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A Detailed Insight into Down's Syndrome

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ABSTRACT:

Down syndrome (DS) is a birth defect with significant medical and social costs that is caused by trisomy of all or part of chromosome 21. It is the most common genetic disease in the world and the most common genetic cause of intellectual disabilities, affecting approximately 1 in 400-1500 newborns. Despite the fact that the syndrome had been described thousands of years before, it was named after John Langdon Down, who described it clinically in 1866. Scientists have discovered candidate genes that play a role in the development of specific DS features. These advancements, in turn, may aid in the development of targeted therapy for people with trisomy 21. Screening for Down syndrome is an essential part of routine prenatal care. Until recently, noninvasive screening for aneuploidy relied on maternal serum analytes and ultrasonography. Recent advancements have resulted in the development of a noninvasive prenatal screening (NIPS) test that uses cell-free foetal DNA sequences isolated from a maternal blood sample. There is a discussion of those accomplishments.

Key Words: Down syndrome, trisomy 21, prenatal diagnosis, chromosome abnormality, cell-free fetal DNA (cffDNA); noninvasive prenatal screening (NIPS)

1. INTRODUCITON

1.1 Genetic basis

Chromosome 21 is the smallest human autosome with forty eight million nucleotides and depicts nearly 1–1.five% of the human genome. The duration of 21q is 33.five Mb and 21 p is five–15 Mb. More than four hundred genes are predicted to be on chromosome 21 (Table 1). Chromosome 21 has 40.06% repeat content material comprising brief interspersed repeatitive elements (SINEs), lengthy interspersed repeatitive elements (LINEs), and lengthy terminal repeats (LTRs) (1, 2, 3). The maximum suitable concept for the pathogenesis of trisomy 21 is the gene-dosage speculation, which announces that each one modifications are because of the presence of an additional reproduction of chromosome 21 (4). Although it's miles tough to choose candidate genes for those phenotypes, information from transgenic mice propose that only a few genes on chromosome 21 can be worried withinside the phenotypes of DS and a few gene merchandise can be extra touchy to gene dosage imbalance than others. These gene merchandise encompass morphogens, mobileular adhesion molecules, additives of multi-subunit proteins, ligands and their receptors, transcription regulators and transporters. A "essential location" inside 21q22 turned into idea to be answerable for numerous DS phenotypes inclusive of craniofacial abnormalities, congenital coronary heart defects, clinodactyly of the 5th finger, intellectual retardation and numerous different capabilities (1, 2)

1.2 Genetics of the disease

The maximum not unusualplace reason of getting a DS infants is presence greater reproduction chromosome 21 ensuing in trisomy. The different reasons may be Robertsonian translocation and isochromosomal or ring chromosome. Ischromosome is a time period used to explain a situation wherein lengthy palms of chromosome separate collectively in preference to the lengthy and brief arm isolating collectively at some stage in egg sperm improvement. Trisomy 21 (karyotype 47, XX, + 21 for women and 47, XY, + 21 for males) is as a result of a failure of the chromosome 21 to split at some stage in egg or sperm improvement. In Robertsonian translocation which

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happens simplest in 2-4% of the instances, the lengthy arm of the chromosome 21 is hooked up to any other chromosome (usually chromosome 14). While mosaicism offers with the mistake or misdivision happens after fertilization in some unspecified time in the future at some stage in mobileular division. Due to this human beings with mosaic DS have mobileular lineages which make contributions to tissues and organs of people with Mosacism (one with the regular variety of chromosomes, and different one with an additional variety 21) [5].

2. Chromosome 21 Genes and Their Over expression

The cutting-edge chromosome 21 transcription map offers us with a few thrilling sequences with which to research the effects of overexpression. Such research continuously take region with transgenic mice in order that the consequences at the entire frame may be evaluated. Mice aren't human and, therefore, we are able to simplest use them to version dosage consequences, in preference to DS. Nevertheless, mouse fashions permit us to dissect organic pathways and mechanisms despite the fact that the final results of overexpression is probably extraordinary from what happens in humans . In the future, different version systems, which includes fly or yeast, are probably to turn out to be vital to useful research of human aneupoloidy, specially as many partial trisomies are recognized in those organisms[6].

While those mice permit us to take a look at the overexpression of unmarried genes, they do now no longer mimic the viable interactions that arise from more than one genes on a trisomic chromosome. In addition, overexpression from a unmarried transgene is frequently considerably extra than the diffused 3:2 dosage distinction visible among DS and regular people; one current exception is furnished with the aid of using transgenic mouse traces wherein the Ets2 transcription element is overexpressed at ranges similar with that visible in human DS. These mice expand skeletal abnormalities much like the ones discovered in DS people [7].

3. Various medical situations related to Down syndrome

The diverse medical situations related to DS are Alzheimer's disease, coronary heart defects, leukemia, high blood pressure and gastrointestinal problems[8]The molecular pathogenesis mechanism of those DS associated phenotype should be studied together with its causative marketers so that it will have a higher know-how of the disease. Below are a few DS associated phenotype mentioned in element which might be as follows:

4. Neurological problems

DS sufferers have significantly expanded threat of early onset AD. After the age of 50, the threat of growing dementia will increase in DS sufferers as much as 70% [9-11]. There are diverse genes said to reason early onset AD. Some of the genes defined withinside the cutting-edge literature are APP (amyloid precursor protein), BACE2 (beta secretase 2), PICALM (Phosphatidylinositol binding clathrin meeting protein) and APOE(Apolipoprotein E) etc. APP is an necessary membrane protein that is focused in synapse of neurons and trisomy of this protein is probably to make big contribution to the expanded frequency of dementia in DS people[12]. The triplication of Hsa 21 together with APP in human beings with out DS has been these days proven to be related to early onset AD.

Neurological phenotypes in Down syndrome .The neurological phenotype in Down syndrome (DS) is the product of genetic expression and environmental influences. Like the other forms of genetically determined developmental disability, the neurological phenotype in DS changes across the life span[14]. Changes in gene expression can determine differentiation of tissue involved in development and in functional decline associated with aging. Put differently, from the moment of conception we begin to age, a process involving decay in cellular structures, gene regulation, and DNA sequencing. Biological findings indicate that individuals with DS provide a link between development and aging. This review will examine the neurological phenotype at different age epochs in DS[16].

5. Neuroanatomic abnormalities and cognitive implications:

The morphology of the brain in DS is a characteristic of the disorder and includes reduced brain weight with diminished proportions in the volumes of the frontal and temporal lobes[17]. The brains of adults with DS are about 20% smaller than typically developing brains even when the measure is corrected for reduced body [18]. This reduction in brain size appears in 4–5-month fetuses and progresses during the last 3months of gestation.

Guihard-Costa et al., 2006). Magnetic resonance imaging (MRI) studies show an approximate 17% decrease in children with DS between 10 and 20years[19]. MRI studies confirm a selective decrease in the volumes of the

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hippocampus and the temporal lobes. The brain is brachycephalic with a small cerebellum, simplified gyral appearance, and a narrow superior temporal gyrus [20]. These anatomic findings have also been seen by voxel-based morphometric MRI studies of the brain in children and adults with DS [21]. The MRI studies have shown a remarkable preservation of subcortical gray matter structures in the face of a generally diminished brain volume, suggesting that there may be a temporal disassociation in development between the cortical versus subcortical areas. This may be an example of the disruption of developmental timing and homeostasis that occurs in DS and possibly other examples of aneuploidy[22]. Unexplainably, the parahippocampal gyrus may be larger than normal in DS [23]

6. Congenital Heart Disease

Congenital coronary heart disease (CHD) is a famous co-going on situation in Down syndrome (DS). The general incidence of CHD said in DS ranged from 20 to 57.nine%. In later decades, the superiority remained regular at 40—55%. Category of CHD numerous notably among research. Some research suggest a fashion in the direction of a milder phenotype, however this turned into now no longer consistent. Over time, a few research discovered an advanced diagnosis for CHD in DS. Studies investigating screening for CHD with the aid of using bodily examination, chest X-ray, and electrocardiogram record sensitivities of 71–95%.[24]

The prevalence of CHD in new child infants with DS is as much as 50% [8]. Endocardial cushion illness additionally known as as atrioventricular cushion illness is maximum not unusualplace shape which influences as much as 40% of the sufferers. Ventricular septal illness (VSD) is likewise found in those populace which influences as much as 35% of the sufferers [25]. The vital morphological hallmark of an AVSD is the presence of a not unusualplace atrioventricular junction in comparison to the separate proper and left atrioventricular junction withinside the regular coronary heart. Other morphological capabilities encompass defects of the muscular and membranous atrioventricular septum and an ovoid form of the not unusualplace atrioventricular junction[26]. There is disproportion of outlet and inlet dimensions of the left ventricle, with the previous extra than the latter in comparison to the regular coronary heart in which each dimensions are comparable [27]. While in case of VSD, the illness lies in ventricular septum of the coronary heart because of which a number of the blood from the left ventricle leaks into the proper ventric main to pulmonary high blood pressure. Mutation in non Hsa 21 CRELD1 (Cysteine wealthy EGF like domain1) gene contributes to the improvement of AVSD in DS [11].

7. Hematological problems

Studies suggest that sufferers with DS have a 10–20 fold expanded relative threat of leukemia, with a cumulative threat of 2% with the aid of using age five and 2.7% with the aid of using age 30 [28]. They represent about 2% of all pediatric acute lymphoblastic leukemia(ALL) and about 10% of pediatric acute myeloid leukemia (AML). Leukemogenesis of acute megakaryoblastic leukemia (AMKL) in DS sufferers is related to the presence of somatic mutations regarding GATA 1 gene (or additionally known as as GATA-binding element 1) [13]. GATA 1 is a chromosome X- related transcription element that is vital for erythoid and megakaryocytic differentiation.

8. Transient abnormal myelopoiesis

TAM, also called transient myeloproliferative disorder and transient leukaemia, is a haematological disorder virtually confined to Down syndrome and presents during fetal life or in the neonatal period. An identical disorder with the same natural history can also be found in neonates without Down syndrome but who have an acquired trisomy 21 confined to the haematopoietic cell[29]. A similar, but distinct, disorder can be seen in some neonates with Noonan syndrome.6 However, true TAM is strictly associated with trisomy 21. The importance of TAM is its potential to transform into an acute leukaemia, known as myeloid leukaemia of Down syndrome (ML-DS), which is estimated to occur in ~20–30% of babies with TAM, although the exact frequency is not known.7,8 TAM can therefore be considered as a leukaemic or "pre"-leukaemic syndrome (reviewed by Zipursky7). Clinically, TAM is conventionally defined by a combination of its haematological and clinical features (see box 2, and discussed in detail below). Using these criteria, about 10% of all newborns with Down syndrome have TAM. However, molecular genetic studies have recently shown that neonates with TAM have mutations in the key megakaryocyte transcription factor GATA1,9,10,11,12,13 which offers the opportunity to more accurately identify the true incidence of TAM in Down syndrome, since some infants with TAM do not have symptoms and may not previously have been diagnosed as having the condition[30]. All cases of TAM should be referred to a paediatric haematologist because the neonate may need specialised intervention and also to ensure the appropriate tests are done to clinch the

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diagnosis (see below). Another reason for referral is that follow-up is required as there is risk of the infant developing ML-DS later.

9. Hypertension

People with DS were said to have a discounted prevalence of high blood pressure [31]. Trisomy of the Hsa21 microRNA hsa-miR-one hundred fifty five contributes to this [32]. Hsa-miR-one hundred fifty five is proposed to especially goal one allele of the type-1 angiotensin II receptor (AGTR1) gene, ensuing in it's under- expression, which make contributions to a discounted threat of high blood pressure. Further research are required to validate this speculation and decide whether or not different genes may additionally defend human beings with DS towards high blood pressure[43].

Low blood pressure is reported in Down's syndrome (DS). To assess this and determine whether low pressure results from the disease or from long-term residence in hospital, we measured blood pressure with a random-zero sphygmomanometer in three groups of patients: 52 DS inpatients, 62 DS outpatients, and 60 outpatients with other forms of mental handicap. Relative to normal reference populations, blood pressure was low in both DS inpatients (systolic, score −33 mm Hg, $P<.0001$) and DS outpatients (−25 mm Hg, $P<.0001$). It was normal in non-DS outpatients (−4.0 mm Hg, $P=.3$)[44]. Blood pressure rose normally with age in the non-DS group but not in the DS group. We conclude that blood pressure is low in DS and that this is a feature of the disease rather than of the protected environment in which patients live. A mechanism related to trisomy 21 is likely, and there may be a link with Alzheimer's disease (AD) because blood pressure is also low in Alzheimer's and a high proportion of DS patients develop this disease[45]. If, as is likely, blood pressure is lowered in Alzheimer's by the neuropathy, the same neuropathy developing early in DS may also reduce blood pressure[46].

10. COVID-19 in sufferers with Down syndrome

The goal of the cutting-edge take a look at turned into to decide whether or not COVID-19 is related to a extraordinary supplying medical photo or a extra extreme route of infection in human beings with Down syndrome (DS). Down syndrome (DS) is a genetic sickness with numerous congenital defects (e.g., cardiac, respiration, immunological) [47].

All consecutive sufferers who had been admitted at healthcare centers everywhere in Fars province (placed withinside the south of Iran with a populace of 4,851,000 human beings) from 19 February 2020 to twenty November 2020 had been blanketed[48]. For each affected person with DS, 3 age- and sex-matched sufferers with COVID-19 and with none underlying scientific situations had been decided on as controls[49].

11. Otorhinolaryngological (ENT) Disorders

Ear, nose, and throat problems are also quite common in patients with Down syndrome. The anatomical structure of the ear in Down syndrome patients predisposes them to hearing deficits. Hearing loss is usually conductive because of impaction of cerumen and middle ear pathologies that include chronic middle ear effusion due to the small eustachian tube, acute otitis media, and eardrum perforation. These patients usually require pressure equalization tubes for the treatment.

The sensorineural hearing loss has also been associated with Down syndrome because of the structural abnormalities in the inner ears such as narrow internal auditory canals[42].

12. Musculoskeletal Disorders

Children with Down syndrome are at an increased risk of reduced muscle mass because of hypotonia increased ligamentous laxity which causes retardation of gross motor skills and can result in joint dislocation[43]. These patients also have vitamin D deficiency due to several factors like inadequate exposure to sunlight, inadequate intake of vitamin D, malabsorption secondary to celiac disease, increased breakdown because of anticonvulsant therapy, among other factors. These factors increase the risk of decreased bone mass in children with Down syndrome and predispose them to recurrent fractures[50]

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Conclusion:

To summarise, DS is a birth defect with significant medical and social costs, and there is currently no medical cure for DS. As a result, all pregnant women must be screened for DS. NIPS for foetal aneuploidy, which has been in clinical use since November 2011, is not yet considered a diagnostic test because false positive and false negative test results continue to be generated. Following a positive cfDNA foetal aneuploidy screening test, invasive diagnostic testing such as CVS or amniocentesis is recommended.

The described performance of the cffDNA test for screening for trisomy 21 is superior to other screening methods, with a diagnostic rate of more than 99 percent and a false positive rate of less than 0.1 percent. Despite widespread acceptance, the test's high cost prevents it from being used on all patients who have been identified as such by another traditional first-line screening method. The nuchal scan is regarded as the most appropriate first-line method of screening when using DNA testing.

Conflict of Interest:

The authors declared no conflict of interest

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