INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Down Syndrome: An Insight Of The Disease

Musku Srivani*[1], Gudivada Himaja Lakshmi[2], Aashutosh Sinwal[3], Ishu[4], Mohit Nair[5], Smrithimol Baby[6]

[12]Malla Reddy College Of Pharmacy, Maisammaguda, Hyderabad, Telangana, India- 500100.
[3456]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India,302017.

ARTICLE INFO

Received: 27 June 2024
Accepted: 02 July 2024
Published: 12 July 2024

Keywords:
Down syndrome, Chromosome 21, Congenital heart abnormalities, Chorionic villus sampling, Paralogous sequence quantification, Speech-language therapy.

DOI:
10.5281/zenodo.12733651

ABSTRACT

Down syndrome (DS) is the most commonly observed genetic anomaly linked to intellectual disability, resulting from the trisomy of Homo sapiens chromosome 21 (HSA21). The prevalence of Down syndrome (DS) is experiencing a notable increase during an individual's lifespan, primarily attributed to the global population growth. Down syndrome phenotype encompasses a range of symptoms that exert an influence on several physiological systems, such as the musculoskeletal, neurological, and cardiovascular systems. The primary cause of having a Down syndrome (DS) baby is trisomy, which is characterized by the presence of an extra copy of chromosome 21. Down syndrome is associated with several health issues as a result of its influence on specific physiological systems. The most common cardiac abnormality associated with Down syndrome is an atrioventricular septal defect. Hematological abnormalities, such as neutrophilia, thrombocytopenia, and polycythemia, are frequently observed in neonates diagnosed with Down syndrome. The technique of paralogous sequence quantification (PSQ) is a modern approach that uses paralogous sequences to measure the number of copies of Hsa 21.

INTRODUCTION

Down syndrome (DS) is the most commonly observed genetic anomaly linked to intellectual disability, resulting from the trisomy of Homo sapiens chromosome 21 (HSA21). The illness is named after Down, who presented a thorough account of its clinical symptoms in 1866. The Down syndrome phenotype encompasses a range of symptoms that exert an influence on several physiological systems, such as the musculoskeletal, neurological, and cardiovascular systems. [1] Individuals who have received a diagnosis of Down syndrome (DS) may display various physiological manifestations, including but not limited to stunted growth, muscle weakness, instability in the atlantoaxial region, reduced neuronal density, cerebellar hypoplasia, cognitive impairment, and congenital heart

***Corresponding Author:** Musku Srivani
Address: *Malla Reddy College Of Pharmacy, Maisammaguda, Hyderabad, Telangana, India- 500100*
Email : singheshu827@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

abnormalities (CHDs), such as atrioventricular septal defects (AVSDs). People who have been diagnosed with Down syndrome (DS) demonstrate a heightened vulnerability to a range of health conditions, including but not limited to hypothyroidism, autoimmune diseases, obstructive sleep apnea, epilepsy, hearing and vision impairments, hematological disorders (including leukemia), recurrent infections, anxiety disorders, and early-onset Alzheimer's disease (AD). Individuals diagnosed with DS demonstrate a condition known as inverse comorbidity, meaning they have a lower likelihood of having other illnesses, including most types of solid tumors, in comparison to the general population. [2] The study conducted in 1959 marked an important milestone in the field of genetic medicine by establishing a correlation between a supernumerary chromosome 21 and the DS phenotype. The inception of mice models for studying DS took place in 1990, and subsequently, a global group of researchers published the whole nucleotide sequence of the long arm of HSA21 in 2000. Over the last 19 years, substantial progress has been made in understanding the molecular pathophysiology behind the diverse phenotypic manifestations of Down syndrome (DS), a disorder currently acknowledged as a disruption in gene expression. Moreover, the implementation of widely used screening methods has been observed in the prenatal detection of Down syndrome (DS). Significant advancements have been made in the management of various symptoms and the general quality of life for individuals diagnosed with Down syndrome (DS). However, there are still major challenges that remain, including understanding the precise molecular mechanism that causes each characteristic aspect of the disease, effectively managing different symptoms like cognitive impairment, and integrating individuals with Down syndrome into various global societies. Furthermore, the task of studying the effects of duplicating more than 200 protein-coding genes on HSA21, as well as the duplication of non-coding genes and the resulting indirect repercussions, presents considerable challenges when doing research in animal models.[3]

Epidemiology And Prevalence

The prevalence of Down syndrome (DS) is experiencing a notable increase during an individual's lifespan, primarily attributed to the global population growth. According to unpublished data, the prevalence of Down syndrome (DS) in the United States increased from 50,000 individuals in 1950 (3.3 per 10,000 individuals) to 212,000 individuals in 2013 (6.7 per 10,000 individuals). The observed rise can primarily be ascribed to the progress made in enhancing the survival rates of individuals with Down syndrome during their early developmental years. [4] The United States witnessed a significant rise in the average life expectancy of individuals with Down syndrome (DS) from around 26 years and 4 years in 1950 to 53 years and 58 years, respectively, by the year 2010. The projected prevalence of Down syndrome (DS) in Europe in 2015 was 4.9 cases per 10,000 individuals. A prevalence rate of 6.0 per 10,000 inhabitants was observed in Europe, excluding the former Eastern Bloc republics. [2,4] The incidence rate in former Eastern Bloc nations rose to 3.3 per 10,000 inhabitants. However, it is not possible to calculate a precise global estimate until further birth registries are established in countries and more data is available on the historical and current survival rates of individuals with Down syndrome in different parts of the world. Disproportional sex (DS) is a prevalent phenomenon observed in all populations. Nevertheless, the number of live births is influenced by variations in maternal age at conception across different countries and ethnicities13–16. Based on unverified data from 2013, the incidence of DS10 in the United States was found to be 1 in 779 infants, corresponding to

a rate of 12.8 per 10,000 live births. There is heterogeneity in the incidence of Down syndrome (DS) among different countries, which is influenced by the maternal age at conception. The estimated occurrence rate of this disease at a gestational age of 10 weeks is 1 in 365 fetuses. Based on data obtained from England and Wales, it has been observed that around 32% of these pregnancies will result in spontaneous miscarriage during the timeframe of 10 weeks gestation to the scheduled date of delivery, while roughly 25% of these pregnancies will terminate spontaneously between 16 weeks gestation and the intended date of birth. [5] The incidence of spontaneous miscarriage is contingent upon the age of the mother. The occurrence of deliberate pregnancies depends on various factors, such as the availability and accuracy of screening tests in each country, the extent of engagement in prenatal screening and subsequent prenatal testing, and parental decisions after receiving a prenatal diagnosis of Down syndrome. In 2013, the United States witnessed approximately 3,400 elective terminations about Down syndrome (DS), resulting in a notable reduction of 33% in the anticipated count of babies with DS during that particular year. In contrast, Australia witnessed a decline in its proportion to 55% in 2004, while Europe observed a fall of 54%. Specifically, Europe, excluding the former Eastern Bloc nations, had a decrease of 66%. Furthermore, the former Eastern Bloc countries witnessed a decrease of 32% between the years 2010 and 2015. Between the years 2003 and 2011, there was a notable reduction of 55% in the total perinatal prevalence of terminations for fetuses diagnosed with Down syndrome (DS) in China. [6] The findings of studies conducted in England and Wales, Slovenia, Australia, and EUROCAT regions have indicated that there is a negative correlation between maternal age and the utilization of prenatal screening. This correlation has resulted in a consistent or slightly decreasing prevalence of Down syndrome in live births from the 1990s to the present. There has been a slight decrease in the occurrence of Down syndrome (DS) in live births in Europe since the 1990s, however, there are significant differences across different locations. Between 1980 and 2015, the incidence of Down syndrome in live births in southern Europe had a reduction of almost 50%. By contrast, the live birth prevalence in the Netherlands saw a moderate rise between 1980 and 2000, followed by a marginal decline after 2005. [7] The increase in the prevalence of Down syndrome (DS) among live births in the United States began in the 1980s and subsequently stabilized around 2005. Since 2011, many nations have made noninvasive prenatal screening (NIPS) or noninvasive prenatal testing (NIPT) available. This includes sequencing cell-free placental DNA in maternal plasma. However, a thorough assessment of the impact of surveillance programs on birth rates is still lacking due to a lack of adequate time that has passed. Furthermore, it is expected that the absence of consistency in the accessibility of prenatal care will affect the implementation of surveillance initiatives.[8]

Genetics Of The Disease

The primary cause of having a Down syndrome (DS) baby is trisomy, which is characterized by the presence of an extra copy of chromosome 21. Furthermore, it is worth considering Robertsonian translocation and the presence of isochromosome or ring chromosomes as probable etiological factors. The term "chromosome" refers to a condition when two long arms of a chromosome are separated at the same time, rather than the usual separation of both long and short arms during egg and sperm development. [9] Trisomy 21, which is defined by the karyotype 47, XX, + 21 in females and 47, XY, + 21 in males, occurs when chromosome 21 is not properly separated during the production of eggs or sperm. In approximately 2-4% of cases, Robertsonian

translocation is an infrequent phenomenon characterized by the fusion of the elongated arm of chromosome 21 with another chromosome, commonly chromosome 14. In the context of cell division, mosaicism refers to the presence of mistakes or misdivisions that occur during fertilization. Mosaic Down syndrome (DS) is characterized by the presence of two different cell lineages that contribute to the functioning of tissues and organs in affected individuals. The first cell lineage exhibits the standard number of chromosomes, whereas the second cell lineage possesses an additional 21 chromosomes.[10]

Genotype-Phenotype Correlation

The hypothesis of gene dosage imbalance suggests that individuals diagnosed with Down syndrome (DS) demonstrate an increased dosage or copy number of genes located on the Hsa21 locus, which may lead to enhanced gene expression. The conceptual framework has been broadened to include the potential impact of certain genes or gene subsets on unique aspects of Down syndrome (DS).[11] Amplified developmental instability theory suggests that an uneven distribution of some trisomic genes leads to a genetic modification that has a substantial impact on the expression and regulation of several genes throughout the genome. Furthermore, this collection incorporated the critical region idea. A phenotypic study was conducted on individuals exhibiting partial trisomy for Hsa21, which unveiled the existence of "Down syndrome critical regions" (DSCR). The majority of Down syndrome characteristics were attributed to specific areas on the 21q21.22 gene, which span from 3.8 to 6.5 Mb. [12] The main factors to these DS traits were identified as approximately 30 genes. Before this, it was recognized that a region spanning from 1.6 to 2.5 megabases (Mb) played a substantial role in the development of the Down syndrome (DS) phenotype. The examination of Hsa 21 sequencing has been pivotal in the progression of DS research and has yielded further insights into the connections between genotype and phenotype in DS, along with precise delineations of DSCR regions. Prior research has hypothesized that a distinct region within the 21q22 gene is responsible for many characteristics commonly observed in individuals with Down syndrome (DS), including craniofacial abnormalities, congenital cardiac issues impacting the endocardial cushions, clinodactyly of the fifth finger, and cognitive impairment. It has been reported that Dual-specificity tyrosine phosphorylation-regulated kinase (DYRK1A) and regulator of calcineurin 1 (RCAN1), Down syndrome cell adhesion molecule (DSCAM), may have potential relevance in the process of brain development. Moreover, it has been determined that DSCAM may serve as a plausible gene linked to the increased vulnerability to coronary heart disease (CHD) in persons diagnosed with Down syndrome (DS). [13] In neuronal differentiation, axon guidance, and the establishment of neural networks, the DSCAM protein assumes a pivotal function. The hypothesis posits that the dysfunction of these cognitive processes plays a role in the neuropsychological characteristics observed in persons diagnosed with Down syndrome. After conducting thorough investigations on human individuals and mouse models of Down syndrome (DS), it becomes evident that there is no solitary genetic region that possesses the ability to induce all traits associated with DS. On the contrary, multiple pivotal regions or genetic factors are likely contributing to the expression of a particular symptom or a group of symptoms associated with Down syndrome (DS). [14]

Various Clinical Conditions Associated with Down Syndrome

Down syndrome is associated with several health issues as a result of its influence on specific physiological systems. The subjects under

consideration display a wide array of indications and manifestations, encompassing intellectual and developmental deficits or neurological traits, congenital heart defects, gastrointestinal (GI) irregularities, unusual facial characteristics, and abnormalities. [15]

Congenital Cardiac Defects (CHD)

The most common and leading cause of disease and mortality in individuals with Down syndrome, especially in the first 2 years of life, is congenital cardiac problems. Numerous explanations have been posited concerning the oscillations in the occurrence of specific congenital heart abnormalities in individuals with trisomy 21, concerning geographical and seasonal variations. Nevertheless, up until now, none of the research outcomes have produced conclusive findings. Infants with Down syndrome may have a prevalence of congenital heart disease (CHD) that can reach as high as 50%. [11,13] The most common cardiac abnormality associated with Down syndrome is an atrioventricular septal defect (AVSD), which makes up about 40% of all congenital cardiac abnormalities in persons with Down syndrome. It is hypothesized that the mutation of the non-Hsa21 CRELD1 gene is connected to this disorder. Approximately 32% of persons with Down syndrome are affected by the ventricular septal defect (VSD), making it the second most common cardiac defect in this population. These abnormalities, when combined with AVSD, cumulatively account for approximately 50% of congenital heart defects reported in persons diagnosed with Down syndrome. Trisomy 21 has been associated with several cardiac anomalies, such as secundum atrial defect (10%), tetralogy of Fallot (6%), and isolated PDA (4%). In addition, around 30% of individuals impacted by trisomy 21 experience various cardiac complications. The prevalence of cardiac defects in individuals with Down syndrome varies across different geographical regions. [16] In Asia, ventricular septal defect (VSD) is the most common variant, while in Latin America, secundum type ASD is more commonly observed. The etiology of the disparity in the prevalence of different types of coronary heart disease (CHD) across diverse geographical areas remains ambiguous, as other factors, such as proximity to neighbouring regions, have been recognized as potential determinants. It is recommended that individuals identified with Down syndrome receive an echocardiogram within the first few weeks after birth due to the increased prevalence of coronary heart disease (CHD) in this population. [14,15]

Gastrointestinal (GI) Tract Abnormalities

Trisomy 21 is characterized by a multitude of morphological and functional abnormalities that are closely linked to the gastrointestinal tract in affected individuals. Various anatomical locations, including the mouth cavity and the anal region, might exhibit structural anomalies. Studies have shown that persons with these disorders had a greater occurrence of certain abnormalities, such as duodenal and small intestinal atresia or stenosis, annular pancreas, imperforate anus, and Hirschsprung disease, compared to the general population. [13] Hirschsprung disease exhibits a prevalence rate of approximately 2% among individuals diagnosed with Down syndrome, with a notable occurrence observed in approximately 12% of patients with Down syndrome. [17] This pathological condition manifests as a functional obstruction within the lower intestines, impeding the movement of neural cells toward the distal end of the rectum. Consequently, an aganglionic segment is formed, characterized by abnormal movement, and leads to the inability to perform the normal defecation reflex, resulting in a functional obstruction. The newborn usually exhibits clinical symptoms and signs related to intestinal blockage. Duodenal atresia and imperforate anus are frequently observed in neonates. In addition to

their structural defects, individuals with Down syndrome are prone to several gastrointestinal illnesses such as gastroesophageal reflux disease (GERD), chronic constipation, sporadic diarrhea, and celiac disease. [18] Due to the significant association between celiac disease and Down syndrome, seen in around 5% of affected persons, it is recommended to undergo annual testing for celiac disease. After receiving a diagnosis, these patients will need to strictly follow a gluten-free diet for the rest of their lives. [17]

Hematologic Disorders

The condition known as Down syndrome is distinguished by the existence of several haematological abnormalities. Haematological abnormalities, such as neutrophilia, thrombocytopenia, and polycythaemia, are frequently observed in neonates diagnosed with Down syndrome (HANDS). The prevalence of these disorders is estimated to be around 80%, 66%, and 34% in infants with Down syndrome, respectively. Hand, Foot, and Mouth Syndrome (HANDS) generally presents as a mild ailment and tends to resolve within the first three weeks after birth. Down syndrome is characterized by a distinct and temporary myeloproliferative disease. Down syndrome is a condition marked by the existence of blast cells in infants below the age of three months. [18] This syndrome is characterized by the rapid growth of megakaryocytes, which occurs within the first week of a person's life and is often resolved within three months following birth. Transient aberrant myelopoiesis, often known as transient leukemia, has been documented in around 10% of individuals who have received a diagnosis of Down syndrome. If the fetus exhibits spontaneous abortion, it can be induced. [19] There is a tenfold higher probability for individuals with Down syndrome to develop leukemia, which constitutes approximately 2% of acute lymphoblastic leukemia cases in children and 10% of acute myeloid leukemia cases in children. 30% of Down syndrome patients with acute lymphoblastic leukaemia had a functional mutation in the Janus Kinase 2 gene. Research has demonstrated that over 10% of individuals who are diagnosed with chronic myeloid leukaemia (TML) develop acute megakaryoblast leukaemia (AMKL) before they become four years old. There is evidence to suggest that the interaction between AMKL and the GATA1 gene, which is an X-linked transcript or factor, leads to an uncontrolled increase in the number of immature megakaryocytes. [20]

Neurologic Disorders

The association between trisomy Hsa21 and a reduction in brain volume, namely in the hippocampus and cerebellum, has been established. Hypotonia, a distinctive characteristic exhibited in infants with Down syndrome, is present in almost all instances. The condition is characterized by a reduced ability to resist passive muscular stretch, which is linked to delayed motor development in affected individuals. Individuals with Down syndrome experience hypotonia, which causes joint laxity, reduced gait stability, and increased energy demand during physical activity. These individuals also tend to have lower bone mass and are more prone to fractures due to their limited physical activity. Moreover, the presence of ligamentous laxity in these structures increases their vulnerability to atlantoaxial subluxation. Seizures occur in from 5% to 13% of children who have been diagnosed with Down syndrome. Within this cohort, 40% will experience seizures before attaining their initial birthday. [16,18] In such cases, the seizures commonly present as infantile spasms. In comparison to their counterparts, children with Down syndrome who experience infantile spasms demonstrate a more positive reaction to antiepileptic drugs. [19] Therefore, the implementation of early intervention and therapy is of utmost importance in improving their developmental outcomes. The

prevalence of Lennox-Gestaut syndrome is greater in children who have been diagnosed with Down syndrome. This condition is marked by a delayed start of symptoms, as well as the presence of reflex seizures and an increased frequency of abnormalities in electroencephalogram (EEG) readings. During the early stages of life, approximately 40% of individuals diagnosed with Down syndrome encounter tonic-clonic or myoclonic seizures. [20] The prevalence of dementia is higher among individuals aged 45 and above with Down syndrome, with nearly 84% of this population being at an elevated risk of experiencing seizures. The occurrence of seizures in these individuals is linked to the rapid decline of their cognitive functions. The prevalence of early-onset Alzheimer's disease is significantly higher among individuals with Down syndrome, with approximately 50% to 70% of individuals experiencing dementia by the age of 60. The amyloid precursor protein (APP), which is associated with an increased susceptibility to Alzheimer's disease, is encoded in the Hsa21 gene. [21] The increased prevalence of dementia in persons with Down syndrome may be attributed to the trisomy of this protein. Recent studies have shown evidence suggesting a correlation between the replication of APP and an increased susceptibility to early-onset Alzheimer's disease, even in persons without any pre-existing medical disorders. Most persons who have been identified with Down syndrome often demonstrate a moderate-to-moderate degree of learning impairment. Cognitive deficits in mice have been documented as a consequence of trisomy in various genes, including DYRK1A, synaptojanin 1, and single-minded homolog 2 (SIM2). The implications of this research suggest that the upregulation of these genes could potentially play a role in the development of learning disabilities reported in persons diagnosed with Down syndrome. [22]

Endocrinological Disorders

An observed correlation exists between thyroid gland malfunction and Down syndrome. Congenital or acquired hypothyroidism can occur at any stage of a person's life. The New York newborn screening program has found that infants diagnosed with Down syndrome have a higher occurrence of congenital hypothyroidism compared to their peers. Individuals diagnosed with Down syndrome who developed hypothyroidism had a range of 13% to 34% of anti-thyroid autoantibodies. [23] Moreover, it was observed that the concentrations of these antibodies showed an increasing pattern after the age of 8. Around 50% of individuals diagnosed with Down syndrome display subclinical hypothyroidism, which is characterized by elevated levels of thyroid-stimulating hormone (TSH) and normal levels of thyroxine. [24] The occurrence of hyperthyroidism in individuals with Down syndrome is slightly lower than that of hypothyroidism, but it still exceeds the occurrence of hyperthyroidism in the entire pediatric population. Individuals with delayed puberty, irrespective of their gender, have exhibited notable deviations in sexual development. In girls, primary hypogonadism is distinguished by a postponement of menarche or adrenarche. Conversely, in boys, it manifests as cryptorchidism, ambiguous genitalia, micropenis, diminutive testes, diminished sperm count, and scanty proliferation of axillary and pubic hair. The potential role of insulin-like growth factor (IGF) in the delayed skeletal maturation and shorter stature reported in individuals diagnosed with Down syndrome has been established. [25]

Musculoskeletal Disorders

Children who have been identified with Down syndrome are more prone to experiencing a reduction in muscle mass as a result of hypotonia, which is marked by increased flexibility of the ligaments. This condition is characterized by a

decrease in the speed of gross motor skills and can potentially result in joint dislocation. The individuals in question demonstrate a deficiency of vitamin D due to various factors, such as inadequate exposure to sunlight, inadequate intake of vitamin D, impaired absorption associated with celiac disease, and increased breakdown caused by anticonvulsant medication, among other contributing factors. Multiple variables are implicated in the heightened vulnerability of children diagnosed with Down syndrome to diminished bone mass, hence augmenting their susceptibility to recurring fractures. [26]

Refractive Errors and Visual Abnormalities

Ocular and orbital abnormalities are commonly observed in children who have been diagnosed with Down syndrome. The conditions mentioned above include blepharitis (2-7%), keratoconus (5-8%), cataract (25% to 85%), retinal anomalies (0% to 38%), strabismus (23% to 44%), amblyopia (10% to 26%), nystagmus (5% to 30%), refractive errors (18% to 58%), glaucoma (less than 1%), iris anomalies (38% to 90%), and optic nerve anomalies (very few cases). Untreated ocular abnormalities can significantly impair the quality of life for those affected. Furthermore, all persons who have been identified with Down syndrome must get an ocular checkup during the first six months following their birth, followed by an annual test thereafter. [27]

Otorhinolaryngological (ENT) Disorders

Individuals diagnosed with Down syndrome commonly encounter challenges related to the ear, nose, and throat. The sensitivity to hearing abnormalities is heightened in individuals with Down syndrome due to the anatomical shape of the ear. Conductive hearing loss commonly occurs due to the blockage of the cerumen and the existence of middle ear conditions, including chronic middle ear effusion caused by the short Eustachian tube, acute otitis media, and eardrum perforation. The utilization of pressure equalization tubes is commonly required for the management of these individuals. Sensorineural hearing loss in individuals with Down syndrome is associated with structural abnormalities in the inner ears, specifically the presence of small internal auditory canals. [28]

Diagnostic Methods

Prenatal diagnosis using amniocentesis and chorionic villus sampling (CVS) is crucial for the prevention of Down syndrome in pregnancies with a high risk. Amniocentesis and cesarean section (CVS) are considered to be procedures with a good level of reliability, however with a potential risk of miscarriage ranging from 0.5% to 1%. The identification of Down syndrome (DS) risk in the fetus at 14 to 24 weeks of gestation may generally be accomplished by the utilization of ultrasound, which involves the examination of soft indicators such as the presence or absence of nasal bone, enlarged ventricles, and increased thickness of the nuchal fold. [24,26] An increased level of fetal nuchal translucency indicates an increased vulnerability to Down syndrome. In several places, traditional cytogenic analysis is widely utilized as a prominent method for prenatal diagnosis. However, there are various efficient molecular approaches used for prenatal diagnosis, including FISH (fluorescent in situ hybridization), QF-PCR (quantitative fluorescence PCR), and MLPA (multiplex probe ligation assay). [27]

Rapid aneuploidy testing methods

Over the past ten years, several alternative methods have been developed and utilized to quickly detect trisomy 21, either before or after birth. The study of interphase nuclei using the FISH technique typically involves the use of Hsa 21-specific probes or whole-Hsa 21. Quantitative polymerase chain reaction (QF-PCR), a frequently utilized alternative method in specific countries, entails the application of DNA polymorphic markers (microsatellites) on Hsa 21 to determine the presence of three different alleles. This

methodology is contingent upon pertinent indicators and the existence of DNA. [29] The application of polymorphic STR markers in PCR-based techniques holds promise in addressing the limitations associated with traditional methodologies. The technique using STR markers exhibits a detection rate of 86.67% for trisomy in circumstances when just two markers are employed. Augmenting the quantity of markers has the potential to augment the dependability of the test. Simultaneous determination of the paternal origin of the nondisjunction is also a viable option. The technique known as MLPA, which was first introduced in 2002, functions as a supplementary method for determining the copy number of DNA sequences. MLPA offers numerous advantages, such as a quick diagnostic timescale of 2-3 days, high effectiveness, user-friendly interface, and cost-effectiveness. [30] The procedure is dependent on the use of hybridization and polymerase chain reaction (PCR) methodologies, which consist of four distinct phases: DNA denaturation, DNA probe hybridization to the target sequence, probe ligation, and PCR amplification. In conclusion, the products amplified by PCR are subjected to capillary electrophoresis. However, MLPA cannot completely remove low-level placental and true mosaicism. [27]

Advancement in the diagnosis

The technique of paralogous sequence quantification (PSQ) is a modern approach that uses paralogous sequences to measure the number of copies of Hsa 21. The technique known as paralogous sequence quantification (PSQ) utilizes the polymerase chain reaction (PCR) method to detect and characterize certain abnormalities in chromosomal numbers. This approach depends on the use of genes that are related to each other. Paralogous sequences exhibit a notable degree of sequence similarity, however, they undergo nucleotide alterations that are exclusive to the locus. Pyrosequencing technology can be used to quantify paralogous sequence mismatches (PSMs), which are variances in sequence. This methodology facilitates the determination of the comparative dosage among different chromosomes. PSQ is a dependable, uncomplicated, and easy-to-execute method for detecting prevalent aneuploidies. The procedure can be accomplished within a time frame of 48 hours, rendering it a feasible choice for broader implementation in diagnostic laboratories. Pyrosequencing is used to produce quantitative sequences. In summary, the application of comparative genomic hybridization (CGH) on BAC chips offers a feasible method for detecting complete trisomy or monosomy, as well as partial (segmental) aneuploidies. [31,32]

Common Treatments For Down Syndrome

There is no single, globally acknowledged treatment for Down syndrome. Residing at home or in the community, individuals with Down syndrome can get suitable care that considers their unique physical and intellectual needs, as well as their strengths and limits. People with Down syndrome are more prone to various health difficulties and illnesses in comparison to individuals without Down syndrome. Many of these associated illnesses may require immediate care after birth, intermittent therapy during childhood and adolescence, or continued therapies throughout an individual's lifespan. [16,17] For example, a neonate who has been diagnosed with Down syndrome may undergo surgical intervention shortly after birth to correct a cardiac anomaly. Similarly, an individual with Down syndrome may encounter gastrointestinal challenges that require a lifelong specialized dietary regimen. The concept of "early intervention" encompasses a range of specialized programs and resources provided by professionals to young children diagnosed with Down syndrome and their families. This group of professionals may

include individuals who are special educators, speech therapists, occupational therapists, physical therapists, and social workers. [30]

Treatment Therapies

Various treatment methods can be used in early intervention programs and throughout a person's life to promote optimal development, independence, and effectiveness. The following section enumerates several therapies. [31] Physical therapy involves a variety of activities and exercises that are designed to improve motor skills, increase muscle strength, and maintain proper alignment and balance. Physical therapy has a key role, especially in the initial phases of a child's growth, as it lays the groundwork for subsequent functional capacities. Infants gain an understanding of their environment and learn abilities to interact with it by flipping over, crawling, and extending their reach. Physical therapists can provide support to children with Down syndrome in managing physical challenges, such as reduced muscle tone, in a way that minimizes the risk of long-term consequences. To provide an example, a physical therapist may aid a child in cultivating an ideal gait, rather than one that may potentially lead to arthralgia. [21,29]

Research has demonstrated the efficacy of speech-language therapy in improving the communication skills and language proficiency of children who have received a diagnosis of Down syndrome. [29] Children diagnosed with Down syndrome often develop language abilities at a later stage in comparison to their peers. A speech-language therapist possesses the capacity to aid clients in developing fundamental communication skills, including the aptitude to imitate sounds. In addition, the therapist may aid a newborn with breastfeeding as it aids in strengthening the muscles responsible for speech production. Frequently, children diagnosed with Down syndrome exhibit a cognitive understanding of language and a propensity for active communication before developing the capacity to engage in verbal communication. [25] Speech-language therapists can help youngsters use other forms of communication, such as sign language and visual aids until they develop the ability to speak. Individuals with Down syndrome can benefit from participating in speech and language therapy during their scholastic years and in their future pursuits, as the development of communication skills is an ongoing process. Therapists can aid individuals in developing their conversational skills, honing their pronunciation, expanding their reading comprehension, and helping the acquisition and retention of words.[30]

Occupational therapy plays a crucial role in enabling individuals to modify their everyday activities and environments to accommodate their unique needs and talents. This therapeutic approach teaches individuals self-care strategies, encompassing tasks such as eating, dressing, writing, and using the Internet. Specialized equipment, such as a pencil specifically developed to enhance grip, may be provided by occupational therapists to improve daily functioning. The role of an occupational therapist at the secondary education level involves providing support to teenagers in the process of identifying jobs, professions, or competencies that are in line with their interests and aptitudes. [32] The primary objective of emotional and behavioral treatments is to ascertain efficacious approaches for the management of both psychologically desirable and psychologically undesirable habits. Children with Down syndrome may encounter frustration as a result of communication difficulties, display compulsive behaviours, and develop attention-deficit/hyperactivity disorder and other mental health disorders. The primary objective of these therapists is to gain a comprehensive understanding of the fundamental factors contributing to a child's disruptive behavior. [33] They then develop strategies and techniques to

prevent or mitigate such circumstances, while also providing instruction on more efficient and productive methods for managing such issues. Professionals in psychology, counselling, and other mental health professionals have the necessary knowledge and skills to support children in effectively controlling their emotions and cultivating coping strategies and interpersonal skills. The heightened levels of aggression observed in adolescents can be attributed to the hormonal variations that transpire during the period of puberty. Behavioral therapists can help adolescents recognize their intensified emotions and teach them how to use effective techniques to attain a state of calmness. Additionally, parents might benefit from obtaining guidance on how to properly support a child with Down syndrome in overcoming daily challenges and reaching their full potential. [34]

Drugs and Supplements

Some persons diagnosed with Down syndrome may undergo cognitive impairment as a result of consuming amino acid supplements or drugs. However, a considerable proportion of recent clinical trials examining these medications demonstrated insufficient control procedures and revealed adverse effects linked to their utilization. Following this, there has been a development of more sophisticated psychoactive drugs that exhibit improved specificity. [33] Nevertheless, a dearth of controlled clinical trials exists that have yielded empirical data about the safety and effectiveness of these pharmaceutical interventions in the context of persons diagnosed with Down syndrome. The sample size of several studies examining the effectiveness of drugs in mitigating dementia symptoms in individuals with Down syndrome has been constrained. The research findings have not provided conclusive evidence on the benefits of these medications. Similarly, studies on antioxidants for dementia in individuals with Down syndrome have shown that these supplements are considered safe, although they do not exhibit significant effectiveness. [34, 35]

Assistive Devices The utilization of assistive devices has become more prevalent in interventions for children diagnosed with Down syndrome. These devices cover a diverse array of materials, equipment, instruments, or technologies that are specifically designed to enhance learning or streamline task completion. Amplification devices, mobility bands, specialist writing aids, touchscreen computers, and computers outfitted with keyboards that accommodate larger letter sizes are among the assistive technologies available for those with hearing impairments. [35]

CONCLUSION

In conclusion, Down syndrome is a genetic anomaly caused by the trisomy of chromosome 21, leading to intellectual disability and a range of health conditions. The prevalence of Down syndrome has increased over time, but there are variations among countries and it is influenced by maternal age. While there is no single treatment, individuals with Down syndrome can receive appropriate care through various therapies and assistive devices to promote development and independence.

REFERENCE

1. Holmes, G. (2014). Gastrointestinal disorders in Down syndrome. Gastroenterol Hepatol Bed Bench. Gastroenterol Hepatol Bed Bench, 7(1), 6–8.
2. Antonarakis, S. E., Lyle, R., Dermitzakis, E. T., Reymond, A., & Deutsch, S. (2004). Chromosome 21 and down syndrome: from genomics to pathophysiology. Nature Reviews. Genetics, 5(10), 725–738.
3. Asim, A., Kumar, A., Muthuswamy, S., Jain, S., & Agarwal, S. (2015). Down syndrome: an insight of the disease. Journal of Biomedical Science, 22(1), 41.
4. Choi, J. K. (2008). Hematopoietic disorders in Down syndrome. International Journal of

Clinical and Experimental Pathology, 1(5), 387–395.

5. Wallace, R. A. (2007). Clinical audit of gastrointestinal conditions occurring among adults with Down syndrome attending a specialist clinic. Journal of Intellectual & Developmental Disability, 32(1), 45–50.
6. Miller, M., & Cosgriff, J. M. (1983). Hematological abnormalities in newborn infants with Down syndrome. American Journal of Medical Genetics, 16(2), 173–177.
7. Wechsler, J., Greene, M., McDevitt, M. A., Anastasi, J., Karp, J. E., Le Beau, M. M., & Crispino, J. D. (2002). Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. Nature Genetics, 32(1), 148–152.
8. Jain, S., Agarwal, S., Panigrahi, I., Tamhankar, P., & Phadke, S. (2010). Diagnosis of Down syndrome and detection of origin of nondisjunction by short tandem repeat analysis. Genetic Testing and Molecular Biomarkers, 14(4), 489–491.
9. Skotko, B. G., Davidson, E. J., & Weintraub, G. S. (2013). Contributions of a specialty clinic for children and adolescents with Down syndrome. American Journal of Medical Genetics. Part A, 161A(3), 430–437.
10. Asim, A., Kumar, A., Muthuswamy, S., Jain, S., & Agarwal, S. (2015b). "Down syndrome: an insight of the disease." Journal of Biomedical Science, 22(1).
11. Lyle R, Béna F, Gagos S, Gehrig C, Lopez G, Schinzel A, et al. Genotype-phenotype correlations in Down syndrome identified by array CGH in 30 cases of partial trisomy and partial monosomy chromosome 21. Eur J Hum Genet [Internet]. 2009;17(4):454–66.
12. Wahab, A. A., Bener, A., & Teebi, A. S. (2006). The incidence patterns of Down syndrome in Qatar: Letter to the Editor. Clinical Genetics, 69(4), 360–362.
13. Wiseman, F. K., Al-Janabi, T., Hardy, J., Karmiloff-Smith, A., Nizetic, D., Tybulewicz, V. L. J., Fisher, E. M. C., & Strydom, A. (2015). A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. Nature Reviews. Neuroscience, 16(9),
14. Gardiner, K. J. (2010). Molecular basis of pharmacotherapies for cognition in Down syndrome. Trends in Pharmacological Sciences, 31(2), 66–73.
15. Levitas, A. S., & Reid, C. S. (2003). An angel with Down syndrome in a sixteenth century Flemish Nativity painting. American Journal of Medical Genetics. Part A, 116A(4), 399–405.
16. Salehi, A., Ashford, J. W., & Mufson, E. J. (2016). The link between Alzheimer's disease and down syndrome. A historical perspective. Current Alzheimer Research, 13(1), 2–6.
17. Bull, M. J. (2020). Down syndrome. The New England Journal of Medicine, 382(24), 2344–2352. Weerakkody, Y., & Stanislavsky, A. (2011). Down syndrome. In Radiopaedia.org. Radiopaedia.org.
18. Antonarakis, S. E., Skotko, B. G., Rafii, M. S., Strydom, A., Pape, S. E., Bianchi, D. W., Sherman, S. L., & Reeves, R. H. (2020). Down syndrome. Nature Reviews. Disease Primers, 6(1).
19. Parker, S. E., Mai, C. T., Canfield, M. A., Rickard, R., Wang, Y., Meyer, R. E., Anderson, P., Mason, C. A., Collins, J. S., Kirby, R. S., Correa, A., & for the National Birth Defects Prevention Network. (2010). Updated national birth prevalence estimates for selected birth defects in the United States, 2004–2006. Birth Defects Research. Part A, Clinical and Molecular Teratology, 88(12), 1008–1016.

20. Minear, M. A., Alessi, S., Allyse, M., Michie, M., & Chandrasekharan, S. (2015). Noninvasive prenatal genetic testing: Current and emerging ethical, legal, and social issues. Annual Review of Genomics and Human Genetics, 16(1), 369–398.
21. Zerres, K., Rudnik-Schöneborn, S., & Holzgreve, W. (2021). Do non-invasive prenatal tests promote discrimination against people with Down syndrome? What should be done? Journal of Perinatal Medicine, 49(8), 965–971.
22. Karmiloff-Smith, A., Al-Janabi, T., D'Souza, H., Groet, J., Massand, E., Mok, K., Startin, C., Fisher, E., Hardy, J., Nizetic, D., Tybulewicz, V., & Strydom, A. (2016). The importance of understanding individual differences in Down syndrome. F1000Research, 5, 389.
23. Hickey, F., Hickey, E., & Summar, K. L. (2012). Medical update for children with down syndrome for the pediatrician and family practitioner. Advances in Pediatrics, 59(1), 137–157.
24. Patterson, D., & Costa, A. C. S. (2005). Down syndrome and genetics — a case of linked histories. Nature Reviews. Genetics, 6(2), 137–147.
25. Daunhauer, L. A., & Fidler, D. J. (2011). The down syndrome behavioral phenotype: Implications for practice and research in occupational therapy. Occupational Therapy in Health Care, 25(1), 7–25.
26. Desai, S. S. (1997). Down syndrome. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics, 84(3), 279–285.
27. Guralnick, M. J. (2002). Involvement with peers: comparisons between young children with and without Down's syndrome. Journal of Intellectual Disability Research: JIDR, 46(5), 379–393.
28. Fidler, D. J. (2005). The emerging down syndrome behavioral phenotype in early childhood: Implications for practice. Infants and Young Children, 18(2), 86–103.
29. Roizen, N. J., & Patterson, D. (2003). Down's syndrome. Lancet, 361(9365), 1281–1289.
30. Capone, G. T., Grados, M. A., Kaufmann, W. E., Bernad-Ripoll, S., & Jewell, A. (2005). Down syndrome and comorbid autism-spectrum disorder: Characterization using the aberrant behavior checklist. American Journal of Medical Genetics. Part A, 134A(4), 373–380.
31. Celani, G., Battacchi, M. W., & Arcidiacono, L. (1999). Journal of Autism and Developmental Disorders, 29(1), 57–66.
32. Kasari, C., Freeman, S. F. N., & Hughes, M. A. (2001). Emotion recognition by children with down syndrome. American Journal of Mental Retardation: AJMR, 106(1), 59.
33. Wetter, S., & Murphy, C. (1999). Individuals with Down's syndrome demonstrate abnormal olfactory event-related potentials. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 110(9), 1563–1569.
34. Cecchini, M. P., Viviani, D., Sandri, M., Hähner, A., Hummel, T., & Zancanaro, C. (2016). Olfaction in people with down syndrome: A comprehensive assessment across four decades of age. PloS One, 11(1), e0146486.
35. Head, E., Silverman, W., Patterson, D., & Lott, I. T. (2012). Aging and down syndrome. Current Gerontology and Geriatrics Research, 2012, 1–6.

HOW TO CITE: Musku Srivani*, Gudivada Himaja Lakshmi, Aashutosh Sinwal, Ishu, Mohit Nair, Smrithimol Baby, Down Syndrome: An Insight Of The Disease, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 7, 750-762. https://doi.org/10.5281/zenodo.12733651