Diyala Journal of Medicine

ORIGINAL RESEARCH
Published: 30 June 2023
Doi: 10.26505/DJM.24027180102

Molecular Biology View on Down syndrome: Review article

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Abstract

Background: Down Syndrome (DS) is a resulting from a defect of the genotype in patients affected by it. The occurrence of this type of disease is very common. It has been associated with causing many genetic diseases with a significant change in phenotypic pattern. People with this type of disease suffer from intellectual disability that ranges from mild to moderate, delay in growth and the emergence of some distinctive signs in the face. It leads to Alzheimer's in some cases. The treatment cost is very high and exorbitant, many laboratories have sophisticated diagnoses methods, but they are expensive and require high skill. Therefore, this disease still needs to develop many genetic methods to facilitate its diagnosis infection rates reduction among humans.The present review article empasied an overview of DS-associated phenotypes diagnosis and managment of the disease. Furthermore,we have also Reviewed further parental diagnosis methods to facilate moleculr methods CSV, MLPA, FISH, QF-PCR, PSQ, and NGS and noninvasive dignosis in details.

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Received: 2 January 2023
Accepted: 19 March 2023
Published: 30 June 2023

Introduction

Dermatophytosis Down syndrome (DS),named as trisomy 21, is a genetic syndromeproduceddue tooccurrence of all or part of a third chromosome number 21. Patients usually have minor to modest mental retardation, developmental delays, and prominent facial structures [1].DS was first termed by British physician,John Langdon Down on 1866 who discovered the chromosome number 21.The existence of the third duplicate of chromosome 21 or portion of it leads to DS, the most communal chromosomal abnormal in humans [2].It waproposed that the most common aneuploidy is trisomy 21, as sourcesof this disorder [3].

The incidence of DS increases with motherly age a rate raged from 1 / 319 to 1 / 1,000 live deliveries [4,5].It wasrecognizedthat fetuses with DS is compeletly healthy at the period of gestation, but 50% to 75% of these fetuses die prematurely. The autosomal trisomies are more common than trisomy 21, but postpartum existence is at low in this case. The survival rate of patients with trisomy 21

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Published: 30 June 2023
Doi: 10.26505/DJM.24027180102

is believed to be due to a few genes on chromosome number 21 namedHsa21, that is the least and smallest dense autologous gene [6]. In most cases, Down syndrome is caused by an extra copy of a person's chromosome21, causing a defect in gene expression, which increases the abnormal intellectual function. Controlling of DS is challenging when considerate the effects of dose inequity due to trisomy 21 (T21) and the sequencing of genome, genome comparison investigation, genome function scanning, This has steered to novelindication that based on therapeutic methods to prevent the effects of T21 on brain construction and cognition which has significantassociationswith investigation of cognition and behaviorin the neurogenomics [7].

Etiology

Most patients with DS have an extra duplicate of chromosome #21. There are several theories regarding the genetic basis of DS and the connection between its diverse genotypes and phenotypes.

These include gene dose imbalances in which an increase in the dose or number of Hsa21 genes leads to increase genetic proliferation. This also includes the possibility that different genes may be associated with different Down syndrome phenotypes. Another popular suggestion is the evolutionary variability hypothesis, which is stated that the genetic defect is caused by a set of triploid genes, resulting in a more influence on the expression of numerous genes [8].DS is a major cause of mental retardation, and millions of people who suffer from it suffer from various health problems such as education and remembrance problems, Alzheimer's disease (AD), congenital heart disease (CHD) and leukemia,and Hirschsprung's disease (HD) [9,10].

Down syndrome is a challenging syndrome at genetic and phenotypiclevel [11,12]. Patients with Trisomy are at high risk of miscarriage and its sequences [13].

Medical defect of DS

Several medical defectshave been found in the DSpeople, includingcraniofacial malformations,comprising learning disabilities and hypotension at childhood age. [14]. DS individuals with diabetes of various phenotypes, may have leukemia, atrioventricular septal defects (AVSD) (both AMCL and AD), acute lymphoblastic leukemia (ALL)and HD. The clinical signs of individuals DS include; small eye, muscular weakness, flat nose, small mouth and tongue, one palm and one side [15].

The geneticdefect of the DS

As mentioned above, the most communalreason of children with DS is the existence of an additional copy of chromosome #21 which leads totrisomy. Other causesare related to the translocation of Robertson and isochromatic or annulus chromosomes. Ichromosome is a term used to describe the separation of the long arms of a chromosome, rather than the separation of the long and short arms, during the development of a sperm cell into an egg. Trisomy 21, karyotype 47, XX, +21 for females and 47, XY, +21 for males occurs when chromosome #21 does not discretefduring sperm or egg progress. In Robertsonian translocation, which happensin merely(2% to 4%) of cases, the lengthyof chromosome 21 arm fuses with alternative chromosome (usually chromosome 14). On the other hand, mosaic

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type DS deals with post-fertilization errors or incorrect division that occurs somewhere during cell division. As outcome, individuals with mosaic DS have dual cell lines (one with a usualchromosomes count and single with an extra 21 chromosomes) that contribute to the tissues and organs of the mosaic people [16].

The phenotypic - Genotypic correlation

Evidence for a gene number defect indicates that patients with Down syndrome have a higher dose or number of copy of the Hsa21gene, which may indicatean increasing in the expression of the gene. This theory have been prolonged to comprise the suggestion that certain genes or subgroups of genes regulate some phenotypes of Down syndrome[17].The hypothesis of increasing developing instability conditionsproposed that a nonspecific dose of numerous triploid genes results in a genetic defect that has a significant influence on the regulation and expression of numerous genes [15]. Phenotypic analysis were done on persons with limited trisomy Hsa21, in which about 30 genes are responsible for one or more minor chromosomal areas called DS critical regions (DSCR), which ranging from 3.8 to 6.5 Mb at 21q21.22 [17].Earlier a region of 91.6 - 2.5 Mb was recognized as adequatereason for phenotype of DS [18]. The sequence of Hsa21 has been shown to be an essentialfeature in the development and diagnosis of DS. In addition, it has led to a better understanding of the relationships between genotype and phenotype features of DS and accurate characterization of the regions of DSCR. The 'critical zone' within 21q22 is thought to be accountable for a variety of diabetes phenotypes, comprising craniofacial malformations, congenital heart defects in the endocardium, subclinical fifth toe, and mental retardation [19].The double specificity regulator tyrosine phosphorylation kinase (DYRK1A) and DS cell adhesion molecule 1 (RCAN1) (DSCAM) is thought to production a seriouspart in brain development and has as well been recognized as anapplicant gene. To increase the risk of coronary artery disease in patients with diabetes. DSCAM is a serious factor in neuronal distinction, axon guidance, neural network formation, and disturbance of these progressions has been suggested to contribute to the neurocognitive phenotype of DS [20].Based on the comprehensive analysis of human and mouse DS models, it is clear that a single serious gene region is not a singlereasonfor all DS variants. On the other hand, there are many serious regions or genes that contribute to the phenotypic, or set of phenotypic,relatedto DS[21].

Methods of DS Diagnosis

Down syndrome could be determined bydiagnosis of prenatal of high danger pregnancies usingchorionic villus sampling (CVS)and amniocentesis. CVS,as well asAmniocentesis, are completely safe, however there is a 0.5% to 1% risk of miscarriage [22]. The risk of the fetus having DS can usually be determined by ultrasound between 14 and 24 weeks of pregnancy [23]. Improved transparency of the posterior cavity of the fetus shows an augmented risk of developing DS. Other prenatal diagnostic systems, isbased on the traditionalcytology, commonly using in several countries. Nevertheless, a number ofquick molecular tests, QF-PCR (quantitative fluorescent PCR) FISH (fluorescent in situ hybridization), and

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MLPA (multiple probes ligation assay) are likewise using for diagnosis of prenatal [24] as they are explained below:.

Cytogenetically analysis(Giemsa banding)

It is achieved at metaphase time on amniocytes on fetal cells (grown-up in vitro) or CVS.This test is appropriate for low-income countries where the medical doctors should ensure their great analytical ability in the deficiency of research laboratory facilities. The disadvantage of this method is a time-consuming assay. In addition, the recognition of fundamental abnormalities may be fairly little, as the division of impulsive cells is further reduced compared to the in vitro cell culture.In CVS, the existence of restrained mosaicism of the placenta also the incidence of cells that abnormality that does not recognize the state of fetal. It gives probabilities of a wrong positive and/or a negative outcome.

Fluorescence In Situ Hybridization(FISH)

FISH includessequences specificDNAof chromosomehybridizationthat brandedby a fluorescent color to the chromosome prepare. Thesequences thatfluorescentlytagged are inserted into the analogous DNAmolecules on the chromosome then can be seen byusing a microscope. As smaller sensors are used, the indicators appear more clearly as points. It uses more interface cores for examination, thus the problematic of questionable mosaicism is solved by FISH.

Quantitative Fluorescent-Polymerase Chain Reaction(QF-PCR)

It includes amplify and finding STRs using fluorescent labeling primers. Thus, the creation is envisioned and counted as crests of appropriate length using an automatic DNA sequencer with genetic screening software. The method is very reliable and repeatable. The probability of receiving false positive and false negative results is low. It is easy to identify the infection of the mother. A faster approach to diagnosis can be made within 24 hours. However, it is difficult to take into account the shortcomings of the mosaic example. At the time of testing, samples with sex chromosome deformities from a normal female XX may display a homozygous QF-PCR pattern vague from that from a single X sample, as in Turner disorder.

Multiplex Probe Ligation Assay (MLPA)

MLPA is performed based on PCR andneucleic acid hybridization. It is separated into 4 steps: denaturation of DNA, the probe hybridization withprobe ligation,complementary target sequences and amplification of PCR the fused probe. These improvedproducts are examined by capillary electrophoresis. This method is a very short diagnostic time assay (2 to 4 days) and a fairly low cost. However, placental depression and a failure to exclude true mosaicism could not be identified in this method.

Paralogous Sequence Quantification (PSQ)

A polymerase chain reaction-based techniquefor finding anomalies in target chromosome sum created on the usage of aberrant genes. The sequences that are paralogous have a greatgrade of sequence characteristics,however,collection of nucleotide substitutions in a site-specific way. Those mismatches homologous sequence could be measured using thermal sequence. The main advantage of first-generation assay development is that 10

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individual PCR reactions are required per sample, which considerablydecreases sample volume and increase the potential of processing errors. It is cheaper, compared to other methods, and can process 30-40 testers per day and report outcomes in less than 48 hours.

Next Generation Sequencing(NGS)

The magnified DNA templates are relatively arranged in large parallels because the reading of each string can be counted 'sequence tag' and represents as a single clonal of DNAmoleculeor template.NGS provides numerical quantitative information. In this test, the time available for sample dispensation, sequencing, and data explanation is 5 to 8 days, but the unanticipated cost of sequencing and compound documents analysis is about 700 to1000 $ per test [25].

Rapid Aneuploidy testing

Previously, ten years ago, many furthertechniques have been developed and used for identification of trisomy 21, both in uterus after the second birth. FISH is the best at interphase nuclei using all Hsa21 probes or specific probes. QF-PCR is anothertechnique currently used in a number ofcountries.QF-PCR usesDNA polymorphism (microsatellite) tags in Hsa21 to detect existence of three diverse alleles [26].This process depends on presence of DNA and the information content of the indicators. The rapidanalysis by PCR-based techniques by usingSTR polymorphismindicators can limit these complications with the conservativemethod. Using the STR indicatorprocess, it can identify trisomy 21 in 86.67% of cases using only two indicators. Using additionalindicators can rise the consistency of the test [27,28].Another method,MLPA, is used for measuring DNA sequences copy number [29].MLPA was firstlypresented in 2002 as a virtualway for DNA quantification. MLPA is a test of very short diagnostic time (2-4 days), efficient, ease and fairly low cost. It is used in the hybridization and PCR and includes four steps: denaturation of DNA, hybridization of the probe with complementary target sequences, probe ligation and PCR amplification. Lastly, capillary electrophoresis of the PCR amplification produces is performed. Nevertheless, MLPA cannot rule out low true placenta and mosaicism [30].

Non-Invasive Prenatal analysis

Based on the detection of fetal lymphocytes in the mother's circulation in 1969, researchers have sought to develop a non-invasive prenatal genetic diagnosis (NIPD) method. Despite the many benefitsaccessiblevia this assay, the usage of the fetus cells in NIPD havecertainly not been implemented clinically,due to the paucity of these cells (cells/ml of mother’s blood) and fears of that fetal cells remain in the blood of mothers fetus cell-freefrom DNA in motherly serum: This new process was suggested in 1997. Fetus cell-free from DNA, which makes up 5% to 10% of DNA molecules inplasma mother, and risesthrough pregnancy,thenquickly removed from the blood circulation after birth . Various medical applications have been developed and establishedin order to examin thefetus cell-free from DNA, including; determination of fetusRh factor D in Rh-negative females (31). Gender in sex syndromes (32) and discovery of recessive and dominant genetic mutations

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inherited from the father [33]. However, using cell-free fetal DNA to detect aneuploidy, especially trisomy 21, 18 and 13, remains a major challenge. Mother cells obtain free DNA from motherly leukocytes [34]. The method is to examine variances in genomic DNA methylation between placental and conjugated motherly leukocytes.It was identified that placenta-specific epigenetic indicators [35]. In addition, the discovery of placenta-derived cell-free mRNA enables the determination of placental-specific mRNA production [36]. The next method to add near the grade is followingnext generation sequences (NGS), that is created on the standard of clonal amplificationtemplates of DNA (or, more newly, single DNA molecule) sequencing in a large similarprocess in a current cell. The NGS delivers numerical quantifiableevidence where the reading of every sequence is a countable "sequence tag" and represents a DNA clonal of template molecule. This NGS quantification extends the perception of digital PCR to enumerate cell-free from DNA molecules [37, 38] It was designated that the non-invasive finding of NGS, trisomy 21 [39]. The authors extract cell-free from DNA inplasmamother samples of the chromosomal andlineages of trisomy. The DNA sequences of every sample were entered into the Illumina Genome Analyzer and every read sequence was compared toreferenceofgenome of human. Another builds on previous effort with the Illumina gene analyzer and demonstrates the discovery of non-invasive NGS-based trisomy 21 using a linkage sequencing method on Life Technologies' SOLiD platform [40].

Epidemiology of DS

The prevalence of DSrises with motherly age and differs across populations (from 1 in 319 to 1 in 1,000 live births) [41]. It is as wellidentified that the occurrence of fetuses with DS is very great at the period of conception, but 50% - 75% of those fetuses die prematurely. Other autosomal trisomies are more communal than trisomy 21, but postpartum endurance is very low equaled to DS. The great survival rate of patients with trisomy 21 is believed to be due to a few genes on chromosome 21 termedas Hsa21, which is the least and smallest dense autologous gene [42].

Pathophysiology of DS

An additional copy of chromosome 21 is related with DS, which happens when chromosome 21 does not discrete during genomics, result in an additional chromosome in every single cell in the body. Chromosome and Robertsonian translocation or ring chromosome are other probablesources of trisomy 21. Isochromosome is a state in which two long arms diverge as an alternative of the long and short arms during the Robertsonian translocation. It appears in 2-4% of patients. The long arm of chromosome 21 is devoted to alternative chromosome, commonly chromosome number14. There are two diverse cell lines in the mosaic due to mitotic errors after fertilization [43].

Medical circumstancesrelated to DS

Neurological problems

People with DS have a significant risk of developing early Alzheimer's disease. After age 50, the danger of emerging dementia increases to 70% in people with diabetes [21]. Several genes have been describedas a

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sourceof early inception of Alzheimer's disease. These genes are associated withthe amyloid precursor protein (APP), BACE2 (beta 2 chain), PICALM (phosphatidylinositol-associated clathrin assembly protein), APOE (apoprotein E), etc. APP is afundamental membrane protein found in synapses. Localized Trisomy of this protein may be considered lost to the augmented incidence of dementia in those with DS. Recently, Hsa21 replication by APP has been revealed to be associated with initial onset of Alzheimer's disease in individuals without diabetes. A tetranucleotide reappearance in intron 7 of the APP, ATTT, is relatedto the beginning of Alzheimer's disease in DS in aninitialtraining [44]. Numerousmodels mouse are used to monitor the regeneration of forebrain cholinergic neurons (BFCNs). Ts65Dn mice rely on trisomy to express APP for retrograde axonal transportation [45]. The autors showed that BACE2, which codes the beta-secretase 2enzyme, is implicated in AD. The BACE2 and APP genes are situated on chromosome number 21. Recent documents on DSprovision the relationship of BACE2 haplotypes withAD [46]. In addition to theBACE2and APP genes, further genes such as APOE andPICALM have also been originate to be related with the starting of Alzheimer [47].

Complications of Cardiac

The prevalence of coronary artery disease in newborns with diabetes is up to 50%. An endocardial cushion fault, likewise known as an atrioventricular cushion fault, is the bestcommunal form, affecting 40% of patients. Ventricular septal defect (VSD) is also existing in this population and disturbs 35% of patients [48, 49]. The most significant morphological feature of the AVSD is the incidence of a communal AV junction in the normal heart paralleled to the right and left separate AV junctions. The other morphological characters include;comprisemembranous atrioventricular septal, muscular defects and the oval-shaped of the communal atrioventricular junction. There is a mismatch between the inlet and outlet of the left ventricle, with the first being larger than the second paralleled to a regular heart where both volumes are the same [50]. For ventricular septal defect, the fault is in the ventricular septum of the heart because blood is leaking from the left ventricle into the right ventricle, causing pulmonary hypertension. A mutation in the cysteine-rich EGF-like domain (1) gene other than Hsa21.The Creld1 transferred to the improvement of AVSD in DS [51]. *Creld1* is situated on chro 3p25. It codes a protein cell surface that roles as a cell adhesion molecule and is articulatedthrough cardiac cushion progress. The Creld1 gene comprises 11 exons of ~12 kb in size. To date, two genetic locus specific for AVSD have been recognized. One of these locus was the AVSD loci 1 located on chro 1p31-p21 [52]. The further locus was on chro 3p25 and the analogous gene was *Creld1* [53].

Hypertension

The incidence of hypertension is low in the patirnts with DS [53]. Presence of the trisomy of microRNA Hsa21 hsa-miR-155 is believed to speciallytarget an allele of the receptor type 1 (AGTR) gene, which is providing a comprehensive understanding of the expression process. There is more

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speculation about whether this strategy and/or other genes can protect people with DS from high blood pressure [54].

Gastrointestinal problems

Down syndrome patients account for about 12% of all HD cases. Duodenal stenosis (TSD) and anal stenosis (AI) are 260 and 33 times, respectively, more likely to accompany DM [55]. Hepatic encephalopathy is a form of intestinal obstructioninitiated by absence ofusual IBD cells at a portion of the colon [56]. The deficiency of ganglion cells in children with HD happens whentheirlarge (distal) intestine cannot relax generally. This casewill slow/ceases the intestinal peristaltic movements through the nodular part and influence on the usual defecation leading to functional impairment of the digestive system. Flatulence, enterocolitis, abnormal meconium secretionandbiliary nausea are the main symptoms and signs occur in the days following delivery. Biliary vomiting occurs early in the neonatal period in infants with duodenal atresia or DST. If left untreated, this leads to austereelectrolyte and dehydration imbalance. AI is also a congenital defect in which the rectum is deformed. AI enhances the occurrence of a severalparticularabnormalities, which namedas VACTERL relationship: anal atresia,,vertebral malformations, cardiovascular malformations, esophageal atresia, renal failure,tracheoesophageal fistula, darn and limbs. Defective changes in about 10 genes other than Hsa21 are associated with this disease. Several studies have shown that Huntington's disease involves thegene of DSCAM, which is articulated in the neural crest and gives increase to the system of enteric nervous. An overlyingseriousarea for DST and IA is described. To date, no other Hsa21 genes have been included [57].

Hematologic Disorders

The following are some of the blood syndromesrelated with DS. Several hematological abnormalities in children with DSwere identified including, neutropenia, thrombocythemia, and polycythemia, occurring in 80%, 66%, and 34%, respectively of children with DS. Hands are frequently soft,identified during the first three weeks of life [58]. Another disorder characteristic of DS is temporary myeloproliferative disease, which is well-defined as the appearance of eraptions in children less than 3 months of age with DS. It is described by clonal reproduction of megakaryocytes, which is identified in the first week of life and disappears by the age of 3 months. Also known as transient myelodysplasia or transient leukemia, it occurs in about 10% of patients with DS. If this happens in a fetus during the gestation peroid, it may cause a miscarriage [59]. Individuals with DS are ten times more likely to develop leukemia [60]. Thirty percentage of DS patients with acute lymphocytic leukemia are associated with a functional mutation in the gene of Janus kinase 2. [61].

Alternative control of DS

Previously, a wide range of alternative treatments have proposed in order to improve the development and growth of children with DS. The community demands for complementary and alternative medical care(CAM) to controlthe developmental disorders. The safety and efficacy of the alternative therapies should be evaluated

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Published: 30 June 2023
Doi: 10.26505/DJM.24027180102

through clinical research projects and centers [62]. To improve their health and developmental potential of child as a person with DS, the parents has to acceptusing CAM. In this situation, parents worked as a committed advocate and service coordinator for their child [63].The most commonly used CAMwasnutritional supplements [63]. The authors found that (70.0%) of families have children with DS, tried more than two therapies; 16.7% had tried only one treatment, and 13.3% had not tried therapy [64]. Of the families who had used CAM therapies, most parents (67%) had communicated none or only some of this use to their pediatricians [64]. The published trials, which were methodological shortcomings,were few randomized and controlled trials. It was reported that a systematic, exhaustive information to identify appropriatedietary supplements, medicines and their effect on the cognitive function of individuals with DS[65]. Using combined search strategies, the author identified more than 20000 studies, all subjects had DS, treated with drugs and/or dietary supplements, cognitive function was used as an outcome measure, a placebo group was used as a control.These scientific studies demonstrated that the traditional treatment showed no effect. The possible, the rationale, and the outcomes of studies in vitro and in vivo and in animals and humans was discussed in several reviews. Some studies refereed to using vitamin therapies, and other antioxidants, and some medications, such as piracitam and donepezil, to control DS.

Conclusions

Down syndrome(DS) is one of the common diseases in many countries. Although many theories and studies have been conducted in-depth regarding DS, more efforts are needed to investigate the genetic and functional form of the defects-associated DS. Moreover, Anan innovation, rapid and safe laboratory methods are urgently requiredfor early diagnosis of DS in pregnant women. In addition, tThe relationship of this chromosomal abnormality with the other gentic infections should be explored. Since various clinical conditions were associated with DS, we recommend to a continuous monitoring and multidisciplinary approaches for these as discussed in this review article.

Recommendations

Based on the information provided in this mini-review, this study recommended taking good care ofthe style and quality of life, which could increase the life expectancy of people with DS.In addition, The typical diagnosis of DS using recent techniques, such as chromosome analysis after suspected by prenatal screening, could reduce some its consequences including cognitive impairment. A continued research is essential for directing the care for optimal outcomes of people with DS.

Source of funding: The current study was funded by our charges with no any other funding sources elsewhere.

Ethical clearance: Ethical approval was obtained from the College of Medicine / University of Diyala ethical committee for this study.

Conflict of interest: Nil

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Diyala Journal of Medicine

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Published: 30 June 2023
Doi: 10.26505/DJM.24027180102

نظرة بيولوجية جزيئية لمتلازمة داون

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الملخص

خلفية الدراسة: إن متلازمة داون هي سمة غير طبيعية للكروموسومات شائعة في البشر الذين لديهم تثلث صبغي للكروموسوم (٢١) تحدث نتيجة خلل في التركيب الوراثي التي يكون فيها خارج الصبغيات وان حدوث هذا النوع من الاضطراب شائع جدا حيث يرتبط بالعديد من الأمراض الوراثية، كما ان تكلفة التشخيص باهظة للغاية. حيث يعاني الأشخاص المصابون بهذا النوع من المرض من إعاقة ذهنية تتراوح من خفيفة إلى متوسطة وتأخر في النمو وظهور بعض العلامات المميزة في الوجه. يؤدي في بعض الحالات إلى الإصابة بمرض الزهايمر. هناك العديد من طرق التشخيص المخبرية ، لكنها باهظة الثمن وتتطلب مهارة عالية. لذلك ، لا يزال هذا المرض بحاجة إلى تطوير العديد من الأساليب الجينية لتسهيل تشخيصه و بالتالي تقليل معدلات الإصابة بين البشر. هذه الدراسة تهدف الى إبراز أهمية هذا المرض والطرق المهمة المعتمدة في تشخيصه.

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