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Down Syndrome Compendium: Article Review

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Received: February 21, 2020; **Published:** March 14, 2020

Abstract

Down syndrome is the most common genetic syndrome caused by trisomy 21. Individuals with DS are at an increased risk of heart defects, gastro esophageal reflux, celiac disease, hypothyroidism, hearing and vision problems, leukemia, and Alzheimer disease (AD), as well as intellectual disability of varying degrees. The objective of this review is to provide a framework for understanding different aspects of Down syndrome such as brief historical background, Genetics contributions, risk factors, various types, Common features of abnormal phenotype, developmental deficiencies associated with several health problems due to the some genes overexpression.

Keywords: *Down Syndrome; Trisomy 21; Chromosome Anomaly*

Background

Down syndrome (DS) is the common genetic disease cause of intellectual disabilities worldwide [1]. It discovered about 150 years ago [2]. In 1959, Jerome Lejeune identified that Down syndrome as a chromosomal anomaly; he found 47 chromosomes Instead of the usual 46 chromosomes in each cell of individuals with Down syndrome. It was later determined that an extra partial or complete chromosome 21 results in the characteristics associated with Down syndrome. The genes of this extra chromosome produced an excessive amount of certain proteins in the cell, which disturbs the normal growth in the body of the fetus, causing the characteristic features of Down syndrome and health problems associated with this condition [3].

Advanced maternal age is considering a primary risk factor of DS [4]. The incidence of this syndrome is less than 1 in 3000 for women under age 30, increases to 1 in 300 in the 35 to 39 age group, and to 1 in 9 at age 48. Some studies suggest that there are other various environmental and occupational factors that may increase the susceptibility to DS such as alcohol and nicotine, medications (oral contraceptives and spermicides, hormonal therapy, radiation therapy and fertility medications), toxic wastes and infections [5,6].

Genetics aspect of the DS

Knowledge the of normal structures and numbers of chromosomes are the corner stone for understanding process of the disease. The human bodies are consisting of billions of cells; each cell contains the hereditary units, known as genes which are packages into structures called chromosomes. Normally, males and females have 23 pairs of chromosomes; give a total of 46 chromosomes. 22 pairs are autosomes (non-sex) homologous chromosomes, these chromosomes are numbered according to their sizes from 1 to 22 [7]. The 23rd pair is the sex chromosomes, they differ between the sexes. The humans, males have a Y chromosome and an X chromosome while the females have XX chromosomes (Figure 1). Each chromosome consists of two arms separated by the centromere. The long arm and short arm are labeled q (queue) and p (petit), respectively [8].

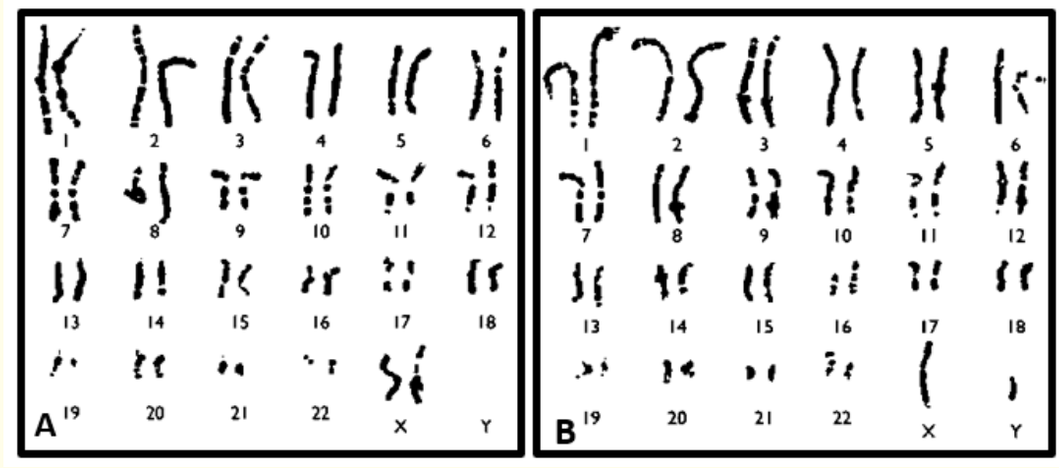

Figure 1: *Show Human karyotype autosomes and sex chromosomes, A. Females and B. Males (www.sdsa, 2001).*

In meiosis, two members of a pair of homologous chromosomes normally separate during the first meiotic division so that each daughter cell receives one member of each pair [10] (Figure 2a). Sometimes, separation does not occur (nondisjunction), and both members of a pair move into one cell (Figure 2b and 2c). As a result of nondisjunction of the chromosomes, one cell receives 24 chromosomes, and the other receives 22 instead of the normal 23, at fertilization, when a gamete having 23 chromosomes fuses with a gamete having 24, the result is an individual with 47 chromosomes (trisomy) as in the Down syndrome [10].

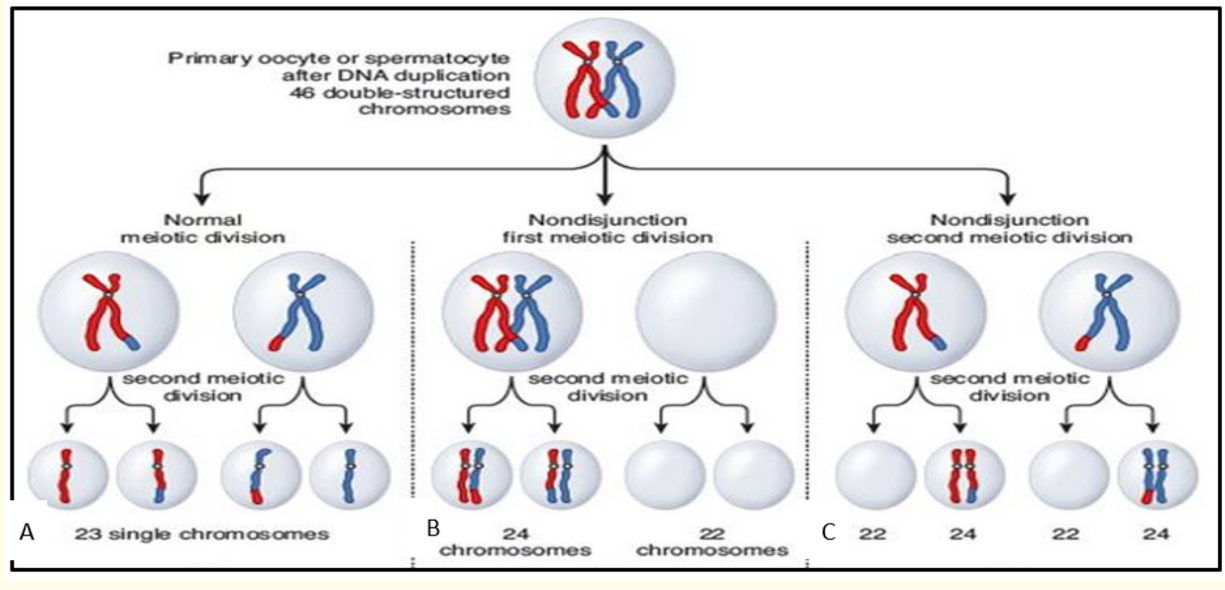

Figure 2: *A. Normal divisions. B. Nondisjunction in the first meiotic division. C. Nondisjunction in the second meiotic division [9].*

Down syndrome is most often occurred during meiosis caused by an error of nondisjunction that leads to individual with three copies of chromosome 21 (Figure 3). Chromosome 21 is the smallest human chromosome and contains 200 to 300 genes [11]. DS individual have an extra copy of chromosome 21 resulting in trisomy, so this type of DS is called trisomy 21 and is consider the major cause of DS, accounting for about 95% of cases [12]. 3 - 4% of DS cases are caused by chromosomal translocations, the long arm of the chromosome 21 is attached to another chromosome, generally chromosome 14 (Figure 3) this condition is called Robertsonian translocation DS [13]. Less than 2% cases of DS caused by mitotic nondisjunction which result in some cells with the normal number of 46 chromosomes, and others cell with an extra chromosome 21, containing 47 chromosomes [5]. These cases may exhibit few or many of the characteristics of Down syndrome, this condition is called mosaic Down syndrome.

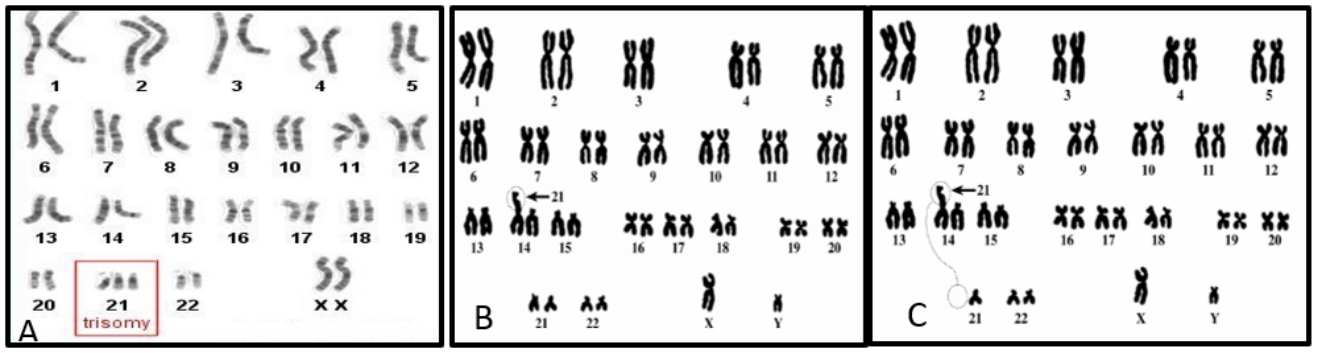

Figure 3: *Down syndrome karyotype A. trisomy 21. B. Unbalanced translocation (14; 21). C. Balanced translocation www 2.palomar.edu/anthro/abnormal/abnormal [14].*

Down syndrome types

People with DS have extra chromosome 21 in some or all of their cells, according to the nature of the abnormality of the chromosome 21, three types of DS are known, trisomy 21, translocation and mosaic [15].

Trisomy 21 means that each cell in the body has three copies of chromosome 21 instead of the usual two copies resulted in 47 chromosomes. It is the most common type of DS.88% of cases of trisomy 21 is of maternal origin and occurs in all cells bodies, trisomy 21 is usually not hereditary [16].

Robertsonian translocation DS, translocations refer to the rearranged chromosome material. There are two forms of Robertsonian translocation DS: familial and de novo. In case of the familial form, a parent is carrier of a translocation and this can transmit that translocation in an unbalanced form (Figure 3B) to the child [13], Affected child I has two normal copies of chromosome 21, in addition to an extra attached chromosome 21 [5]. While for the de novo cases, parents have a normal karyotype and the abnormal chromosome occurs as a spontaneous event in maternal meiosis I from a chromatid translocation [13]. The mother has a higher (10%) risk of transmission than the father (1%). Patients with translocation DS are physically indiscernible from those with Trisomy 21 but they have 46 chromosomes not 47 and one chromosome is larger because it carries the extra 21 (Figure 3B).

Mosaic down syndrome

Is a rare form of Down syndrome, a person has only some cells with an extra copy of chromosome 21. This mosaic of normal and abnormal cells is caused by nondisjunction after fertilization [5]. This type is not inherited [15]. It is not passed down by parents. The chance of having baby with Down syndrome is approximately 1% and may be slightly higher depending on the age of the mother.

Down's syndrome common features

DS individual have variety of anatomical characteristics like, craniofacial abnormality which include brachycephaly (head is small and flattened posteriorly), round face, a flat nasal bridge, small ears, small chin, protruding tongue due to small oral cavity, eye slanted slightly upwards caused oblique palpebral fissures and epicanthic fold (small skin folds at the medial corner of the eyes). Other features include short neck, arms, legs, toes and fingers in relation to the body size, a single horizontal crease of palm (normally double crease across palm), wider space between the large toe (first toe) and the second toe, muscle hypotonia (poor muscle tone), Hyper-flexibility (an

excessive ability to extend the joint) and dry skin, etc. [17-19]. Other features include the brain, decreased sizes of the cerebrum (frontal, occipital and temporal lobes, hippocampus and corpus callosum). Furthermore, cerebellum and brainstem are smaller in size, there are fewer dendrites (main receptive of neurons) and synapse irregularly [20-22].

Down syndrome complications and some genes

Chromosomes contain the genetic information that controls the normal growth of the body systems and their function. Products of the genes on extra chromosome 21 overexpressed in cells and tissues of DS patients [23], these genes have a variety of effects on health and development, but the effects depending on the extent of abnormality [19]. Neurological defects of DS patients includes an assortment of anatomical, physiological and biochemical changes in the brains of patients at various ages [24], for example alterations in neural mechanisms at a chemical level resulting from changes due to replication of chromosome 21 at the cellular level affect the brain development processes [22]. Down syndrome is the most common genetic cause of intellectual disability (ID) in the population due to a gene over expression [25]; in DS abnormal development of the dendritic structures is a sign of ID [24] which affects learning and cognition [19] in addition atrophy of the temporal lobe could account for specific memory and language impairment as it contains the hippocampus, primary auditory area (region responsible for sound) as well as Wernicke's area (region responsible for speech and language recognition) [21,22]. Down syndrome predisposes patients to early onset Alzheimer's disease (AD) due to over-expression of genes on chromosome 21, such as amyloid precursor protein (APP) gene [26,27]. A smaller cerebellum contributes to problems of hypotonia (poor muscle tone), motor coordination, articulation, as well as language and general intelligence in DS [22].

Other severe condition is Cardiac defect with incidence up to 50% [28]. Down syndrome cell adhesion molecule (DSCAM) gene has been identified as a candidate gene for the increased risk of CHD in DS patients [29]. Cardiac abnormalities in DS include atrioventricular septal defect (AVSD), ventricular septal defect (VSD), isolated secundum atrial septal defect (ASD), isolated persistent patent ductus arteriosus (PDA) and isolated tetralogy of Fallot (TOF) [30].

Additional conditions with higher incidence in Down syndrome are gastrointestinal defect include celiac disease [31], feeding difficulties, duodenal atresia or Duodenal stenosis (DST) (short part of the bowel is completely blocked), imperforate anus (IA) and Hirschsprung's disease (HD) (Holland., *et al.* 2000). HD is a form of low intestinal obstruction caused by the absence of normal myenteric ganglion cells in a segment of the colon results in the failure of normal relaxation of the intestine [32].

Patients with Down syndrome have an underactive thyroid gland (hypothyroidism), diabetes and leukemia [31,32], which is a cancer of the white blood cells, mutation of GATA1gene predispose to leukemia [34]. Vision anomalies such as refractive, binocular anomalies, as well as ocular diseases are prevalent in DS patients [4]. Snoring and obstructive sleep apnea due to flattened face and a large tongue.

Conclusion

To better understand Down syndrome this review presents physical characteristics, types, genetic aspects and highlighted some complications and genes associated with DS. To manage clinical problems of DS patient's, medical examinations should be done as soon as they are born to find out if they have additional medical problems such as vision and hearing problems. Early diagnosis of medical problems, frequent visits to the doctor and continuous monitoring of these patients increase life expectancy in a good quality. Parents are advised to adopt a treatment program appropriate for development and needs of the child such as speech and language therapy programs, physiotherapy and Social communication with others.

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