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World Down Syndrome Day

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HUMAN

Shraddha Dingare*[1], Maruf Shikalgar[2], Dipasha Sugnani[2], Omkar Shendge[2]

1) *Assistant Professor, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune 411044, India*

2) *Students of Second Year Bachelor of Pharmacy, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune 411044, India*

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ABSTRACT

Down syndrome (DS), an important cause of intellectual disability (‘mental retardation’), results from the presence of three copies of human chromosome 21. Down syndrome is a multisystem disorder affecting one in 650–1000 births worldwide. The trisomy, affecting more than 300 genes, is associated with a variety of manifestations, including cardiac anomalies, thyroid dysfunction, leukemia, digestive disorders, and intellectual disabilities. DS significantly impacts the lives of those with the disorder as well as their families and the society in which they live, causing both human suffering and economic burden. Since the discovery of the genetic basis of DS, the possibility of linking individual genes to particular manifestations of DS has been an intensive focus of research. These efforts are especially relevant to the goal of understanding and treating cognitive disability and decline in people with DS. DS is the most common cause of intellectual disability and results in a greater susceptibility to early-onset Alzheimer disease, with over 75% of people with Down syndrome above the age of 65 years having a clinical diagnosis of dementia. Remarkable progress in advancing technology, medical treatment, and social intervention has dramatically increased life expectancy in Down syndrome. In addition, mouse models of Down syndrome have provided an unequivocal contribution to understanding the genetic and molecular pathogenesis underlying Down syndrome, leading to the emergence of potential therapeutic targets and the development of clinical trials for candidate drugs in humans.

World Down Syndrome Day

The 21st of March is World Down Syndrome Day. World Down Syndrome Day (WDSD) was declared by the United Nations General Assembly in December 2011. [1] The 21st day of March (the 3rd month of the year) was selected to signify the uniqueness of the triplication (trisomy) of the 21st chromosome which causes Down syndrome. [2]

WDSD is an event created to raise public awareness, promote inclusivity, encourage advocacy, and support the wellbeing of those living with Down syndrome. [3]

The day helps educate the public on what Down syndrome is and how to encourage those with Down syndrome to participate in daily activities so they can live a full life and play a vital role in their community. [2]

Blue and Yellow colors represent Down Syndrome Awareness. [4]

Wrist bands, Ribbons or Lapel Pins of Blue or Yellow colors can be used to show your support or fund-raising at World Down Syndrome Day. [5]

World Down Syndrome Day Timeline:

1990: AFRT—the French Association for Research on Trisomy 21 was founded in order to support research for Down Syndrome.

2005: This year marks not only the first meeting held by AFRT but also the year that March 21 is recognized as a symbolic day to represent Down syndrome.

2007: The World Health Organization acknowledges March 21 as World Down Syndrome Day.

2011: The United Nations supports WHO's acknowledgement of March 21 and also recognizes this date as World Down Syndrome Day.

2012: This year marks the first year that World Down Syndrome Day is to be celebrated annually on March 21. [6] [7]

Introduction/About Down Syndrome

Down syndrome is one of the most leading causes of intellectual disability and millions of these patients face various health issues including learning and memory, congenital heart

diseases (CHD), Alzheimer's diseases (AD), leukemia, cancers and Hirschprung disease (HD). The incidence of trisomy is influenced by maternal age and differs in population (between 1 in 319 and 1 in 1000 live births). [8] Down Syndrome has high genetic complexity and phenotype variability. [9] Trisomic fetuses are at elevated risk of miscarriages and Down Syndrome people have increased incidence of developing several medical conditions. [10] Recent advancement in medical treatment with social support has increased the life expectancy for Down Syndrome population. In developed countries, the average life span for Down Syndrome population is 55 years. [12]

History:

It is named after British doctor John Langdon Down, who fully described the syndrome in 1866. Some aspects of the condition were described earlier by French psychiatrist Jean-Étienne Dominique Esquirol in 1838 and French physician Édouard Séguin in 1844. The genetic cause of Down syndrome was discovered in 1959. [11]

For centuries, people with Down syndrome have been alluded to in art, literature and science. It wasn't until the late nineteenth century, however, that John Langdon Down, an English physician, published an accurate description of a person with Down syndrome. It was this scholarly work, published in 1866, that earned Down the recognition as the "father" of the syndrome. [13] Although other people had previously recognized the characteristics of the syndrome, it was Down who described the condition as a distinct and separate entity. [14]

In recent history, advances in medicine and science have enabled researchers to investigate the characteristics of people with Down syndrome. In 1959, the French physician Jérôme Lejeune identified Down syndrome as a chromosomal condition. Instead of the usual 46 chromosomes present in each cell, Lejeune observed 47 in the cells of individuals with Down syndrome. [15] It was later determined that an extra partial or whole copy of chromosome 21 results in the characteristics associated with Down syndrome. In the year 2000, an international team of scientists successfully identified and catalogued each of the approximately 329 genes on chromosome 21. This accomplishment opened the door to great advances in Down syndrome research. [4]

Etiology and Pathophysiology:

- Down syndrome is usually caused by an error in cell division called nondisjunction:

- During meiosis, one pair doesn't divide & the whole pair goes to one daughter cell.
- In the resulting cells, one will have 24 chromosomes & the other will have 22. [16]
- So if a sperm or egg with an abnormal of chromosomes merges with a normal mate, the resulting fertilized egg will have an abnormal of chromosomes.
- In Trisomy 21, one cell has two 21st chromosomes instead of one, so the resulting fertilized egg has three 21st chromosomes.
- Most commonly recognized genetic cause of mental retardation: prevalence of 9.2 cases per 10,000 live births. [17]

Diagnosed by Karyotype:

- 95% - Trisomy 21
- 2% - Mosaicism
- 3% - Robertsonian translocation [6]

Prognosis:

- Is variable depending on the types of complications of each individual baby.
- The severity of the retardation can also vary significantly.
- Without the presence of heart defects, about 90 percent of children with Down syndrome live into their teens. [18]
- People with Down syndrome appear to go through the normal physical changes of aging more rapidly, however.
- The average age at death for an individual with Down syndrome is about 50 to 55 years.
- Because of modern medical treatments, including antibiotics to treat infections and surgery to treat heart defects and duodenal atresia, life expectancy has greatly increased.
- Men with Down syndrome appear to be uniformly sterile (unable to have offspring). [19]
- Women with Down syndrome, however, are fully capable of having babies. About 50 percent of these babies, however, will also be born with Down syndrome.

- Most people have a six in 100 risk of developing Alzheimer's, but people with Down syndrome have a one-in-four chance of the disease. [20]

- As people with Down syndrome age, they face an increased chance of developing the brain. Disease called Alzheimer's (sometimes referred to Dementia or Senility). [21]

Epidemiology:

Down syndrome is the most common chromosomal abnormality in human. Globally, as of 2010, Down syndrome occurs in about 1 per 1,000 births and results in about 17,000 deaths. More children are born with Down syndrome in countries where abortion is not allowed and in countries where pregnancy more commonly occurs at a later age. About 1.4 per 1,000 live births in the United States and 1.1 per 1,000 live births in Norway are affected. [22] In the 1950s, in the United States, it occurred in 2 per 1000 live births with the decrease since then due to prenatal screening and abortions. The number of pregnancies with Down syndrome is more than two times greater with many spontaneously aborting. It is the cause of 8% of all congenital disorders. [3]

Maternal age affects the chances of having a pregnancy with Down syndrome. At age 20, the chance is 1 in 1,441; at age 30, it is 1 in 959; at age 40, it is 1 in 84; and at age 50 it is 1 in 44. [23] Although the probability increases with maternal age, 70% of children with Down syndrome are born to women 35 years of age and younger, because younger people have more children. The father's older age is also a risk factor in women older than 35, but not in women younger than 35, and May partly explain the increase in risk as women age. [12]

Clinical Manifestations:

- Microcephaly

- Flat face with upward slant to the eye, short & wide neck, small, low-set ears, flat nasal bridge & a protruding tongue.

- Brush field spots (tiny white spots on iris of eye). [24]

- Short broad hands & feet with a single crease on the palm of their hands.

- Small pinky fingers that sometimes curve towards the thumb.

- Excessive space between large toe & second toe.

- Muscle hypotonia[18]

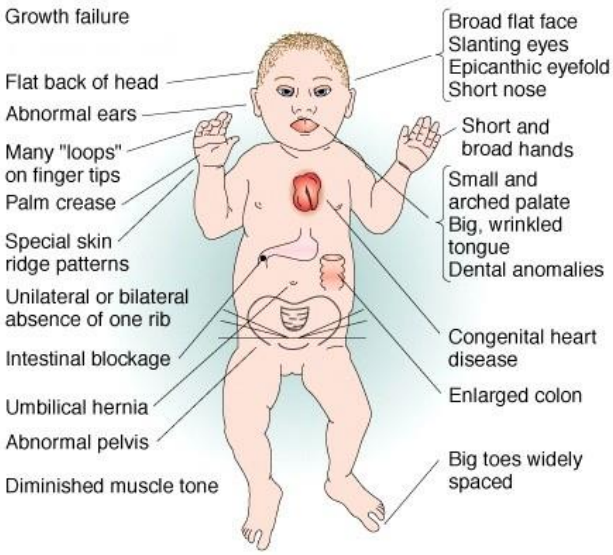
Features of Down Syndrome

Each person with Down syndrome is an individual — intellectual and developmental problems may be mild, moderate or severe. Some people are healthy while others have significant health problems such as serious heart defects.

Children and adults with Down syndrome have distinct facial features. Though not all people with Down syndrome have the same features, some of the more common features include:

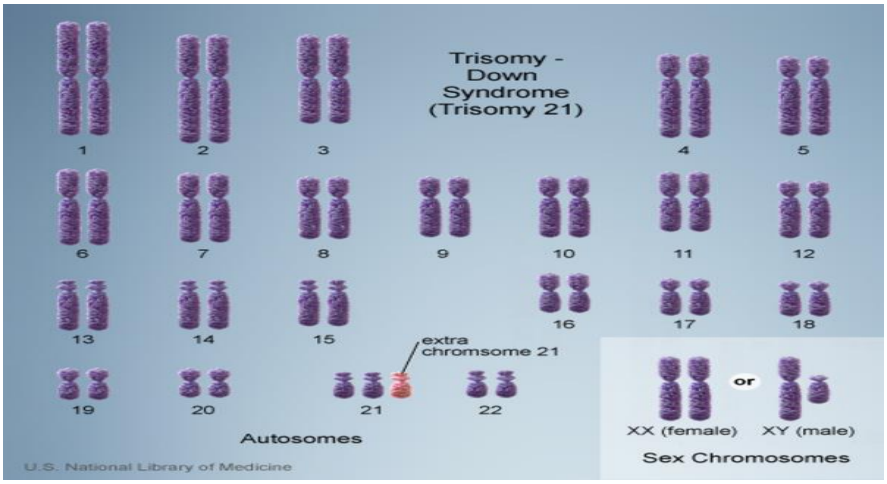
- Flattened face
- Small head
- Short neck
- Protruding tongue
- Upward slanting eye lids (palpebral fissures)
- Unusually shaped or small ears
- Poor muscle tone
- Broad, short hands with a single crease in the palm
- Relatively short fingers and small hands and feet
- Excessive flexibility
- Tiny white spots on the colored part (iris) of the eye called Brushfield's spots
- Short height

Infants with Down syndrome may be average size, but typically they grow slowly and remain shorter than other children the same age. [25]



Genetics of the disease

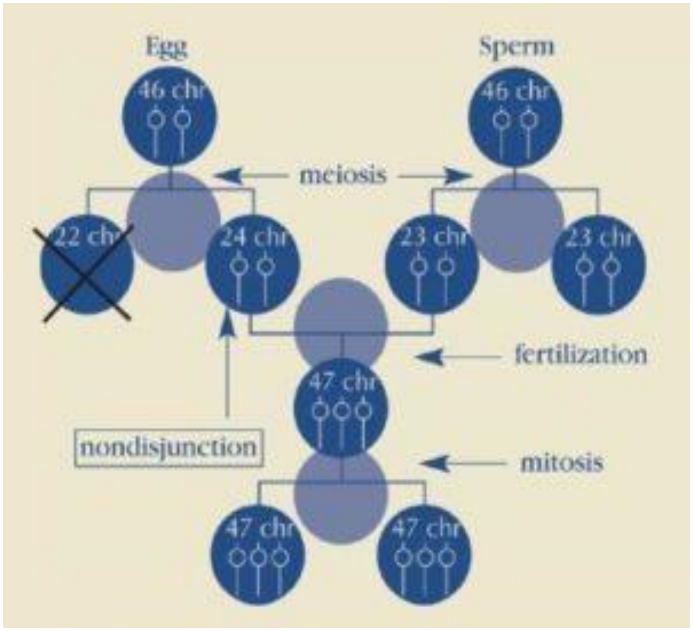
The most common cause of having a Down Syndrome babies is presence extra copy chromosome 21 resulting in trisomy. The other causes can be Robertsonian translocation and isochromosomal or ring chromosome. Isochromosome is a term used to describe a condition in which two long arms of chromosome separate together rather than the long and short arm separating together during egg sperm development. [1] Trisomy 21 (karyotype 47, XX, + 21 for females and 47, XY, + 21 for males) is caused by a failure of the chromosome 21 to separate during egg or sperm development. In Robertsonian translocation which occurs only in 2-4% of the cases, the long arm of the chromosome 21 is attached to another chromosome (generally chromosome 14). While mosaicism deals with the error or misdivision occurs after fertilization at some point during cell division. Due to this people with mosaic Down Syndrome have two cell lineages which contribute to tissues and organs of individuals with Mosacism (one with the normal number of chromosomes, and other one with an extra number 21). [26]



Different Types of Down Syndrome

i) TRISOMY 21 (NONDISJUNCTION)

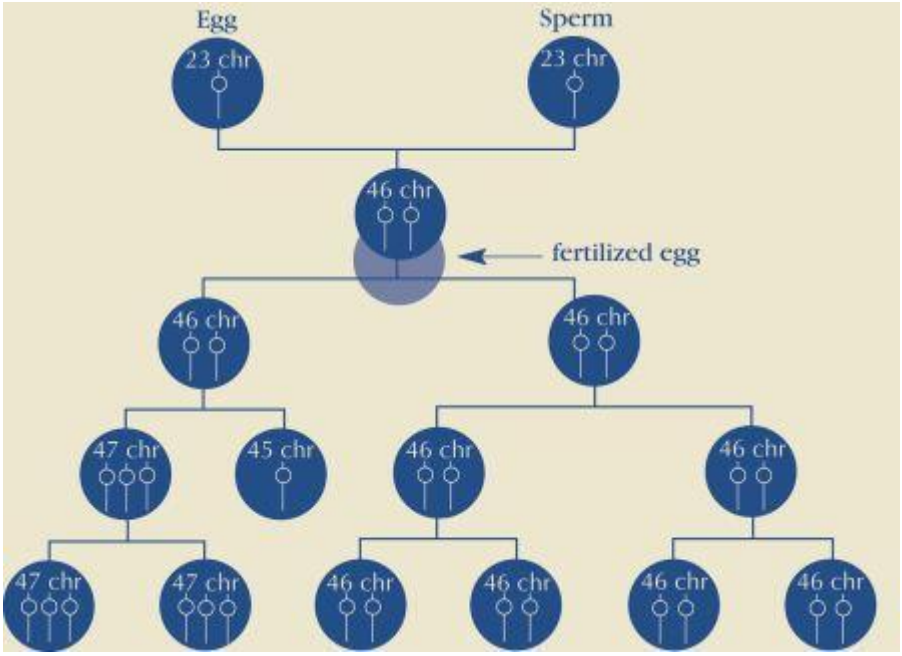
Down syndrome is usually caused by an error in cell division called "nondisjunction." Nondisjunction results in an embryo with three copies of chromosome 21 instead of the usual two. Prior to or at conception, a pair of 21st chromosomes in either the sperm or the egg fails to separate. As the embryo develops, the extra chromosome is replicated in every cell of the body. This type of Down syndrome, which accounts for 95% of cases, is called trisomy 21. [27]



ii) MOSAICISM

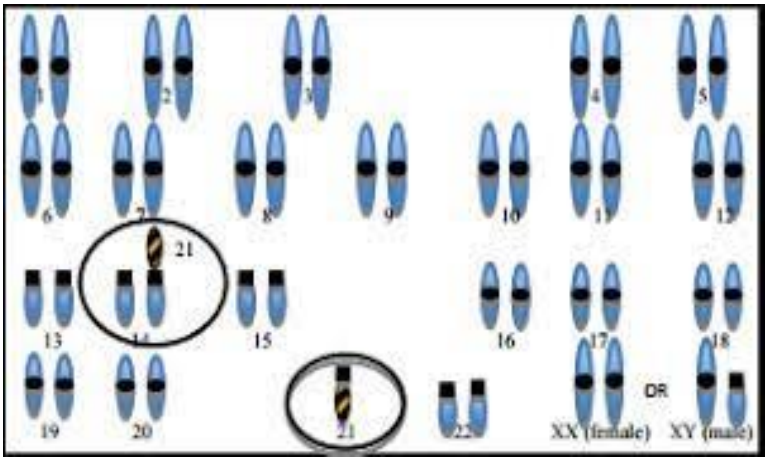
Mosaicism (or mosaic Down syndrome) is diagnosed when there is a mixture of two types of cells, some containing the usual 46 chromosomes and some containing 47. Those cells with 47 chromosomes contain an extra chromosome 21.

Mosaicism is the least common form of Down syndrome and accounts for only about 1% of all cases of Down syndrome. Research has indicated that individuals with mosaic Down syndrome may have fewer characteristics of Down syndrome than those with other types of Down syndrome. However, broad generalizations are not possible due to the wide range of abilities people with Down syndrome possess. [28]



iii) TRANSLOCATION

In translocation, which accounts for about 4% of cases of Down syndrome, the total number of chromosomes in the cells remains 46; however, an additional full or partial copy of chromosome 21 attaches to another chromosome, usually chromosome 14. The presence of the extra full or partial chromosome 21 causes the characteristics of Down syndrome. [27]



Is it inherited?

Most of the time, Down syndrome isn't inherited. It's caused by a mistake in cell division during early development of the fetus.

Translocation Down syndrome can be passed from parent to child. However, only about 3 to 4 percent of children with Down syndrome have translocation and only some of them inherited it from one of their parents. [29]

When balanced translocations are inherited, the mother or father has some rearranged genetic material from chromosome 21 on another chromosome, but no extra genetic material. This means he or she has no signs or symptoms of Down syndrome, but can pass an unbalanced translocation on to children, causing Down syndrome in the children. [14]

Risk factors

Some parents have a greater risk of having a baby with Down syndrome. Risk factors include:

Advancing maternal age. A woman's chances of giving birth to a child with Down syndrome increase with age because older eggs have a greater risk of improper chromosome division. A woman's risk of conceiving a child with Down syndrome increases after 35 years of age. However, most children with Down syndrome are born to women under age 35 because younger women have far more babies. [30]

Being carriers of the genetic translocation for Down syndrome. Both men and women can pass the genetic translocation for Down syndrome on to their children.

Having had one child with Down syndrome. Parents who have one child with Down syndrome and parents who have a translocation themselves are at an increased risk of having another child with Down syndrome. A genetic counselor can help parents assess the risk of having a second child with Down syndrome. [31]

Complications

People with Down syndrome can have a variety of complications, some of which become more prominent as they get older. These complications can include:

Heart defects. About half the children with Down syndrome are born with some type of congenital heart defect. These heart problems can be life-threatening and may require surgery in early infancy.

Gastrointestinal (GI) defects. GI abnormalities occur in some children with Down syndrome and may include abnormalities of the intestines, esophagus, trachea and anus. The risk of developing digestive problems, such as GI blockage, heartburn (gastro esophageal reflux) or celiac disease, may be increased.

Immune disorders. Because of abnormalities in their immune systems, people with Down syndrome are at increased risk of developing autoimmune disorders, some forms of cancer, and infectious diseases, such as pneumonia. [21]

Sleep apnea. Because of soft tissue and skeletal changes that lead to the obstruction of their airways, children and adults with Down syndrome are at greater risk of obstructive sleep apnea.

Obesity. People with Down syndrome have a greater tendency to be obese compared with the general population.

Spinal problems. Some people with Down syndrome may have a misalignment of the top two vertebrae in the neck (atlantoaxial instability). This condition puts them at risk of serious injury to the spinal cord from overextension of the neck. [19]

Leukemia. Young children with Down syndrome have an increased risk of leukemia.

Dementia. People with Down syndrome have a greatly increased risk of dementia — signs and symptoms may begin around age 50. Having Down syndrome also increases the risk of developing Alzheimer's disease.

Other problems. Down syndrome may also be associated with other health conditions, including endocrine problems, dental problems, seizures, ear infections, and hearing and vision problems.

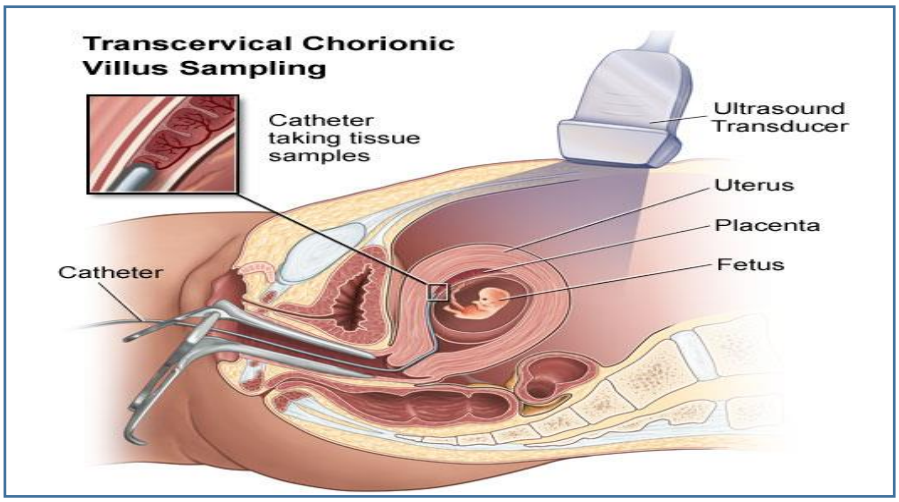
For people with Down syndrome, getting routine medical care and treating issues when needed can help with maintaining a healthy lifestyle. [29]

Diagnostic methods

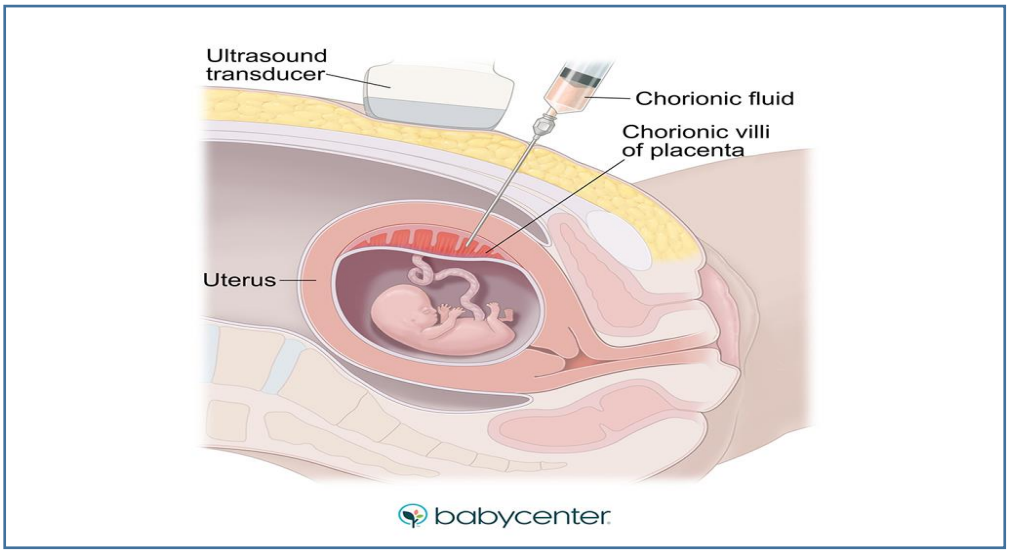
Prevention of DS depends upon offering prenatal diagnosis to high risk pregnancies via amniocentesis and chorionic villus sampling (CVS). Amniocentesis and CVS are quite reliable but offers risk of miscarriage of between 0.5 to 1%. Based soft markers like small or no nasal bone, large ventricles and nuchal fold thickness, the risk of DS for fetus can be identified through ultrasound generally at 14 to 24 weeks of gestation. Increased fetal nuchal translucency indicates an increased risk of DS. The other methods used for prenatal diagnosis in which traditional cytogenic analysis is still widely used in different countries. However some rapid molecular assays- FISH (**fluorescentin situ hybridization**),QF-PCR (**quantitative fluorescence PCR**), and MLPA (**multiplex probe ligation assay**)- also used for prenatal diagnosis. [22]

- Pregnant women be offered screening with the option for invasive diagnostic testing for DS, regardless of age.

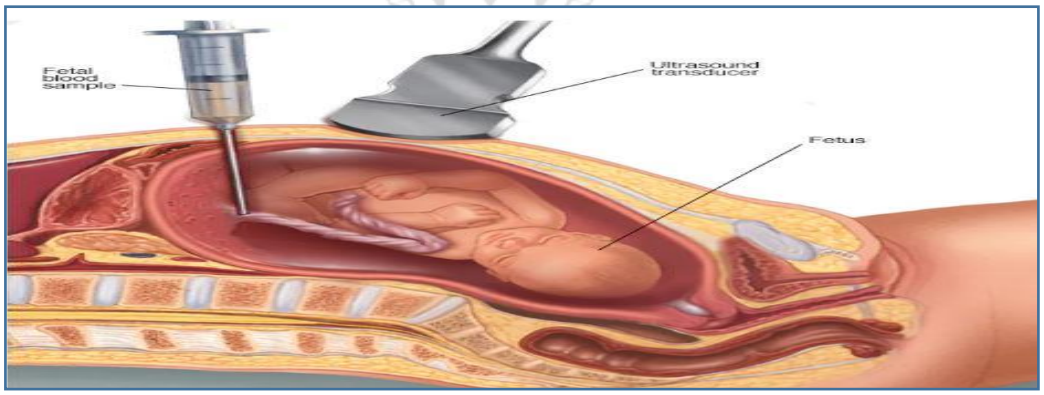
- **Chorionic Villus Sampling (CVS):** sample of placenta taken either through the cervix or through a needle inserted through the abdomen. Test can be performed between 8 and 12 weeks. [17]



• **Amniocentesis:** Removal of a small amount of amniotic fluid through a needle inserted in the abdomen. Cells are analyzed for the presence of chromosomal abnormalities. Test performed between 12 and 20 weeks of pregnancy. [19]



• **Percutaneous Umbilical Blood Sampling (PUBS):** Uses a needle to retrieve a small sample of blood from the umbilical cord. Usually performed after 20 weeks. [19]



• After the baby is born, if DS is suspected, a Karyotype – a blood or tissue sample stained to show chromosomes grouped by size and shape – can be performed to confirm the diagnosis. [19]

Advancement in the diagnosis

A recent method, termed paralogous sequence quantification (PSQ), uses paralogous sequences to quantify the Hsa 21 copy number. PSQ is a PCR based method for the detection of targeted chromosome number abnormalities termed paralogous sequence quantification (PSQ), based on the use of paralogous genes. Paralogous sequences have a high degree of

sequence identity, but accumulate nucleotide substitutions in a locus specific manner. These sequence differences, which are termed as paralogous sequence mismatches (PSMs), can be quantified using pyro sequencing technology, to estimate the relative dosage between different chromosomes. PSQ is a robust, easy to interpret, and easy to set up method for the diagnosis of common aneuploidies, and can be performed in less than 48 h, representing a competitive alternative for widespread use in diagnostic laboratories. The sequencing is quantitatively done by using pyro sequencing. Finally, **comparative genomic hybridization** (CGH) on BAC chips can be used for the diagnosis of full trisomy or monosomy, and for partial (segmental) aneuploidies. [16]

Treatment and Therapies

Medical Treatments:

- People with Down syndrome are at increased risk for certain medical problems.
- Some of the problems commonly faced by people with Down syndrome include heart defects, thyroid, muscle, joint, vision and hearing problems.
- Other conditions seen less frequently in Down syndrome include leukemia, and seizures. [8]

Medications:

- Medications can be used to treat certain conditions that occur in people with Down syndrome.
- For example, if a person with Down syndrome has a seizure disorder, they would benefit from taking anti-seizure medications. [13]
- People with thyroid problems often take thyroid replacement hormones.
- While these medications help with their medical condition, they do not have any effect on their Down syndrome.
- At this point in time, there is no medicine that will cure Down syndrome. [7]

Surgical Treatments:

- Some medical conditions seen in children with Down syndrome require surgery.

- For example, about 40% of children with Down syndrome have congenital heart defects. Some of these defects are mild and may fix themselves, and some heart defects are more severe and will require surgery. [11]
- Children with Down syndrome can have intestinal defects that also require surgery.
- The need for surgery does not correlate with the cognitive defect in Down syndrome.
- In other words, just because a baby needs surgery, there is no reason to suspect that they have a "more severe case of Down syndrome. [26]

Physical Therapy:

- Physical therapy focuses on motor development.
- Since most children with Down syndrome have hypotonia or low muscle tone, the goal of physical therapy is to teach the children with Down syndrome to move their bodies in appropriate ways, and to improve their muscle tone.
- Working with their muscles and movements will help children reach some of their motor milestones and will prevent them from developing problems, such as bad posture, that can accompany low muscle tone. [12]

Speech Therapy (Young Children):

- Although most children with Down syndrome learn to speak and will use speech as their primary means of communication, they will understand language and have the desire to communicate well before they are able to speak.
- Because children with Down syndrome often have small mouths and slightly enlarged tongues, they can have trouble speaking clearly. [23]
- A speech therapist will work with an individual to help them learn to communicate clearly.
- This can be achieved through talking, or in the case of many children using sign language, pictures, and/or electronic synthesized speech can serve as a transitional communication system. [29]

Occupational Therapy:

- Occupational therapists focus on the child's ability to master skills for independence. These can include:
- Self care skills (feeding, dressing, grooming, etc.) Fine and gross motor skills
- Skills related to school performance (eg: printing, cutting, etc.)
- Play and leisure skills [31]

Life expectancy

Life spans have increased dramatically for people with Down syndrome. Today, someone with Down syndrome can expect to live more than 60 years, depending on the severity of health problems. [30]

Prevention

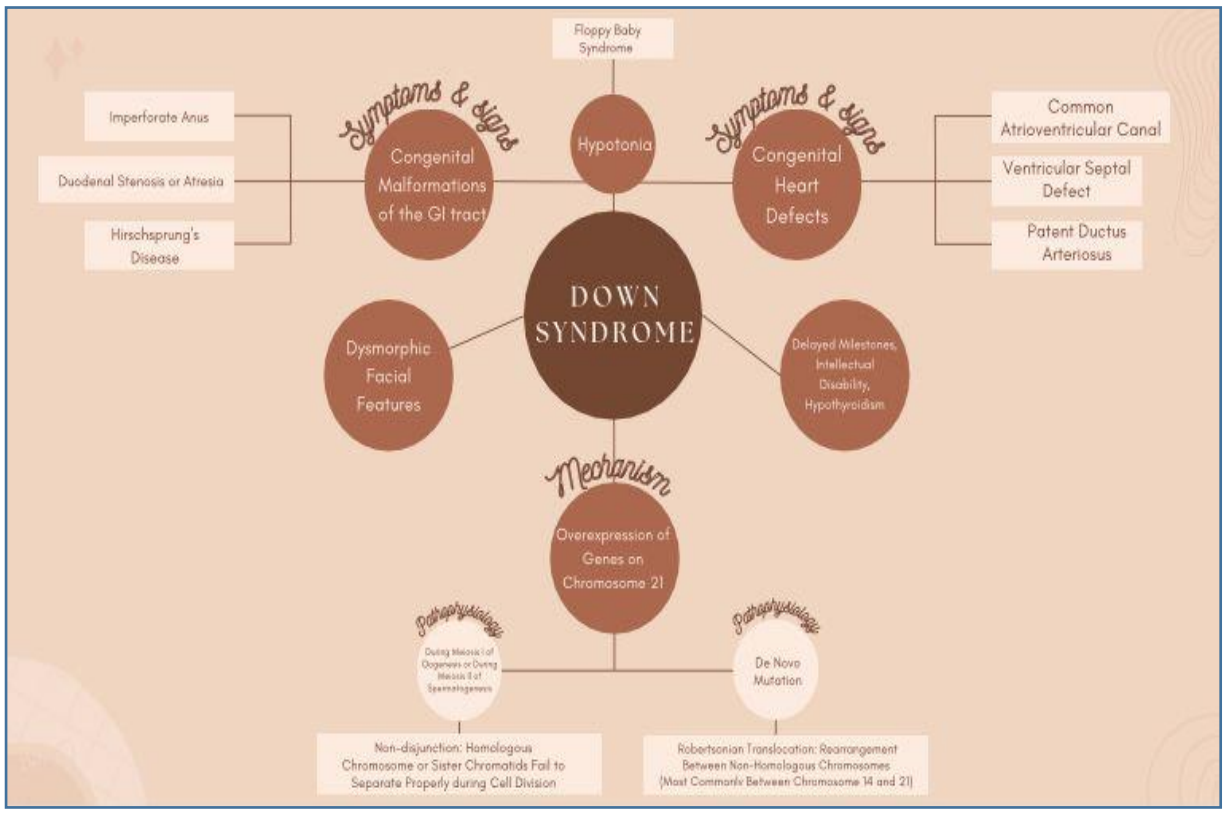
There's no way to prevent Down syndrome. If you're at high risk of having a child with Down syndrome or you already have one child with Down syndrome, you may want to consult a genetic counselor before becoming pregnant. [4]

A genetic counselor can help you understand your chances of having a child with Down syndrome. He or she can also explain the prenatal tests that are available and help explain the pros and cons of testing. [5]

Conclusion

Down syndrome or Trisomy 21, being the most common chromosomal abnormality among live born infants, is associated with a number of congenital malformations. Several theories have been put forward to increase our understanding in phenotype and genotype correlation. A “critical region” within 21 and 22 was believed to be responsible for several Down syndrome phenotypes including craniofacial abnormalities, congenital heart defects of the endocardial cushions, clinodactyly of the fifth finger and mental retardation and several other features. The primary goal of this review is to unravel the common genes involved in Down syndrome associated phenotypes, including APP, BACE2, PICALM, APOE, GATA 1, JAK 2, CRELD 1 and DSCAM. This reviews also provides the detailed description on the application of techniques to prenatal diagnosis in Down syndrome. Rapid aneuploidy testing has been introduced in mid-1990’s in the form of FISH where testing can be done on

uncultured amniocytes. Within a couple of years, MLPA and QF-PCR has been added in the list of rapid aneuploidy testing. The other methods includes: NGS for cell free fetal DNA screening for maternal plasma. Except, FISH, MLPA and QF-PCR other method are not commercialized for aneuploidy diagnosis due to their running cost, labor intensive protocol and complex data analysis. Since various clinical conditions are associated with Down syndrome, hence the management of these patients requires an organized multidisciplinary approach and continuous monitoring of these patients which has been discussed in this review article.



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