



GENETIC CAUSES OF DOWN SYNDROME AND EARLY DIAGNOSIS METHODS IN PEDIATRICS

Mamajonova Sarvinoz Toxirjon qizi

Kokand University, Andijan Branch Faculty
of Pediatrics, Group 25-04 Student:

Akramjonova Xalimaxon O'rmonbek qizi

Department of Clinical and Pathological Anatomy Instructor:

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Abstract

Down syndrome trisomy 21 is one of the most common chromosomal abnormalities, caused by the presence of an extra copy of chromosome 21. This genetic condition results in characteristic physical features, developmental delays, and varying degrees of intellectual disability. The underlying causes of Down syndrome include nondisjunction, translocation, and mosaicism, which disrupt the normal chromosomal segregation process during gametogenesis or embryonic development. This article provides an in-depth review of the genetic mechanisms that lead to Down syndrome and explores modern methods of early diagnosis used in pediatric and prenatal care. It also highlights the epidemiology, risk factors, and socio-medical importance of early detection. Early diagnosis plays a critical role in preventing complications, guiding parental counseling, and ensuring timely interventions that enhance the child's quality of life. Recent advances in genetics and molecular testing, including non-invasive prenatal testing NIPT and cytogenetic analyses, have significantly improved the accuracy and accessibility of early detection. Ultimately, integrating genetic understanding with pediatric practice not only helps in reducing diagnostic delays but also strengthens multidisciplinary approaches in managing children with Down syndrome.

Keywords

Down syndrome, Trisomy 21, genetic disorders, nondisjunction, translocation, mosaicism, early diagnosis, pediatrics, prenatal screening, cytogenetics, child development, genetic counseling.

Introduction

Down syndrome, also known as Trisomy 21, is the most common chromosomal disorder affecting live births worldwide. It occurs when a person has a full or partial extra copy of chromosome 21, which alters the course of development and causes the distinctive physical and intellectual characteristics associated with the condition. Although the syndrome was first described by the British physician John Langdon Down in 1866, the genetic basis of the disorder was not discovered until 1959, when Jérôme Lejeune identified the presence of an additional chromosome 21 in affected individuals. Since then, significant progress has been made in understanding the genetic mechanisms, diagnostic techniques, and management of Down syndrome within the field of pediatrics.

The prevalence of Down syndrome varies across populations, but on average, it occurs in approximately 1 out of every 700 live births. Factors such as advanced maternal age, chromosomal nondisjunction, and genetic translocations contribute to its occurrence. In the pediatric context, early detection of Down syndrome is crucial for timely medical intervention, family support, and developmental care planning. Advances in modern genetics, particularly

prenatal screening and non-invasive prenatal testing NIPT, have greatly improved the ability to diagnose the condition even before birth.

From a clinical perspective, children with Down syndrome often present with a range of features including hypotonia, distinct facial morphology, congenital heart defects, and developmental delays. Early and accurate diagnosis allows pediatricians and genetic counselors to provide individualized management strategies, improving the child's physical health and cognitive development outcomes. Moreover, understanding the genetic causes helps guide future research into prevention and therapeutic interventions. In recent decades, there has been a growing emphasis on integrating genetic research with pediatric care. By combining molecular genetics, cytogenetic testing, and prenatal diagnostics, healthcare professionals can detect chromosomal abnormalities earlier and with greater precision. This integration not only enhances early diagnosis but also strengthens family counseling, supports ethical decision-making, and fosters a multidisciplinary approach to child development and rehabilitation. This, studying the genetic causes of Down syndrome and exploring effective early diagnosis methods are essential components of modern pediatric practice. This knowledge enables clinicians to predict potential complications, design appropriate care strategies, and improve the overall quality of life for children affected by this genetic disorder.

Main body

Genetic Causes of Down Syndrome

Down syndrome is primarily caused by an error in chromosomal division known as nondisjunction, which results in an individual having three copies of chromosome 21 instead of the usual two. This abnormality leads to an overexpression of genes located on chromosome 21, disrupting the normal developmental processes. The extra genetic material affects various systems of the body, including the nervous, cardiovascular, and immune systems, resulting in the clinical features characteristic of the syndrome.

There are three major genetic types of Down syndrome:

Trisomy 21, Nondisjunction Type – This type accounts for about 95% of all cases. It occurs when a pair of chromosome 21 fails to separate during the formation of the egg or sperm, leading to an embryo with three copies of chromosome 21. Most cases of Trisomy 21 are sporadic and not inherited. The likelihood of this error increases with maternal age, particularly after the age of 35.

Translocation Type – Approximately 3–4% of cases result from a translocation, where part of chromosome 21 becomes attached to another chromosome, often chromosome 14. In this case, the total number of chromosomes remains 46, but there is extra genetic material from chromosome 21. Unlike the nondisjunction type, this form can be hereditary, meaning it can recur in families where one parent carries a balanced translocation.

Mosaic Type – this rare form arises when nondisjunction occurs in one of the early embryonic cell divisions, leading to two populations of cells: some with the normal 46 chromosomes and others with 47. The clinical manifestations tend to be milder compared to classical Trisomy 21, depending on the proportion and distribution of affected cells. The discovery of these genetic mechanisms has significantly improved our understanding of the syndrome's origin. Molecular cytogenetic techniques such as fluorescence in situ hybridization and karyotype analysis have become essential tools for confirming the diagnosis and identifying the specific chromosomal pattern. Recent research also focuses on identifying

specific genes on chromosome 21 that contribute to the phenotypic features of Down syndrome. For example, overexpression of genes like DYRK1A, APP, and SOD1 has been linked to neurodevelopmental delay, premature aging, and oxidative stress in affected individuals. These findings help scientists explore potential molecular therapies aimed at minimizing the effects of trisomy on brain function and overall development.

Epidemiology and Risk Factors

The global incidence of Down syndrome is estimated at 1 in 600–1000 live births, with slight regional variations depending on maternal health, genetic counseling availability, and prenatal screening programs. According to the World Health Organization WHO, approximately 3,000–5,000 infants are born with Down syndrome each year worldwide. In developing countries, where prenatal screening is less accessible, the prevalence tends to be higher. One of the strongest risk factors for Down syndrome is advanced maternal age. The risk of having a baby with Down syndrome increases significantly after the age of 35, reaching approximately 1 in 350 births, and continues to rise with age. This is due to an increased likelihood of nondisjunction during oogenesis. However, it is important to note that about 70–80% of children with Down syndrome are born to younger mothers, simply because younger women give birth more frequently.

Other risk factors include - paternal age over 40 years, which slightly raises the risk due to sperm cell mutation rates. Familial translocation carriers, where a parent has a balanced translocation involving chromosome 21. Environmental factors, such as exposure to ionizing radiation, infections, or toxins during early pregnancy. Epidemiological studies also show that Down syndrome affects all ethnic and socioeconomic groups equally, although survival rates and access to healthcare differ widely. In high-income countries, due to improved medical care and early intervention programs, the life expectancy of individuals with Down syndrome has increased dramatically—from less than 10 years in the 1960s to over 60 years today. The early identification of risk factors allows pediatricians and obstetricians to provide targeted genetic counseling, helping families understand the recurrence risks and make informed reproductive decisions. This approach reflects the growing importance of integrating genetic education into public health and pediatric practice.

Early Diagnosis Methods in Pediatrics

The early diagnosis of Down syndrome plays a vital role in modern pediatrics, as it allows healthcare professionals to initiate timely medical, developmental, and social interventions. Diagnostic strategies can be divided into two main categories: prenatal screening and postnatal confirmation.

Prenatal Screening

Prenatal screening aims to identify pregnancies at risk of Down syndrome before the baby is born. These tests are non-invasive and serve as an initial step before diagnostic confirmation. Maternal Serum Screening - this test measures specific biochemical markers in the mother's blood, including alpha-fetoprotein AFP, human chorionic gonadotropin hCG, and unconjugated estriol uE3. Abnormal levels of these substances can indicate a higher probability of chromosomal abnormalities. The "triple test" and "quadruple test" are commonly used between the 15th and 20th weeks of gestation. Though not definitive, they help stratify risk and guide further testing.

Ultrasound Examination

Ultrasound remains one of the most important non-invasive tools in prenatal care. Specific markers, such as nuchal translucency thickness, absent nasal bone, and cardiac anomalies, can suggest an increased risk of Trisomy 21. Ultrasound is typically performed between 11 and 14 weeks of pregnancy as part of first-trimester screening.

Non-Invasive Prenatal Testing NIPT

In recent years, NIPT has revolutionized prenatal diagnostics. This technique analyzes fragments of cell-free fetal DNA circulating in the mother's blood. NIPT can detect chromosomal abnormalities with over 99% sensitivity and specificity for Down syndrome. It can be performed as early as 10 weeks of gestation and poses no risk to the fetus. Despite its accuracy, a positive NIPT result still requires confirmation through invasive tests.

Diagnostic Tests

When a screening test indicates increased risk, diagnostic procedures are performed to confirm the presence of chromosomal abnormalities.

Chorionic Villus Sampling - CVS involves taking a small sample of placental tissue between the 10th and 13th weeks of pregnancy. The fetal cells are analyzed to determine the chromosomal pattern through karyotyping or FISH analysis.

Amniocentesis - this procedure, usually performed between 15 and 20 weeks, involves extracting a sample of amniotic fluid containing fetal cells. These cells are then cultured and analyzed for chromosomal anomalies. Though slightly invasive, amniocentesis remains a gold standard for confirming prenatal diagnosis.

Cordocentesis - in rare cases, fetal blood is obtained from the umbilical cord for genetic testing. This is typically used when other methods are inconclusive.

Postnatal Diagnosis

When Down syndrome is suspected after birth, diagnosis is confirmed through. Karyotyping - the most definitive test showing three copies of chromosome 21. FISH, Fluorescence In Situ Hybridization - a rapid test that can provide results within 24-48 hours. Chromosomal Microarray Analysis, CMA - detects subtle genetic imbalances, including partial trisomies and translocations. Early diagnosis not only provides clarity to families but also allows pediatricians to monitor and manage medical conditions from infancy, such as congenital heart defects, thyroid dysfunction, and hearing problems. Moreover, it facilitates genetic counseling, helping parents understand recurrence risks and make informed reproductive decisions.

Clinical Manifestations and Pediatric Management

Down syndrome presents with a wide spectrum of clinical features that vary from one individual to another. The condition affects multiple organ systems, necessitating a comprehensive and multidisciplinary approach to management in pediatrics.

Physical and Developmental Characteristics

Children with Down syndrome often exhibit distinctive facial and physical traits, including. Flat facial profile and nasal bridge Almond-shaped eyes with upward slant, small ears and mouth, short neck with excess skin folds, hypotonia, short stature and broad hands with a single palmar crease. In terms of neurodevelopment, affected children experience delayed motor milestones such as sitting, crawling, and walking. Speech and cognitive development are also delayed, although early intervention can significantly enhance learning and communication outcomes.

Associated Medical Conditions

Down syndrome is frequently accompanied by congenital and systemic disorders, including. Congenital heart defects. Gastrointestinal anomalies, such as duodenal atresia or Hirschsprung disease. Endocrine disorders, particularly hypothyroidism. Hematological issues, including transient myeloproliferative disorder and leukemia predisposition. Hearing and vision problems, often due to recurrent infections and anatomical differences. Sleep apnea and immune dysfunction. Comprehensive medical screening is therefore essential. Pediatricians typically perform echocardiography, thyroid function tests, audiometry, and ophthalmologic evaluations during infancy.

Pediatric Management and Interventions

The cornerstone of Down syndrome management lies in early and multidisciplinary intervention. This includes.

Medical management - regular health monitoring, timely treatment of infections, and surgical correction of congenital anomalies.

Developmental therapy - early physiotherapy, speech therapy, and occupational therapy to improve motor, language, and social skills.

Educational support - tailored educational programs adapted to the child's cognitive level promote inclusion and self-sufficiency.

Nutritional care - balanced diet and weight management to prevent obesity, which is common in adolescence and adulthood.

Parental education and counseling - equipping parents with knowledge and emotional support to manage day-to-day challenges.

With these interventions, children with Down syndrome can lead fulfilling lives, attend school, and participate in community activities. The role of the pediatrician extends beyond clinical care to advocating for social inclusion and early developmental support.

Psychological and Social Aspects of Early Intervention

Down syndrome not only affects physical development but also has profound psychological and social implications for both the child and the family. Therefore, pediatric management must consider mental health, emotional resilience, and family dynamics.

Parental Reactions and Adaptation

The birth of a child with Down syndrome can evoke a range of emotional responses — shock, denial, guilt, and eventually acceptance. Early counseling is essential to help families adjust and build realistic expectations. Parents benefit from meeting other families with similar experiences and participating in support groups, which reduce stress and feelings of isolation.

Child Development and Social Inclusion

Children with Down syndrome are capable of forming meaningful social relationships and achieving educational milestones when provided with the right environment. Inclusive education systems, which integrate children with and without disabilities, foster empathy and confidence. Regular interaction with peers enhances language skills, emotional stability, and cognitive progress.

Psychological Interventions

Early psychological support focuses on. Behavioral therapy - to address attention difficulties or stubbornness. Speech-language therapy - to enhance communication. Cognitive stimulation programs - to promote problem-solving and memory. Moreover, emotional well-

being must be prioritized during adolescence, when individuals may face identity challenges and social barriers.

Social Integration and Long-Term Outlook

In modern pediatric practice, emphasis is shifting from mere survival to quality of life. Adults with Down syndrome increasingly participate in employment, community life, and independent living. Societal awareness and legal support systems—such as inclusive education policies and employment programs—are vital for ensuring dignity and equality. Research shows that early diagnosis, combined with family-centered care, significantly improves psychosocial adaptation and self-sufficiency in individuals with Down syndrome. Therefore, pediatricians, educators, and policymakers must work collaboratively to create a sustainable and inclusive environment. In conclusion, understanding the genetic mechanisms, epidemiological patterns, and diagnostic advancements of Down syndrome forms the foundation of effective pediatric care. Early detection through NIPT and cytogenetic analysis allows for prompt medical and psychosocial interventions. Furthermore, ongoing collaboration between medical professionals, families, and society ensures that individuals with Down syndrome can reach their full developmental potential and live meaningful lives.

Conclusion

Down syndrome Trisomy 21 remains one of the most well-studied and socially significant genetic disorders in modern pediatrics. Its genetic basis—primarily caused by nondisjunction, translocation, or mosaicism—reveals the complexity of human chromosomal behavior and the delicate balance of genetic development. The discovery of chromosome 21's role not only transformed our understanding of hereditary disorders but also laid the foundation for molecular genetics and prenatal diagnostics. Today, the combination of genetic science and pediatric medicine has made early detection of Down syndrome more accurate and accessible than ever. Non-invasive prenatal testing NIPT, ultrasound screening, and cytogenetic methods such as FISH and karyotyping enable clinicians to confirm the diagnosis early in pregnancy. This early recognition allows families to prepare emotionally and medically, while pediatricians can initiate timely interventions that prevent complications and support optimal development. From a clinical standpoint, Down syndrome is associated with multiple systemic conditions—cardiac, endocrine, gastrointestinal, and neurological—which require a multidisciplinary approach. The pediatrician's role extends beyond treating physical symptoms; it encompasses coordinating therapies, counseling families, and advocating for inclusive education and social integration. Early developmental programs, physiotherapy, speech and occupational therapies, and parental education are essential to maximize each child's potential. When supported by compassionate care and an inclusive environment, individuals with Down syndrome can achieve remarkable progress, participate actively in society, and live longer, healthier, and more fulfilling lives than ever before. Ultimately, understanding the genetic causes and improving early diagnosis methods in pediatrics not only strengthen clinical practice but also embody a broader humanistic mission — to value diversity, promote dignity, and empower every child to reach their full potential.

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