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REVIEW

# Analysis of Downs syndrome with molecular techniques for future diagnoses

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**Abstract** Down syndrome (DS) is a genetic disorder appeared due to the presence of trisomy in chromosome 21 in the G-group of the acrocentric region. DS is also known as non-Mendelian inheritance, due to the lack of Mendel's laws. The disorder in children is identified through clinical symptoms and chromosomal analysis and till now there are no biochemical and molecular analyses. Presently, whole exome sequencing (WES) has largely contributed in identifying the new disease-causing genes and represented a significant breakthrough in the field of human genetics and this technique uses high throughput sequencing technologies to determine the arrangement of DNA base pairs specifying the protein coding regions of an individual's genome. Apart from this next generation sequencing and whole genome sequencing also contribute for identifying the disease marker. From this review, the suggestion was to perform the WES is DS children to identify the marker region.



**Contents**



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## 1. Introduction

Down syndrome (DS) is an autosomal genetic disorder that causes Intellectual disability and increased risk of organic disorders caused by the trisomy 21 (~21q22 region), appearance of additional chromosome leading to birth defects (Mendioroz et al., 2015). Chromosomal aneuploidy is one of the main causes of developing trisomy 21 (Kamhieh-Milz et al., 2014). DS affects ~1 in 1000 in live born children throughout the globe. Earlier studies have reported the risk of DS when the maternal age is greater than 40 years, and increased age of the maternal grandmother may increase the risk of DS. Maternal age plays an important role in the frequency of DS (Ellaithi et al., 2008). The phenotypic characters are brachycephaly, flat facies, upward slanting palpebral fissures, epicanthus, and low-set round ears with abnormal folds, epicanthus, and unique transverse palmar crease, among others. Diagnosis is purely based on clinical features, and cytogenetic analysis (Garduno-Zarazúa et al., 2013). The clinical symptoms of DS are protruding tongue, small head, poor muscle tone (hypotonia), short height, flattened facial features, short hands and fingers (Patil et al., 2014). The initial identification of DS was based upon the clinical symptoms followed by karyotyping and fluorescent in situ hybridization analysis. There are no biochemical, histological, pathological and molecular tests to diagnose the DS. Unfortunately, the diagnosis of DS was performed with the chromosomal analysis. Cytogenetics is the time taking process (> 72 h) for the identification of the diagnosis. The development of extra chromosome is due to the error in cell division (chromosomal non-disjunction in meiosis 1). Trisomy 21 is an error in meiosis, i.e. failure of normal chromosomal pairing or premature unpairing and has a recurrence risk of about 1 in 100. The appearance of trisomy 21 is due to the improper development of egg/sperm cells during meiosis and subsidizes extra chromosome.

## 2. History

Escorel was the first person to describe the Down syndrome (DS) in children in 1838 (Weijerman, 2011). Later on, the DS was discovered by British physician Prof. John Langdon Haydon Down (John Down) as a mental disorder in 1866. From his research, he analyzed the children with DS has common physical characteristics, similar to Mongolian race and termed the disease as Mongolian Idiocy or Mongolism and patients were denoted as Mongoloids. Later on Lejeune, Turpin and Gautier identified the third chromosome 21 in patients with DS in 1959. From this turning point, discovery lead to an understanding of DS as trisomy of chromosome 21 (Weijerman, 2011). The accurate cause of DS was discovered in 1959 with the clinical symptoms. In 1974, Nebuhr suggested that the "Down syndrome phenotype" might be caused by the duplication of only a part of chromosome 21 band q22, which represents about one-half of the long arm (Desai, 1997). Turkel (1985) proposed Down syndrome as a biochemical disease. If the whole chromosome was present in triplicate, then each gene was also in triplicate. Considering one gene at a time could reduce one large problem to many smaller ones (Baggot and Baggot, 2014).

## 3. Genetics and cytogenetics

The study of chromosomes is known as cytogenetics or chromosomal aberrations. Mendel's laws were rediscovered in 1900 and in 1903, the scientist Walter Sutton noted that chromosomes follow Mendel's laws and speculated that genes might be contained on chromosomes. In 1915, Morgan and colleagues published a synthesis of years of work entitled "The Mechanism of Mendelian Heredity", which made an almost incontrovertible case that genes are located on chromosomes. By 1920, the concept that chromosomes carry genes was widely accepted (Patterson and Costa, 2005). Finally in 1958, Tjio and Puck had confirmed that humans consist of 46 chromosomes (Tjio and Puck, 1958). James et al. (1999) were the first to observe an increased risk of chromosome non-disjunction due to abnormal folate metabolism, and this is responsible for abnormalities in the pattern of DNA methylation. Aneuploidy is defined as an abnormal number of copies of a genomic region and is the common cause for the development of genetic disorders. Aneuploidy was restricted to the presence of supernumerary copies (trisomy), or the absence of chromosomes (monosomy), but the definition includes deletions or duplications of subchromosomal regions (Antonarakis et al., 2004). DS are (i) non-disjunction, (ii) translocation and (iii) mosaicism. The 95% cases appear to be regular trisomy 21 (non-disjunction) in both males and females (47 XX or XY + 21). Robertsonian translocation is defined as the exchange of genetic material between chromosome 14 and 21/D and G groups (46 XX or XY rob (D or G; 21) (q10; q10), + 21. Mosaicism is termed as the presence of more than 2 different cell lines in the same individuals. Mosaicism is defined as the appearance of two or more populations of cells with different genotypes in one individual with a single fertilized egg or

**Table 1** Frequencies of different modes of karyotypes.

| Causes of DS | Mode of karyotype | Percentage |
|---|---|---|
| Non-disjunction | 47 XX + 21/47XY + 21 | 95% |
| Robertsonian translocation | 46 XX or XY rob (D or G; 21) (q10; q10), + 21 | 4% |
| Isochromosomes | 46 XX/XY + 21, i (21) (q10) | |
| Mosaicism | 47 XX/XY + 21 46 XX/XY | 1–3% |
| Partial trisomy (21q22.3) | 46 XX/XY, dup (21) (q22.3) | < 1% |

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