p15.3
der	derivative chromosome	der(22)	a chromosome derived from chromosome 22 and containing the chromosome 22 centromere
dup	duplication	46, XY, dup(21)(q21)	A male with a duplication of band q21 on chromosome 21
inv	inversion	46, XX, inv(9)(p12q13)	A female with a pericentric inversion on chromosome 9
mar	marker chromosome	47, XX, +mar	A female with an extra (unidentified) chromosome
mat	of maternal origin	46, XY, del(15)(q12)(mat)	A boy with Angelman syndrome
pat	of paternal origin	46, XX, del(15)(q12)(pat)	A girl with Prader-Willi syndrome
t	translocation	46, XY, t(1;2)(p21;p24)	A boy with a reciprocal translocation between band p21 on chromosome 1 and band p24 on chromosome 2
ter	the end of the chromosome arm	pter or qter	
+	gain of material	47, XY, +21	A boy with trisomy 21
-	loss of material	46, XX, 5p-	A less precise definition of the girl with Cri du chat above
/	mosaic	46,XX / 45, X	A mosaic case of Turner's syndrome