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# Down Syndrome: Clinical and Genetic Aspects, Genetic Counseling and Prenatal Screening and Diagnosis

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## 1. Introduction

### 1.1. Clinical and genetic aspects

Down syndrome (DS) or trisomy 21 is the most common genetic disorder with a prevalence of 1 in 660 live births [1]. In 1959, Lejeune and colleagues discovered the genetic basis of DS and named as trisomy of chromosome 21, which is the smallest human autosomal chromosome [2]. Trisomy 21 can occur as three types of chromosomal abnormalities: free trisomy 21, translocation or mosaicism. Free trisomy 21 is characterized by the presence of three complete copies of chromosome 21, occurring in about 90-95% of DS cases [3-5]. More than 90% of the cases of chromosomal nondisjunction are of maternal origin, mainly during meiosis I, about 5% involve an additional paternal extra chromosome and a small proportion (2%) is consequence of post-zygotic mitotic non-disjunction [6]. Translocations are attributed to 1-7% of the cases, with Robertsonian translocation involving chromosomes 14 and 21 being the most common type. Mosaicism, characterized by some cells containing 46 chromosomes and others with 47 chromosomes (with an extra chromosome 1), is reported in 1-7% of DS cases [3-5].

DS phenotype is complex and varies among individuals, who may present a combination of dysmorphic features and developmental delay [7]. The intellectual disability is a characteristic observed in all cases and the most frequent clinical features include muscular hypotonia (99%), diastasis of the muscle rectus of abdomen (90%), upslanted palpebral fissures (90%), microcephaly (85%), flat occipital (80%), joint hyperextension (80%), broad hands with short fingers (70%), short stature (60%), clinodactyly of fifth finger (50%), epicanthal fold (40%), low-set ears (50%), single palmar crease (40%), atlantoaxial instability (15%) and label-femoral instability (10%) [8]. On average, 50-70% of children with DS have congenital heart defects, such as ventric-

ular septal defect, atrial septal defect, tetralogy of Fallot, patent ductus arteriosus and atrioventricular septal defect [3,4,9]. There are also ocular problems, such as refractive errors, nystagmus, abnormalities of the retina, among others [10]. About 80% of cases present hearing loss, which can be conductive, sensorineural, or mixed [11]. Thyroid dysfunction, particularly hypothyroidism [9], periodontal diseases [10], upper airway obstruction [12] and hypogonadism [14] are more frequent in individuals with DS than in the general population. Other important clinical aspects of DS include immunodeficiency [15], increased risk for hematological disorders and leukemia [16] and early onset of Alzheimer's disease [17].

The development of secondary sexual characteristics in DS is similar to other adolescents. The fetal oogenesis of women with the syndrome appears to be normal and, therefore, they are capable of reproduction [18]. On the other hand, men have diminished reproductive capacity, showing testicular histology compatible with oligospermia and, frequently, hypogonadism [19]. However, there have been reports of men with Down syndrome who have fathered pregnancies [20].

## 2. Genetic counseling

Genetic counseling can be defined as a communication process that takes care of the human problems associated with the occurrence or recurrence of a genetic disease in a family with the purpose of providing individuals and families comprehensive understanding of all the implications related to genetic disease under discussion, the options that the current medicine offers for therapy or for reducing the risk of occurrence or recurrence of the disease and psychotherapeutic support [21,22].

For DS, a well-established risk factor is advanced maternal age at conception [23,24]. The estimated risk for fetal trisomy 21 for a woman aged 20 years at 12 weeks of gestation is about 1 in 1000, and the risk of such woman delivering an affected baby at term is 1 in 1500. The risk for this aneuploidy for a woman aged 35 years at 12 weeks of gestation is about 1 in 250 and the risk of delivering an affected baby at term is 1 in 350 [25].

Although there is considerable variation in the physical features of individuals with DS, most individuals present with a range of characteristics that enable clinical diagnosis of the syndrome [3,4,7]. However, cytogenetic investigation of individuals who present with clinical characteristics of DS is fundamental to establish a precise diagnosis, which may have implications in the genetic counseling process, once it is very important in determining the recurrence risk of the syndrome. In addition, the karyotype analysis of affected individuals identifies cases that may have been inherited making necessary the investigation of the parents' karyotypes. In this case, the cytogenetic investigation of the genitors is essential to establish the risk of recurrence of the syndrome in future generations. Thus, all individuals with a diagnosis suggestive of DS should be referred to a genetic counseling service.

Accurate estimation of recurrence risks depends upon the verification of the individual's karyotype. Cases of free trisomy 21 and mosaicism generally do not recur in siblings of individuals with DS. For women with maternal age <35 at previous trisomy 21, the revised risk

is the age-related risk times 3.5. For those with maternal age  $\geq 35$  at previous trisomy 21, the revised risk is the age-related risk times 1.7 [26]. So, these risk times implies that other factors might influence the risk for DS in young mothers [27]. On the other hand, translocation may be recurrent. If neither parent carries a balanced translocation, the DS recurrence risk is low, probably similar to that of free trisomy 21. However, if one of the parents is the carrier of a balanced translocation, the risk of recurrence is dependent on the type of translocation and the sex of the carrier parent. In the case of Robertsonian translocations involving chromosome 13, 14, 15 or 22 and the chromosome 21, the recurrence risk at time of amniocentesis is of up to 17% when the mother is the carrier and of up to 1.4% when the carrier of this balanced translocation is the father. On the other hand, if one of the parents is the carrier of a balanced translocation involving two chromosomes 21, the recurrence risk of DS is 100% [26]. Thus, once diagnosed as a case of DS due to a translocation, a karyotype analysis of both parents is recommended.

For an individual with DS, the theoretical chance to have a child with DS is 50%, and 66% when both partners have DS. However, empiric risks are difficult to estimate, once the reproduction rates are low. Empiric data indicate a 30–50% chance of a woman with DS have a child with DS [26]. However, considering that the rate of fetal death between 11 weeks and term is about 43% for trisomy 21 [28], the chance of birth of a child with DS decreases. For individuals with mosaicism, the maximum theoretical recurrence risk is as high as 50%, but is dependent upon the proportion of trisomic gonadal cells and whether the other partner has DS as well [26].

Genetic counseling is also important to guide the parents about caring for the child with DS. Because individuals with DS often experience delays in reaching various developmental milestones, early intervention with speech therapy, occupational therapy, and physical therapy is recommended as it maximizes long-term outcomes [29]. As healthcare has improved for individuals with DS, the average life expectancy has increased by more than 30 years, from an average of 25 years of age in 1983 to almost 60 years of age in 2000 [30]. A study performed between 1985–2004 in England showed that the one-year survival of live births with DS increased, especially in babies with cardiovascular malformations, reaching almost 100% [31], and a more recent study showed that the 25-year survival of DS individuals is about 87.5% [32].

Genetic counselors should balance the negative aspects of DS, such as birth defects, medical complications, and developmental delay, with positive aspects like available treatments, therapies, and the ability for people with DS and their families to enjoy a high quality of life [33].

### 3. Prenatal screening and diagnosis

There are several methods that allow the early detection of DS in prenatal phase. At this point, it is not possible avoid congenital malformations or genetic diseases, but the objective is its early detection, looking for emotional and psychological preparation for parents and family and adequate medical support and monitoring for the child's birth. Furthermore, early detection allows treatment of malformations of the complications that may occur, preventing or attenuating their evolution through surgical correction in utero.

There are some methods used to screen fetus with DS that allow the prenatal diagnosis of the syndrome. Among the screening methods are the nuchal translucency test, the measurement of maternal serum concentrations of various fetoplacental products and fetal ultrasound. The nuchal translucency (NT) test is the measurement of the fluid filled fold at the back of the fetal neck in the first trimester of pregnancy, performed through transabdominal or transvaginal sonography. The test is performed between the 11th and 13th weeks of gestation and the minimum fetal crown-rump length (CRL) should be 45 mm and the maximum 84 mm. Fetal NT increases with CRL and therefore it is essential to take gestation into account when determining whether a given NT thickness is increased [25]. The excess skin in the fetus may be the consequence of excessive accumulation of subcutaneous fluid behind the fetal neck which could be visualized by ultrasonography as increased NT in the third month of intrauterine life [34]. Nowadays, it is well established that the measurement of fetal NT thickness provides effective and early screening for trisomy 21 and other major aneuploidies, such as Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13) [34-36] besides for screening of congenital heart disease [37]. In case of abnormality in NT measurement, additional tests are needed to elucidate the cause of increased nuchal fold.

Pregnancies with fetal aneuploidies are associated with altered maternal serum concentrations of various fetoplacental products, including alpha-fetoprotein (AFP), free chorionic gonadotropin ( $\beta$ -hCG), unconjugated estriol (uE3), inhibin A (INH-A) and pregnancy associated plasma protein-A (PAPP-A) [38-42]. The measurement of concentrations of maternal serum AFP,  $\beta$ -hCG and uE3, the triple test, is one of a range of screening tests that are used to identify pregnant women whose fetus is likely to be affected by trisomy 21 and who should then be offered a diagnostic test. AFP is produced in the yolk sac and fetal liver, while uE3 and hCG are produced by the placenta. Elevated  $\beta$ -hCG concentration and low levels of AFP and uE3 suggests the presence of a fetus with DS [38-40]. The test is performed in second trimester of pregnancy and the values should be adjusted to gestational age. The expected detection rate and false-positive rate are about 73 - 78% and 7.5 - 9%, respectively [43].

The incorporation of INH-A into maternal serum DS screening in the second trimester, along with AFP, hCG and uE3, is named quadruple test. INH-A is a glycoprotein mainly secreted from the corpus luteum and the placenta [44] and its concentration is raised in the serum of pregnant women carrying a fetus with DS [42]. The quadruple test presents expected detection rate and false-positive rate about 79 - 82% and 6.5 - 7.8%, respectively [43]. The measurement of PAPP-A is also used as a screening gestations of fetus with DS in the first trimester, once the maternal serum concentration of this protein are reduced in these women [41]. The measurement of PAPP-A at 10-14 weeks of pregnancy is used to screen for fetal DS during the first trimester of pregnancy [45,47].

The fetal ultrasound is also considered a method of screening for DS, once any change in the development of organs or structures is easily visualized. The objective is the detection of major and soft markers of aneuploidy, including alterations in central nervous system, face, neck, heart, gastrointestinal tract, genitourinary tract among others [47]. Besides increased nuchal translucency in the first trimester, alterations commonly detected in DS in the second trimester of gestation include lack of visualization of the nasal bone [48], reduced femur and humerus, mild pyelectasis, hyperechoic bowel and echogenic intracardiac focus [47,49].



Importantly, any suspect result of the markers mentioned implies the genetic analysis of the fetus, the only way to accurate diagnosis. The methods for obtaining fetal cells for analysis vary with gestational age. Among the invasive methods for obtaining fetal cells, chorionic villus sampling (CVS) allows diagnosis in the first trimester of pregnancy (between the 10th and 13th weeks of gestation) [50]. The procedure involves aspiration of trophoblastic tissue under continuous ultrasound monitoring, performed via trans-cervical or trans-abdominal. Studies have showed that the risk miscarriage associated to this procedure is about 0.6-1.1% [51,52] and the procedure is not recommended for pregnant women that present bleeding due to an increase in the procedure-related fetal loss rate [51].

The amniocentesis is the method indicated for obtaining fetal cells after 15 weeks of gestation [53]. This requires taking a small sample of amniotic fluid transabdominally under ultrasound guidance. The procedure-related fetal loss rate is about 0.4-0.8 % [51,52]. After 20th week of gestation, the option is percutaneous umbilical blood sampling or cordocentesis, which involves direct sampling of fetal blood from the umbilical cord. The procedure-related loss rate is about 1.0-1.5% and cordocentesis with placenta penetration had a significantly higher rate of fetal loss [54-56].

Considering the risks which accompany invasive methods for obtaining fetal cells [51,52,56], the use of noninvasive methods could be a good option. Several methods to develop a non-invasive prenatal test for trisomy 21 and other aneuploidies have been investigated, including the use of cell-free fetal nucleic acids [57-60] and nucleated red blood fetal cells present in maternal peripheral blood [61,62]. Although studies have showed that noninvasive methods for obtaining fetal cells allow noninvasive prenatal diagnosis for a variety of genetic conditions and may in future form part of national antenatal screening programs for DS and other common genetic disorders, a major obstacle in the widespread application of noninvasive methods for obtaining fetal cells in clinical diagnostics is still that fetal cells / DNA constitutes a small percentage of total cell / DNA in maternal blood and the inconsistencies in enrichment strategies of these fetal samples [62,63].

After obtaining fetal cells, conventional karyotype analysis has been used for the past few decades as the gold standard for the prenatal diagnosis of numerical and major structural chromosomal abnormalities. Nevertheless, it is labor intensive and requires skilled chromosomal analysis with an average reporting time of 14 days. However, the availability of molecular techniques such as fluorescence in situ hybridization (FISH) has allowed the prenatal diagnosis of most frequent trisomies (21, 13, 18) and aneuploidy of sex chromosomes quickly and accurately, obtaining result from one to two days [64,65]. In addition, the technique of polymerase chain reaction quantitative fluorescent (QF-PCR), besides other molecular techniques such as the multiplex ligation-dependent probe amplification (MLPA) test and DNA sequencing, can also be used for a rapid diagnosis of aneuploidies [66-68]. It has been showed that QF-PCR technique presents 95.4% sensitivity, 100% specificity, 99.5% efficiency and is less laborious than the FISH technique, less time consuming, and some results were obtained in eight hours. The sensitivity, specificity, and efficiency of the assay for detecting DS using this technique are about 95.4%, 100%, and 99.5%, respectively [69]. Molecular techniques also enable the diagnosis of pre-implantation embryos in assisted reproduction [70].

It is important to note that the examinations of prenatal diagnosis should not be offered without the guidance of a geneticist to explain the risks to the parents and especially the implications of possible results. Early diagnosis helps couples to program for the treatment of the consequences of the syndrome diagnosed, preventing further damage and making possible the early stimulation of the patients, aiming their better integration into society.

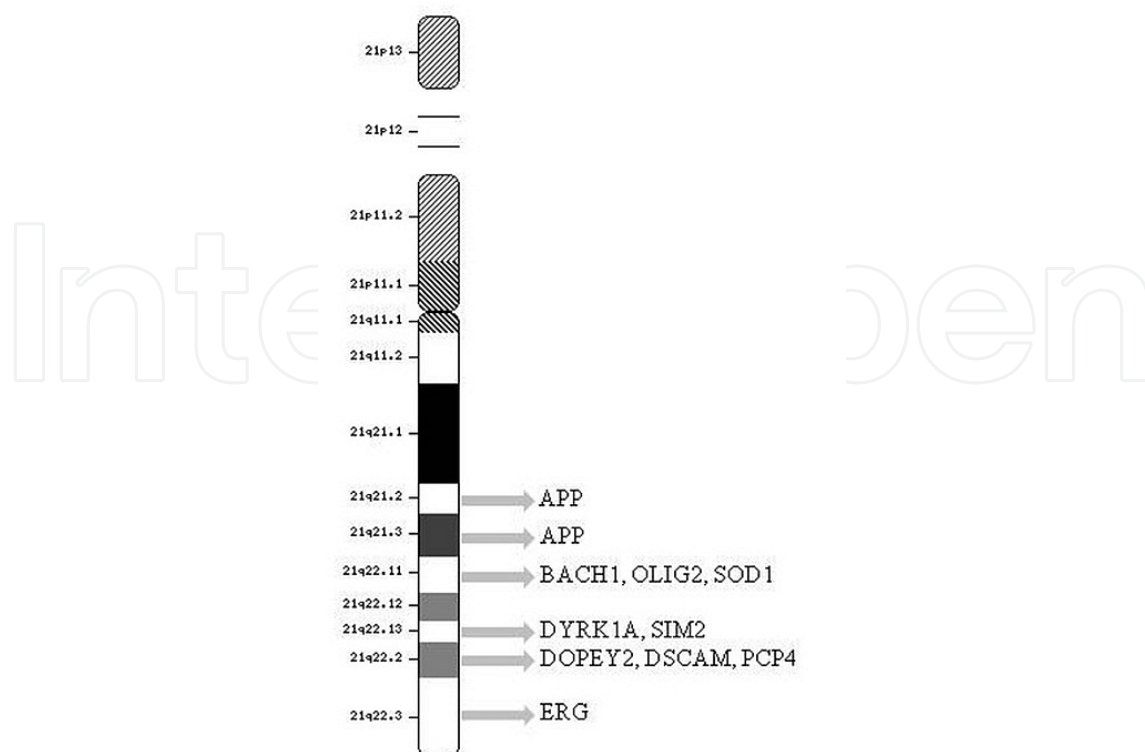
#### 4. Gene expression and DS phenotype

In a recent review of chromosome 21 content, 552 genes were identified in the long arm of the chromosome (21q) [71], including 161 protein-coding genes cataloged in the Reference Sequence database of the National Center for Biotechnology Information (NCBI). The remaining 391 gene models are referred to as novel genes or non-cataloged genes, which could be protein-coding genes or functional RNA genes. Considering that the genetic basis of DS is the presence of three copies of chromosome 21, the first and most commonly accepted hypothesis for DS phenotype is that the genes in triplicate are overexpressed and, thus, the dosage imbalance of genes on chromosome 21 is responsible for the molecular dysfunctions in DS [72]. Among the genes present in chromosome 21, may be highlighted some described in the literature with overexpression associated with phenotypes of DS, most influencing the structure or function of the central nervous system (Table 1). Location of these genes on chromosome 21 is presented in Figure 1.

Gene symbol*	Gene location*	Candidate gene for	Reference
APP	21q21.3	Neurodegeneration	[73,74]
BACH1	21q22.11	Alzheimer's disease-like neuropathological changes	[75]
DOPEY2	21q22.2	Functional brain alterations and mental retardation	[76]
DSCAM	21q22.2	Mental retardation and the precocious dementia	[77]
DYRK1A	21q22.13	Leukemogenesis	[78]
		Impaired brain development	[79]
		Early onset of neurofibrillary degeneration	[80]
ERG	21q22.3	Alzheimer's disease-like neuropathological changes	[75]
OLIG2	21q22.11	Developmental brain defects	[81]
SIM2	21q22.13	Impairment of learning and memory	[82]
		Pathogenesis of mental retardation	[83]
SOD1	21q22.11	Neurodegeneration	[84]
PCP4	21q22.2	Abnormal neuronal development	[85]

\* <http://www.ncbi.nlm.nih.gov/gene>

**Table 1.** Chromosome 21 gene-located with overexpression in DS influencing the structure or function of the central nervous system.



**Figure 1.** Location of genes overexpressed in DS influencing the structure or function of the central nervous system. Figure adapted from the NCBI Map Viewer database (<http://www.ncbi.nlm.nih.gov/mapview/>).

However, although elevated levels of gene expression on chromosome 21 in trisomy 21 tissues have been reported in several studies, there are evidences that increased copy number does not always correspond with increased gene expression level or even less with increased gene function [86,87]. In addition, studies have showed up- or downregulation of genes located on disomic chromosomes, indicating that the phenotype is due to an unstable environment resulting from the dosage imbalance of the hundreds of genes on chromosome 21 which determines a non-specific disturbance of genomic regulation and expression [88-90].

Besides altered pattern of gene expression, regulatory mechanisms are also altered in trisomy 21. Individuals with DS present altered pattern of DNA methylation in genes present in two or three copies with functional consequences in gene expression [91,92]. More recent studies have shown that trisomy 21 results in altered expression of microRNAs, small molecules of noncoding RNA involved in post-transcriptional gene regulation, which could result in abnormal expression of specific proteins and contribute to the DS phenotype [93-97]

The complete sequencing of chromosome 21 provided basis for the identification of candidate genes for DS phenotype manifestations. Currently, there are several genes located on chromosome 21 associated to DS phenotype and the involvement of other genes still will be elucidated with advances of genomics and proteomics. The knowing of these gene functions and their contribution for DS phenotype are fundamental for the understanding of the syndrome and for providing basis for the planning of therapeutic strategies that could contribute to improve the quality of life of DS individuals.



## 5. Conclusion

Although individuals with trisomy 21 present several characteristics that make possible the clinical diagnosis of DS, the confirmation of the diagnosis by cytogenetic analysis is essential to establish the recurrence risks of the syndrome. We highlight the importance of the prenatal diagnosis of DS to provide the needed healthcare for the child, to prepare the family emotional and psychologically and to plan early intervention therapies. The successful control of pharmacological and clinical problems of patients with DS is the biggest medical challenge and depends on the understanding of unbalanced metabolism induced by high expression of the genes located on chromosome 21.

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