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A COMPREHENSIVE REVIEW OF DOWNS SYNDROME

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ABSTRACT:

The most common viable autosomal trisomy and the primary genetic cause of intellectual disability globally is Down syndrome (DS), also known as trisomy 21. Although inherited translocations and mosaicism also contribute to its genetic variety, this disorder results from a dosage imbalance brought on by an extra copy of chromosome 21, which is frequently produced by maternal age-related meiotic nondisjunction. In addition to multisystem involvements like congenital heart problems, early-onset Alzheimer's disease, and an elevated risk of leukaemia, DS is typified phenotypically by unique craniofacial traits such epicanthic folds and a flat nasal bridge. The Gene Dosage Imbalance, Amplified Developmental Instability, and Critical Region hypotheses explain pathogenic pathways by emphasising the involvement of particular genes such as DYRK1A and DSCAM in neurodevelopmental and cardiac outcomes. Non-invasive prenatal testing (NIPT) and postnatal karyotyping are

examples of modern diagnostic frameworks that have revolutionised early detection. Meanwhile, multidisciplinary management through speech-language and physical therapies has greatly improved quality of life and increased life expectancy to an average of 55 years. The complex genotype-phenotype correlations and genetic mechanisms of Down syndrome are covered in this article along with the main maternal and genetic risk factors, current prenatal and postpartum diagnostic procedures, and key therapeutic approaches used in clinical management.

INTRODUCTION:

The most prevalent viable autosomal trisomy, Down syndrome, is the primary hereditary reason for intellectual impairment and is triggered by an extra copy of chromosome 21. [1]

John Langdon Down, an English physician, first identified Down syndrome's unique set of physical and developmental characteristics in 1866. Trisomy 21, another name for Down syndrome, is the most prevalent viable autosomal trisomy and the primary genetic cause of intellectual disability. It is characterised by a unique constellation of physical characteristics, developmental abnormalities, and multisystem involvement and results from an extra copy of chromosome 21. [2] Congenital defects and neurodevelopmental abnormalities affecting several organ systems are common in people with Down syndrome. [3] People with Down syndrome still confront particular health issues throughout their lives, despite the fact that survival and life expectancy have significantly increased over the past few decades due to advancements in medical care. [4] Down syndrome (DS), or Trisomy 21, is one of the most prevalent genetic causes of intellectual disability worldwide. Its occurrence is notably influenced by maternal age, with incidence rates varying across different populations between 1 in 319 and 1 in 1000 live births. [5] While recent medical advancements have significantly increased life expectancy now averaging around 55 years in developed countries the condition remains characterized by high genetic complexity and a diverse range of physical and medical phenotypes. [6]

The dosage imbalance of genes on chromosome 21 is a common cause of the distinct range of health problems that people with Down syndrome frequently experience.[7]

One of the main causes of intellectual disability is Down syndrome, and millions of people with this condition deal with a variety of health problems, including

- **Neurological and Cognitive:** The majority of people struggle with memory and learning. Notably, the triplication of the APP gene is frequently associated with a markedly increased risk for early-onset Alzheimer's disease (AD). [8]
- **Cardiovascular:** Congenital heart disease (CHD), with atrioventricular septal defects (AVSD) being the most prevalent, affects about 50% of newborns with Down syndrome.
- **Haematological:** Leukaemia, particularly Acute Megakaryoblastic Leukaemia (AMKL) and Acute Lymphoblastic Leukaemia (ALL), is ten to twenty times more likely to occur. [9]
- **Gastrointestinal:** This demographic is far more likely to have conditions like duodenal stenosis and Hirschsprung disease (HD), which results in intestinal blockage. [10]

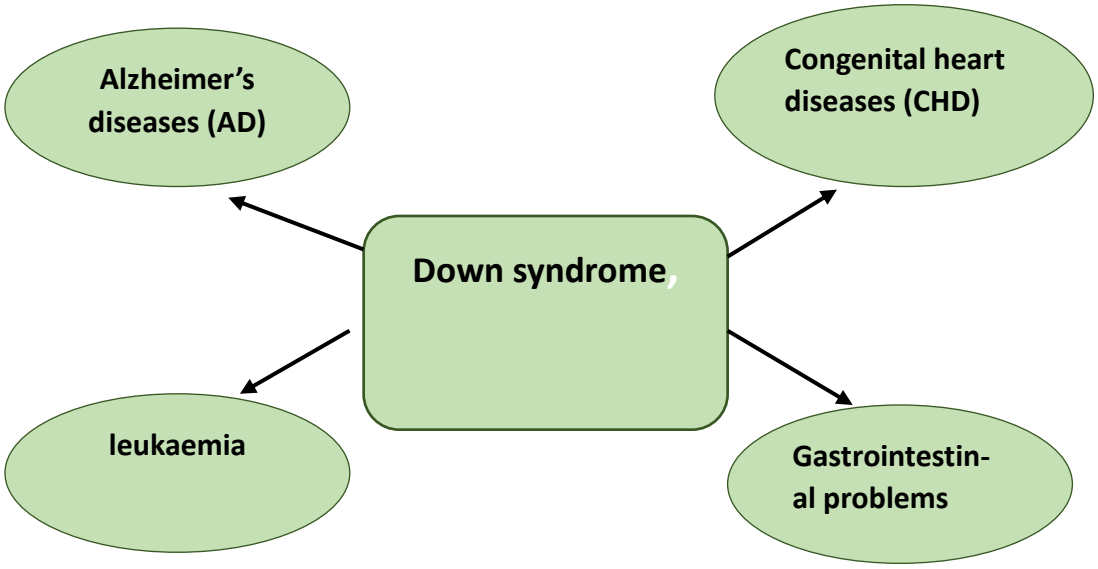

Fig1: Numerous disorders linked to Down syndrome. [11]

Genotype-Phenotype Correlations:

➢ **Physical and Neonatal Indications**

The majority of people with DS have certain dysmorphic traits that are identifiable from birth, such as:

- **Features of the face** include a flat face, epicanthic folds (upper eyelid skin folds), brachycephaly (flattened back of the head), and a flat nasal bridge.
- **Oral/Cranial:** A tiny mouth with small ears and a large, projecting tongue.
- **Extremities:** Broad hands with a prominent sandal gap between the first and second toes and a single transverse palmar crease (commonly referred to as a Simian fold).

- **Musculoskeletal:** excessive flexibility and hypotonia (low muscle tone) Genetic Variations [12]
- **Depending on the particular genetic aetiology, these traits' existence and severity may differ:**
- **Trisomy 21 (90–95%):** The "full" or primary form in which chromosome 21 is present in three copies per cell.
- **Mosaicism (2–4%):** A situation in which certain cell lines are euploid (normal), while others are trisomic. A milder manifestation of the trait may occasionally result from this.
- **Translocation (2–4%):** The outcome of chromosome 21 rearrangement**.** [13]

The additional genetic material from Chromosome 21 (HSA21) is present in every person with DS, however the way those genes "express" themselves varies greatly. This variant is caused by the "Gene Dosage Effect," in which the body's delicate balance of protein creation is upset by having three copies of a gene rather than two. [14]

➢ **Hereditary Mechanism:**

Three main scientific theories that describe how an additional copy of chromosome 21 (Hsa21) causes particular clinical features characterise:

- **The genotype-phenotype association in Down syndrome.** According to the Gene Dosage Imbalance Hypothesis, over-expression and functional abnormalities result directly from a 1.5-fold increase in the "copy number" of genes**.** [15]
- **The Amplified Developmental Instability Hypothesis**, on the other hand, contends that this additional genetic material results in a global, non-specific imbalance that disrupts gene regulation across the genome.[16]
- **The Critical Region Hypothesis**, which identifies particular segments known as Down Syndrome Critical Regions (DSCR)—particularly a 3.8 to 6.5 Mb area on $21q22$—as being responsible for fundamental characteristics like intellectual disability, congenital heart defects (CHD), and craniofacial abnormalities, is central to these theories. Certain "candidate genes" are crucial in various areas: DSCAM is critical for the formation of neural networks and is associated with a higher risk of cardiac abnormalities, whilst DYRK1A and RCAN1 are critical for brain development and neurocognitive performance. In the end, studies employing human data and mouse models indicate that several crucial regions and genes interact to

produce the varied and changeable phenotype observed in the Down syndrome community, rather than a single region being accountable for every symptom. [18,17,18,19]

RISK FACTORS:

- **Advanced maternal age:** A known risk factor for Down syndrome is the advanced age of the mother. The prevalence of Down syndrome rises with age in women. [20]

The risk exists at any age, but after the age of 35, it greatly increases. Although the exact cause of this correlation is unknown, the ageing process of eggs in the ovaries is thought to be involved. Women are more likely to experience chromosomal mistakes during meiosis as they age, which can result in the development of eggs with an additional copy of chromosome 21. [21]

Down syndrome runs in the family:

It raises the possibility of having a child with the illness. The likelihood of producing a child with Down syndrome is increased if a parent has a translocation, which is a rearrangement of genetic material between chromosomes. [22] Translocations can happen on their own during the development of reproductive cells or they might be inherited from a parent. For families with a history of Down syndrome to appropriately determine the risk, genetic counselling is crucial. [23]

Previous Down syndrome history:

The likelihood of having another child with Down syndrome is higher for couples who have already had a child with the disorder. Depending on the kind of Down syndrome the prior child had, there are different risks. For example, there is little chance of a recurrence if the prior child had trisomy 21, a non-inherited form of Down syndrome. However, there is a greater chance of recurrence if the child had the genetic form (translocation Down syndrome). [24]

Some genetic differences:

There is evidence linking specific genetic variants to a higher incidence of Down syndrome. For example, compared to those with full trisomy 21, people with mosaic Down syndrome, in which only a portion of the body's cells have an extra copy of chromosome 21, may be less likely to experience physical and cognitive deficits. The chance of having a child with Down

syndrome can also be increased by other uncommon genetic abnormalities, such as Robertsonian translocations. [25]

Environmental influences: Although genetics is the main cause of Down syndrome, various environmental factors may also be involved. Nevertheless, there is scant and conflicting data connecting environmental influences to Down syndrome. It has been suggested that exposure to specific chemicals or poisons, such as radiation or specific drugs, during pregnancy increases the chance of DS. [26]

Diagnosis:

Pregnancy or the early postpartum period are two possible times for diagnosis.

1. Prenatal Examinations

➢ **Screening tests:** They do not offer a conclusive diagnosis, but they do assess the risk.

- **First Trimester:** Combines a nuchal translucency ultrasound, which detects fluid at the back of the baby's neck, with a blood test to measure PAPP-A and hCG.
- **Second Trimester:** Four chemicals are measured by a "quad screen" blood test (AFP, oestriol, hCG, and inhibin A).
- **Cell-free DNA (NIPT):** This extremely precise blood test, which is available starting at 10 weeks, examines the mother's blood for foetal DNA.[27,28,29,30]

➢ **The diagnostic test:**

- **Chorionic Villus Sampling (CVS):** The placenta (usually 10–13 weeks) is used to extract cells.
- **Amniocentesis:** This procedure involves testing a sample of amniotic fluid, usually after 15 weeks.[31,32]

2. Postpartum Evaluation:

- **Physical Exam:** Based on physical characteristics, such as weak muscle tone, a single palmar crease, or upward-slanting eyes, doctors frequently suspect Down syndrome from birth.
- **Karyotype Test:** To determine whether the newborn has an extra copy of chromosome 21, a blood sample is drawn from them.[33,34]

Treatment and Management:

There is no "cure" for Down syndrome; instead, co-occurring medical issues are managed and developmental milestones are supported.

1. Early Intervention (Birth to Age 3):

For people with Down syndrome to thrive and become independent, early intervention and ongoing therapy are crucial. Below is a synopsis of the main therapy modalities:

- **Speech-language therapy:** Speech-language therapy aims to improve communication deficits by strengthening muscles and imitating sounds (often with the help of nursing). In order to close the gap between understanding and speaking, therapists frequently use alternate methods, such as sign language or graphics, before moving on to more complex dialogue and reading comprehension. [35]
- **Occupational therapy:** Improves day-to-day functioning by teaching self-care techniques including eating and dressing. In addition to helping with vocational training and job identification during adolescence, therapists offer adaptive equipment (such as specialised grips) to increase productivity. [36]
- **Behavioural and emotional therapies:** Offer coping mechanisms for dissatisfaction brought on by mental health issues like ADHD or communication difficulties. These treatments emphasise training constructive coping strategies and social reactions while figuring out the "why" behind particular behaviours.[37]

2. Health Care Throughout Life:

Regular testing for common related health concerns is necessary for people with Down syndrome:

- **Heart Health:** An echocardiography is typically performed at birth; around 50% of people are born with congenital heart abnormalities.
- **Thyroid Function:** To monitor for hypothyroidism, yearly blood tests are advised.
- **Vision and Hearing:** Regular examinations to check for hearing loss, ear infections, and cataracts.
- **Sleep:** Since facial structure can affect breathing, screening for obstructive sleep apnoea is routine. [38,39]

CONCLUSION:

Down syndrome is a complicated genetic disorder that continues to be the leading inherited cause of intellectual disability worldwide. As discussed in this article, the disorder stems from

the Trisomy 21 genotype, in which normal biological development is disrupted by a gene dosage imbalance, notably involving an extra copy of chromosome 21. We have explored the genetic processes, such as the Gene Dosage and Critical Region hypotheses, that account for these clinical presentations, as well as the specific physical and neonatal markers, such as hypotonia and distinctive craniofacial traits. We also discussed the important risk variables, focusing on the relationship with advanced maternal age and the consequences of family history. From non-invasive prenatal screening (NIPT) to conclusive postnatal karyotyping, the study also described the key diagnostic paths.

Lastly, we examined the transforming power of early intervention, highlighting the critical role that physical and speech-language treatments play in managing medical comorbidities and enhancing long-term independence. The notable rise in life expectancy to 55 years shows the effectiveness of contemporary multidisciplinary care and social involvement, even while problems like a greater risk of Alzheimer's and cardiovascular problems still exist.

In the future, the emphasis of care will be on creating a society that is truly inclusive rather than just clinical management. People with Down syndrome can live more independent lives provided certain educational demands are met and career options are encouraged. The combination of medical attention, community support, and the celebration of neurodiversity will continue to improve the trajectory for both individuals and families, even though genetic complexity remains at the center of the disorder.

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