Genetic Etiology of Chromosome 21 Nondisjunction and Down syndrome Birth: Aberrant Recombination and Beyond

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Abstract

Aberrant recombination pattern is known as risk factor for Chromosome 21 nondisjunction in oocyte and subsequent Down syndrome child birth. A considerable fraction of recombining chromosomes that missegregates exhibits erroneous pattern of single chiasma placement along the length of chromosome 21, either very close to centromere or very close to telomere. This pattern differs significantly from the chromosomes that segregate correctly. Researchers have also found an interaction of maternal age with aberrant pattern of single chiasma positioning on the chromosome and the interaction differs according to stage of meiotic origin of error i.e., meiosis I or meiosis II. Moreover, study on nondisjoined chromosome 21 that carries two simultaneous chiasmata revealed such chromosomes have tendency to missegregate in meiosis II. In meiosis I error double chiasmate chromosome exhibits shifting of distal chiasma towards centromere. Genome wide recombination profiling revealed recombination regulation at the maternal level predisposes meiosis I error, but additional oocyte-specific dysregulation contributes to the nondisjunction event. Very study has characterized certain genomic features that are associated with aberrant recombination pattern of nondisjoined chromosome 21, though confirmation of this notion is contingent to replication of such study in other population.

Keywords: Down syndrome; Chromosome 21; Nondisjunction; Recombination; Chiasma

Introduction

Down syndrome (DS) represents the most frequent live born aneuploidy and genetic form of intellectual disability. The overwhelming majority of live born DS is caused by trisomy 21 condition i.e. presence of extra copy of chromosome 21(Ch21) originates from nondisjunction (NDJ) i.e., nonseparation at anaphase. In ~90% of cases the error occurs in oocyte and often designated as maternal meiotic error. Among maternal errors, about 70% originates in meiosis I (MI errors) and 30% originates in meiosis II (MII errors). Many of the apparent MII errors are actually initiated in MI, but end with an oocyte containing sister chromatids [1]. This preferential occurrence of maternal meiotic error is probably due to the mechanism of oocyte maturation in the ovary. Meiosis is initiated in the human foetal ovary at 11–12 weeks of gestation [2], but becomes arrested after completion of homologous chromosome pairing and recombination. This meiotic-halt lasts for several years until the elevated level of LH and FSH resume the process at the onset of puberty. Then the oocyte completes meiosis I (MI) and enters meiosis II (MII) and again undergoes a phase of pause. It completes the meiosis II after the sperm enter its cytoplasm following fertilization. Thus, the oocyte, whose ovulation marks the menarche, remains in pause for shortest period and that ovulate just preceding menopause experiences longest period of arrest. This long tenure of oocyte development makes it vulnerable to acquire environmental hazards within its microenvironment which inevitably increases the risk of chromosomal NDJ.

The first documented risk factor for maternal NDJ is advancing maternal age of conception [3]. The first molecular correlate found to associate nondisjoined chromosome 21 is altered recombination along 21q. Chiasma formation and subsequent recombination between homologous chromosome pair are essential for proper segregation at anaphase. Chiasma holds the two chromatids in physical contract and counterbalances the pull by spindle fibres from the poles up to a certain time. Following chiasma formation recombination is initiated by double stranded break on DNA molecules. The resultant single stranded DNA then invades homologous duplex and the recombining pair is then resolved in either in exchanged (crossover) or non-exchanged (non-crossover) products [4]. Deviation from optimal chiasma positioning at the middle of arm of chromosome pair and reduction in crossover frequency impose risk of nondisjunction on the chromosome pair (Figure 1).

The pioneering study by Warren et al. [5] provided the first evidence to suggest that a proportion of maternal NDJ errors was associated with reduced recombination along Ch21. Further examination has shown that in addition to the absence of an exchange along the nondisjoined Ch21, the suboptimal placement of an exchange is an important susceptibility factor for NDJ. Realizing the mechanistic and temporal difference in MI and MII many researchers have hypothesized the risk factors associated with NDJ of Ch21 in MI and MII are different. In present review we have discussed a detail of aberrant pattern of recombination as risk factor that differentially associated with MI or MII NDJ of Ch21.

Absence of Recombination is Associated with MI Error

After initial finding by Warren et al. [5] absence of recombination along the length of 21q has been documented as risk factor for Ch21 NDJ in several studies in different ethnic populations. In their study...
on US population Oliver et al. [6] found that the lack of an exchange would increase the risk for NDJ, regardless of maternal age, particularly at MI. Here we should mention that Ch21 without exchange may nondisjoin at MII, but owing to technical definition this group may be misidentified as post zygotic mitotic error. Study of Ghosh et al. [7] on Indian DS population sample revealed only 22% of recombinant Ch21 that nondisjoin at MI and they estimated reduced genetic map length of 21q [7].

In their study on US sample Oliver et al. [6] found that the frequency of MI errors with no detectable exchange on Ch21 was the highest among the youngest maternal age group (<29 years) compared with the middle (29-34 years) and older age (>34 years) groups. This finding suggests that absence of detectable exchange is maternal age independent risk factor as the trend of decrease in proportion was not associated linearly with increasing maternal age of conception. Almost similar trend was observed in the study conducted by Ghosh et al. [8] on DS sample from India. In US sample there was a less proportion of non-exchange event in middle age group than expected and in Indian sample middle age group exhibited highest proportion of non-exchange events. These two sets of results provide primary evidence for a secondary backup mechanism that helps to distribute non-exchange bivalents which is age dependent. Existence of such ‘back-up’ system is also evident in experiments with model organisms [9,10]. Human Proteins with similar function as those in yeast that are involved in regulation of meiotic recombination. The mutant/null alleles of synaptonemal complex candidates Sycp1 and Sycp3 in mouse exhibit lack of synthesis and abolishment of MLH1-MLH3-dependent crossovers maturation and the structural integrity of chromosomes was drastically impaired [14]. In a different study mutant allele of chtf 18 causing impairment in spermatogenesis and defective meiotic recombination with premature chromatid separation in prophase I in male mouse has been documented. Additionally reduction in MLH1 foci has been found in this mouse strain [15]. These findings are suggestive of probable existence of similar etiology in Ch 21 nondisjunction in human, though such study is yet to be conducted.

**Single Telomeric Chiasma Increases Chance of MI Error**

Beside absence of recombination, single telomeric chiasma increases the risk for Ch21 NDJ at MI. Usually a single chiasma at the middle of chromosome arm ensures proper segregation of chromosome at meiosis (Figure 2). In both the studies on US and Indian populations [6,7], the single telomeric chiasma was found in highest frequency among the women of younger age group (<29 years), who had a NDJ error at meiosis I stage of oogenesis and there was a trend of gradual decrease in telomeric chiasma frequency with advancing maternal age. The US study [5] revealed the majority of single exchange occurred in the distal 6.5 Mb of chromosome 21. In Indian study [7] the single exchange was scored at terminal 5.1Mb region. These observations suggest that the single telomeric chiasma formation is the risk of NDJ of Ch 21 even in younger women who otherwise do not suffer from deterioration...
Single Centromeric Chiasma Increases the Chance of MII Error

The etiology of MII NDJ is pretty different from MI NDJ. A single chiasma very close to centromere has been proved as risk of MII NDJ in both the US and Indian studies [6,7]. A trend of gradual increase in centromeric chiasma frequency with increasing maternal age was recorded in both the studies with gradual shifting of chiasma from middle of the chromosome in younger age group (<29 years) to more proximal to centromere in older age group (>34 years). In explaining the effect of centromeric chiasma on chromosome segregation two hypotheses have been put forward [24], Chiasma that is positioned very close to centromere may cause ‘chromosomal entanglement’ at MI, with the bivalent being unable to separate, passing intact to MII metaphase plate [24]. Upon MII division, the bivalent divides reductionally, resulting in disomic gamete with identical centromeres. In this manner, proximal pericentromeric exchange, which occurs at MI, is resolved and visualized as MII error. According to an alternate model which is an outcome from the study in Drosophila [21], proximal chiasmata lead to a premature sister chromatid separation just prior to anaphase I. Resolution of chiasmata requires the release of sister chromatid cohesion distal to the site of exchange [20]. Attempt to resolve chiasmata that are very near to centromere could result in premature separation of chromatids. If the sister chromatids migrate to a common pole at MI, they have 50% probability to move randomly into the same product of meiosis at MII, resulting in an apparent MII NDJ (Figure 4). Similar observation is reported from the study in Yeast in which centromere-proximal crossover promotes local loss of sister-chromatid cohesion [25]. Studies of NDJ in both humans [23] and Drosophila [26] have provided preliminary supports for this model.

Multiple Chiasma Associated with MI & MII Errors

The frequency of multiple chiasma formation on recombining tetrad is less than the frequency of single chiasma formation and cytological evidence from meiosis in diverse species has shown that the number of chiasmata and their position on the chromosome are nonrandom. This non-random positioning of multiple chiasmata generates genetic ‘interference’ which ensures optimal functioning of multiple chiasmata in chromosome segregation. This observation on model organisms led scientist to evaluate the association of multiple chiasma formation on Ch21 segregation. In their study for analyzing the spatial distribution of two exchange events on Ch21 that non-disjoined at MI Oliver et al. [27] found that the position of proximal chiasma remains same as that on the normally disjoined Ch21, but it is the distal chiasma that dislocates more proximally. In other words the distal chiasma displaces more proximally on the nondisjoined chromosome and it reduces the distance between two chiasmata and the authors hypothesized that is reduction of distance between chiasmata reduces the ‘good effect’ of two chiasma formation as two or more chiasmata usually stabilizes the chromosome and ensure proper segregation. The author did not find any correlation between maternal age and the position of distal chiasma.

In extending their analyses to examine MII errors with two observed recombination events Oliver et al. [27] Found that the average location of proximal recombination event was closer to the centromere in compare to normally disjoined Ch21. With respect to maternal age the proximal exchange, not the distal exchange, exhibits statistically significant displacement towards centromere. This trend was very concordant to that of age-related shift of single chiasma in MII NDJ as observed in previous studies [6, 7]. Further replicative study is warrant to confirm this result.

Alteration in Genome Wide Recombination Frequency Associated with Ch21 NDJ

Study of Brown et al. [28] provided the first evidence that oocyte...
with nondisjoined non-exchange Ch21 experience overall reduction in genome wide recombination. The author reported a linear increase in the mean genome-wide recombination depending on the inferred number of exchange along the nondisjoined Ch21. They inferred that specific chromosomes may be at higher risk for NDJ when the number of genome-wide recombination events is less than some threshold. The same group of researchers continued their study recruiting larger sample size and very recently they have published the data on genome wide variation in recombination in oocyte carrying nondisjoined Ch 21 [29]. In this study Middlebrooks et al. [29] examined two levels of recombination regulation in oocytes: Firstly, regulation at the maternal level that leads to correlation in genome-wide recombination across her oocytes and secondly, regulation at the oocyte level that leads to correlation in recombination count among the chromosomes of an oocyte. The authors used Golden Gate linkage panel and analyzed nearly 6000 SNP markers across the genome. They found that the correlation in recombination count among the chromosomes of an oocyte is reduced in oocytes with MI errors compared with that of their siblings or controls. These results suggest that disregulation at the maternal level and subsequent reduced level of recombination predisposes MI error, but additional oocyte-specific dysregulation contributes to the nondisjunction event. The author did not found any significant genome wide recombiant reduction for MII nondisjoined group. Moreover, author did not find any genome wide alteration in placement of chiasma probably owing to limitation in sample size. This study is very much pioneering and has shed a new light in this field of research.

Recombination Hotspots and Their Relationship with Ch21 NDJ

Very recently, Oliver et al. [30] has analyzed the molecular features and distribution of recombination hotspots along the length of nondisjoined Ch21 to get more insight on the relationship between recombination and Ch21 NDJ. Studies of normal meiotic events in humans show that the placement of recombination is not a random event. Rather, both cis and trans-acting factors have been found to be associated with the placement of recombination. Specifically, GC content, CpG fraction and Poly(A)/Poly(T) fraction have each been found to be significant predictors of placement of sex-averaged recombination events in the human genome [31]. In addition, sequence variation in the zinc-finger domain of the gene Proline Rich Domain Containing 9 (PRDM9) has a major impact on the location of recombination in humans [32]. The observation that both cis and trans-acting factors are associated with the placement of recombination led authors to enquire whether the altered patterns of recombination associated with NDJ of Ch21 could be explained by differences in the relationship between recombination and genomic features (i.e., GC content, CpG fraction, Poly(A)/Poly(T) fraction or gene density) on 21q or differential hot-spot usage [30].

Oliver et al. [30] used Illumina Golden gate platform for trisomy genotyping which included ~509000 SNP markers and found that for single recombiant events only the location of recombination hotspot has been proved to a significant predictor for MI NDJ and for MII NDJ both centromeric location and GC content have been proved to predictor of the error. Among the nondisjoined chromosomes with two exchange, authors found MI and MII proximal recombiant events occur in GC rich regions more often than statistically expected if there was no relationship between the amount of recombination and GC (or CpG) content. For meiosis with two detectable recombinants, the authors found a positive correlation among proximal chiasma, GC content and CpG cluster with both MI and MII error, but not with euploid samples. Poly(A)/Poly(T) fraction was found to be inversely correlated with the amount of recombination among MI and MII errors and euploids. Collectively these observations suggest that MI and MII proximal recombinant events occur in GC rich regions more often than statistically expected if there was no relationship between the amount of recombination and GC (or CpG) content [30]. This relationship was not detectable for distal recombination events.

Further, the authors analyzed the relation between single chiasma position and hotspot used in recombination and found hotspot density to be a positively correlated with the proportion of recombination both in MI error as well as with controls. For MI errors with two crossover events the authors did not detect a significant relationship between hotspot density and the proportion of recombination for proximal exchange, but a significant relationship was found for distal exchange though pattern of association did not differed from MI and controls. For MII cases with single recombination events a significant positive correlation between hotspot density and the proportion of recombination across 21q was detected, which differs from control, in that with MII single recombinant events being less correlated with hotspot density than controls. Among MII errors with two recombinant events, as with MI errors, the authors did not detect a significant correlation between the proportion of recombination and the density of LD-defined hotspots in the proximal region . For MII distal events, there was a significant positive association between LD-defined hotspot density and the proportion of recombination was detected.

Conclusion

Study on recombination dysregulation in the context of aneuploid gene formation is an emerging trend of research. Alternation in frequency and placement of chiasma on Ch 21 leads to NDJ of the chromosome particularly in oocyte. But the reasons behind this dysregulation remain intriguing. It is not yet clear whether failure of Ch21 to recombine properly is a stochastic event or some genetic susceptibilities do play background role in it. Genome wide analyses have identified some specific genetic candidates or regions on the chromosome that may have certain role in the origin of recombination anomaly. For example PRDM9 is a gene known to be involved in the placement of recombination events and alleles have also been associated with a significant change in crossover rate within recombination hotspots [31] of the chromosome. Mouse lacking functional PRDM9 exhibits inefficient homolog recognition and synopsis, with aberrant repair of meiotic DNA double-strand breaks and transcriptional abnormalities characteristic of meiotic silencing of unsynapsed chromatin. [32] Similarly, allelic variants in the RNF212 have been identified to cause variation in recombination count in males and females mice [31]. Heterozygous mutant allele of this gene exhibits reduced recombination [33]. The product of this gene is essential for mammalian cross-over and it may stabilize other recombination proteins [34]. In addition, an inversion at genomic region 17q21.31 was also found to be associated with elevated recombination in female carriers versus non-carrier [35]. This inversion carries two different haplotypes, namely H1 and H2 which differ from each other in gene expression profile [35-37] Data from the recent study of Middlebrooks et al. [31] have shown that chromosome 17 is a strong predictor of genome-wide recombination count. The future research should be directed towards the characterization of all these genes or genetic loci so that more close understanding the etiology of Ch21 NDJ and subsequent DS birth could be achieved.
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