COMMON ANEUPLOIDY AND MICRODELETION SYNDROMES
# COMMON ANEUPTLOYIDY AND MICRODELETION SYNDROMES

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Down syndrome, also called trisomy 21, is associated with the presence of an extra copy of chromosome 21. It is the most common genetic disorder and single cause of human birth defects.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 750–800 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• The syndrome is statistically more common with older parents.</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>INHERITANCE</th>
<th>Sporadic / not inherited</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Most cases of Down syndrome are not inherited, including mosaicism.</td>
</tr>
<tr>
<td></td>
<td>• Translocation Down syndrome can be inherited. A carrier can have a rearrangement of genetic material between chr 21 and another chromosome. This is called a balanced translocation because there is no extra material from chr 21. Although they do not have signs of the syndrome, people who carry this type of balanced translocation are at an increased risk of having children with the condition.</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>LIFE EXPECTANCY</th>
<th>Lifespan close to normal average</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• The median life expectancy is above 50 years.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>A third chromosome 21 appearing in all or some of the cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Primary trisomy: the presence of an entire third chr 21 in all cells (95% of cases).</td>
</tr>
<tr>
<td></td>
<td>• Unbalanced translocation: part of chr 21 becomes attached (translocated) to another chromosome (usually chr 14) during the formation of reproductive cells or very early in fetal development. Affected people have two copies of chr 21, plus extra material from chr 21 attached to another chromosome.</td>
</tr>
<tr>
<td></td>
<td>• Mosaicism: some normal cells with 46 chromosomes, others with extra chr 21.</td>
</tr>
<tr>
<td></td>
<td>• The only well known risk factor for conceiving a child with Down syndrome is advanced maternal age:</td>
</tr>
<tr>
<td></td>
<td>– 1:385 risk at 35 years</td>
</tr>
<tr>
<td></td>
<td>– 1:106 at 40 years</td>
</tr>
<tr>
<td></td>
<td>– 1:30 at 45 years</td>
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</tbody>
</table>
Symptoms and medical problems

Trisomy 21 symptoms vary from person to person and can range from mild to severe. In mosaic trisomy 21 cases the percentage of cells with extra chr 21 varies, and they often do not have all the typical physical characteristics and may not be as severely intellectually impaired as people with full trisomy 21.

Key features:
- Round, flat face
- Upward slanting eyes with skin folds at the upper eyelid (epicanthal fold)
- Brushfield spots (small white/gray spots on the periphery of the iris)
- Abnormally shaped nose and ears
- Small mouth with protruding tongue
- Lateral teeth
- Excess skin at the nape of the short neck
- Short hands with short fingers
- Single line in the palm (simian crease)
- Hearing problems
- Hip problems and risk of dislocation
- Hypotonia and ligamental laxity
- Congenital heart defects
- Digestive malformations
- Sleep apnea (because of narrowed mouth, throat and airway)
- Autoimmune and endocrine problems
- Infertility in males and severely decreased fertility in females
- Earlier aging

Children with Down syndrome may also have delayed mental and social development. Common problems may include:
- Impulsive behavior and poor judgment
- Short attention span
- Slow learning with mild to moderate learning disabilities
- Delayed language development and slow motor development
- Intellectual deficiency

People with Down syndrome have an increased risk for developing epilepsy, leukemia, Alzheimer’s disease and immune deficiencies.

Treatment

Early intervention can help people with trisomy 21 live productive lives well into adulthood. Corrective surgery for heart defects, gastrointestinal irregularities and other health issues is necessary for some individuals. Regular screening is needed for other medical conditions and disorders.

Patients can and should be fully included in family and community life. Educative programs are essential, aiming at the best possible personal fulfillment and integration in society, including physical, occupational and speech therapy.

DID YOU KNOW?

The syndrome was named after John Langdon Haydon Down, an English physician who first described the syndrome in 1866. Although Down made some important observations about the syndrome, he did not correctly identify what causes the disorder. The condition was identified as a chromosome 21 trisomy by Jérôme Lejeune in 1959.
Edwards syndrome, also called trisomy 18, is a genetic disorder associated with the presence of an extra chromosome 18. It is the second most common autosomal trisomy among liveborn children.

**Frequency of Occurrence**
- Seen 1 in 6000 live births
- About 1 in 3000 conceptions is diagnosed as having an extra copy of chromosome 18, but most fetuses with trisomy 18 die during pregnancy.

**Inheritance**
- Sporadic / not inherited
- Most cases of Edwards syndrome (primary trisomies) are not inherited including mosaicism.
- Trisomy 18 due to a translocation can be inherited. A carrier can have a rearrangement of genetic material between chr 18 and another chromosome. This is called a balanced translocation, because there is no extra material from chr 18. Although they do not have signs of the syndrome, people who carry this type of balanced translocation are at an increased risk of having children with the condition.

**Life Expectancy**
- Limited lifespan, median survival of 4 days
- Survival rates:
  - 40% chance of surviving to 1 month
  - 5% chance of surviving to 1 year
  - 1% chance of surviving to 10 years

**Cause**
- A third chromosome 18 appearing in all or some of the cells
  - Primary trisomy: the presence of an entire third chr 18 in all cells.
  - Unbalanced translocation: an extra portion of chr 18 attached to another chromosome, which may be due to a balanced translocation of one parent.
  - Mosaicism: some normal cells with 46 chromosomes, others with extra chr 13.
Symptoms and medical problems

- Low birth weight
- Neonatal hypotonia followed by hypertonia
- Growth delay
- Small head (microcephaly)
- Long head (dolichocephaly)
- Craniofacial abnormalities
- Eye malformations (microphthalmia, coloboma)
- Skeletal abnormalities (clenched fist, thumb aplasia, malformed feet)
- Incomplete development of lungs (pulmonary hypoplasia)
- Congenital heart defects
- Gastrointestinal abnormalities
- Urogenital malformations
- Neurological problems (anencephaly, hydrocephaly and other brain malformations)
- Severe learning disability

People with Edwards syndrome can have a range of severe medical problems. For the most part of their lives they require specialised nursing in a hospital or hospice.

The majority of non-mosaic patients develop only limited autonomy (absence of speech and ambulation).

For unknown reasons, the rate of survival is higher in females than in males, leading to a female predominance among live-born trisomy 18 infants.

Treatment

Medical management of patients with trisomy 18 is planned on a case-by-case basis and depends on their individual circumstances of the patient. Treatment is usually supportive only.

Surgical treatment of the malformations does little to improve the poor prognosis associated with this syndrome: more than 90% of infants die within the first year of life from cardiac, renal or neurological complications, or from repeated infections.

Prolonged survival (in some cases into adulthood) mainly happens in cases involving mosaic or partial trisomy.

DID YOU KNOW?

Trisomy 18 was named after John Hilton Edwards, a British medical geneticist. Edwards and his coworkers first described the syndrome in 1960.
**Patau Syndrome**

Patau syndrome, also called trisomy 13, is a genetic disorder caused by the presence of an extra chromosome 13. It is the least common and the most severe of the viable trisomies.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 10,000 births</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>In utero death occurs in over 95% of fetuses with this chromosomal anomaly.</td>
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</table>

<table>
<thead>
<tr>
<th>INHERITANCE</th>
<th>Sporadic / not inherited</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Most cases of Patau syndrome are sporadic, and not inherited, including mosaicism.</td>
</tr>
<tr>
<td></td>
<td>Patau syndrome caused by a translocation can be inherited. A carrier can have a rearrangement of genetic material between chr 13 and another chromosome. This is called a balanced translocation, because there is no extra material from chr 13. Although they do not have signs of Patau syndrome, people who carry this type of balanced translocation are at an increased risk of having children with the condition.</td>
</tr>
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</table>

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<thead>
<tr>
<th>LIFE EXPECTANCY</th>
<th>Limited lifespan, with 2.5 days of median survival</th>
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<tbody>
<tr>
<td></td>
<td>90% of infants die before 1 year of age. Prolonged survival is more common in cases of mosaic or partial trisomy and in the absence of severe brain malformations.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>A third chromosome 13 appearing in all or some of the cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary trisomy: the presence of a third chr 13 in all cells (75% of all cases).</td>
</tr>
<tr>
<td></td>
<td>Unbalanced translocation: an extra portion of chr 13 attached to another chromosome, which may be due to a balanced translocation of one parent.</td>
</tr>
<tr>
<td></td>
<td>Mosaicism: some normal cells with 46 chromosomes, others with extra chr 13.</td>
</tr>
</tbody>
</table>
Symptoms and medical problems
People with Patau syndrome have multiple congenital abnormalities, which result in severe physical and mental impairment. The syndrome carries a high mortality rate. It causes such serious birth defects that only few babies survive to their first birthday. Profound mental retardation and developmental delay occur in survivors. Seizures and feeding difficulties are also common.

Key features:
- Intrauterine growth retardation
- Low birth weight
- Low muscle tone (hypotonia)
- Small head (microcephaly)
- Brain malformations (holoprosencephaly)
- Craniofacial abnormalities
- Ocular anomalies
- Extra fingers or toes (polydactyly)
- Clenched hands
- Hyporeactivity
- Congenital heart defects
- Problems with control of breathing (central apnoea)
- Gastrointestinal abnormalities
- Urogenital malformations
- Severe psychomotoric retardation

Treatment
Management of children with trisomy 13 is planned on a case-by-case basis and depends on the individual circumstances of the patient. The treatment of the syndrome focuses on the particular physical problems with which each child is born.

Surgery may be necessary to repair heart defects or body abnormalities. Many infants do not survive the first few days or weeks due to severe neurological problems or complex heart defects.

DID YOU KNOW?
The syndrome was named after Klaus Patau, a German-born, American human geneticist. Patau and his colleagues described the syndrome in 1960, the same year that Edwards and his coworkers described trisomy 18. The clinical appearance of trisomy 13 was first observed and described by Thomas Bartholin in 1657, but he was unaware of the chromosomal nature of the disease.
Trisomy X, also called triple X syndrome, is the most common female trisomy and has a variable phenotype caused by the presence of an extra X chromosome in each cell of a human female.

| FREQUENCY OF OCCURRENCE | Seen 1 in 1000 female births  
• As most individuals are only mildly affected or asymptomatic, it is estimated that only 10% of individuals with trisomy X are actually diagnosed.  
• Advanced maternal age is noted in approximately 30% of trisomy X cases. |
|-------------------------|-------------------------------------------------------------------|
| INHERITANCE             | Sporadic / not inherited  
• Most cases of trisomy X are not inherited, including mosaicism. |
| LIFE EXPECTANCY         | Normal lifespan |
| CAUSE                   | Presence of an extra X chromosome  
• A random chromosomal change during cell formation - an error in chromosome separation during cell division (nondisjunction) - can result in reproductive cells with an abnormal number of chromosomes. As a result of the extra X chromosome, each cell has a total of 47 chromosomes instead of the usual 46.  
• 46,XX / 47,XXX mosaicism occurs as a random event during cell division in early embryonic development. As a result, some of an affected person’s cells have two X chromosomes (46,XX), and other cells have three X chromosomes (47,XXX). The extent to which an individual is affected by the condition will depend upon the proportion of XXX to XX. |
Symptoms and medical problems

Due to the X-inactivation (lyonization), only one X chromosome is active at any time in a female cell. Triple X syndrome most often causes no unusual physical features or medical problems, although females with this condition may be taller than average.

There are rare cases when a female with this syndrome is affected by various symptoms. The most common features associated with trisomy X:

- Taller stature than average
- Weak muscle tone (hypotonia)
- Skin folds at the upper eyelid (epicanthal fold)
- Inward bend of the small finger (clinodactyly)
- Seizures
- Renal and genitourinary abnormalities
- Motor and speech delays with cognitive deficits and learning disabilities
- Behavioral and emotional difficulties (attention deficits, anxiety, depression)

Fertility in women with trisomy X is generally considered normal; most females with triple X syndrome have normal sexual development and are able to conceive children. However, adolescents and adult women presenting with late menarche, menstrual irregularities, or fertility problems should be evaluated for hormonal abnormalities that may signal ovarian insufficiency.

Treatment

Following diagnosis, clinical evaluation is conducted to identify any manifesting features of the disorder.

Patients diagnosed in the prenatal period are followed closely for developmental delay so that early intervention therapies can be implemented as needed. School-aged children and adolescents benefit from a psychological treatment with an emphasis on identifying and developing an intervention plan for problems in cognitive skills, language, and/or social-emotional development.

DID YOU KNOW?

The first published report of a woman with a 47,XXX karyotype was by Patricia Ann Jacobs and her coworkers at Western General Hospital in Edinburgh, Scotland, in 1959. It was found in a 35-year-old, 176 cm tall, 58.2 kg woman who had premature ovarian failure at age 19. Her mother was age 41 and her father was 40 at the time of her conception.
**KLINEFELTER SYNDROME**

Klinefelter syndrome (KS) defines a group of chromosomal disorders in which there is at least one extra X chromosome compared with the normal (46,XY) male karyotype. It is the most common chromosomal disorder in humans, and the second most common condition caused by the presence of extra chromosomes.

| FREQUENCY OF OCCURRENCE | Seen 1 in 500–1000 male births  
• Despite its relatively mild phenotype, it is estimated that at least half of the 47,XXY conceptions are spontaneously aborted. |
<table>
<thead>
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<tbody>
<tr>
<td>INHERITANCE</td>
<td>Sporadic / not inherited</td>
</tr>
<tr>
<td>LIFE EXPECTANCY</td>
<td>Normal lifespan</td>
</tr>
</tbody>
</table>
| CAUSE                   | Addition of an extra X chromosome  
• The addition is a random event that happens when paired chromosomes fail to separate in the first or second stage of meiosis.  
• The extra chromosome can come from either parent, the addition can occur in the sperm, in the egg or after conception. |
Symptoms and medical problems

- Infertility
- Small testicles (microorchidism)
- Increased breast tissue (gynecomastia)
- Above-average height
- Disproportionately long arms and legs
- Reduced muscle bulk
- Feminine distribution of body fat
- Sparse facial and body hair
- Low serum testosterone level
- High serum FSH and LH levels
- Reduced IQ, but usually not mentally retarded

Some males with Klinefelter syndrome have the extra X chromosome in only some of their cells; this condition is described as mosaic Klinefelter syndrome (46,XY / 47,XXY). Individuals with mosaicism may have milder signs and symptoms depending on how many cells have an additional X chromosome.

A variety of other physical and behavioral differences and problems can occur, though severity and personality characteristics vary among males with this condition. The syndrome can affect different stages of physical, cognitive and social development (communication problems, language learning deficits).

Klinefelter syndrome can lead to osteoporosis, varicose veins and various autoimmune diseases. XXY males have an increased risk for breast cancer, germ cell tumors and hypothyroidism. They also tend to have heart and blood vessel diseases and type 2 diabetes.

Treatment

The XXY chromosome pattern is irreversible, but there is a variety of ways to treat the symptoms of this condition. With treatment, most males grow up to have normal sex lives, successful careers and normal social relationships.

Medical treatment – Testosterone replacement therapy (TRT) can help XXY males get their testosterone levels into normal range. Having a more normal testosterone level can help develop bigger muscles, deepen the voice, and grow facial and body hair. Androgen replacement begins at puberty (around 12 years of age) and the dose should be increased so that it is sufficient to maintain age-appropriate serum concentrations of testosterone, estradiol, follicle stimulating hormone (FSH), and luteinizing hormone (LH). Some XXY males can also benefit from fertility treatment to help them father children.

Therapeutic options – A variety of physical, speech, occupational, behavioral, and mental therapies can help reduce or eliminate some of the symptoms of the condition, such as poor muscle tone, speech or language problems, or low self-confidence.

Educational treatments – Many XXY males qualify for special services to help them in school.
XYY SYNDROME

XYY syndrome is characterized by the abnormal number of sex chromosomes when a human male has an extra copy of the Y chromosome in each of his cells.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 1000 male births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The incidence of XYY syndrome is not affected by advanced paternal or maternal age.</td>
</tr>
<tr>
<td>INHERITANCE</td>
<td>Sporadic / not inherited</td>
</tr>
<tr>
<td></td>
<td>The occurrence of 47,XYY is not inherited, including 46,XY / 47,XYY mosaicism.</td>
</tr>
<tr>
<td>LIFE EXPECTANCY</td>
<td>Normal lifespan</td>
</tr>
<tr>
<td>CAUSE</td>
<td>Presence of extra Y chromosome</td>
</tr>
<tr>
<td></td>
<td>A random chromosomal change during cell formation - an error in chromosome separation during cell division (nondisjunction) - can result in sperm cells with an extra copy of the Y chromosome. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra Y chromosome in each of his cells.</td>
</tr>
<tr>
<td></td>
<td>In some cases, the addition of an extra Y chromosome results from nondisjunction during a post-zygotic mitosis in early embryonic development. This produces 46,XY / 47,XYY mosaics.</td>
</tr>
</tbody>
</table>
Symptoms and medical problems

The 47,XYY chromosome pattern is irreversible, but the syndrome is usually asymptomatic, the extra Y chromosome causes no unusual physical features or medical problems. The condition is usually detected only during genetic analysis for another reason.

Intellectual disability ranges from mild to severe in patients. Compared to people with other forms of intellectual disability, their socialization skills are stronger, while verbal communication and language skills tend to be weaker.

Key features of XYY:
- Normal appearance, often tall stature
- No increase in medical problems or illnesses
- Intellectual ability usually in the normal range
- No problems with sex organs, puberty and fertility
- Increased vulnerability to behaviour problems and stress

XYY boys have an increased risk of learning difficulties, delayed development of speech, language and motor skills. Developmental delays are also possible, but these characteristics vary widely among affected boys and men, are not unique to 47,XYY and are managed no differently than in normal 46,XY males.

A small percentage of males with this syndrome is diagnosed with autistic spectrum disorders, affecting their communication and social interactions.

Treatment

Although this chromosomal disorder has no cure, with treatment, males with 47,XYY syndrome grow up to have normal lives, successful careers and normal social relationships.

Screening and early intervention, optional speech therapy, psychological and social skills treatment make it easier to overcome any possible difficulties.

DID YOU KNOW?

Some medical geneticists question whether the term "syndrome" is appropriate for this condition because its phenotype is normal and the vast majority of 47,XYY males do not even know they have this karyotype.
Monosomies

TURNER SYNDROME

Turner syndrome, also called monosomy X, is the only viable monosomy in humans. It is associated with the complete or partial absence of the X chromosome.

| FREQUENCY OF OCCURRENCE | Seen 1 in 2500 female births
|                         | • 15% of spontaneous abortions have the 45,X karyotype.
|                         | • The missing chromosome is of paternal origin.
| INHERITANCE            | Sporadic / not inherited
|                         | • Most cases of monosomy X are not inherited, including mosaicism.
| LIFE EXPECTANCY        | Slightly reduced lifespan
| CAUSE                  | The absence or structural alteration of one X chromosome
|                         | • The chromosomal abnormality occurs as a random event during the formation of reproductive cells. The missing genetic material affects development before and after birth, leading to the characteristic features of the condition.
|                         | • About half of individuals with Turner syndrome have primary monosomy X, which means that each cell in the individual’s body has only one copy of the X chromosome instead of the usual two sex chromosomes.
|                         | • A large number of the cases are caused by the presence of mosaicism and/or an abnormal X or Y chromosome (partial deletion, isochromosome X, dicentric chromosome).
Symptoms and medical problems

- Short stature (becomes evident by about age 5)
- Low hairline at the back of the neck
- Low-set ears
- Webbed neck
- Swelling of the hands and feet (lymphedema)
- Broad chest with widely spaced nipples
- Poor breast development
- Skeletal abnormalities
- Increased weight (obesity)
- Premature ovarian failure
- Infertility
- Deficiency of thyroid hormone (hypothyroidism)
- High blood pressure (hypertension)
- Kidney problems
- Congenital heart defects

Even though females with Turner syndrome have only one normal X chromosome, they are 100% female. They can have a wide variety of symptoms, some of them may have more severe problems, and others may have mild symptoms.

Short stature is present in all cases. Ovarian failure, with variable onset depending on the chromosomal anomalies, is frequent. Other visceral manifestations (bone anomalies, lymphoedema, deafness, and cardiovascular, thyroid and gastrointestinal involvement) are less common but should be screened for at diagnosis, and then surveyed during adolescence and adulthood.

Most girls and women with Turner syndrome have normal intelligence. Developmental delays, nonverbal learning disabilities, and behavioral problems are possible, although these characteristics vary among affected individuals. Studies show that many women with Turner syndrome have higher-than-average educational achievements.

Treatment

There is no cure for Turner syndrome, however, there are treatments that help to minimize its symptoms. Prognosis depends on the presence of heart disease, obesity, arterial hypertension and osteoporosis, therefore, a long-term follow-up is necessary.

Appropriate medical treatment and support allows a woman with Turner syndrome to lead a normal, healthy and happy life. Management includes:

- Human growth hormone (hGH) and low-dose androgen therapy, which leads to a significant increase in final height.
- Estrogen replacement therapy, which is used to promote the development of secondary sexual characteristics and to maintain good bone integrity and tissue health (preventing osteoporosis).

Modern assisted reproductive technologies can help some women with Turner syndrome to become pregnant if they desire. A donor egg can be used to create an embryo, which is then carried by the monosomy X woman.

DID YOU KNOW?

The syndrome was named after Henry Hubert Turner, an American endocrinologist, who described the condition in 1938. In Europe, it is often called Ullrich-Turner syndrome or even Bonnevie-Ullrich-Turner syndrome to acknowledge that earlier cases had also been described by European doctors.
**ANGELMAN SYNDROME**

Angelman syndrome (AS) is a complex genetic disorder that affects the nervous system and causes developmental delay.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 12,000–25,000 births</th>
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<tbody>
<tr>
<td>INHERITANCE</td>
<td>Sporadic / not inherited</td>
</tr>
<tr>
<td></td>
<td>• Most cases of AS are not inherited, particularly those caused by a deletion in the maternal chr 15 or by paternal uniparental disomy.</td>
</tr>
<tr>
<td></td>
<td>• Sometimes, a genetic change responsible for AS can be inherited. For example, it is possible to pass a mutation in the UBE3A gene from one generation to the next.</td>
</tr>
<tr>
<td>LIFE EXPECTANCY</td>
<td>Normal lifespan</td>
</tr>
<tr>
<td></td>
<td>• People with AS usually have good general health, but are not able to live independently.</td>
</tr>
<tr>
<td></td>
<td>• Patients generally do not show developmental regression as they age.</td>
</tr>
<tr>
<td>CAUSE</td>
<td>Loss of gene function in q11.2–q13 region of maternal chromosome 15, subject to genetic imprinting</td>
</tr>
<tr>
<td></td>
<td>• If the deletion is in the chromosome of maternal origin, the child has AS. Loss of the maternally contributed AS region can occur by five genetic mechanisms:</td>
</tr>
<tr>
<td></td>
<td>– deletion</td>
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<td></td>
<td>– paternal uniparental disomy</td>
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<tr>
<td></td>
<td>– imprinting defects</td>
</tr>
<tr>
<td></td>
<td>– mutation of UBE3A gene</td>
</tr>
<tr>
<td></td>
<td>– unidentified mechanisms</td>
</tr>
<tr>
<td></td>
<td>• The causes of AS are unknown in 10 to 15% of affected individuals. Changes involving other genes or chromosomes may be responsible for the disorder in these cases.</td>
</tr>
<tr>
<td></td>
<td>• AS has a sister disorder called Prader-Willi syndrome, in which paternally derived genetic material is affected in the same genetic region.</td>
</tr>
</tbody>
</table>
Symptoms and medical problems
The phenotype of Angelman syndrome is well-known in infancy and adulthood, but the clinical features may change with age. Infants with this syndrome appear normal at birth, but often have feeding problems in the first months of life and exhibit noticeable developmental delays by 6 to 12 months. Other symptoms usually appear in early childhood. Diagnosis is commonly made at age 3–7 years, when the clinical features and behaviour patterns become more apparent. Children with AS typically have happy, excitable demeanor with frequent smiling, laughter and hand-flapping movements. They are contented people who like human contact and play. They tend to develop strong non-verbal skills to compensate for their limited use of speech. Some affected individuals have unusually fair skin and light-colored hair.

Other key features:
- Small head (microcephaly)
- Dysmorphic facial features
- Developmental delays
- Severe mental retardation
- Epileptic seizures
- Speech impairment
- Motor difficulties
- Hyperactivity
- Sleeping problems

With age, people with AS become less excitable and their sleeping problems tend to improve. However, affected individuals continue to have intellectual disability, severe speech difficulties, and seizures throughout their lives.

People with AS are sometimes known as “angels,” both because of the syndrome’s name and because of their youthful, happy appearance.

Treatment
There is no specific treatment for Angelman syndrome. Early diagnosis followed up by tailored interventions and therapies help to improve the patients’ quality of life.

Medical control for seizures and sleep disorders is usually necessary. Physical, occupational, speech and behavioral therapies are important in allowing individuals with AS to reach their maximum developmental potential.

DID YOU KNOW?
The syndrome was first described in 1965 by Harry Angelman, an English physician. Angelman explained the choice of his paper’s title *Puppet Children* to describe these cases as being related to an oil painting he had seen while on vacation in Italy: *Boy with a Puppet* or also known as *A child with a drawing* by Giovanni Francesco Caroto.
**Cri du Chat Syndrome**

Cri du chat syndrome (CdCS), also known as chromosome 5p deletion syndrome and 5p monosomy, is a genetic disorder caused by the deletion of variable size of genetic material occurring on the short arm of chromosome 5.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 15,000–50,000 live births • The condition is more common in females by a 4:3 ratio.</th>
</tr>
</thead>
<tbody>
<tr>
<td>INHERITANCE</td>
<td>Sporadic / not inherited • The deletion occurs most often as a random event during the formation of reproductive cells or in early fetal development. Affected people typically have no history of the disorder in their family. • About 10% of people with CdCS inherit the chromosome abnormality from an unaffected parent. In these cases, the parent carries a balanced translocation, in which no genetic material is gained or lost. Balanced translocations usually do not cause any health problems, but they can become unbalanced as they are passed to the next generation. Children who inherit an unbalanced translocation can have a chromosomal rearrangement with extra or missing genetic material.</td>
</tr>
<tr>
<td>LIFE EXPECTANCY</td>
<td>Normal lifespan • A small number of children are born with serious organ defects and other life-threatening medical conditions, although most individuals with CdCS have normal life expectancy.</td>
</tr>
<tr>
<td>CAUSE</td>
<td>Partial deletion of the short (p) arm of chromosome 5 • Approximately 90% of cases results from a sporadic, de novo deletion. The remaining 10% may be due to unequal segregation of a parental balanced translocation, where 5p monosomy is often accompanied by a trisomic portion of the genome. These individuals may have more severe disease than those with isolated monosomy of 5p because the duplicated material from the other chromosome is involved in the translocation. • The symptoms of CdCS are related to the loss of multiple genes on the short arm of chr 5. The size of the deletion varies among affected individuals; larger deletions tend to result in more severe intellectual disability and developmental delay.</td>
</tr>
</tbody>
</table>

**Affected chr region**

chr 5p
Symptoms and medical problems

- High-pitched cat-like cry
- Low birth weight and slow growth
- Feeding problems because of difficulty with swallowing and sucking
- Weak muscle tone (hypotonia)
- Small head (microcephaly)
- Small jaw (micrognathia)
- Wide-set eyes
- Broad and flat nasal bridge
- Low-set or abnormally shaped ears
- Partial webbing or fusing of fingers and toes
- Single line in the palm (simian crease)
- Mental retardation and behavioral problems
- Slow or incomplete development of motor skills
- Severe cognitive and speech delays

The symptoms of cri du chat syndrome vary among individuals. Cardiac, neurological and renal abnormalities and malformations may be present.

People with CdCS are fertile and can reproduce. Affected females reach puberty, develop secondary sex characteristics, and menstruate at the usual time. The female genital tract is usually normal except for a bicornate uterus. In males, testes are often small, but spermatogenesis is normal.

Most individuals who have CdCS have difficulty with language, but they learn sufficient verbal skills to communicate. Both children and adults with this syndrome are usually friendly and happy, they enjoy social interaction.

Treatment

The diagnosis of cri du chat syndrome is generally made at birth based on typical manifestations. The cat-like cry is the most prominent clinical feature in newborn children and is usually diagnostic for the syndrome. Additionally, karyotype analysis may be performed to identify the missing portion of the short arm of chr 5.

No specific treatment is available for this syndrome. Patients require ongoing support to help them achieve their maximum potential, cardiac abnormalities often require surgical correction. With early and consistent rehabilitative and educational intervention, as well as physical and language therapy, people with CdCS can lead full and meaningful lives.

DID YOU KNOW?

Cri du chat syndrome was first described by a French geneticist, Jérôme Lejeune in 1963. Its name is a French term (cry or call of the cat) referring to the characteristic high-pitched cat-like cry of affected children. This typical cry, similar to that of a meowing kitten, is caused by problems with the larynx and the nervous system. The cry usually becomes less apparent with time, about 1/3 of children lose it by age 2.
DiGeorge syndrome (DGS), also called monosomy 22q11, velocardiofacial syndrome (VCFS), and 22q11.2 deletion syndrome, is caused by the deletion of a small piece of chromosome 22. It is one of the most common causes of mental retardation, and next to Down syndrome, DGS is the most common genetic cause of congenital heart disease.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 4000–5000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• The condition may actually be more common than this estimate, as some individuals with the deletion have few symptoms and may not be formally diagnosed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INHERITANCE</th>
<th>Sporadic / not inherited</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• For most cases, the deletion occurs as a random event during the formation of reproductive cells or in early fetal development. Affected people typically have no history of the disorder in their family, but they can pass the condition to their children.</td>
</tr>
<tr>
<td></td>
<td>• DGS can be inherited, but this is the case in the minority of newly diagnosed individuals. Its inheritance is autosomal dominant because a deletion in one copy of chr 22 is sufficient to cause the condition. Only 5–10% inherit the deletion from a parent, whereas about 90–95% of cases have a de novo deletion. This is because the 22q11.2 region has a structure that makes it highly prone to rearrangements during reproductive cell formation. The deletion is almost equally likely to occur when an egg is formed as when a sperm is formed. An individual with DGS has a 50% chance of passing the deletion to their offspring.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIFE EXPECTANCY</th>
<th>Reduced lifespan</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>Deletion on the long (q) arm of chromosome 22, in region q11.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• A small percentage of affected individuals have shorter deletions in the same region of chr 22.</td>
</tr>
<tr>
<td></td>
<td>• Some cases of DGS have defects in other chromosomes, notably a deletion in 10p14.</td>
</tr>
</tbody>
</table>
Symptoms and medical problems

- Skeletal abnormalities
- Significant feeding problems
- Characteristic facial features
- Palatal abnormalities (e.g. cleft palate)
- Neuromuscular problems with closure (velopharyngeal insufficiency)
- Hypocalcemia (due to hypoparathyroidism)
- Congenital heart and kidney anomalies
- Seizures
- Hearing loss (both conductive and sensorineural)
- Growth hormone deficiency
- Immunodeficiency, autoimmune disorders
- Learning disabilities
- Speech impairments

The features of DiGeorge syndrome vary widely and affect many parts of the body, ranging from mild to very serious conditions. The clinical course of the syndrome is mainly determined by the nature of the congenital malformations involved. Patients are highly susceptible to infections.

Individuals with DGS have a specific profile in neuropsychological tests. They usually have a borderline normal IQ. Cognitive functioning involving space and time usually shows significant impairment, which generally slows down the development of numerical and arithmetical skills.

Patients are a high-risk group for developing schizophrenia. 30% have at least one incident of psychosis and about a quarter develop actual schizophrenia.

Treatment

There is no cure for the syndrome. Certain symptoms are manageable using standard treatments. The key is to identify each of the associated features and manage each using the best available methods.

It is important that the immune problems are identified early as special precautions are required regarding blood transfusion and immunization with live vaccines. Transplantation of thymus tissue can restore normal immune function to infants with this syndrome. Cardiac surgery is often required for congenital heart abnormalities. Hypoparathyroidism causing hypocalcemia requires lifelong vitamin D and calcium supplements.

DID YOU KNOW?

The syndrome was described in 1968 by Angelo DiGeorge, an American endocrinologist. The symptoms are so varied that different groupings of its features were once regarded as separate conditions (velocardio-facial syndrome, Shprintzen syndrome, DiGeorge syndrome, Sedlakova syndrome, conotruncal anomaly face syndrome). When the genetic basis was identified, doctors determined that they were all part of one syndrome with many possible symptoms. To avoid confusion, this condition is usually called 22q11.2 deletion syndrome, a description based on its underlying genetic cause.

DiGeorge 22q11.2 Coverage

DiGeorge 10p14 Coverage
Deletions

**CHR 8q23.2–q24.13**

The Langer-Giedion Syndrome (LGS) is a rare genetic disorder that causes bone abnormalities, intellectual disabilities, and distinctive facial features. Since the features include abnormalities in the hair (tricho), nose shape (rhino), and fingers and toes (phalangeal), another name for LGS is tricho-rhino-phalangeal syndrome, type 2.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Prevalence is unknown, LGS is a very rare condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>INHERITANCE</td>
<td>Sporadic / not inherited</td>
</tr>
<tr>
<td></td>
<td>• Most cases of LGS are not inherited, but occur as random events during the formation of reproductive cells in a parent of an affected individual.</td>
</tr>
<tr>
<td></td>
<td>• LGS can be inherited in rare cases. Its inheritance is autosomal dominant, one copy of the altered chr 8 is sufficient to cause the condition.</td>
</tr>
<tr>
<td>LIFE EXPECTANCY</td>
<td>Normal lifespan</td>
</tr>
<tr>
<td>CAUSE</td>
<td>Deletion on the long (q) arm of chromosome 8 in region q23.2–q24.13</td>
</tr>
<tr>
<td></td>
<td>• The loss of genes in the region is responsible for some of the overall characteristics of the disorder. LGS is often described as a contiguous gene deletion syndrome because it results from the loss of several neighboring genes.</td>
</tr>
</tbody>
</table>
Symptoms and medical problems

• Short stature
• Growth retardation
• Low muscle tone (hypotonia)
• Small head (microcephaly)
• Fine and sparse scalp hair
• Broad eyebrows
• Deep-set eyes
• Rounded nose
• Long flat area between the nose and the upper lip (philtrum)
• Thin upper lip
• Missing teeth
• Prominent ears
• Loose redundant skin (typically resolves with age)
• Hearing problems
• Intellectual deficit, learning difficulties
• Cone-shaped phalangeal epiphyses
• Multiple cartilaginous, noncancerous bone tumors (exostoses)

The range, number and severity of malformations and other symptoms varies from case to case.

Bone tumors may result in pain, limited range of joint movement and pressure on nerves, blood vessels, on the spinal cord, and tissues surrounding the tumors. Exostoses and cone-shaped phalangeal epiphyses usually appear during the first 5 years of life.

Treatment

Diagnosis is usually made at birth or in early childhood. Although the syndrome cannot be cured, treatments are available for some of its symptoms. Early diagnosis of Langer-Giedion syndrome is essential in order to provide genetic counseling to affected families, and to assure orthopedic follow-up and management of growth, hearing and other problems.

DID YOU KNOW?
The syndrome was named after two doctors who undertook the main research into the condition in the 1960s, Leonard O. Langer Jr. (American radiologist) and Andreas Giedion (Swiss radiologist). LGS or trichorhinophalangeal syndrome (TRPS) type 2 can be differentiated from TRPS type 1 by the presence of the exostoses.

Langer-Giedion Syndrome Coverage
Deletions

MILLER-DIEKER SYNDROME

Miller-Dieker syndrome (MDS) is an autosomal dominant congenital disorder characterized by a developmental defect of the brain (lissencephaly), which is caused by incomplete neuronal migration.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 100,000–300,000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>INHERITANCE</td>
<td>Sporadic / not inherited</td>
</tr>
<tr>
<td></td>
<td>• Approximately 80% of individuals with MDS have a de novo deletion involving 17p13.3 and approximately 20% have inherited a deletion from a parent who carries a balanced chromosome rearrangement.</td>
</tr>
<tr>
<td></td>
<td>• Individuals can inherit a balanced translocation from an unaffected parent that becomes unbalanced. When MDS is inherited, its inheritance pattern is considered autosomal dominant because a deletion in one copy of chr 17 is sufficient to cause the condition.</td>
</tr>
<tr>
<td>LIFE EXPECTANCY</td>
<td>Reduced life span</td>
</tr>
<tr>
<td></td>
<td>• Most individuals with this condition do not survive beyond childhood.</td>
</tr>
<tr>
<td>CAUSE</td>
<td>Deletion on the short (p) arm of chromosome 17 at region p13.3</td>
</tr>
<tr>
<td></td>
<td>• MDS is a contiguous gene syndrome caused by microdeletions of 17p13.3 genetic material leading to partial monosomy. The size of the deletion varies among affected individuals. The symptoms of the syndrome are probably related to the loss of multiple genes in this region.</td>
</tr>
</tbody>
</table>
Symptoms and medical problems
MDS is a congenital malformation syndrome characterized by classical lissencephaly, which means that the brain is abnormally smooth with fewer folds and grooves and it has a cerebral cortex 4 layers thick instead of 6.

Other typical features:
• Feeding difficulties
• Small head (microcephaly)
• Characteristic facial appearance
• Severe developmental delay
• Mental retardation
• Epilepsy
• Multiple heart, kidney and gastrointestinal abnormalities
• Seizures and decreased spontaneous activity
• Abnormal muscle stiffness (spasticity)
• Weak muscle tone (hypotonia)

Treatment
There is no cure for MDS, its management is symptomatic and treatment is usually directed towards comfort measures. To avoid the complications of feeding and swallowing problems (poor nutritional state, aspiration pneumonia), nasogastric tubes and gastrostomies can be utilized. Seizure control and close medical control of all symptoms is necessary.

DID YOU KNOW?
The syndrome is named after J. Q. Miller and H. Dieker, two physicians, who independently described the condition in the 1960s. Miller described it in 1963 and in 1969 Dieker emphasized that it should be termed the lissencephaly syndrome because there are malformations beyond the brain.

Miller-Dieker Syndrome Coverage
PRADER-WILLI SYNDROME

Prader-Willi syndrome (PWS), also called Prader-Labhart-Willi syndrome is a highly variable genetic disorder with a recognizable pattern of dysmorphic features and major neurologic, endocrine and behavioral disturbances. PWS is the most common known genetic cause of life-threatening obesity in children.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 10,000–30,000 live births</th>
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<tbody>
<tr>
<td>INHERITANCE</td>
<td>Sporadic / not inherited</td>
</tr>
<tr>
<td></td>
<td>• Rarely, a genetic change responsible for Prader-Willi syndrome (abnormally inactivating genes on paternal chr 15) can be inherited from one generation to the next. This is because the 15q11.2-q13 region has a structure that makes it highly prone to rearrangements during reproductive cell formation.</td>
</tr>
<tr>
<td>LIFE EXPECTANCY</td>
<td>Normal lifespan (if weight is controlled)</td>
</tr>
<tr>
<td>CAUSE</td>
<td>Loss of gene function in q11.2-q13 region of paternal chromosome 15, subject to genetic imprinting</td>
</tr>
<tr>
<td></td>
<td>• If the deletion is in the chromosome of paternal origin, the child has PWS. The loss of the paternally contributed region can occur by the following genetic mechanisms:</td>
</tr>
<tr>
<td></td>
<td>– paternal deletion</td>
</tr>
<tr>
<td></td>
<td>– maternal uniparental disomy</td>
</tr>
<tr>
<td></td>
<td>– imprinting defects</td>
</tr>
<tr>
<td></td>
<td>• PWS has a sister disorder called Angelman syndrome in which maternally derived genetic material is affected in the same genetic region.</td>
</tr>
</tbody>
</table>
Symptoms and medical problems
- Low muscle tone (hypotonia)
- Feeding difficulties in infancy
- Poor growth and delayed development
- Short stature
- High and narrow forehead
- Almond-shaped eyes with thin, down-turned lids
- Thin upper lip and down-turned mouth
- Unusually fair skin and light-colored hair
- Soft skin, which is easily bruised
- Small hands and feet
- Chronic overeating (hyperphagia)
- Excessive weight gain, obesity
- Underdeveloped genitals, hypogonadism
- Low levels of sex hormones
- Delayed or incomplete puberty
- Infertility
- Poor motor skills and physical coordination
- Mild mental retardation and learning disabilities
- Behavioral problems
- Sleep disorders

The part of the brain that controls feelings of hunger does not work properly in people with PWS. Morbid obesity may lead to type 2 diabetes, lung failure with low blood oxygen levels, right-sided heart failure, various orthopedic problems and death.

Treatment
There is no cure for PWS. However, several treatments are in place to manage the symptoms of the condition. Early diagnosis and multidisciplinary care greatly improve the life quality of affected patients.

The largest health problem associated with the syndrome is severe obesity. Limiting caloric intake controls the obesity and allow for a more comfortable and healthier life. Exercises can increase lean body mass. Low levels of sex hormones may be corrected at puberty with hormone replacement.

DID YOU KNOW?
The syndrome was first described in 1956 by Andrea Prader, Heinrich Willi and Alexis Labhart of Switzerland, on the basis of nine children with small stature, mental retardation, obesity and small hands and feet. Prader and Willi reviewed the condition in 1961, expanded the phenotype and drew attention to the presence of hypotonia in infancy and the development of diabetes mellitus in later childhood. The term Prader-Willi syndrome is now commonly used, but by historical precedence Labhart’s name is sometimes also added.

Prader-Willi Syndrome Coverage
SMITH-MAGENIS SYNDROME

Smith-Magenis syndrome (SMS) is a relatively rare genetic disorder that affects many parts of the body and is characterized by a specific pattern of physical, behavioral, and developmental features.

**FREQUENCY OF OCCURRENCE**
- Seen 1 in 25,000–50,000 live births
  - Researchers believe that many people with this condition are not diagnosed, so the true prevalence may be closer to 1 in 15,000 individuals.

**INHERITANCE**
- Sporadic / not inherited
  - The 17p11.2 region has a structure that makes it highly prone to rearrangements during reproductive cell formation.

**LIFE EXPECTANCY**
- There is insufficient data regarding the average life expectancy of those diagnosed with SMS. Some individuals have lived well into their 70s.

**CAUSE**
- Deletion on the short (p) arm of chromosome 17 in region p11.2
  - Although multiple genes have been mapped to this region, researchers believe that the loss of one particular gene, RAI1, in each cell is responsible for most of the characteristic features of this condition.
  - A small percentage of people with Smith-Magenis syndrome have a mutation in the RAI1 gene instead of a chromosomal deletion.
Symptoms and medical problems

- Short stature
- Broad, square-shaped face
- Deep-set eyes with eyelid folds
- Flat mid-face area
- Broad nasal bridge
- Full cheeks
- Protruding jaw
- Mouth turning downward with an outward-curving upper lip
- Short fingers and toes
- Abnormal curvature of the spine (scoliosis)
- Reduced sensitivity to pain and temperature
- Hoarse, deep voice
- Chronic ear infections leading to hearing loss
- Heart and kidney defects
- Seizures
- Mild to moderate mental retardation
- Disrupted sleep patterns
- Speech delay
- Learning disabilities

Facial differences can be subtle in early childhood, but they typically become coarser and more distinctive later on.

People with SMS have engaging and endearing personality but they also have behavioral problems including frequent temper, tantrums and outbursts, aggression, anxiety, impulsiveness, and attention deficit. Self-injury, including biting, hitting, head banging, and skin picking, is very common. Repetitive self-hugging is a behavioral trait that may be unique to Smith-Magenis syndrome. People with this condition may also compulsively lick their fingers and flip pages of books and magazines (a behavior known as “lick and flip”), as well as possessing an impressive ability to recall a wide range of small details about people or subject-specific trivia.

Treatment

Although there is no cure for SMS, early diagnosis can help the successful management of symptoms. Early behavioral and educational therapies, language therapy and medication are necessary to provide support and treatment for developmental deficits.

Regarding sleep disturbances, beta-adrenergic antagonists and melatonin treatment improve inappropriate behavior and restore sleep. Support is often required throughout an affected person’s lifetime.

DID YOU KNOW?

The syndrome was first described in 1982 by genetic counselor Ann C. M. Smith and medical geneticist Ellen Magenis. Until the mid 1990s, SMS was not a well-known disorder, even among genetics experts as the chromosome deletion is small (a microdeletion) and difficult to detect. Most individuals are not diagnosed until they receive specialized genetic tests, usually in mid-childhood or adulthood.
**WILLIAMS-BEUREN SYNDROME**

Williams–Beuren syndrome (WBS), also known as Williams syndrome (WS), is a rare genetic disease caused by missing genes. It is characterised by elflike facial dysmorphism, cardiac malformation, mental retardation, and a specific cognitive and behavioural profile.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 7500–20,000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>INHERITANCE</td>
<td>Sporadic / not inherited</td>
</tr>
</tbody>
</table>
|                         | • It occurs as a random event during the formation of reproductive cells in a parent of an affected individual. These cases occur in people with no history of the disorder in their family.  
|                         | • A person with WBS has a 50% chance of passing the disorder on to each of his or her children. The syndrome is considered an autosomal dominant condition because one copy of the altered chr 7 is sufficient to cause the disorder.  
|                         | • The 7q11.23 region has a structure that makes it highly prone to rearrangements during reproductive cell formation. |
| LIFE EXPECTANCY         | Shorter lifespan than average (due to possible medical complications) |
| CAUSE                   | Deletion on the long (q) arm of chromosome 7 in region q11.23 |
|                         | • The deleted region includes more than 25 genes, their loss contributes to the characteristic features of the disorder.  
|                         | • The deletion of the Elastin gene causes heart defects. |
Symptoms and medical problems

• Low birth-weight / slow weight gain
• Feeding problems including colic, reflux, and vomiting
• Puffiness around the eyes
• Skin folds of the upper eyelid (epicanthal folds)
• Stellar iris
• Flattened nasal bridge with small upturned nose
• Long ridges in the skin that run from the nose to the upper lip (philtrum)
• Small chin
• Wide mouth with prominent lips
• Dental abnormalities (missing teeth, defective tooth enamel, small, widely spaced teeth)
• Inward bend of the small finger (clinodactyly)
• Sunken chest (pectus excavatum)
• Sensitive hearing (hyperacusis)
• Low muscle tone (hypotonia) and joint laxity
• Heart and blood vessel problems
• Kidney abnormalities
• Elevated blood calcium levels (hypercalcemia)
• Developmental delay and learning disabilities
• Attention deficit disorder (ADD)
• Mild to moderate mental retardation
• Friendly, excessively social personality

Most individuals with Williams syndrome are highly verbal and overly sociable, having what has been described as a “cocktail party” type personality, and exhibit a remarkable blend of cognitive strengths and weaknesses and affinity for music. There is a higher prevalence of left-handedness and left-eye dominance.

Medical problems involving the eyes and vision, the digestive tract, the heart and the urinary system are possible.

Treatment

There is no cure for WBS. Treatment is based on the patients’ particular symptoms. Most medical problems require life-long surveillance, and most of the patients require full-time caregivers, adult patients are rarely self-sufficient.

Physical therapy is helpful to patients with joint stiffness
Developmental and speech therapy is beneficial for all patients. Vascular malformations can be a significant health problem and require regular follow-up as well as dedicated management. Hypercalcemia is treated by a calcium-restricted diet.

DID YOU KNOW?
The syndrome was first identified in 1961 by J. C. P. Williams, a cardiologist working in Auckland. A. J. Beuren in 1962 described a similar syndrome with additional features of dental anomalies and periferal pulmonary artery stenosis. In the wake of his discovery, Williams was offered a position at the Mayo Clinic, USA, but he did not appear as scheduled. Williams then went to London to work. When the Mayo Clinic offered him another post later in the 1960s, he again failed to appear. Williams then disappeared, his family did not know of his whereabouts only that he had left a suitcase at a baggage office in London, which was never claimed. Interpol traced him to Salzburg in 1972 when his mother died. Nobody has heard of him ever since.
**WOLF-HIRSCHHORN SYNDROME**

Wolf-Hirschhorn syndrome (WHS), also known as deletion 4p and 4p- syndrome, is a condition that affects many parts of the body. The major features of this disorder include a characteristic facial appearance, delayed growth and development, intellectual disability, and seizures.

<table>
<thead>
<tr>
<th>FREQUENCY OF OCCURRENCE</th>
<th>Seen 1 in 50,000 births</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• This may be an underestimate as it is likely that some affected individuals are never diagnosed.</td>
</tr>
<tr>
<td></td>
<td>• For unknown reasons, WHS occurs in about twice as many females as males.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>INHERITANCE</th>
<th>Sporadic / not inherited</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Most (nearly 90%) cases of the syndrome are not inherited but are due to de novo partial deletions of the short (p) arm of chr 4.</td>
</tr>
<tr>
<td></td>
<td>• In the remaining 10% of cases, the disorder is either the result of an unusual chromosomal abnormality such as a ring chr 4, or one of the parents has a balanced translocation involving chr 4p. The translocation can become unbalanced as it is passed to the next generation and deletes genes near the end of the short arm of chr 4.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIFE EXPECTANCY</th>
<th>Limited lifespan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• About one third of all affected infants die within the first two years of life.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>Partial deletion on the short (p) arm of chromosome 4, in region p16.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• The symptoms of WHS are related to the loss of multiple genes on the short arm of chr 4. The severity of symptoms and the expressed phenotype differ based on the amount of genetic material deleted.</td>
</tr>
</tbody>
</table>
Symptoms and medical problems

- Short stature
- Weak muscle tone (hypotonia)
- Small head (microcephaly)
- Increased distance between the eyes (hypertelorism)
- Prominent glabella
- Dysplastic ears
- Broad and/or beaked nose
- Shortened distance between nose and upper lip (short philtrum)
- Small chin (micrognathia)
- Downturned mouth
- Cleft palate
- Abnormal curvature of the spine (scoliosis and kyphosis)
- Seizures (that tends to diminish with age)
- Congenital heart defects and renal anomalies
- Absence of one or both testes from the scrotum (cryptorchidism)
- Immunodeficiency
- Developmental and mental retardation

People with WHS experience delayed growth and development. Slow growth begins before birth, and affected infants tend to have problems feeding and gaining weight. Motor skills, such as sitting, standing, and walking, are significantly delayed.

Intellectual disability ranges from mild to severe in patients. Compared to people with other forms of intellectual disability, their socialization skills are stronger, while verbal communication and language skills tend to be weaker.

Treatment

There is no specific treatment for WHS. Physiotherapy and occupational therapy are recommended to improve overall condition. Patients with congenital heart defects and cryptorchidism are surgically treated and those with seizures need regular EEG control and antiepileptic drugs.

DID YOU KNOW?
The syndrome is named after Kurt Hirschhorn, an Austrian-born American geneticist and Ulrich Wolf, a German human geneticist, who independently found the 4p- chromosome abnormality in the 1960s. The syndrome was first described in 1961 by Herbert L. Cooper and Kurt Hirschhorn. The disease gained worldwide attention through publications by Wolf and their co-workers, specifically their articles in the German scientific magazine Humangenetik.

Wolf-Hirschhorn Syndrome Coverage
The information in this publication was adapted from the following resources:

http://www.orpha.net
http://www.rarechromo.org
http://www.medicinenet.com
http://www.patient.co.uk