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Review

The Role of NIPT and the DYRK1A Gene in the Prenatal Diagnosis of Down Syndrome: Sleep Disorders, Melatonin, and Psychopharmacological Approaches

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ABSTRACT

Down syndrome (DS) is one of the most common genetic anomalies associated with trisomy 21, with a clinical spectrum ranging from congenital heart defects to cognitive impairment. In recent years, non-invasive prenatal testing (NIPT) has become an important tool in prenatal diagnosis due to its high sensitivity and specificity. However, the molecular basis of DS cannot be explained solely by chromosomal excess; overexpression of critical genes, particularly dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A), amyloid precursor protein, superoxide dismutase 1, and regulator of calcineurin 1, plays a decisive role in neurodevelopmental disorders, immune dysregulation, and neurodegenerative processes. DYRK1A is associated not only with synaptic plasticity and cognitive functions but also with sleep disturbances through its effects on circadian rhythm and melatonin metabolism. In this context, melatonin therapy emerges as a promising pharmacological approach for improving both sleep and cognitive functions in DS. This review discusses the significance of NIPT in the prenatal diagnosis of DS and examines the molecular mechanisms linking the DYRK1A gene to sleep regulation, while also addressing potential psychopharmacological interventions.

Keywords: Down syndrome, DYRK1A, melatonin, NIPT, psychopharmacology, sleep disorders.

One of the most frequently observed congenital genetic abnormalities is Down syndrome (DS). Down syndrome results from the presence of an extra copy of chromosome 21 (trisomy 21). While the general population has 46 chromosomes, individuals with DS have a total of 47 chromosomes. This additional genetic material leads to numerous clinical manifestations, including intellectual disability, congenital heart diseases, immune dysregulation, and gastrointestinal anomalies.[1]

Immune system dysregulation (autoimmune diseases) in individuals with DS manifests as increased susceptibility to infections, a higher prevalence of autoimmune disorders (e.g., thyroiditis, celiac disease), and functional impairments of immune cells.[2] Gastrointestinal anomalies include congenital and functional disorders such as duodenal atresia (obstruction of the duodenum), Hirschsprung disease (a developmental defect of enteric nerve cells), gastroesophageal reflux, and chronic constipation.[3]

Nearly half of infants with DS have congenital heart disease. The most common defects include atrioventricular septal defect (42%), ventricular septal defect (22%), and atrial septal defect (16%). An atrioventricular septal defect results from incomplete development of the wall between the atria and ventricles, leading to abnormal blood flow between the chambers. A ventricular septal defect is characterized by a hole in the wall separating the ventricles, whereas an atrial septal defect involves a hole in the septum between the atria. In recent years, a decrease in the prevalence of severe cardiac defects has been observed.[4]

The primary reasons for this decline include advances in prenatal diagnostic methods such as ultrasound imaging, fetal echocardiography, and non-invasive prenatal testing (NIPT); the termination of some pregnancies when severe anomalies are identified; and significant improvements in surgical techniques and neonatal care for affected newborns.[5]

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The risk of leukemia in children with DS is increased by 46- to 83-fold compared with the general population. Mortality is particularly higher during the early years of life, especially in the 0-4 age group. The risk of developing acute megakaryoblastic leukemia is markedly elevated in children with DS, occurring hundreds of times more frequently than in other children. In addition, pneumonia and other severe respiratory infections occur more often and substantially contribute to increased mortality.[6]

The life expectancy of individuals with DS is generally shorter, with an elevated risk of mortality during childhood, particularly between ages 0 and 4. The primary contributors to this increased risk are congenital heart diseases and immune system deficiencies. From 1980 to 2021, the global number of deaths among children and adolescents with DS decreased by approximately 22.8% (from 26,950 to 20,810). During the same period, the mortality rate declined from 1.31 to 0.79 per 100,000 individuals.[1,7]

Research on sex distribution in DS shows variability depending on biological and demographic factors. Overall, the prevalence of DS has been reported to be slightly higher in males. However, recent studies suggest a potential association between maternal age and the sex ratio of children born with DS. Pan et al.[8] reported that the proportion of male infants with trisomy 21 rises with increasing maternal age, while a higher proportion of female infants is observed among younger mothers. These results indicate that DS is not simply a chromosomal aneuploidy but a complex biological condition influenced by the interplay between maternal age and sex-related factors.

Mortality rates associated with DS vary according to the level of the sociodemographic index (SDI). In regions with low SDI, death rates remain high, with an increase reported in sub-Saharan Africa. In contrast, substantial declines have been observed in East Asia, South Asia, and North Africa. While mortality rates have generally decreased in most high-SDI countries, increases in adolescent deaths have been reported in some countries, including Poland, the United Kingdom, New Zealand, Australia, and Canada. Recent analyses also indicate that DS-related mortality rates in China have declined more rapidly than the global average and that there is a strong association between SDI level and mortality.[1,9]

In a study by Tu et al.[9], which analyzed global and Chinese data, it is projected that mortality rates and disease burden associated with DS will continue to decline in the coming years. Using a Bayesian age-period-cohort model-a statistical method that analyzes trends simultaneously across age groups, time periods, and birth cohorts to make future projections-the forecasts indicate a global decrease in DS prevalence and mortality rates between 2022 and 2036. However, this decline is expected to be slower in low-SDI regions, and the risk of death in the 0-4 age group will remain high. Therefore, future strategies should prioritize interventions during early childhood.[9,10]

The Role of Prenatal Diagnosis and NIPT in Down Syndrome

Methods used for the prenatal diagnosis of DS are of great importance for pregnancy management. Although conventional screening methods have long been considered the standard approach, NIPT has made significant advances over the past decade. The NIPT, which analyzes cell-free fetal DNA in maternal blood, has become a reliable option for assessing the risk of DS due to its high sensitivity and specificity. According to the systematic review by Sebire et al.,[11] the integration of NIPT into prenatal screening programs has reduced the need for invasive tests in many countries, influenced pregnancy outcomes, and demonstrated uptake rates ranging from 20% to 93%. These findings indicate that NIPT stands out not only for its diagnostic accuracy but also for its role in prenatal decision-making processes. Non-invasive prenatal testing is performed from the 10th week of pregnancy by analyzing cell-free fetal DNA (cffDNA) present in a maternal venous blood sample. The cffDNA isolated from plasma is examined using next-generation sequencing (NGS) or single-nucleotide polymorphism-based methods. Bioinformatic analyses assess copy number variations in target chromosomes, such as chromosome 21, to detect potential trisomies. The results are reported as a risk assessment, and in cases requiring definitive diagnosis, confirmation is performed using invasive methods such as amniocentesis or chorionic villus sampling. This process is safer compared with invasive procedures and minimizes the risk of complications for both the mother and the fetus.[12] Currently, cffDNA isolation is mostly performed using magnetic bead–based automated systems. These systems efficiently separate fetal DNA from maternal DNA, reducing the risk of contamination. Additionally, liquid handling robots such as the Hamilton Microlab STAR or Tecan Freedom EVO automate pipetting procedures, minimizing human error and enhancing the reproducibility of analyses.[13]

The isolated cffDNA is prepared for analysis during the library preparation stage. In this process, DNA fragments are generated, adapter sequences are added, and PCR amplification is performed. Kits such as Illumina TruSeq or NEBNext Ultra II are commonly used. The prepared libraries are assessed using quality control instruments (e.g., Agilent Bioanalyzer, Qubit) and then loaded onto NGS platforms. These methods provide reliable results for DS screening due to their high sensitivity and specificity.[14]

When evaluating the clinical performance of NIPT, sensitivity for DS (trisomy 21) has been shown to approach 99%, with false-positive rates lower than those of other biochemical screening methods. These high accuracy rates enable NIPT to be used as a reliable screening tool in early pregnancy. Furthermore, when combined with ultrasound findings, NIPT enhances screening accuracy and provides significant support to clinicians in pregnancy management.[15]

Non-invasive prenatal testing is used not only for the detection of trisomy 21 but also for screening trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome), and sex chromosome abnormalities. However, studies have shown that sensitivity and specificity are somewhat lower for these aneuploidies compared with DS. Nevertheless, NIPT is considered superior to conventional screening methods for Edwards and Patau syndromes. Additionally, applications for detecting rare chromosomal disorders and microdeletions are being explored, although there is not yet a consensus on their clinical accuracy.[16]

The implementation of NIPT is influenced not only by technical accuracy but also by cost, accessibility, and ethical considerations. High costs limit the use of the test in low- and middle-income countries, whereas in high-income countries, NIPT is increasingly becoming routine. Moreover, the impact of positive results on pregnancy termination decisions raises ethical debates at both clinical and societal levels. Differences in healthcare policies, cultural values, and legal regulations across countries create significant variations in NIPT utilization. Therefore, NIPT is regarded not only as a biomedical innovation but also as a development with ethical and socio-political dimensions.[17]

Genetic Factors in Down Syndrome and the Role of the DYRK1A Gene

Not all genes on chromosome 21 contribute equally to the phenotype in trisomy 21; some genes are located within the "critical region" and exert a determining effect. Overexpression of these genes disrupts fundamental biological balances during developmental processes, leading to clinical manifestations across different organ systems. The nervous system, cardiovascular structures, and immune responses are particularly affected by these imbalances. Therefore, the distribution of genetic dosage plays a key role in explaining the phenotypic variability of DS.[18]

The phenotypic variability observed in DS arises from differences in gene-dosage effects among individuals. In some cases, cognitive impairments are predominant, whereas in others, cardiac or gastrointestinal anomalies are more pronounced. This indicates that genes interact with environmental factors and epigenetic mechanisms. Therefore, understanding DS requires not only detecting chromosomal excess but also analyzing the combined effects of gene dosage and environmental interactions.[19]

Recent studies have shown that overexpression of genes on chromosome 21 disrupts fundamental molecular mechanisms such as signal transduction pathways, protein phosphorylation, and oxidative stress. These alterations compromise cellular homeostasis, creating the basis for the development of DS-specific clinical manifestations. The role of critical genes that directly affect these mechanisms is particularly noteworthy in understanding the molecular underpinnings of DS. Therefore, investigating these mechanisms contributes not only to explaining clinical variability but also to the development of novel therapeutic approaches.[20]

Although there are hundreds of genes on chromosome 21, not all exert the same phenotypic effect. Genes located within the "critical region" are particularly important in determining the clinical variability of DS. Among the most studied genes are amyloid precursor protein (APP), superoxide dismutase 1 (SOD1), regulator of calcineurin 1 (RCAN1), and dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A). Overexpression of these genes has been associated with neurological disorders, immune system dysfunction, and metabolic imbalances. Therefore, these genes are considered a starting point for understanding the molecular basis of DS.[21]

Amyloid precursor protein is one of the most well-known genes located on chromosome 21 and plays a crucial role in Alzheimer-like neurodegenerative processes. In individuals with DS, overexpression of

APP leads to the accumulation of amyloid-β in the brain, contributing to early cognitive decline. This represents one of the key mechanisms explaining the high susceptibility of DS individuals to Alzheimer's disease. Therefore, APP is considered a central gene at the intersection of DS and neurodegenerative processes.[22]

The SOD1 gene is responsible for the production of the superoxide dismutase enzyme and plays a critical role in regulating oxidative stress. In trisomy 21, overexpression of this gene leads to the accumulation of reactive oxygen species, increasing cellular damage. This contributes to functional impairments in both the nervous system and cardiovascular tissues. Considering the role of oxidative stress in the pathophysiology of DS, SOD1 is regarded as one of the key molecular targets.[23]

Regulator of calcineurin 1 disrupts intracellular calcium homeostasis and stress responses by inhibiting the calcineurin signaling pathway. In DS, overexpression of RCAN1 leads to imbalances in immune system function and nervous system development. Additionally, this gene is suggested to play a role in the vascular system and may contribute to atherosclerotic processes. The multifaceted effects of RCAN1 provide an important molecular link in explaining the systemic complications of DS.[24]

Among these genes, DYRK1A is one of the most notable. DYRK1A is a protein kinase located within the critical region of chromosome 21 and is capable of phosphorylating both tyrosine and serine/threonine residues. It plays a central role in neuronal proliferation, differentiation, and synaptic maturation. Overexpression of DYRK1A has been directly associated with synaptic plasticity impairments, cognitive delay, and Alzheimer-type tau pathologies. Therefore, DYRK1A is considered one of the most critical genes for understanding the neurological features of DS.[25]

DYRK1A functions as a key regulator of the cell cycle and neuronal differentiation in normal brain development. Overexpression of this gene disrupts the timely division of neural cells, leading to a reduced neuronal population. This is directly associated with microcephaly and decreased cerebral volume, which are commonly observed in individuals with DS. Therefore, DYRK1A emerges as one of the primary genetic determinants of structural brain differences in DS.[26]

In addition, DYRK1A exerts indirect effects on neurotransmitter systems. It regulates learning, memory, and motivation processes by phosphorylating synaptic proteins, particularly within dopaminergic and glutamatergic pathways. Overexpression disrupts these neurotransmitter balances, forming the molecular basis of cognitive and behavioral impairments in DS. These effects may also help explain why psychoactive drugs elicit different response profiles in individuals with DS.[27]

DYRK1A also plays a critical role in neurodegenerative processes associated with tau protein and APP. Hyperphosphorylation of tau is a well-known mechanism of Alzheimer-type neurodegeneration and is observed at an early age in DS. DYRK1A accelerates this process, contributing to the concurrent development of both tau and amyloid pathologies. Therefore, DYRK1A is considered one of the strongest molecular candidates explaining the increased susceptibility to Alzheimer's disease in DS.[28]

The effects of DYRK1A are not limited to the nervous system; they are also linked to circadian rhythm and melatonin metabolism. Its interactions with pineal gland functions and biological clock genes provide a genetic basis for the sleep disturbances commonly observed in DS. Dysregulation of melatonin synthesis adversely affects both cognitive performance and mood. Therefore, DYRK1A is considered a central hub integrating sleep, neurodegeneration, and behavioral phenotypes in DS.[29]

Sleep disturbances are an important yet often overlooked component of the phenotype in individuals with DS. Obstructive sleep apnea, circadian rhythm disruptions, and irregularities in melatonin secretion have been frequently reported. These sleep problems are directly associated with reduced cognitive performance, attention deficits, and exacerbation of behavioral issues. Recent studies emphasize that sleep disturbances are among the factors most significantly affecting quality of life in DS.[30]

Melatonin is the primary regulator of the sleep-wake cycle and is secreted by the pineal gland. In individuals with DS, disruptions in melatonin metabolism have been observed, with irregular nocturnal melatonin levels that disturb sleep architecture. Additionally, low melatonin levels have been associated with increased oxidative stress and neurodegenerative processes. Therefore, melatonin deficiencies contribute not only to sleep disturbances but also to accelerated aging processes in DS.[31]

Overexpression of the DYRK1A gene can disrupt

circadian rhythms by interacting with biological clock genes that regulate melatonin synthesis. This mechanism may explain common sleep disturbances in DS, such as difficulty falling asleep, frequent nighttime awakenings, and excessive daytime sleepiness. Furthermore, the indirect effects of DYRK1A on serotonin-melatonin pathways reinforce the neurological basis of these sleep problems. Thus, genetic and biochemical factors reveal the intertwined nature of sleep disturbances in DS.[32,33]

From a pharmacological perspective, melatonin supplementation is one of the most extensively studied approaches in individuals with DS. Clinical studies have shown that melatonin use shortens sleep onset latency, increases total sleep duration, and improves behavioral regulation. Additionally, due to its antioxidant properties, melatonin may reduce oxidative stress burden and provide a neuroprotective effect. Therefore, melatonin therapy is considered a promising intervention for both sleep and cognitive functions in DS.[34]

However, pharmacological approaches are not limited to melatonin. Benzodiazepines, antihistamines, and certain antidepressants can also be used to manage sleep problems in individuals with DS. These drugs, however, may have more pronounced side effect profiles. Cognitive decline, daytime drowsiness, and risk of dependence should be carefully considered. Therefore, current research recommends combining low-dose melatonin with behavioral interventions as the safest and most effective strategy.[35,36]

In conclusion, this review highlights that DS is not merely a result of chromosomal excess; critical genes, particularly DYRK1A, play a fundamental role in shaping phenotypic variability. The clinical success of NIPT has enhanced the reliability of prenatal diagnosis and reduced the need for invasive procedures. Overexpression of DYRK1A exerts a broad spectrum of effects, ranging from neurodegenerative processes to circadian rhythm disruptions, and its association with melatonin metabolism explains the genetic basis of the sleep disturbances commonly observed in DS. Melatonin therapy emerges as a promising approach for improving both sleep and cognitive functions; however, pharmacological strategies should be tailored by considering individual differences and side effect profiles. In the future, advanced screening methods such as NIPT and gene-editing technologies like CRISPR/Cas9 may enable the development of more targeted interventions addressing the genetic basis of DS. Thus, a comprehensive evaluation of genetic, molecular, and clinical dimensions will pave the way for substantial advancements in both early diagnosis and therapeutic strategies for DS.

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