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# Chromosomal deletion syndromes: common types, causes and detection methods

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## Summary

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Chromosomes are structures composed of a DNA molecule and histone proteins that carry genetic information. They are located in the cell nucleus and become visible under light microscope during cell division. A karyogram is used to depict the number and structure of chromosomes, whereby a normal human karyogram has 46 chromosomes arranged in 23 homologous pairs. Changes in the number or structure of chromosomes lead to various genetic conditions and syndromes. Chromosomal deletions represent one of the most severe forms of chromosomal aberrations as they involve the loss of genetic material, causing severe disorders such as cri-du-chat, Wolf-Hirschhorn, Prader-Willi and Angelman syndromes. Prenatal diagnostic methods are used to check fetal growth and development and determine a type of fetal abnormality, if present, with commonly performed procedures including ultrasound, amniocentesis, chorionic villus sampling and cordocentesis. Final diagnosis is established through laboratory methods such as karyotyping, fluorescence in situ hybridization and chromosomal microarray analysis.

## Chromosomes and chromosomal aberrations

DNA molecules situated in the cell nucleus contain genetic instructions for the development and functioning of an entire organism. By coiling around histone proteins, DNA forms chromosomes, of which there are 46 in human cells, including 44 autosomes and two sex chromosomes. Cells prepare for division by duplicating their chromosomes and condensing them into thread-like structures that become visible during cell division, particularly in the metaphase stage when they are fully condensed. At this stage, a chromosome consists of two chromatids connected at a narrowed region called the centromere which facilitates the movement of chromosomes during cell division through the spindle apparatus. Additionally, the centromere partitions the chromosomes into short p arms and long q arms. Chromosomes are classified into several distinct types depending on the position of the centromere: metacentric, submetacentric, acrocentric and telocentric, the latter being absent in humans.<sup>2</sup> Special staining techniques enable visual distinction of particular chromosomes, as these stains colour specific regions on each chromosome differently.<sup>1</sup> A karyogram represents a graphical depiction of a karyotype, i.e. the chromosomal set of an individual.

During meiosis, a type of cell division that gives rise to reproductive cells, errors sometimes occur that trigger chromosome breaks or non-separation of sister chromatids or homologous chromosomes, leading to various numerical and structural chromosomal aberrations. These are mostly detrimental and in many cases lethal. Numerical chromosomal anomalies are categorised as aneuploidies or polyploidies. An aneuploidy involves the gain or loss of one or more chromosomes, whereas a polyploidy is defined by the presence of three or more sets of chromosomes and is typically lethal in humans. Numeric anomalies occur due to the non-separation of chromosomes or sister chromatids during meiosis I or meiosis II, giving rise to gametes with  $n+1$  or  $n-1$  number of chromosomes.<sup>1</sup> Structural chromosome changes are classified as translocations, deletions, duplications, inversions, and insertions. These changes occur due to chromosome breaks and rearrangements with other chromosome segments.<sup>2,4</sup>

## Chromosomal aberrations arise during meiosis

Meiosis is a cellular division that halves the number of chromosomes and generates gametes. It involves two divisions, meiosis I and meiosis II.<sup>1</sup> Meiosis I, also known as the reduction division, cuts the number of chromosomes by half. During prophase I, chromosomes consist of two sister chromatids connected by a centromere, and homologous pairs of chromosomes of the same size and shape and carrying the same genes align side by side allowing for crossing over to occur between non-sister chromatids so that genetic material can be exchanged. Paired homologous chromosomes are at this stage called bivalents. If homologous chromosomes carry different alleles, new allele combinations may be formed and genetic diversity is generated because each resulting gamete will have a unique allele combination. Therefore, crossing over has a pivotal role in ensuring genetic diversity in offspring.<sup>1,7</sup> In the next stage, during metaphase I, chromosomes align at the cell's equatorial plane, attached to the spindle fibres. During anaphase I, the spindle fibres contract, thereby separating the homologous chromosome pairs and pulling them towards the opposite cell poles. Subsequently, telophase I occurs, resulting in the formation of two daughter cells. Each of these cells contains a haploid number of chromosomes composed of two chromatids, therefore another division must occur to separate the sister chromatids.<sup>1</sup> Meiosis II begins with prophase II when chromosomes condense, and the spindle apparatus is formed. In metaphase II the chromosomes align along the cell's equatorial plane and during anaphase II microtubules of the spindle apparatus separate sister chromatids and pull them apart to opposite poles of the cell. Finally, in telophase II, two new cells are formed, each containing a haploid number of chromosomes, but this time each chromosome consists of a single chromatid.<sup>1</sup>

Occasionally, errors occur during crossing over, leading to duplications or deletions. If homologous chromosomes do not align precisely opposite each other or if they connect unevenly, unequal crossing over occurs.<sup>8</sup> In unequal crossing over, the alleles being exchanged are not in alignment, causing one gene to transfer to the homologous chromosome that already has that gene, resulting in a duplication of the gene. On the other chromosome, the gene that was supposed to be exchanged does not transfer, leading to a gene loss on that chromosome, i.e., a deletion. These errors result in structural chromosomal changes and the formation of cells with chromosomes carrying duplications or deletions.<sup>8</sup>

## Overview of chromosomal deletions

Chromosomal deletions are among the most severe structural changes as they involve the loss of genetic material. Deletions of more than 2% of the total haploid genome are considered lethal and mostly result in spontaneous miscarriages.<sup>1</sup> Smaller deletions can result in various syndromes such as Wolf-Hirschhorn syndrome, Angelman syndrome, cri-du-chat syndrome, and many others, which can have varying degrees of impact on the patient. Although there is currently no cure for these syndromes, they are managed symptomatically. The magnitude of deletion has a major influence on the clinical variability of symptoms such as characteristic facial and body features, organ impairments, intellectual disabilities, etc. (Table 1). Many of these anomalies can be identified during the initial stages of pregnancy (first trimester) using diverse prenatal diagnostic techniques. Ultrasound examinations can detect certain fetal abnormalities, and further in-depth information

can be obtained through diagnostic procedures such as amniocentesis or chorionic villus biopsy and subsequent cytogenetic and molecular genetic analyses.<sup>1</sup>

Deletions can involve an entire chromosome segment, a set of genes or a specific gene.<sup>5</sup> Large chromosomal deletions can be observed using a light microscope and are associated with syndromes like Wolff-Hirschhorn and cri-du-chat, while microdeletions can be identified using cytogenetic methods such as FISH (fluorescence in situ hybridization) and high-resolution karyotyping of prometaphase chromosomes. Examples of syndromes caused by microdeletions include Prader-Willi syndrome and Angelman syndrome. Some microdeletions result in the loss of multiple genes located in close proximity, leading to the so-called contiguous gene syndromes.<sup>1,2</sup>

Chromosomal deletions are classified into terminal and interstitial deletions (Figure 1). Terminal deletions involve the loss of the ends of the p or q arms of a chromosome due to a single break, while interstitial dele-

**Table 1. Main characteristics of several chromosomal deletion syndromes**

Chromosomal deletion syndrome	Chromosome involved	Location	Occurrence	Main genes affected	Main symptoms
Cri-du-chat	5	5p-	1:15000 to 1:50000	SEMAF, CTNND2	high pitched cry, microcephaly, severe psychomotor and intellectual disability
Wolf - Hirschhorn	4	4p-	1:50000	NSD2, MSX1, LETM1	characteristic facial features, intellectual disability, seizures, delayed growth and development
Angelman	15	15q11-13	1:12000 to 1:20000	UBE3A	severe speech impairment, delayed development, intellectual disability, problems with movement and balance, seizures
Prader - Willi	15	15q11-13	1:10000 to 1:3000	snoRNA genes (SNORD116 cluster)	constant hunger, obesity, behavioral problems, distinctive facial features
Kleefstra	9	9q34.3	1:25000 to 1:35000	EHMT1	developmental delay, intellectual disability, speech impairment
22q11	22	22q11.2	1:4000	TBX1, COMT	heart abnormalities, recurrent infections, distinctive facial features, submucosal cleft palate
Smith - Magenis	17	17p11.2	1:25000	RAI1	distinctive facial features, sleep disturbances, behavioral problems, delayed speech and language skills
Williams	7	7q11.23	1:7500 to 1:18000	ELN, GTF2I, GTF2IRD1, LMK1	mild to moderate intellectual disability, unique personality characteristics, distinctive facial features, cardiovascular problems

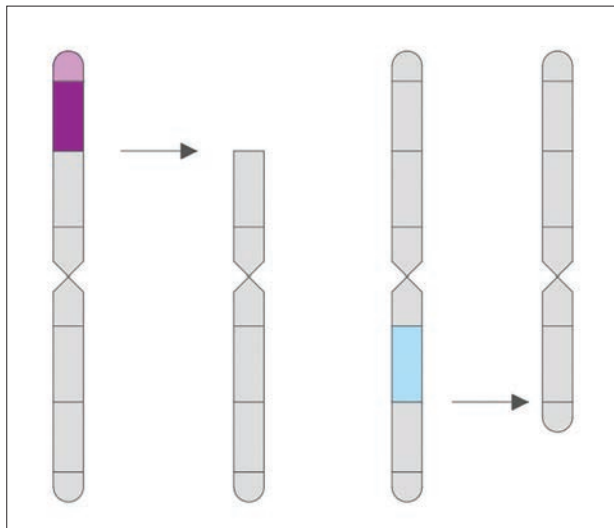


Figure 1. **Terminal and interstitial deletion**

tions involve two breaks on the p or q arm, causing the loss of the region between them. If both p and q arms undergo terminal deletions, the remaining chromosome retains sticky ends that subsequently join to form a ring, resulting in a so-called ring chromosome. If it involves an autosomal chromosome, the consequences of a ring chromosome formation can be very severe.<sup>2,5</sup>

## Cri-du-chat syndrome

Cri-du-chat syndrome (CdCS) is a genetic condition caused by a deletion of the short arm of chromosome 5 (5p). It occurs in approximately 1 in every 15000 to 1 in every 50000 live births. The most recognizable characteristic of CdCS, a high-pitched cry resembling a “cat’s cry”, occurs in newborns due to improperly developed small and narrow larynx and small and loose epiglottis.<sup>9,10</sup> Additionally, the high-pitched cry can be associated with neurological and structural changes, such as neurocranial malformations. This syndrome exhibits significant clinical variability due to the varying size of the deleted chromosome segment, ranging from 5 to 40 megabases (Mb), with more severe symptoms when a larger portion is lost. Common clinical features include microcephaly, an asymmetric face with a mouth unable to close properly, a wide nose, low-set ears, small jaw (micrognathia), and severe psychomotor and intellectual impairments. During the neonatal period, specific manifestations include asphyxia and cyanosis due to insufficient oxygen supply and airway obstruction

caused by anomalies of the larynx and epiglottis.<sup>9</sup> Less frequently, cardiac and renal problems as well as syndactyly occur. The postnatal mortality rate is approximately 10%, with the majority of deaths occurring within the first year of life. However, if a child survives the first year, the mortality rate decreases, and individuals can have a normal lifespan. The muscular hypotonia present in newborns transitions to hypertonia in adulthood, and microcephaly becomes increasingly apparent. Metabolic abnormalities have also been reported in patients with CdCS, such as difficulty in synthesizing purine nucleotides that are needed in purinergic neurotransmission. Approximately 50% of patients are diagnosed with hyperactivity, which can be accompanied by aggression. A smaller percentage of patients display characteristics such as self-injury, repetitive behaviours and hypersensitivity to sound stimuli. The CdCS diagnosis in newborns or prenatally is based on the clinical features, karyotyping and/or a specific FISH test.<sup>9,10</sup>

Most of the symptoms of cri-du-chat syndrome result from deletions at positions 5p13.33, where the telomerase reverse transcriptase (*h-TERT*) gene is located, and 5p15.2, where the semaphorin F (*SEMAF*) gene is located.<sup>9</sup> Deletion of the  $\delta$ -catenin (*CTNND2*) gene, also located on 5p15.2, is associated with severe intellectual difficulties, as this protein is expressed during early intellectual development. The prevalent causes of this syndrome include spontaneous terminal deletions of 5p as the most common cause, interstitial deletions, and *de novo* translocations. About 80 to 90% of deletions originate from the father, indicating that they likely occur due to errors during spermatogenesis. Parents of children with spontaneous deletions usually have normal chromosomes, therefore the likelihood of conceiving another child with chromosomal abnormalities is very low. Approximately 10 to 15% of cases arise from translocations between chromosome 5 and another chromosome.<sup>10</sup>

## Wolf - Hirschhorn syndrome

Wolf - Hirschhorn Syndrome (WHS), also referred to as 4p-syndrome, is a very rare genetic disorder arising from deletion near the end of the chromosome 4 short arm. WHS is an example of contiguous gene deletion and exhibits a wide range of clinical variability depending on the size of the deletion. The estimated incidence of WHS is approximately 1 in 50000 live births and occurs approximately twice as often in females as in males.<sup>1,13</sup> Clinical symptoms

include seizures, slowed growth, developmental delays and a distinct facial phenotype described as a “Greek warrior helmet” with a prominent and broad area between the eyebrows (glabella) and a high forehead, which is associated with widely spaced and protruding eyes.<sup>12</sup> Additionally, there is a shortened distance between the upper lip and nose (short philtrum), micrognathia, and underdeveloped ears with small ear openings. Typical features present in the majority of patients include short stature and low body weight, low muscle tone, intellectual disabilities, and seizures. Motor skills are significantly limited, while the severity of intellectual disabilities can vary from mild to severe. Congenital heart defects such as atrial septal defects are frequent in individuals with WHS. Additionally, many individuals with this syndrome are prone to infections due to primary immunodeficiency. Feeding difficulties are prevalent and can be quite severe, with many a patient requiring tube feeding. Some individuals experience significant gastrointestinal problems, including malrotated intestine and poor absorption of nutrients. The life expectancy varies, and many affected children do not survive infancy, while a small percentage may reach their twenties. Those who survive often experience severe intellectual and physical impairments, are prone to infections and epilepsy, and have significant challenges in their daily lives.<sup>11,12,13</sup> The syndrome was first recognized in 1961, but it wasn't until 1965 that it was described as the syndrome we know today.<sup>1</sup> It should be noted that the Pitt-Rogers-Danks Syndrome (PRDS) was initially described as a separate disorder from WHS.<sup>13</sup> However, it was later discovered that individuals diagnosed with PRDS also have a deletion in the same region of chromosome 4 as seen in WHS. Therefore, PRDS is now considered a milder form of WHS.<sup>11,12,13</sup>

*NSD2*, *MSX1*, and *LETM1* are genes that are deleted in individuals with typical WHS symptoms.<sup>12</sup> Although many specific functions of these three genes are still unknown, it is known that they play a significant role in embryogenesis and early development. Experts believe that the loss of the *NSD2* gene is associated with many characteristic features of WHS, including the recognizable facial appearance and developmental delay. The deletion of the *LETM1* gene is believed to be linked to seizures and other abnormal brain activities, while the loss of the *MSX1* gene could be associated with dental abnormalities and cleft lip or palate, which are characteristic features of WHS cases. Scientists continue to research and discover other genes located on the distal end of the fourth chromosome that may also be associated with the distinctive features of WHS. Approximately 85 to 90% of all WHS cases result from spontaneous chromosomal deletions, while

a smaller percentage of individuals with WHS acquire the syndrome as a result of a ring chromosome 4.<sup>12</sup> The diagnosis of WHS is made based on characteristic clinical symptoms and by detecting the deletion on the fourth chromosome using cytogenetic analysis, a FISH test, which can be employed in prenatal diagnosis of WHS, and the diagnostic test CMA (chromosomal microarray analysis), which can detect nearly all WHS deletions and their sizes. For families of children with Wolf-Hirschhorn syndrome genetic counselling is recommended.<sup>13</sup>

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## Angelman syndrome and Prader - Willi syndrome

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Angelman syndrome and Prader - Willi syndrome (PWS) are examples of genomic imprinting, an epigenetic phenomenon in which a gene is active on only one parental allele, while the allele inherited from the other parent is inactive<sup>1</sup>. Therefore, the phenotype of the individual is influenced by only one allele, not both. Both syndromes are caused by lack of expression of genes in the 15q11-13 region, but the difference lies in the parental inheritance of the chromosome. If the deletion occurs on the paternal chromosome, PWS will manifest, and if the deletion occurs on the maternal chromosome, Angelman syndrome will occur. *SNORD116* gene cluster appears to be critical for the PWS phenotype and *UBE3A* gene for the Angelman.<sup>14,18</sup> However, these syndromes may also occur due to uniparental disomy. If an individual inherits both chromosome 15 copies from the father, Angelman syndrome will occur, while in the case of PWS, the individual inherits both chromosome 15 copies from the mother.<sup>1</sup> The incidence of Angelman syndrome is approximately 1 in 12000 to 1 in 20000 births, while the incidence of PWS is approximately 1 in 10000 to 1 in 30000 births.<sup>14,18</sup>

Angelman syndrome primarily affects the nervous system.<sup>14</sup> Children with Angelman syndrome experience seizures, poor coordination, severe cognitive developmental delay, intellectual disabilities and severe speech impairments. Early in childhood, problems with movement and coordination (ataxia) become apparent. Hypotonia or hypertonia may be present. Motor skills generally develop late. In less severe cases, children may start walking between the ages of 2 and 3, while in more severe cases, walking may be delayed until between the ages of 5 and 10, and it will probably be slow, stiff, and jerky. Approximately 10% of children with An-

gelman syndrome may not walk or require assistance to walk. Children with this syndrome are characterized by a happy personality and often have episodes of unprovoked laughter. Most children also experience sleep difficulties and require less sleep than usual. As individuals with Angelman syndrome grow older, they become less excitable, and sleep problems may improve. Adult patients often have characteristic facial features described as rough.<sup>14,15,16,17</sup>

On the other hand, children with PWS have hypotonia, mild to moderate cognitive impairment, poor feeding in infancy, and later develop hyperphagia and obesity due to constant hunger that is typical of this syndrome. Hypotonia diminishes as they grow, but it remains present throughout life. Individuals have short stature, underdeveloped and small genitalia, which often leads to sterility. Appetite is excessive and patients still feel hungry even after consuming a meal, despite reduced calorie requirement due to low muscle mass, decreased metabolism, and reduced physical activity, which leads to overeating and life-threatening obesity. Patients may also exhibit unusual food-related behaviours, including hoarding, food-seeking, or consuming spoiled food. Therefore, constant supervision is necessary for these patients. Individuals with PWS have varying degrees of cognitive impairment, ranging from low-normal intelligence with learning difficulties to mild and moderate intellectual disabilities. Behavioural problems are common and may include outbursts of anger, obsessive-compulsive disorder, and self-injury in the form of excessive skin picking, leading to sores and bleeding. People with this syndrome also have characteristic facial features, including almond-shaped eyes, a thin upper lip, narrow forehead and an elongated and narrow head. Recognizable facial features may be evident shortly after birth or develop gradually over time.<sup>18,19,20</sup>

The diagnosis of Angelman syndrome or PWS is based on a detailed patient history and clinical examination. In approximately 80% of cases, confirmation of Angelman can be obtained through specialized blood tests such as methylation-specific DNA testing, which detects the syndrome but does not differentiate between deletion and uniparental disomy. However, FISH and CMA can detect these specific abnormalities. About 10% of patients with this syndrome do not have a deleted *UBE3A* gene on the maternal chromosome; instead, the gene is active but mutated. Therefore, the DNA methylation test will be normal and an additional *UBE3A* gene mutation test must be ordered.<sup>15</sup> Similarly, specialized tests such as DNA methylation and FISH, as well as

CMA, are necessary to diagnose PWS. Unlike Angelman syndrome, 99% of patients with PWS can be confirmed through DNA methylation testing alone; however, the diagnosis should always be confirmed using FISH or the newer CMA, which can determine the size of the deletion.<sup>19</sup> Families of patients with these two syndromes are recommended to seek genetic counselling.<sup>14,15,18,19</sup>

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## Microdeletion syndromes

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### Kleefstra syndrome

Kleefstra syndrome is caused by the deletion or a mutation of the the *EHMT1* gene located at the end of the long arm of chromosome 9, specifically at the region designated as 9q34.3. This gene provides synthesis instructions for an enzyme which modifies histone formation. The loss of the *EHMT1* gene underlies the characteristic features of Kleefstra syndrome, and the potential loss of other genes in that region can lead to additional health complications in affected individuals. Approximately 25% of patients with this syndrome do not have a deletion of the *EHMT1* gene but instead have a mutation in the same gene.<sup>21</sup> Kleefstra syndrome is a disorder that affects multiple parts of the body. Characteristic features include developmental delay, intellectual disabilities, severely limited or absent speech, and hypotonia.<sup>22</sup> These patients also have microcephaly and brachycephaly (wide and short skull) and distinctive facial features, including connected eyebrows, widely spaced eyes, nostrils that open forward rather than downward, inverted lips, and a large tongue. They are also characterized by high birth weight and childhood obesity. People with Kleefstra syndrome may also have structural abnormalities of the brain, congenital heart defects, seizures, hearing loss, and a predisposition to severe respiratory infections. During childhood, they may exhibit features of autism or similar developmental disorders that affect communication and social interaction. The prevalence of this syndrome is estimated at between 1:25000 to 1:35000, given that testing to differentiate this syndrome from other disorders with similar characteristics has only recently become available. Nevertheless, based on genome-wide studies, it is estimated to be around 1 in 500 individuals with a neurodevelopmental disorder.<sup>1,21,22</sup>

## 22q11 microdeletion syndrome

The 22q11 microdeletion syndrome is caused by a deletion of a small portion of chromosome 22 near the middle of its long arm. It was previously known by various names such as Sedlackova syndrome, DiGeorge syndrome and velocardiofacial syndrome.<sup>1</sup> After identifying the genetic cause of all these disorders, it was established that they are all part of the same syndrome now called the 22q11 microdeletion syndrome. The wide range of symptoms in this syndrome is evident from the fact that its features vary greatly even among affected members of the same family. The most common symptoms are cardiac abnormalities, frequent infections resulting from immune system problems, characteristic facial features, submucous cleft palate and nasal-sounding voice, and others.<sup>24</sup> These patients may also have breathing difficulties, kidney abnormalities, low calcium levels in the blood leading to seizures, feeding difficulties, and hearing loss. Shortened stature may be present, as well as bone and spinal abnormalities. Many children with this syndrome experience delays in development, growth and speech, and some may have mild intellectual disabilities and learning difficulties. Older individuals have difficulties reading, performing tasks involving mathematics, and solving problem-based tasks. Additionally, children with this syndrome have a highly increased risk of developing ADHD and autism spectrum disorders that affect communication and social interaction. This syndrome has an estimated occurrence of 1 in 4000 births, making it one of the most frequent microdeletion syndromes.<sup>23</sup> The deletion in this syndrome is usually around 3 Mb and includes up to 30 or 40 genes. The 22q11 microdeletion syndrome is referred to as a syndrome of contiguous gene deletion in which many genes on a single chromosome are missing.<sup>23</sup> It has been determined that the loss of the *TBX1* gene on chromosome 22 is likely responsible for many characteristic features of the syndrome, such as heart defects, cleft palate, low calcium levels, and characteristic facial features. Furthermore, some studies associate the loss of this gene with behavioural problems. The loss of the *COMT* gene in the same region of chromosome 22 can also lead to behavioural problems and mental illnesses. Individuals with the 22q11 microdeletion can pass it on to their children. However, the deletion is inherited in 7% of cases and occurs *de novo* in 93% of affected individuals. The risk of inheriting the deletion from the affected parent is 50% for each pregnancy. As with all the other mentioned syndromes, there is no cure for this syndrome, and treatment focuses on managing the symptoms. Genetic counselling is recommended for parents.<sup>1,23,24</sup>

## Smith - Magenis syndrome

Smith-Magenis syndrome is a developmental disorder that affects multiple body parts. It arises from chromosomal deletion on 17p11.2 approximately 3.7 Mb in size and occurs in approximately 1 in 25000 births.<sup>1,25,26</sup> Although there are several genes in that region, it seems that the deletion of the *RAI1* gene contributes to the majority of the characteristic features of Smith-Magenis syndrome. The *RAI1* gene codes for a protein that aids in regulating the expression of genes involved in circadian rhythms, for example, the sleep and wake cycle. A smaller percentage of individuals with this syndrome do not have a deletion of the *RAI1* gene but rather a mutation. While these individuals exhibit most of the main characteristics of the syndrome, they also experience a range of other symptoms indicative of deletions in other genes. The primary features of this syndrome include delayed development of speech and language skills, unique facial features, mild to moderate intellectual disabilities, behavioural problems and sleep disorders. Most patients have a broad square-shaped face with deep-set eyes, full cheeks, pronounced lower lip curved outward and a prominent lower jaw, which all becomes more evident in adulthood. Other symptoms include typically short stature, scoliosis, reduced pain and temperature sensitivity, as well as ear and eye abnormalities leading to hearing loss and vision problems. Sleep disturbance is characteristic of this syndrome, and affected individuals may experience excessive daytime sleepiness while struggling with sleep initiation and interrupted sleep during the night, which is associated with a reversed melatonin circadian rhythm but can be managed through cautious administration of melatonin.<sup>26</sup> Individuals with this syndrome have an affectionate personality, but the majority also exhibit behavioural problems characterized by frequent outbursts of anger, aggression, and anxiety. They are also prone to self-injury, which often includes head-banging, nail-biting, inserting objects into body openings, and possibly unique to this syndrome, constant self-hugging.<sup>1</sup>

## Williams syndrome

Williams-Beuren syndrome or Williams syndrome is a rare developmental genetic disorder characterized by mild to moderate intellectual disabilities, learning difficulties, unique and characteristic personality traits and behaviours, heart and blood vessel problems, short stature, drooping shoulders, and distinctive facial features that become more pronounced with age. A key behavioural feature of patients with this syndrome is a pronounced

communicativeness, friendliness and open personality inclined towards engaging with other people. Children with Williams syndrome often have a cheerful and friendly disposition, and are talkative, sometimes exhibiting remarkably enhanced language usage and vocabulary. However, in adulthood, they may become withdrawn and sensitive, with mild to moderate intellectual impairment, although they typically have average intelligence with some learning difficulties. Facial features include full lips, full cheeks, large open mouths, and a broad nasal bridge with nostrils that flare forward. These patients may also have unusually short eyelid folds, bushy eyebrows, small jaw, prominent ears, and dental abnormalities like small and underdeveloped teeth that are widely spaced or misaligned and have small roots. Difficulties with visual-spatial tasks such as drawing and puzzle-solving are commonly present but generally these individuals excel in tasks involving speech, memorization, and music. Patients with this syndrome experience cardiovascular problems, with congenital heart defects occurring in approximately 75% of cases of Williams syndrome, as well as supra-aortic stenosis which, if left untreated, can lead to shortness of breath, fatigue, chest pain and heart failure.<sup>28</sup> Other blood vessels may also be affected. Some infants may have elevated blood levels of calcium, leading to loss of appetite, irritability, confusion, weakness, and abdominal and muscle pain. Calcium levels usually normalize around the first year of life, but in some cases, hypercalcemia may persist into adulthood.

The prevalence of Williams syndrome is estimated to be around 1 in 7500 to 1 in 18000 births and it is caused by a deletion of genetic material on chromosome 7, specifically on the long arm at the location 7q11.23.<sup>27</sup> This region contains 25 to 27 genes, some of which contribute to the characteristic features observed in individuals with this syndrome. *ELN*, *GTF2I*, *GTF2IRD1*, and *LIMK1* are genes that are typically deleted in individuals with Williams syndrome. The loss of the *ELN* gene is associated with connective tissue abnormalities, lax skin, and cardiovascular diseases (particularly supra-aortic stenosis). The *LIMK1* gene is believed to be related to the visual-spatial problems that are common in this syndrome, and the loss of the *GTF2IRD1* gene may contribute to the characteristic facial features. The *NCF1* gene is located in a region that is sometimes included in the deletion and sometimes not, and it is presumed that this gene is associated with the risk of developing hypertension in individuals with the deleted *NCF1* gene. Diagnosis of this syndrome is based on clinical evaluation, patient medical history, and laboratory tests, including specialized

blood tests that detect elevated calcium levels, as well as the application of the FISH method that detects the deletion on the seventh chromosome. Genetic counselling is recommended for families of affected individuals.<sup>1,27,28</sup>

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## Prenatal diagnostics

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Prenatal diagnostics includes various procedures and tests used to determine the health status of the fetus during pregnancy. It is generally applied to evaluate the potential risk of chromosomal abnormalities in the fetus. Prenatal diagnostics can be classified into invasive and non-invasive diagnostics. Invasive prenatal diagnostics can sometimes pose a risk to the fetus and, in rare cases, may cause additional harm or result in miscarriage. Non-invasive methods such as ultrasound and certain blood tests are part of routine pregnancy examinations and do not carry a risk to the fetus. However, they cannot confirm the presence of fetal diseases but rather indicate an increased risk for a particular condition. The most common invasive methods include amniocentesis, chorionic villus sampling, and cordocentesis.<sup>29</sup>

### Amniocentesis, chorionic villus sampling and cordocentesis

Amniocentesis is the method commonly used in invasive prenatal diagnostics. It is typically performed between the 15th and 18th week of pregnancy, and the test results are available after two to three weeks. Amniocentesis is a procedure in which the fetus is observed using ultrasound, and a needle is inserted through the abdominal wall into the uterine cavity to collect approximately 10 to 20 mL of amniotic fluid for analysis. The amniotic fluid is then centrifuged to separate fetal cells from the fluid, and then they can be used for chromosomal anomaly detection. The cellular sediment is subsequently resuspended in a cell growth medium. After approximately two weeks of cell culture, enough cells are present for DNA and chromosome analysis. Prior to the procedure, parents must be informed that this method carries a risk of miscarriage ranging from 0.5% to 1%.<sup>29</sup>

Unlike amniocentesis, chorionic villus sampling offers the advantage of early prenatal diagnosis, as it can be performed during the first trimester of pregnancy, specifically between the 11th and 12th week. Before the pro-



cedure, an ultrasound examination is conducted to determine the position of the placenta and the gestational age of the fetus. Under ultrasound guidance, a hollow needle is inserted through the cervix or abdominal wall (more commonly) to obtain a sample of chorionic villi. The term “placental biopsy” is used when the procedure is performed in the later weeks of pregnancy. The results of the biopsy are usually available within one week. The risk of spontaneous miscarriage ranges from 1 to 2%. This procedure is not performed before the 11th week of pregnancy, as it has been shown to potentially cause limb abnormalities if performed earlier.<sup>29</sup>

Cordocentesis or “percutaneous umbilical cord blood sampling” is used to obtain fetal blood from the umbilical cord, usually from 18 weeks onward. This method can be used for rapid chromosomal analysis, and the results are typically available within 48 hours. The procedure is performed with the assistance of ultrasound, where a needle is inserted through the abdominal wall into the umbilical cord to collect a sample of fetal blood.<sup>29</sup>

## Ultrasound and fetoscopy

Ultrasound plays a crucial role in prenatal diagnostics as it allows monitoring of a healthy pregnancy and enables detection of fetal congenital abnormalities and fetal surveillance. Non-invasive nature of ultrasound is highly beneficial for both a mother and a fetus. During pregnancy, a minimum of three ultrasound examinations are recommended, first between weeks 10-14 to confirm pregnancy and measure nuchal fold, second between weeks 18-22 to check fetal growth and development and detect structural anomalies, and the third between weeks 30-34. If certain fetal anomalies are identified with ultrasound, additional procedures such as amniocentesis and chorionic villus sampling are recommended to determine a fetal karyotype.<sup>1</sup>

Fetoscopy is an invasive method performed in the second trimester that involves visualizing the fetus using an endoscope to identify structural abnormalities or to obtain samples of fetal tissue for diagnostic purposes. Fetoscopy carries a higher risk of miscarriage compared to amniocentesis and chorionic villus sampling, ranging from 3 to 5%. Due to its invasiveness, this method is rarely performed as there are significantly safer alternatives. However, if necessary, it is conducted in highly specialized diagnostic centers.<sup>1</sup>

## Laboratory diagnostics

Laboratory diagnostics plays a significant role in diagnosing patients with genetic disorders. When there is a suspicion of a specific diagnosis, laboratory tests are ordered to provide a clearer understanding of the patient's condition. In the diagnosis of chromosomal abnormalities, methods such as karyotyping and cytogenetic techniques like fluorescence in situ hybridization, or FISH, and chromosomal microarray analysis, or CMA, play a key role. Due to their exceptional accuracy and effectiveness, these are the methods that are widely used for chromosomal analysis.

## Karyotyping

Karyotyping allows the analysis of chromosome structure and composition to determine the presence of chromosomal abnormalities. This technique is reliable due to its straightforward analysis and clear interpretation of results, making it the first step in detecting diseases caused by chromosomal abnormalities. The detection limit of this procedure can be up to 3 Mb, but changes in size ranging from 5 to 10 Mb can often be predicted, depending on the location of the change and the resolution of banded chromosomes. The most common samples used are lymphocytes from peripheral blood, but cells can also be collected from bone marrow, amniotic fluid obtained through amniocentesis, and other sources. The sample is then supplemented with cell culture media and grown in sterile conditions at a temperature of 37 °C for three days. Colchicine is added to the cell culture, which stops the formation of the spindle apparatus and stops cell division in metaphase when chromosomes are most visible. Subsequently, a physiological solution is added to the culture, leading to cell lysis and release of chromosomes, which are then fixed onto glass slides, stained, and analysed. The predominantly used method for chromosome staining is Giemsa staining (G-banding) due to its high-quality chromosome analysis. After staining, a detailed banding pattern is determined for each chromosome. Chromosomal banding patterns are specific for each chromosome and are represented in the form of a stylized chromosome map called an idiogram. A cytogeneticist examines each pair of homologous chromosomes using a microscope or photographic image, organizing and arranging them into a karyogram. A normal karyogram will show 46 chromosomes without any de-

letions, translocations, or other structural or numerical anomalies.<sup>1</sup> For research and diagnostic purposes, chromosomes are divided into various segments that are designated by numbers. For example, chromosome 5p15.3 is defined as the 15th segment of the short arm of chromosome 5. Such numbering is important for determining the location of individual genes on the chromosome.

## Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) is a diagnostic technique that combines cytogenetics and molecular genetic technology, enabling direct identification of chromosomes, specific chromosomal regions, and genes. A significant advantage of this method is its ability to visualize changes in metaphase chromosomes as well as in interphase nuclei. FISH is based on the unique ability of short single-stranded DNA to pair with complementary DNA sequences. In order to visualize hybridization, FISH utilizes fluorescence-labelled probes, which become visible when they come into contact with the patient's DNA, using a fluorescence microscope. Each probe binds to a specific location on the chromosome, thereby allowing the identification of specific regions. There are several types of FISH probes used to identify specific conditions. Unique probes specific to individual chromosomes are used for detecting chromosomal deletions and microdeletions, as well as duplications. These probes are specific to precisely defined loci, and through hybridization, they recognize deletions at those loci if they are present. FISH has been used in clinical diagnostics for almost 30 years due to its high accuracy, allowing for the detection of specific chromosomal changes that may not be visible with conventional cytogenetic methods.<sup>1</sup>

## Chromosomal microarray

Chromosomal microarray analysis (CMA) is a diagnostic method that has been used in clinical diagnostics for a little over 15 years. It is employed to identify genetic causes of diseases that lead to developmental and intellectual disabilities, autism spectrum disorders, and congenital anomalies. This test only detects variations in the copy number of DNA, and therefore, it is used for the diagnosis of chromosomal microdeletions or duplications, and numerical abnormalities. The use of chromosomal microarray analysis in the diagnosis of microdeletions has become almost inevitable today due to its significantly higher resolution compared to traditional karyotyping and greater accuracy in detecting micro-

deletions. CMA tests are commonly performed using blood samples. The testing is conducted on a microchip containing probes that hybridize with specific parts of DNA. If a deletion or duplication is present, these differences are referred to as variations in the test results. The test is primarily used for the detection of Angelman syndrome, Wolf-Hirschhorn syndrome, Prader-Willi syndrome, DiGeorge syndrome, and Williams syndrome.<sup>31</sup>

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## Conclusion

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Chromosomal abnormalities cause various malformations and intellectual impairments, organ damage, physical appearance abnormalities, hearing and vision problems, and similar conditions. Chromosomal deletions result in the loss of genes on chromosomes and are commonly caused by errors in meiosis, although they may also be inherited. They are the main cause of syndromes such as cri-du-chat syndrome, Wolf-Hirschhorn syndrome, Angelman syndrome, Prader-Willi syndrome, Williams syndrome, and Kleeftstra syndrome. Almost all fetal abnormalities can be detected through prenatal diagnostics using invasive and non-invasive methods. Invasive tests can pose risks to the fetus and carry a certain risk of miscarriage. After sample collection, laboratory methods are used to analyse the samples and make a diagnosis. Chromosomal deletions can be identified with cytogenetic analyses of prometaphase chromosomes. The predominantly used method is karyotyping, often accompanied by FISH or CMA. Chromosomal microarray analysis is most frequently employed for detecting chromosomal microdeletions due to its high precision. Although there is currently no cure for syndromes caused by chromosomal deletions, early diagnostics and advanced treatment of symptoms allow patients to reach their maximum potential and improve their quality of life.

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## SINDROMI KROMOSOMSKIH DELECIJA: UČESTALI TIPOVI, UZROCI I METODE DETEKCIJE

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### Sažetak

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Kromosomi su strukture sastavljene od molekule DNA-a i histonskih proteina koji nose gensku informaciju. Nalaze se u jezgri stanice i postaju vidljivi pod svjetlosnim mikroskopom tijekom stanične diobe. Kariogram je grafički prikaz broja i strukture kromosoma, pri čemu normalni ljudski kariogram ima 46 kromosoma raspoređenih u 23 homologna para. Promjene u broju ili strukturi kromosoma uzrok su različitih genskih stanja i sindroma. Kromosomske delecije predstavljaju jedan od najtežih oblika kromosomskih aberacija jer uključuju gubitak genskog materijala, uzrokujući teške poremećaje kao što su sindrom *cri du chat* te Wolf-Hirschhornov, Prader-Willijev i Angelmanov sindrom. Prenatalne dijagnostičke metode primjenjuju se za provjeru fetalnog rasta i razvoja i određivanje vrste fetalne abnormalnosti, ako je prisutna, s uobičajenim postupcima koji uključuju ultrazvuk, amniocentezu, biopsiju korionskih resica i kordocentezu. Konačna dijagnoza postavlja se laboratorijskim metodama kao što su kariotipizacija, fluorescentna *in situ* hibridizacija i analiza kromosomskih mikročipova.

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**Ključne riječi:** kromosom, delecija, sindrom, prenatalna dijagnostika, laboratorijska dijagnostika

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