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Research Article

A Comprehensive Review on Down Syndrome Diagnosis and Associated Genes: Diagnosis of DS

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Abstract:

Down syndrome (DS) is an inherited genetic disease characterized with the trisomy of chromosome 21. The major clinical presentation of DS is intellectual disability which is seen among 12-15% of DS patients in the developed countries. Increased maternal age over 30 years increases the risk of having DS child. DS affects various organ systems causing cardiac disorders, GI abnormalities, hematological anomalies, endocrine disorders and skin diseases along with morphological anomalies of face, feet and hands. The current review aims at outlining the genes associated with cardiac, GI and hematological disorders seen in DS patients along with DS itself and also widely used diagnostic tools in identifying the disorder.

Keywords: Down syndrome, Gene Mapping, Genotype-Phenotype correlation, Genetics, Chromosome 21, Trisomy.

Introduction:

Down syndrome (DS) is a genetic disorder characterized with trisomy of chromosome 21, presence of either a portion or full of third copy of chromosome[1]. Patients with down syndrome are presented with mild to moderate intellectual disability and growth retardation[1,2]. It dates back to 1866 when Down Syndrome was first described by an English physician, John Langdon Down but the association of the disease to the trisomy of chromosome 21 came into light almost a century later in 1959 by Dr Jerome Lejeune from Paris[2].

Epidemiology

With incidence rate of 1 among 650 to 1000 live births, it accounts for most inherited intellectual disability. 12-15% of patients with learning disabilities in developing countries were of down syndrome[3]. In India where the consanguineous marriage rates are very high in the enormous population size and the birth rates are high, the prevalence of Down syndrome is also high. Out of 495,000 infants with congenital mutations 21,400 were with down syndrome [4]. 95% of patients with Down syndrome have a karyotype of trisomy of chromosome 21, 4% present translocation and rest 1 % shows a mosaic pattern[5].

Among DS patients 50.7% presented GI abnormalities with Chronic intestinal constipation as seen mostly seen disease. Giardiasis is seen in 22%, GERD is seen in 14%, and digestive tract malformations in about 5% population [6]. Following this, next commonly seen abnormality includes congenital heart disease that is seen in 40-50% of DS patients [7].

Among the DS patient's males contributed majorly with 57.8% and females of 42.1% [8,9]. The risk of having a DS child increase with increase in the maternal age above 30 years [10].

Genotype and Phenotype Correlation

Use of mice models of Down syndrome and sequencing of chromosome 21 elucidated the pathogenesis of the syndrome and association of the genes or sets of genes in the phenotype presentation[11]. Phenotypical complexity of the DS is due to imbalance in the dosage of genes on the chromosome 21 (HSA 21) [12]. Basic approaches in developing the genotype-phenotype correlations can be done by, partial trisomy of chromosome 21 mapping, developing various mouse models with partial trisomy of HSA 21 at different orthologous regions & analysis of gene expression (transcriptome/ aneuploid chromosome genes) [13]. Combination of mice models and genomic analysis unveiled the gene dosage imbalance and its associated functional characteristics [14]. However, there are evidences that support the genes outside D21S55 also contribute significantly for the phenotype presentations of DS [15].

There are 2 hypotheses stated for phenotypical variations and its association with the genotype, viz., gene dosage effect hypothesis & amplified developmental instability hypothesis. The former hypothesis explains the direct cumulative effect of imbalance in the genes located on the extra copy of the chromosome 21 while the latter explains the disruption of homeostasis as a result of non-specific chromosomal imbalance [16].

Genes Responsible for Various Phenotypes

D21S55 or DCR-1 (Down syndromes' Chromosomal Region-1), on 21q22.2-21q22.3 proximal (1/20 of the long arm) is related to the presentation of four cardinal features: Growth retardation, Mental Retardation, Joint hyperlaxity & muscular hypotonia along with 8 of 18 common morphological

anomalies relating to feet, face and hands.

The phenotypes of DS is often linked to the cluster of genes located on the small regions of chromosome 21, viz., D21S55 (DCR) and D21S55-MX1 and the identified genes, viz., ETS2, ERG, HMG14 and MX1 are identified on D21S55-MX1 and no genes were identifies on DCR [17]. The cDNA probes used in the analysis after DNA hybridisation that are mapped on chromosome 21 include D21S46 in 21q11.2-21.05, D21S47 and SF57 in 21q22.1-22.3, and D21S39, D21S42, and D21S43 in 21q22.3 along with 21q22.1 for CuZn-superoxide dismutase (SOD1) gene and 21q11.2-21.05 for amyloid precursor protein (APP) mapping[18]. Trisomy of the HSA 21 between the regions D21S58 and D21S55 down to COL6A1 or of the region distal to D21S17 were greatly responsible for the facial changes, mental retardation and CHD [18,19]. Incurved 5th figure and few facial features were found to be associated with the D21S55-D21S15 and gap between 1st and 2nd toes joint laxity, brachycephaly, hypotonia, mental retardation and gut atresia were associated with the region D21S8 (located between D21S11 – D21S15) [20].

Overlapping of DCR 1 & DCR 2 (21q21.2-21q22.3, 1-10 of the long arm) presents congenital heart defect and other 5 of 18 common morphological anomalies of feet, face and hands along with the features presented by DCR 1 [21].

DS affects various organ systems of the body, hence clinical presentations related to different systems are presented by the patients. Signs and symptoms vary greatly from developmental or intellectual disability (neurological features), GI abnormalities, Congenital Heart defects, hematological abnormalities, morphological abnormalities of feet, face and hands [22].

Among DS infants congenital heart defects are seen in approximately 40-50%, of which approximately half are of Atrio Ventricular Sepal Defects (AVSD) (2,000 of 10,000 DS new born patients have AVSD) [23]. Ventricular septal defects are also seen in 35% of patients [12,23]. Presence of three copies of gene D21S3 would present DS- Specific Congenital Heart Disease (DSCHD)[24]. Most prevalent of DSCHD, AVSD is seen due to CLERD 1 (Cystiene rich EGF like Domain1) mutation at chromosome 3p25.3 [12,25]. A locus related to CLERD 1 is located on chromosome 1p31-p21[26].

In terms of neurological abnormality, DS patients often develop clinical features of Alzheimers Disease (AD)[27]. Genes associated with this include genes of Amyloid Precursor Protein (APP) mapped on 21q11.2-21.05[18], beta secretase 2 (BACE2), Phosphatidylinositol binding clathrin assembly protein (PICALM) and Apolipoprotein E (APOE)[12]. The brain of DS has reduced weight & proportions of volume of the frontal and temporal lobes [28]. Structural changes in the dendrites of the neurons in hippocampus, cerebellum and cerebral cortices are also seen[29] . DS patients often develop AD at an early age due to presence of tetranucleotide repeat, ATTT, in the intron 7 of amyloid precursor protein [30]. About 12% of Hirschsprung disease (HD) is seen in DS patients[12].

The GI abnormalities includes developmental obstructive defects of small intestine and anomalies of colon and anorectal with intestinal duplication [31]. DS patients would present symptoms like vomiting, diarrhoea, constipation & abdominal pain and discomfort[32]. A Swedish case control study reported the risk of Celiac Disease is six folds higher in DS patients on comparison to the healthy volunteers[33]. GI abnormalities in DS patients results in increased morbidity in children, which is seen the most among all, and would require hospitalisation and special setting to treat in case of adults[34]. However, the GI anomalies presented by DS are not linked with the trisomy nature of the genotypical DS patient[35].

The hematological abnormalities in newborn with Down syndrome (HANDS) includes thrombocytopenia, neutrophilia, polycythemia, thrombocytosis, congenital leukemia and transient myeloproliferative disorder (TMD), transient leukemia [36,37]. Various hematological parameters like white blood cell count, hematocrit, platelet count are seen altered in DS patients [38]. Of all the hematological diseases seen, leukemia accounts more which is developed due to GATA 1 mutation [39]. The 2 major genomic linkages to the hematological presentation of DS patients lies within the trisomy of 21 and GATA1 mutation, however, the exact gene location on the trisomy 21 responsible for hematological disorders is mostly unknown [37].

Diagnosis

Diagnosis of DS at an early stage is vital. Prenatal screening for presence of abnormalities/ markers of trisomy of 21 associated with the DS can be done in the second trimester using ultrasound screening for the presence of ventriculomegaly, greater nuchal fold thickness, minimal or no hypoplastic nasal bone, short humeral length, echogenic intracardiac focus and bowel along with choroid plexus cyst that can detect DS with a sensitivity of >90% [40]. However, sonogram will predict the risk of foetal abnormalities the women considered as high risk for DS (increased maternal age, biochemical and sonogram abnormalities) are to be further confirmed with invasive procedures like amniocentesis, chorionic villus sampling and cordocentesis which has a false positive rate of 0.2% but with a miscarriage risk of 1% -2% [41,42]. Other methods developed for diagnosing DS include Fluorescence in situ hybridization (FISH) that uses probes specific for chromosomes, quantitative fluorescent (QF)-PCR that uses PCR technique and 2 tetranucleotide short tandem repeat markers and paralogous sequence quantification (PSQ), a PCR based technique that uses a paralogous gene of Hsa21 [43]. There are few non-invasive procedures used in prenatal screening for estimating the risk of DS which include presence of foetal cells in the maternal bold and also cell free foetal DNA [1]. Recently placental specific epigenetic markers are also identified that are potent markers that can be used as non-invasive prenatal diagnosis of DS [44].

DS patients presents with physical and intellectual symptoms, the former one includes almond shapes eyes, upward slanting eyes with a skin fold that comes out from upper eyelid and cover inner corner of eye, flattened face, short neck with excess skin fold on the back of the neck, head, mouth & ears, protruding tongue, tiny white spots on the iris of eye (Brushfield spots), palmar crease (single line across the palm), small hands and feet, small pinky figure that curves outwards poor muscle tone

and loose joints, shorter height, deep groove between first and second toes and the latter includes short attention span, poor judgement, impulsive behaviour, slow learning and delayed language and speech development [45,46].

Besides these diagnostic tools there is a need of another simpler tool to estimate the risk or confirm the presence of DS in order to make it easily identifiable and start an early intervention to improve patient outcome.

Summary

Down Syndrome is one of the most studied genetic diseases of humans. However, one can find the discoveries or advancements in the correlation of various genes with the phenotypical presentation is done much before 2 decades from now. Although, there are several unanswered questions and numerous phenotypes that are to be corelated with specific genes, the advancement is seen to be slowed down in this area. The major limiting factor for this review to exclude the genotypic correlation with the endocrine and skin diseases in DS, as there are not much articles or papers describing the genes association with these diseases/ disorders. Besides this genetic-phenotype establishments, a major need for a simpler tool in diagnosing the disease or in estimating the risk of disease also still exist.

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