Chapter

What Causes Down Syndrome?

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Abstract

Trisomy 21 (Down Syndrome) is the model human phenotype for all genome gain-dosage imbalance situations, including microduplications. Years after the sequencing of chromosome 21, the discovery of functional genomics and the creation of multiple cellular and mouse models provided an unprecedented opportunity to demonstrate the molecular consequences of genome dosage imbalance. It was stated years ago that Down syndrome, caused by meiotic separation of chromosome 21 in humans, is associated with advanced maternal age, but defining and understanding other risk factors is insufficient. Commonly referred to as Down syndrome (DS) in humans, trisomy 21 is the most cited genetic cause of mental retardation. In about 95% of cases, the extra chromosome occurs as a result of meiotic non- nondisjunction (NDJ) or abnormal separation of chromosomes. In most of these cases the error occurs during maternal oogenesis, especially in meiosis I.

Keywords: trisomy 21, chromosome 21, non- nondisjunction, down syndrome, genetics

1. Introduction

More than 50 years have passed since trisomy 21 was identified as the cause of Down syndrome. After that date, the first link between a clinical disorder and a chromosomal abnormality was established. In the intervening half century, the importance of numerical chromosome abnormalities for human disease pathology has been well established.

Studies with live births in the 1960s and 1970s showed that about 0,3% of newborns were trisomic or monosomic, while subsequent studies of spontaneous abortions found a much higher incidence of about 35%. Taken together, these studies revealed aneuploidy as the leading known cause of congenital birth defects and miscarriages, showing that most cases of aneuploidy disappear in utero [1–3].

In humans, trisomy 21, commonly referred to as Down syndrome (DS), is the most common genetic cause of mental retardation. In about 95% of cases, the excess chromosome occurs as a result of meiotic nondisjunction (NDJ) or incorrect dissociation of chromosomes [4, 5]. In most of the cases, the error occurs during maternal oogenesis, especially in meiosis I (MI) [6]. Advanced maternal age and defective recombination are two risk factors that have been reported to be associated with DS for cases where extra chromosome arises in the oocyte. The process of oogenesis is long and is a cycle that involves meiotic arrest, making it more vulnerable to improper assembly of chromosomes than spermatogenesis. Also, with increasing age, there is a rapid degradation of spindle thread formation in sister chromatid cohesion or anaphase separation of sister chromatids in oocytes, and this poses the risk of NDJ in both MI and MII [7–11].

Through recombinant DNA technology, a new technique has become available to study the origin and mechanisms of chromosomal abnormalities using DNA polymorphism analysis. Initially, such analyzes used chromosome 21-specific DNA probes to detect restriction fragment length polymorphisms. The development of the polymerase chain reaction (PCR) amplification technique has enabled the identification of new and highly informative classes of DNA polymorphisms (microsatellites or simple sequence repeat (SSR) polymorphisms) in the human genome. In particular, multi-allelic and easily typeable micro satellites have contributed to chromosomal nondisjunction studies in recent years [12–14].

Meiotic meiosis I or II examination of nondisjunction in trisomy 21 by DNA polymorphism analysis could not be performed due to the absence of centromeric markers. Alphaid DNA polymorphisms specific to the human chromosome 21 centromere were identified years ago, but these markers were unlikely to provide information on the process and were not useful for routine nondisjunction studies. However, alfoid DNA polymorphisms were localized in the genetic linkage map of chromosome 21(**Figure 1**), and an estimate of the genetic distance between the centromere and the closest pericentromeric markers on the long arm of chromosome 21 was made [4, 9, 16].

Two large collaborative studies used DNA polymorphism involving the long arm of human chromosome 21 to determine the parental origin of separation in trisomy 21. Such studies estimate that only 5% of trisomy 21 (of a total of 304 families studied) originates from the father and attributes the difference in cytogenetic studies to the increased accuracy of DNA polymorphism analysis as shown by inaccurate

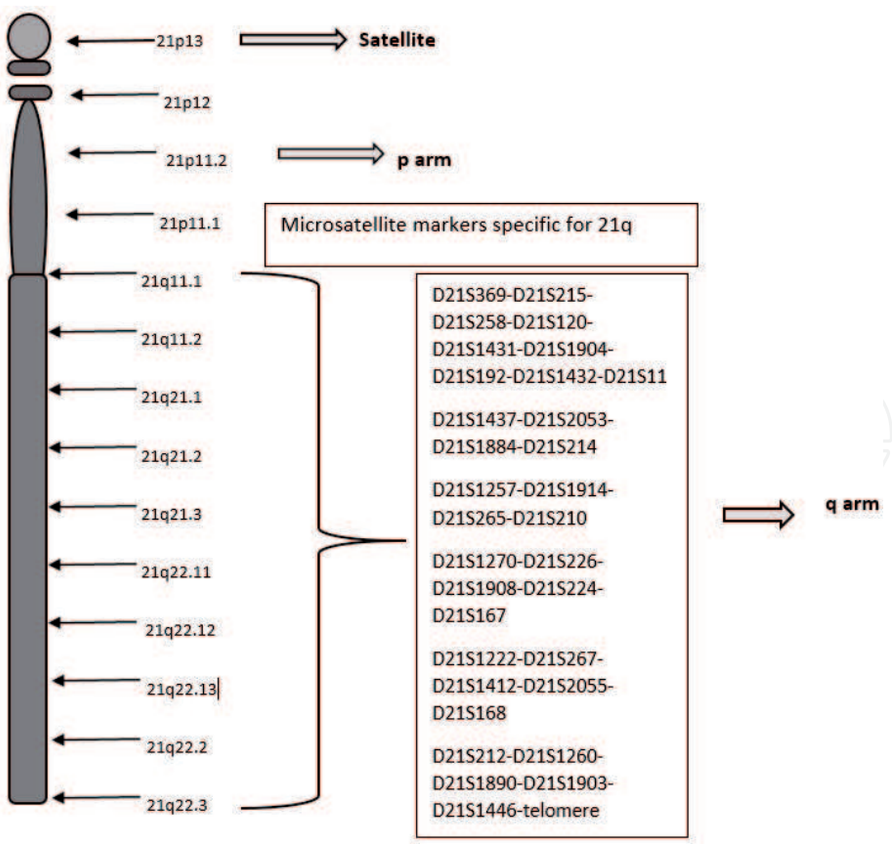

Figure 1.
Short tandem repeat (STR) markers used to infer the origin of the meiotic error and characterization of the recombination profile [15].

cytogenetic determinations in a subgroup of families. Other population-based studies show paternal meiotic errors in the 5–9% range [17, 18].

For example, the absence of detectable recombination or just a single telomeric change may be associated with MI NDJ errors, and this pattern is more common in the younger maternal age group than in the older maternal group. In contrast, it shows that MII errors are clearly associated with pericentromeric changes in older maternal age groups [19].

A molecular study found high differences in mean maternal ages between maternal origin cases and paternal origin cases. This demonstrated that the maternal age effect in Down syndrome is limited to maternal nondisjunction and does not provide evidence for a comfortable selection against trisomic fetuses in older women [20, 21].

2. Sex-specific differences in meiosis

As discussed in many studies, studies of clinically recognized pregnancies indicate that most human aneuploidy is of maternal origin. The question then arises: why is female meiosis so prone to error? In this section, we review oocyte development and summarize the latest evidence that errors in the oocyte that predispose to chromosome misgrouping are increased, and that gender-specific differences in meiotic cell cycle checkpoints allow oocytes with these errors to develop into mature eggs [3, 22].

In mammals, meiotic recombination occurs in the fetal ovary and the significance of the resulting physical connections for chromosome separation has been well observed. Studies in the 1990s identified transitions that could not be recombined and / or optimally positioned as significant contributors to human trisomy.

Changing recombination is essential here. It is related to mother-derived trisomies as well as those originating from the father. However, the female is clearly at greater risk, as most aneuploidy occurs during oogenesis. Therefore, either more recombination errors are made in the female or these errors are removed more efficiently in the male [23, 24].

The immunofluorescence methodology has made it possible to examine cross-linked proteins in pachytene spermatocytes and oocytes and thus test these alternatives. Interestingly, almost all chromosomes in males are joined by at least one crossover, but the same is not true for females [4, 14, 18].

Studies have shown that; The conclusion is that more than 10% of all human oocytes contain at least one “non-crossing” bivalent. Since half of all these divalent ones are expected to result in aneuploidy (**Figure 2**), the stage seems to have been adjusted for meiotic errors from the onset of oogenesis.

As suggested based on cytogenetic studies with no evidence of a difference in mean maternal age between maternal and paternal trisomy 21 cases. A factor associated with aging of the oocyte therefore appears to be responsible for the maternal age effect in Down syndrome.

Among maternal errors, approximately 75% are considered errors in meiosis I and 25% as errors in meiosis II. Maternal meiosis I and II errors are linked to increased maternal age [25–27]. Two studies of cytogenetic short-arm heteromorphisms and microsatellite DNA polymorphisms showed inconsistencies regarding the meiotic period of non-separation and suggested pericentromeric increased recombination associated with nondisjunction. The place where chiasma occurs is the middle of the chromosome arm and then recombination is necessary for proper

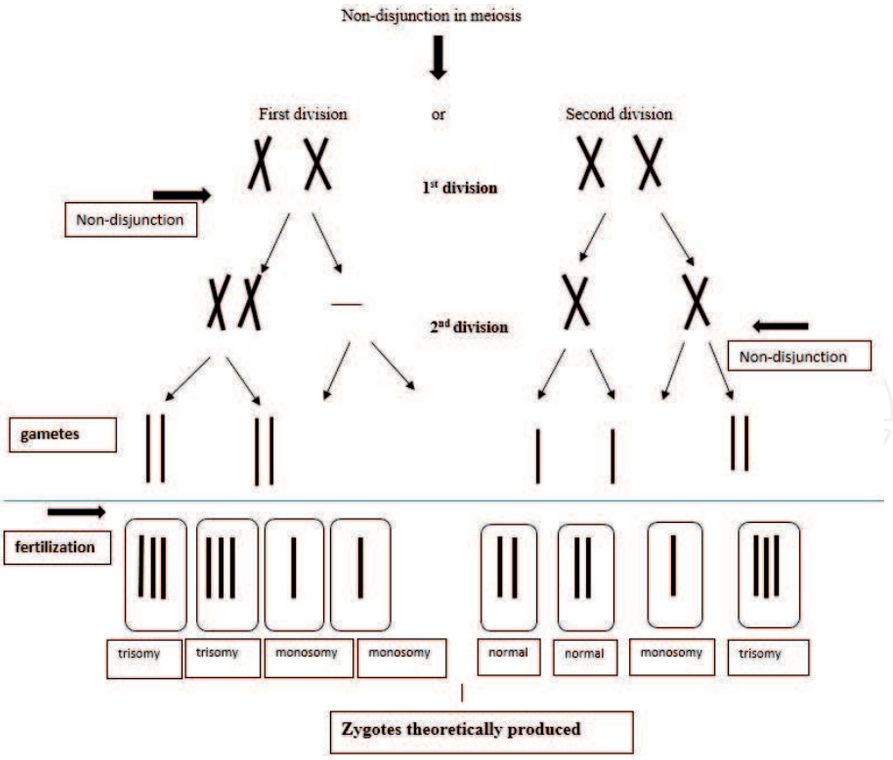

Figure 2.
Homogeneous due to meiotic non-disjunction.

chromosome separation as it holds the chromatids tightly and balances the attraction to opposite poles [28, 29].

Meiotic recombination was thought to stabilize matched homologs to ensure their proper separation. However, the process is stochastic and may not be handled properly even in euploid samples. Thus, achiasmate chromosomes are vulnerable to malsegregation and this condition gradually increases with age due to the rapid degradation of the protein mechanism within oocytes responsible for surveillance and separation of chromosomes. A chiasma located near the telomere of the chromosome probably attaches the homolog to the spindle weaklier due to loss of cohesion and directs the kinetochore precisely towards the opposite pole. On the other hand, chiasmata close to the center occurs during MI, which causes chromosome entanglement so the bivalent cannot be separated correctly. In this way the MII can pass into the anaphase plate and then result in the reduction section; as a result, a disomic gamete is produced [30, 31].

Epidemiological studies have identified some environmental, habitual and socio-economic factors that may pose a risk for Ch21 NDJ. These can be observed in both MI and MII errors depending on maternal age or independent of maternal age. When we consider these findings, it is clear that Ch21 NDJ risk is a multifactorial event that interacts with genetic and environmental factors.

About 5% of trisomy 21 cases are likely due to the mitotic (postzygotic) non-disjunction of chromosome 21 in the early embryo. This was demonstrated by the identification of pericentromeric DNA markers and the lack of recombination observed along the entire long arm of chromosome 21. Mitotic errors are not associated with advanced maternal age and do not show any preference depending on the parental origin of the replica chromosome 21. Mosaic with a normal cell line occurs in about 2–4% of newborns with Down syndrome. By DNA polymorphism analysis performed in 17 families with mosaic trisomy 21 probands, it showed that most cases were caused by a trisomic zygote with mitotic loss of one chromosome (**Table 1**) [32, 33].

Origin	Number of cases	%	Meiotic recombination
Maternal	732	90,7	
MI	556	68,9	Reduced
MII	176	21,8	Increased
Paternal	44	5,5	
MI	17	2,1	Reduced
MII	27	3,3	
Mitotic	31	3,8	
Maternal	17	2,1	
Paternal	14	1,7	

MI: Meosis I, MII: Meosis II, Maternal and Paternal refer to parental origin of the chromosome that was duplicated by postzygotic nondisjunction

Table 1.
Origin of nondisjunction in human trisomy 21 by DNA polymorphism analysis [31, 33–35].

3. Changes in recombination

Failure to nondisjunction in maternal meiosis I is associated with reduced recombination between unallocated chromosomes 21, suggesting an important role for pairing / recombination errors or reduced recombination in the etiology of trisomy 21. Subsequent results showed an overall reduction in recombination, but with increased recombination in the distant region of 21q.

Meiotic outcome group	Maternal age group	Number of observed events	Frequency of observed number recombinants			Frequency of the number inferred exchanges		
			0	1	≥2	0	1	≥2
MI								
	Young (<29 yrs)	175	0,70	0,20	0,10	0,47	0,32	0,21
	Mid (29–34 yrs)	197	0,56	0,35	0,10	0,18	0,64	0,19
	Old (>34 yrs)	243	0,64	0,27	0,09	0,27	0,49	0,24
MII								
	Young (<29 yrs)	58	—	0,66	0,34	—	0,22	0,78
	Mid (29–34 yrs)	69	—	0,78	0,22	—	0,51	0,49
	Old (>34 yrs)	126	—	0,81	0,19	—	0,57	0,44
Euploid								
	All Ages	152	0,52	0,39	0,09	0,20	0,50	0,30

Table 2.
Frequency distribution of observed recombinants and inferred exchanges for each meiotic outcome group stratified by maternal age group [10].

Unpredictably, nondisjunction in meiosis II is due to the increased recombination occurring in meiosis I suggesting that all errors are due to meiosis I. The recombination rate remains constant with advancing maternal age. However, possible chiasmate configurations of chromosome 21 appear more susceptible to nondisjunction in older oocytes than younger oocytes (**Table 2**).

Analysis of the chiasma configuration showed that the failure of a proximal recombination (or the presence of a telomeric recombination) tends to be nondisjunction in meiosis I, while the presence of pericentromeric change appears to be nondisjunction in meiosis II [30, 31, 36, 37].

These findings are very effective in understanding the etiology of trisomy 21 and may explain why both maternal meiosis I and II errors are associated with increased maternal age. A two-hit nondisjunction model has been proposed where the first hit is the prenatal establishment of a sensitive tetrad and the second hit is the disruption of a meiotic process that increases the risk of nondisjunction of the susceptible configuration. The second hit can involve any element of the meiotic process and can be the basis for the maternal age effect. Recent studies have found signs indicating a reduction in the recombination rate in the total genome of eggs with chromosome 21 nondisjoined, meaning that the reduction in recombination is not limited to nondisjoined chromosomes but extends to other chromosomes as well [22].

The two-beat non-separation model needs to be validated with further study from other chromosomes and direct observation with oocytes.

4. Paternal nondisjunction

In the paternal nondisjunction of chromosome 21, there is mainly meiosis II error, as DNA polymorphisms show, in contrast to meiosis I errors and maternal nondisjunction.

Therefore, the mechanisms associated with paternal nondisjunction will likely differ from those associated with maternal nondisjunction.

In live births with Down syndrome; there is a well-known increasing ratio (about 1.15) between the sexes. This effect is limited to free trisomy 21 cases and does not include translocation-style trisomies, suggesting that increased sex ratio is associated with free trisomy 21 per se, not gender-based differential selection. As a result of molecular studies, it has been revealed that among the meiotic errors of the father, a rather high sex ratio (3.50) and male proband excess, in contrast to paternal mitotic errors and maternal errors, are specific to MII errors.

As with maternal meiosis, there is reduced recombination across the nondisjoined 21. chromosome involved in the 22 paternal nondisjunction cases, but there is no difference in recombination between the 27 paternal MII cases compared to controls [14, 18, 34].

5. Recurrence risk of nondisjunction

Two molecular studies with families with free trisomy 21 relapse showed that mosaicism in parents is an important etiological factor and that this possibility alone may explain recurrent trisomy 21 in most families. In only a small number of families, the possibility of genetic predisposition for chromosomal nondisjunction could not be excluded [32, 35].

It has been previously shown that live born children with free trisomy 21 for chromosomally normal parents whose maternal age is less than 30 years have a significantly increased risk of recurrence [35].

6. Risk factors

Many factors have been suggested as risk factors for nondisjunction in the past, but only in the last few studies identified the source of nondisjunction by DNA analysis. The increased frequency of the apolipoprotein E (APOE) allele Â4 was more observed in young mothers with MII errors in a population-scale study of Down syndrome in Denmark. This finding showed an increased risk of Alzheimer's disease in a subgroup of young Down syndrome mothers and suggested the APOE E4 allele as a risk factor for nondisjunction in young mothers [36–38].

An association between an intron polymorphism in the presenilin-1 gene and maternal MII errors was identified in the same population-based study and the function of presenilin proteins in chromosome segregation was determined and thought to be related to subcellular localization.

Another population-based study revealed an association with young MII mothers and maternal smoking and oral contraceptive use.

Both studies have found an association in young MII mothers, and the proposed risk factors support the ovarian risky microcirculation hypothesis to explain the effect of maternal age on nondisjunction, and it should not be overlooked.

Oocytes from hypoxic follicles under heavy exposure showed abnormalities in the organization of chromosomes on the metaphase spindle at high frequencies.

When we look at the two hit nondisjunction model, the findings suggest that aging alone is sufficient to disrupt the meiosis process, but there is a higher requirement for a genetic or environmental factor for nondisjunction to occur in young women.

A different recent study showed abnormal folate metabolism in mothers with Down syndrome; It was reported that the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene was higher in mothers with Down syndrome than in control mothers. However, the study included a small number of mothers and was not population-based, and so the source of nondisjunction could not be determined. Nevertheless, the study may support the at-risk microcirculation hypothesis as hyperhomocysteinemia is a known risk factor for vascular disease and the common MTHFR C677T mutation in the homozygous state is associated with mild hyperhomocysteinemia [39–42].

7. Conclusions

As a result, it shows that there is a high frequency of chromosome abnormalities throughout embryonic development as a result of accumulated errors during gametogenesis and early mitotic divisions. Advancing female age is associated with increased rates of aneuploidy in oocytes and embryos. Especially during female meiosis, excessive chromosome losses, anaphase delay of chromosomes and / or capturing of the spindle by microtubules (congression failure) are important mechanisms that cause aneuploidy during oogenesis and continue to have a significant effect during the first few mitotic divisions. Studies of abortions and molecular genetic analyzes of chromosomal abnormalities revealed that most aneuploidies occur during female meiosis, usually as a result of splitting in the first meiotic division. Aneuploidies and, to a lesser extent, male-meiotic errors due to both premature separation of sister chromatids during female meiotic divisions and mitotic chromosome malsegregation are quite common. The fact that aneuploidies caused by these disturbances are rarely seen later in pregnancy increases the likelihood that the origin of aneuploidy may somehow affect the impact on embryo viability.

While interest in the development and refinement of culture systems to support the development of functional gametes from stem cells for the treatment of infertility has been intense, so far those working in these areas have shown little interest in the meiotic process. Obviously, the successful production of normal gametes in vitro will require great attention to meiotic details and a full understanding of the differences between the sexes.

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Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

DS	Down syndrome
NDJ	Non- nondisjunction
MI	Meiosis I
MII	Meiosis II
PCR	Polymerase chain reaction
SSR	Microsatellites or simple sequence repeat
STR	Short tandem repeat
APOE	Apolipoprotein E
MTHFR	Methylenetetrahydrofolate reductase.

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