

## HEREDITARY FEATURES AND RISK FACTORS OF DOWN SYNDROME

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### Abstract

This article presents a comprehensive and systematic analysis of the genetic inheritance patterns of Down syndrome and the major risk factors influencing its development. As the primary genetic basis of the disorder, trisomy of chromosome 21 is highlighted, and the mechanisms of its occurrence are scientifically explained in relation to chromosomal segregation errors, particularly nondisjunction.

The study compares the genetic characteristics of different forms of Down syndrome, including complete trisomy, translocation, and mosaic variants. It is emphasized that the translocation form may, in some cases, involve partial heritability, while the importance of genetic counseling and karyotype analysis is also underlined.

The main factors contributing to the development of the condition are analyzed, including maternal age and genetic errors during gametogenesis. Environmental factors are also considered from a biological and genetic perspective in terms of their direct impact on the genetic stability of cells and gametes. Ionizing radiation, such as ultraviolet and radioactive exposure, may increase the likelihood of mutations in the DNA of male and female gametes, leading to errors in chromosomal segregation. Certain chemical agents, including pesticides, heavy metals, and pharmacological substances, may cause genetic damage to gametes or embryonic cells during early developmental stages. Additionally, environmental stressors such as high temperature and oxidative stress can contribute to abnormal chromosomal segregation during cell division.

Scientific studies indicate that in women over the age of 35, the genetic stability of gametes decreases, and when combined with environmental factors, the risk of chromosomal abnormalities significantly increases. Furthermore, the article discusses modern prenatal diagnostic methods, including ultrasound examination, biochemical screening, and invasive techniques, which enable early detection of Down syndrome. The obtained findings contribute to a deeper understanding of the etiopathogenesis, inheritance patterns, and preventive strategies of the disease, and are of significant importance in clinical medical practice.

### Keywords

Down syndrome, trisomy 21, inheritance, chromosomal anomaly, genetic mutation, translocation, mosaicism, risk factors, prenatal diagnosis, karyotype, gametogenesis.



## General Definition and Etiology of Down Syndrome

Down syndrome is a congenital genetic disorder associated with an abnormal change in the number of chromosomes in the human body. It is primarily characterized by delayed physical development, reduced intellectual ability, and various morphological and functional abnormalities. The main genetic cause of this syndrome is trisomy of chromosome 21, in which three copies of chromosome 21 are present in the cells. As a result, genetic imbalance occurs in the organism, leading to dysfunction in various body systems.

From an etiological perspective, Down syndrome is most commonly associated with chromosomal errors occurring during gametogenesis. The primary mechanism is nondisjunction, in which chromosomes fail to properly separate during meiosis, resulting in the formation of a gamete with an extra chromosome. When such a gamete fuses with a normal gamete during fertilization, a zygote with three copies of chromosome 21 is formed. This leads to the most common form of the disorder—complete trisomy.

In addition, the translocation mechanism also plays an important role in the etiology of the syndrome. In this case, a segment of chromosome 21 becomes attached to another chromosome, most commonly chromosome 14 or 15. Although the translocation form is relatively rare, it is significant because it can be inherited in some cases; that is, if one of the parents is a carrier of a balanced translocation, the risk of having a child with Down syndrome increases.

Another etiological variant is the mosaic form, in which chromosomal abnormalities occur during the early stages of embryonic development as a result of mitotic cell division. Consequently, part of the organism's cells is normal, while another part carries trisomy. In this form, clinical manifestations are generally milder, since not all cells are affected.

Several risk factors also play an important role in the development of Down syndrome. One of the most significant factors is maternal age. In women over 35 years of age, the age-related decline in oocyte quality increases the likelihood of chromosomal segregation errors, thereby raising the risk of trisomy. In addition, genetic factors, such as the presence of chromosomal rearrangements in one or both parents, are also important. In rarer cases, environmental factors—such as radiation exposure, chemical substances, and unfavorable ecological conditions—are considered additional risk factors.

Thus, the etiology of Down syndrome is multifactorial, with chromosomal abnormalities forming its underlying basis. These abnormalities lead to an excess of genetic material, which disrupts normal developmental processes of the organism and results in the clinical manifestations of the disease.

## Pathogenesis of Down Syndrome

Down syndrome is one of the most common chromosomal disorders in humans, and its development involves complex molecular, cellular, and systemic changes. The most important molecular event underlying the disease is the presence of three copies of chromosome 21 (trisomy 21). As a result, the balance of gene expression within the cell is disrupted, leading to impaired normal developmental processes in the organism.



The primary mechanism in the development of Down syndrome is chromosomal nondisjunction. During the formation of an ovum or sperm cell, chromosomes fail to separate properly, resulting in gametes with an abnormal number of chromosomes. For example, instead of having one copy of chromosome 21, a gamete may contain two copies or none at all. When such a gamete participates in fertilization, the resulting zygote acquires an extra copy of chromosome 21, leading to trisomy 21. This results in the most common form of Down syndrome—complete trisomy.

One of the less common forms is translocation Down syndrome. In this case, a segment of chromosome 21 becomes attached to another chromosome, most commonly chromosome 14 or 15. The translocation form may, in some cases, be inherited from a parent, especially if one parent carries a balanced translocation. In such situations, the risk of having an affected child increases significantly. Therefore, genetic counseling and karyotype analysis are of great importance in translocation cases.

The mosaic form represents another variant of pathogenesis, in which chromosomal abnormalities occur during the early mitotic divisions of the embryo. As a result, some cells in the organism are normal, while others carry an extra copy of chromosome 21. Consequently, clinical manifestations in the mosaic form are generally milder, since not all cells are affected.

The excess of chromosome 21 leads to widespread cellular and tissue-level disturbances. The gene dosage effect causes significant alterations in the development of the central nervous system. Neuronal proliferation, migration, and differentiation are impaired, which negatively affects the formation of brain structures and synaptic connections. These abnormalities in the central nervous system result in delayed intellectual development, reduced cognitive abilities, and impaired motor skills.

In the pathogenesis of Down syndrome, the cardiovascular system is also significantly affected. The excess of chromosome 21 disrupts the normal development of the myocardium and blood vessels, resulting in congenital heart defects. In addition, delayed cellular proliferation and insufficient tissue differentiation lead to impaired cardiac function.

The metabolic and endocrine systems also undergo pathological changes in Down syndrome. Disruption of genetic balance at the cellular level slows metabolism, reduces thyroid gland function, and in some patients leads to disturbances in insulin regulation and other hormonal systems.

Disorders of the immune system are associated with insufficient development of immune cells due to the presence of an extra chromosome. As a result, patients have increased susceptibility to infections, with diseases tending to be more prolonged and recurrent.

Changes are also observed in the musculoskeletal system. Excess gene expression leads to reduced muscle tone (hypotonia), delayed growth, and impaired motor development. Skeletal development is also slowed, and some patients exhibit increased joint laxity.

Furthermore, the pathogenesis is closely associated with phenotypic characteristics. The characteristic facial features of Down syndrome, short stature, hypotonia, delayed intellectual



development, congenital heart defects, and other systemic abnormalities are all the result of trisomy 21 and underlying cellular genetic disturbances.

Thus, the pathogenesis of Down syndrome is a complex process involving chromosomal abnormalities and subsequent changes at the cellular, organ, and systemic levels, which together give rise to all clinical manifestations of the disease. These disturbances begin during embryonic development and persist throughout the individual's life, providing an explanation for the etiopathogenesis and clinical presentation of the condition.

### **Functional Changes in Down Syndrome**

Down syndrome has multifaceted clinical consequences affecting almost all body systems. These outcomes arise from genetic disturbances, chromosomal excess, and functional alterations at the cellular level.

#### **1. Neurological and cognitive consequences:**

The excess of chromosome 21 impairs the development of the central nervous system. As a result, neuronal migration and differentiation are delayed, leading to reduced intellectual development, limited memory and attention capacities, and delayed speech and language development. In some patients, the brain structure may differ slightly, with irregular formation of gyri and brain regions.

#### **2. Effects on the cardiovascular system:**

Congenital heart defects are highly prevalent in children with Down syndrome. The most common include atrial septal defect (a hole between the upper chambers of the heart), ventricular septal defect (a hole between the lower chambers), patent ductus arteriosus (failure of closure of the fetal vessel connecting the aorta and pulmonary artery), and Tetralogy of Fallot (a combination of multiple congenital heart defects). These abnormalities disrupt blood flow, increase cardiac workload, and lead to symptoms such as fatigue, pallor, and respiratory difficulties. In some cases, arrhythmias and blood pressure abnormalities may also occur. Therefore, timely medical evaluation, pharmacological treatment, and, when necessary, surgical intervention are required, significantly improving quality of life and survival.

#### **3. Effects on the musculoskeletal system:**

Hypotonia (reduced muscle tone) leads to delayed motor development. Children often acquire skills such as independent walking later than their peers. Increased joint laxity and abnormalities in the spine and limb development may also be present.

#### **4. Effects on metabolic and endocrine systems:**

The presence of an extra chromosome 21 slows metabolic processes. Some patients develop hypothyroidism, reduced insulin sensitivity, and an increased risk of diabetes. Nutritional difficulties and slowed gastrointestinal function are also observed.

#### **5. Immune system disorders:**

Due to underdevelopment of the immune system, patients are more susceptible to infections. Infectious diseases tend to recur frequently and have a prolonged course. In addition, weakened immune responses may contribute to the development of autoimmune disorders.



## 6. Effects on other organ systems:

- Eye and ear dysfunction: visual and hearing impairments may occur.
- Skin and hair structure: reduced skin elasticity and delayed hair growth.
- Hematological outcomes: some patients have an increased risk of developing leukemia and other blood disorders.

## 7. Social and psychological consequences:

Delayed intellectual development and limited speech abilities affect the patient's behavior, interpersonal relationships, and social integration. Therefore, early rehabilitation, physiotherapy, and speech therapy are of great importance in improving the patient's development and quality of life.

Thus, the consequences of Down syndrome are interrelated and complex, originating from genetic-based cellular abnormalities and spreading across all organ systems. Early detection of these outcomes and effective management can significantly improve patients' quality of life and independence.

## Diagnosis of Down Syndrome

Down syndrome is diagnosed in modern medicine at both prenatal (before birth) and postnatal (after birth) stages. The diagnostic process plays an important role in early detection of the condition, prevention of complications, and selection of appropriate medical management.

Prenatal diagnosis is performed during pregnancy and consists of several stages. Initially, screening methods are used to assess the risk of the condition. Ultrasound examination (USG) may reveal certain morphological features associated with Down syndrome, such as increased nuchal translucency, congenital heart defects, and skeletal abnormalities. In addition, maternal serum biochemical screening tests (including  $\beta$ -hCG, PAPP-A, and others) are used to estimate the risk of chromosomal abnormalities.

In recent years, a highly accurate non-invasive method known as NIPT (non-invasive prenatal testing) has been widely used. This method analyzes cell-free fetal DNA present in the maternal blood to detect the presence of trisomy 21.

If screening results indicate a high risk, invasive diagnostic methods are used to confirm the diagnosis. These include amniocentesis (analysis of amniotic fluid) and chorionic villus sampling. In these procedures, fetal cells are obtained and their karyotype is examined, allowing precise determination of chromosome number. Karyotype analysis is considered the "gold standard" for confirming Down syndrome.

Postnatal diagnosis is based on the clinical phenotypic features of the newborn. Physicians may make a preliminary diagnosis based on characteristic facial features, hypotonia, and a single transverse palmar crease. However, the definitive diagnosis is confirmed only through cytogenetic analysis (karyotyping).

Additional examinations are also important. For example, ECG and echocardiography are performed to detect cardiac defects, specialized tests are used to assess hearing and vision, and



hormonal analyses are conducted to evaluate endocrine function. These investigations help to identify complications early and determine a comprehensive treatment approach.

Thus, the diagnosis of Down syndrome requires a comprehensive approach. The combined use of prenatal screening, non-invasive and invasive genetic testing, as well as postnatal clinical and cytogenetic evaluations, enables accurate and early detection of the condition.

## **Prevention of Down Syndrome**

The prevention of Down syndrome cannot be fully guaranteed; however, modern medicine offers effective preventive measures aimed at reducing the risk of its occurrence and enabling early detection. Prevention is mainly based on the genetic nature of the disorder and is carried out through pregnancy planning, genetic counseling, and prenatal diagnosis.

One of the most important preventive approaches is genetic counseling. It is especially recommended in cases where a family has a child with a chromosomal abnormality or when chromosomal rearrangements (such as translocations) are identified in one of the parents. In such situations, consultation with a genetic specialist before pregnancy is essential. This helps to assess the risk of recurrence and provides appropriate medical recommendations.

Proper pregnancy planning also plays a significant role. The risk of trisomy 21 increases with maternal age; therefore, it is recommended to plan pregnancy during the optimal reproductive age. In addition, maintaining a healthy lifestyle, avoiding harmful habits, and minimizing exposure to radiation and toxic chemical substances are important general preventive measures.

Prenatal screening is one of the most effective preventive strategies. Ultrasound examinations and biochemical blood tests performed during pregnancy allow early detection of possible chromosomal abnormalities in the fetus. In recent years, non-invasive prenatal testing (NIPT) has been widely used, offering high accuracy in detecting the condition by analyzing fetal DNA in maternal blood.

If screening results indicate a high risk, invasive diagnostic methods—such as amniocentesis or chorionic villus sampling—are performed for definitive diagnosis. These procedures allow analysis of the fetal karyotype and precise determination of chromosome number.

Thus, the prevention of Down syndrome requires a comprehensive approach. Genetic counseling, proper pregnancy planning, and the use of modern prenatal diagnostic methods make it possible to detect the condition early and reduce the likelihood of its occurrence. This plays an important role in ensuring the birth of a healthy population.

## **Modern Treatment and Rehabilitation**

Although Down syndrome is a congenital genetic condition that cannot be completely cured, modern medical and rehabilitation approaches can significantly improve patients' quality of life, enhance social adaptation, and increase their level of independent functioning. Treatment



is mainly symptomatic and multidisciplinary, aimed at correcting disorders in various body systems.

One of the important directions of treatment is the correction of congenital anomalies. In particular, congenital cardiovascular defects (such as septal defects) are treated surgically. This significantly improves life expectancy and overall health status. In addition, if endocrine disorders such as hypothyroidism are detected, hormonal therapy is applied.

The rehabilitation process should begin at an early age and includes several components. Physiotherapy plays an important role in improving muscle tone, developing motor coordination, and forming basic motor skills. Speech therapy (logopedics) supports speech and language development and enhances children's communication abilities.

In addition, special pedagogical approaches and inclusive education systems support cognitive development. Individual educational programs, psychological support, and social adaptation training facilitate the integration of patients into society.

Medical follow-up is also essential. Patients should be regularly monitored by specialists such as cardiologists, endocrinologists, neurologists, and others. This allows early detection of complications and timely medical intervention.

Thus, modern treatment and rehabilitation of Down syndrome require a multidisciplinary approach. Early diagnosis, appropriate medical care, and comprehensive rehabilitation measures improve patients' quality of life and increase their social functioning and independence.

Down syndrome is one of the most common chromosomal abnormalities worldwide. On average, it occurs in approximately 1 out of 700–1000 live births, and about 3,000–5,000 children are born with Down syndrome globally each year. This incidence may vary depending on the country and the level of diagnostic capabilities.

The most important risk factor is maternal age. According to statistical data, the risk of Down syndrome is approximately 1:1500 at the age of 20, 1:1000 at the age of 30, 1:350 at the age of 35, 1:100 at the age of 40, and 1:30 at the age of 45. Thus, the risk of Down syndrome increases significantly with maternal age, highlighting the importance of pregnancy planning and early genetic counseling.

The distribution of Down syndrome types is also notable. The most common form is complete trisomy (~95%), in which three copies of chromosome 21 are present. The less common form is translocation (~3–4%), in which a segment of chromosome 21 is attached to another chromosome. The mosaic form (~1–2%) is characterized by chromosomal abnormalities present only in some cells, and clinical manifestations in this form are usually milder.

Congenital heart defects occur in approximately 40–50% of children with Down syndrome. The most common cardiac abnormalities include septal defects, patent ductus arteriosus, and Tetralogy of Fallot. In addition, intellectual development is usually mildly to moderately delayed, and speech and motor skills are typically affected.



Due to underdevelopment of the immune system, children with Down syndrome are 2–3 times more susceptible to infectious diseases, and the risk of developing leukemia is 10–20 times higher compared to the general population.

Life expectancy has significantly increased in recent years. In the 1980s, the average life expectancy was around 25 years, whereas with modern medical care, surgical interventions, and rehabilitation, the current average life expectancy of individuals with Down syndrome has increased to 50–60 years or more.

Thus, statistical data clearly demonstrate the prevalence of Down syndrome, its association with maternal age, distribution of forms, cardiac defects, intellectual development, immune system disorders, and life expectancy. These findings are highly important for genetic counseling, prevention, early diagnosis, and rehabilitation strategies.

**Conclusion:** Down syndrome is a genetic disorder caused by the presence of an extra copy of chromosome 21, leading to complex disturbances at the cellular, organ, and systemic levels. The etiology of the condition is primarily based on chromosomal nondisjunction during gamete formation, and less commonly involves translocation and mosaic forms. These genetic alterations impair the normal development of the central nervous system, cardiovascular system, musculoskeletal system, endocrine system, and immune system, resulting in intellectual developmental delay, congenital heart defects, hypotonia, and impaired nutritional and immune functions.

The clinical consequences of Down syndrome are extensive and significantly affect patients' quality of life and social adaptation. Therefore, early diagnosis and prevention are of great importance. Diagnosis is performed at both prenatal and postnatal stages; prenatal screening and NIPT are used for risk assessment, while amniocentesis and karyotype analysis provide definitive diagnosis. In the postnatal stage, diagnosis is based on phenotypic features and cytogenetic testing.

Preventive measures—including genetic counseling, pregnancy planning, consideration of maternal age, avoidance of toxic factors, and prenatal diagnostics—help reduce the risk of developing Down syndrome. Modern treatment and rehabilitation, including surgical correction of congenital heart defects, hormonal therapy, physiotherapy, speech therapy, special educational approaches, and social integration, significantly improve patients' quality of life.

Statistical data show that Down syndrome occurs in approximately 1 out of every 700–1000 live births worldwide, and the risk increases significantly with advancing maternal age.

The most common form is complete trisomy (~95%), followed by the translocation form (~3–4%) and the mosaic form (~1–2%). Congenital heart defects occur in approximately 40–50% of patients, susceptibility to infectious diseases is increased by 2–3 times, and the risk of developing leukemia is 10–20 times higher. In recent years, due to advances in modern medicine, the average life expectancy has increased to 50–60 years, which is associated with early diagnosis and effective rehabilitation.

Thus, Down syndrome is a complex genetic disorder, and its prevention, early diagnosis, modern treatment, and rehabilitation measures can significantly improve patients' quality of life



and level of independent living. These scientific data serve as a theoretical basis for first-year students in strengthening genetic and medical-biological knowledge and in understanding the clinical approach to this condition.

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