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Etiology of Down Syndrome: Evidence for Consistent Association among Altered Meiotic Recombination, Nondisjunction and Maternal Age Across Populations

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Abstract

Down syndrome caused by meiotic nondisjunction of chromosome 21 in humans, is well known to be associated with advanced maternal age, but success in identifying and understanding other risk factors has been limited. Recently published work in a U.S. population suggested intriguing interactions between the maternal age effect and altered recombination patterns during meiosis, but some of the results were counter-intuitive. We have tested these hypotheses in a population sample from India, and found that essentially all of the results of the U.S. study are replicated even in our ethnically very different population. We examined meiotic recombination patterns in a total of 138 families from the eastern part of India, each with a single free trisomy 21 child. We genotyped each family with a set of STR markers using PCR and characterized the stage of origin of nondisjunction and the recombination pattern of maternal chromosome 21 during oogenesis. Our sample contains 107 maternal meiosis I errors and 31 maternal meiosis II errors and we subsequently stratified them with respect to maternal age and the number of detectable crossover events. We observed an association between meiosis I nondisjuncion and recombination in the telomeric 5.1 Mb of chromosome 21. By contrast, in meiosis II cases we observed preferential peri-centromeric exchanges covering the proximal 5.7 Mb region, with interaction between maternal age and the location of the crossover. Overall reduction of recombination irrespective of maternal age is also evident in meiosis I cases. Our findings are very consistent with previously reported data in a U.S. population and our results are the first independent confirmation of those previous reports. This not only provides much needed confirmation of previous results, but it suggests that the genetic etiology underlying the occurrence of trisomy 21 may be similar across human populations.

Keywords

Trisomy 21; Meiotic nondisjunction; Altered recombination; susceptible chiasma; Maternal age

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INTRODUCTION

Trisomy 21 in humans, commonly referred as Down syndrome (DS), is the most common genetic cause of mental retardation. In approximately 95% cases, the extra chromosome occurs as a result of meiotic nondisjunction (NDJ) or abnormal segregation of chromosomes. Of these, in the majority of cases the error occurs during maternal oogenesis [Antonarakis, 1991; Freeman et al., 2007] particularly at meiosis I (MI) [Antonarakis, 1992; Sherman et al., 2007].

Advanced maternal age [Hassold and Chiu, 1985] and altered recombination [Warren et al., 1987; Sherman et al., 1991] are two established risk factors that have been reported to be associated with DS, at least for the cases in which the extra chromosome has arisen in the oocyte [Sherman et al., 2007]. The process of oogenesis is lengthy and involves meiotic arrest, which makes it more vulnerable to malsegregation of chromosomes than spermatogenesis [Oliver et al., 2008]. Moreover, with increasing age, there is rapid degradation of cellular proteins involved in spindle formation [Hawley et al., 1994], sister chromatid cohesion [Wolstenholme and Angell, 2000] or anaphase separation of sister chromatids in oocytes, which imposes the risk of NDJ both at MI and MII [Yoon et al., 1996].

Recombination, initiated in the fetal ovary, stabilizes the tetrad and ensures proper segregation of chromatids to opposite poles. But the process is random and may be absent even in euploid samples [Cheung et al., 2007]. These achiasmate meioses are at risk for NDJ, and this risk increases with age due to rapid deterioration of ovarian proteins that make up the surveillance and `back-up' system for resolving and separating these non-exchange chromosomes [Cheslock et al., 2005]. It has been shown that nondisjoined chromosomes often show altered patterns of recombination [MacDonald et al., 1994; Hassold et al., 1995; Koehler et al., 1996b] and for trisomy 21, achiasmate meioses contribute about 45% of maternal MI cases [Sherman et al., 2007]. Therefore, the ovarian microenvironment of older women appears to become more error prone due to accumulation of environmental and age related insults [Hassold and Chiu, 1985].

Studies in a U.S. population have also shown that both absence of chiasmata and suboptimally placed chiasmata impose susceptibility for NDJ of chromosome 21 [Lamb et al., 1996, 1997]. A single telomeric exchange leads to an increased risk for MI error, whereas pericentromeric exchanges increase the risk for MII error. A distally placed chiasma probably links the homologue less efficiently to the spindle and imprecisely orients the kinetochore towards opposite pole; this tendency has been proved to be true for a model organism [Hawley et al., 1994]. For pericentromerically placed chiasmata, it has been speculated that a chromosomal error develops during MI, with the bivalent being unable to separate, passing intact to the MII metaphase plate and subsequently resulting in reductional division in MII anaphase, producing a disomic gamete [Lamb et al., 1996, 1997].

More recently, the relationship between maternal age and recombination has been explored in order to further elucidate the causes of chromosomal NDJ [Lamb et al., 2005a, 2005b; Oliver et al., 2008]. These studies indicated that for MI errors, a greater proportion of single telomeric exchange within the distal region was exhibited by younger mothers. This differed statistically from middle and old age group mothers, as well as from euploid samples. On the other hand, for MII cases, older age group mothers exhibited a preferential occurrence of single chiasma within the proximal 5.2 Mb of 21q, and this differed statistically from younger and euploid mothers [Oliver et al., 2008].

Combining these findings, it has been postulated that chromosomal NDJ is a complex and multi-factorial event for which the underlying mechanisms are related to two different sets

of factors; one age dependent and another age independent [Oliver et al., 2008]. Specifically, achiasmate meioses and single telomeric exchanges always place the oocyte at risk of NDJ regardless of maternal age. In contrast, age-dependent factors are evident from the presence of pericentromeric exchange among older mothers for MII [Lamb et al., 2005b; Oliver et al., 2008].

The age-stratified results discussed above were found in a single large sample from the United States, and to our knowledge had not previously been confirmed in any other population. In this paper we report the results of a similar study on a population from the eastern part of India that was conducted in order to confirm whether the previously observed relationships between recombination and NDJ are replicated across geographical/racial divides.

MATERIALS AND METHODS

DS Population Sample

A total of 138 families, each with single DS child having free trisomy 21, were included in our study. Families were referred from different Medical Colleges & Hospitals of Kolkata and adjoining areas. The families were unrelated and heterogeneous in respect to their religion. A detailed family history with informed consent was taken from each participating family. The design of experiments with human tissue samples and subsequent data analyses were reviewed and approved by the ethics committee constituted by West Bengal University of Technology. Peripheral blood samples were collected from father, mother and DS child. The samples were genotyped with 13 STR markers spanning centromere to telomere of 21q. The order of markers was Centromere- **D21S369** - **D21S215** -**D21S258**- **D21S1432** - **D21S11** - **D21S1437** -**D21S1270** - **D21S167** - **D21S1412** - **D21S2055** - **D21S1260** - **D21S1411** - **D21S1446** - **qter.**

Detection of Parental origin and stage of meiotic nondisjunction

The parental origin of the segregation error was determined by detecting the contribution of parental alleles to the probands for multiple markers. Three pericentromeric markers—D21S369, D21S215 and D21S258, were used to infer the stage of NDJ (MI or MII). If parental heterozygosity was retained in the trisomic child at the centromeric markers, we considered the case to be of MI origin. If parental heterozygosity was reduced to homozygosity, we interpreted this as an MII origin. MII events with no evidence of recombination were considered to be mitotic errors and were excluded, as described elsewhere [Oliver et al., 2008].

Detection of crossover events

In addition to the three pericentromeric markers, ten additional markers were used to divide 21q into intervals to monitor the exchange events. After genotyping, the status of each marker was recorded as nonreduced (N), reduced (R), partially informative (PI) and uninformative (U). A matrix was generated by arranging the status of all the markers in a direction from proximal to distal of centromere on 21q arm. The recombination events were detected on a chromosome after observing the change of status of two successive markers, either R→N or N→R in a single family. In cases in which a recombination could not be assigned to a specific interval due to uninformative markers, the position was scored at the midpoint of the two intervals (e.g., a recombination localized to interval 1 or 2 would be scored as 1.5).

Statistical Analysis

We divided families into three groups based on maternal age at the time of the trisomic birth: young (28 yrs and younger), middle (29yrs –34yrs) and old (35yrs and older). We chose these age groups to match previous studies. We had two principal aspects of analyses -----1) amount of recombination and 2) position of recombination. Comparisons of count data (e.g. number of families showing no recombination) between age groups were performed using Chi-squared tests of independence. To examine locations of recombination events by age we performed simple linear regressions of the location (scored as the interval number) on the maternal age. All analyses were performed with observed recombination data. We did not infer underlying exchange patterns, as that is unnecessary (and statistically sub-optimal) for comparing age groups.

RESULTS

MI:MII ratio and age group frequencies

We report results for 138 families with maternal meiotic error. Of these, 107(77.5%) are MI cases and the rest are of MII. The MI cases are younger on average than the MII cases, with 60, 26 and 21 in the MI young, middle and old age groups respectively, as compared to 11,10 and 10 for the MII cases. Both the age difference and overall MI:MII ratio are similar to those observed in previous studies [Oliver et al., 2008].

Maternal MI nondisjunction

Amount of recombination—Because recombination helps to orient the chromosomes properly on the meiotic spindle in order to ensure subsequent anaphase separation to opposite poles, reduction or absence of recombination places them at risk of NDJ. When all age groups are combined, MI mothers exhibit an average of only ~0.22 recombination events per meiosis in our dataset. If this risk is operative during oogenesis irrespective of maternal age, we would expect to observe a greater proportion of achiasmate MI events among the younger mothers, decreasing for the middle and older age groups. This is because, for younger mothers, absence of recombination is the only risk factor (under this simple model) where as for older mothers, other age related factors are also operative.

We found that 80% of young mothers exhibited an absence of recombination, in contrast with 67% for old age group. But the tendency is not linear (Table-II), as the middle age group exhibited a puzzling higher proportion (88%) of non-recombinant meioses. However, none of the pairwise differences among the three groups are statistically significant using a Chi-square test of independence.

Location of Recombination—Along with reduced recombination, a single telomeric exchange had been reported to be associated with risk for MI NDJ among mothers of all ages [Lamb et al., 2005a; Oliver et al., 2008]. Moreover, previous studies observed an age-related shifting of exchange from the telomere towards the middle of the chromosome [Lamb et al., 2005b; Oliver et al., 2008], which is consistent with a model in which the risk due to a telomeric exchange is constant for all age groups (as discussed above for achiasmate chromosomes).

To evaluate this model in our Indian population, we included only maternal MI cases with single recombination events (n =18) and observed the locations of those recombination events among the twelve intervals on the 21q defined by the markers we used (table -II). The peritelomeric 5.1Mb region (marker intervals 11 and 12) accounted for a remarkably high proportion (48%) of exchanges among the young age group mothers. In contrast, among the middle and older groups, peri-telomeric exchange is almost absent. Regression analysis of

location (recorded as marker interval 1–12) on maternal age yields a regression-t value of −2.3 (p value = .02), which clearly indicates preferential occurrence of single crossover events at the telomere and surrounding regions among the younger mothers. With increasing age, the location of chiasmata gradually shifts towards the middle (intervals 4 & 5) of the chromosome.

Maternal MII nondisjunction

Amount of recombination—Previous results [Oliver et al., 2008] showed the frequency of multiple recombinants was decreasing with maternal age in MII cases. Although our sample size (n=31) is too small to achieve statistical significance, we see a similar decrease (Table-I), with only 1 of 6 cases showing a double recombination among older mothers, 2 of 6 in the middle age group, and 3 of 6 in the young age group.

Location of recombination—In a previous study [Oliver et al., 2008] with maternal MII cases, it was shown that pericentromeric exchange was most prevalent in older mothers, with exchanges in young mothers shifting towards the telomere. As noted in [Oliver et al., 2008], this result was quite surprising, as it directly contradicted the model in which susceptible chiasma patterns are age-independent risk factors (as in MI). Rather, this result suggested that peri-centromeric exchange is a strongly age dependent risk factor for MI NDJ.

We repeated this analysis in our Indian dataset to see if this counter-intuitive result would be replicated in a new population. In fact, our dataset showed an even stronger age-dependent effect (Table-II). Despite our small sample size, we observed a highly statistically significant change in chiasma position with age among MII cases. Regression of position of the chiasma on the maternal age yielded a regression `t' value of - 7.1 for p value of < .0001. This indicated a strong linear tendency, with centromeric exchanges (intervals 2, 3 & 4) for older mothers and gradual shifting of chiasma position towards the middle of chromosome (intervals 5,6 & 7) for the younger group.

DISCUSSION

Previous findings in other populations regarding the relationship between NDJ and altered recombination inspired us to carry out a similar study on an Indian DS sample. In particular, previously reported findings in a U.S. population indicated that certain chiasma locations are risk factors for trisomy 21, some in an apparently age-dependent pattern. We wanted to investigate whether these previously reported associations could be replicated in an independent population.

Reduced recombination is a well-established susceptibility factor associated with various types of chromosomal aneuploidy in human and model organisms [Hawley et al., 1994; MacDonald et al., 1994; Rockmill and Roeder, 1994; Koehler et al., 1996a; Freeman et al., 2007]. One of the major aims of our present study was to investigate whether this `reduced recombination' risk factor imposes equal risk of chromosomal NDJ for all age groups of mothers. If this risk is age independent, then the greatest proportion of cases with achismate meioses should be among the youngest group of women. The logic behind this prediction lies in the fact that a single age independent risk factor would be predominant among low age group mothers who are not subject to age-related risk factors.

Our data revealed that 80% of younger mothers of MI cases experienced nonrecombinant meioses, in contrast to 67% of older women (Table I). We do not have any satisfactory explanation for occurrence of a higher proportion (88%) of non-recombinant meioses among the middle age group. This may due to sampling variation, as none of the differences among

the groups were statistically significant. Previous results for a U.S. population [Oliver et al., 2008] showed 70% non-recombinant in the young group, 64% in the old group, and 56% in middle group, with the difference between young and old being statistically significant. Taken together, these two sets of results are still somewhat puzzling, but given sampling variation they are not inconsistent with the expected model of a decrease in nonrecombinant frequency with age.

In addition to absence of recombination, position of chiasmata along 21q, was also an established susceptibility factor for chromosome 21 NDJ [Lamb et al., 1997; Oliver et al., 2008]. We also found associations between recombination location and age in our study. In the younger subgroup of MI cases, about 48% of detectable crossover events took place in marker intervals 11 & 12, covering a region of 5.1 Mb at the telomeric end of chromosome 21, with an additional 35% of all detectable recombination in the adjoining 0.4 Mb peritelomeric region (intervals 9 and 10). In contrast, only 20% of recombination events among the old age group were within that peritelomeric region (intervals 9 & 10) and none were at the telomeric end (interval 11 & 12). This difference was statistically significant by linear regression analysis. Following the same argument made above, we suggest that distally placed chiasmata appear to impose susceptibility for chromosomal malsegregation irrespective of age. Support for this hypothesis was available also among model organisms [Zetka and Ross, 1995; Koehler et al., 1996a; Ross et al., 1996]. Probably this distally placed single chiasma links the homologues less efficiently due to recruitment of a minimum amount of sister chromatid cohesion complex which prevents the bi orientation and subsequent separation of homologues on the meiotic spindle [Hawley et al., 1994; Koehler et al., 1996b; Orr-Weaver, 1996].

In our MII sample, we observed the same apparently age dependent risk pattern that has been reported previously [Oliver et al., 2008]. Of all recombination events among old age group mothers, 71% took place within a ~5.7Mb region proximal to the centromere [intervals 2,3 & 4], in contrast to 19% for the middle age group and none for the younger mothers. This result is highly statistically significant and suggests that pericenromeric single exchange is an age-dependent risk for MII NDJ. This similarity of our Indian data with previously reported findings [Oliver et al., 2008] leads us to postulate the model that proximal chiasmata are a risk factor for `chromosome entanglement' at MI, with the bivalent being unable to separate and remaining intact upto the MII metaphase plate [Lamb et al., 1996]. An alternative model is that a chiasma very close to the centromere causes premature sister chromatid separation at MI and subsequently leads to NDJ during MII [Angell et al., 1994]. Whatever the mechanism is, the factors related to this MII malsegregation are clearly related to an effect of aging. This is also supported from a yeast model in which a protein *shugoshin*, a member of the centromeric cohesion complex, showed age-dependent degradation and subsequent premature sister chromatid separation prior to anaphase II [Marston et al., 2004]. Similar patterns of age dependent degradation of protein apparatus leading to MII NDJ have also been seen in the human female [Steuerwald et al., 2001; Baker et al., 2004].

Despite the smaller sample size of our study, we have observed very concordant results with those of Oliver et al. [2008], which previously examined the same questions in a U.S. population. The frequency of MI (77.5%) in our dataset is quite similar to theirs of 71% (p value for Fisher's exact test is 0.13), as is our observation of a much higher average maternal age among MII cases. We observed similar results to theirs in both the amount and location of exchange, and in the age effects on these factors, in both MI and MII. The most striking result of our present study is the strong replication of Oliver et al.'s [2008] unexpected findings of increased pericentromeric exchange in older MII mothers, indicating a strong age-dependent effect of this risk factor. All of these observations not only provide much

needed confirmation of the previous results but lead us to infer that the genetic etiology behind the incidence of human chromosome 21 NDJ may be almost universal irrespective of geographical, racial and socioeconomic differences. These discoveries bring us a significant step closer to complete picture of the risk factors for DS.

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Table-I

Frequency distribution of observed recombination events for maternally derived NDJ groups among different maternal age groups

Frequency distribution of recombination in meioses among the maternal age groups of both MI and MII cases.

Types of NDJ	Maternal age group	Sample Size	Frequency of observed number of recombination events		
			0	1	≥ 2
MI	Young (≤28yrs)	60	0.8	0.18	0.02
	Middle (29–34yrs)	26	0.88	0.08	0.04
	Old (≥35)	21	0.67	0.24	0.09
MII	Young (≤28yrs)	11	-	0.73	0.27
	Middle (29–34yrs)	10	-	0.8	0.2
	Old (≥35)	10	-	0.9	0.1

NDJ - Nondisjunction, MI-Meiosis I, MII - Meiosis II.

Table-II

Positional distribution of single recombination events for maternally derived NDJ among different maternal age groups

Frequency distribution of recombination events.

Types of NDJ	Maternal age group	Sample Size	Marker intervals along 21q (Centromere to Telomere)											
			1	2	3	4	5	6	7	8	9	10	11	12
MI	Young (≤28yrs)	11	0.00	0.04	0.04	0.09	0.00	0.00	0.00	0.00	0.09	0.26	0.35	0.13
	Middle (29–34yrs)	2	0.00	0.00	0.00	0.5	0.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Old (≥35)	5	0.00	0.00	0.00	0.00	0.00	0.4	0.4	0.00	0.00	0.2	0.00	0.00
MII	Young (≤28yrs)	8	0.00	0.00	0.00	0.00	0.00	0.16	0.08	0.21	0.16	0.13	0.13	0.13
	Middle (29–34yrs)	8	0.00	0.00	0.03	0.16	0.25	0.37	0.03	0.16	0.00	0.00	0.00	0.00
	Old (≥35)	9	0.00	0.2	0.43	0.26	0.11	0.00	0.00	0.00	0.00	0.00	0.00	0.00

NDJ - Nondisjunction, MI-Meiosis I, MII - Meiosis II.