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Relationship between Maternal Aging and Risk of Chromosome 21 Nondisjucntion: Where We Are and Where We Have To Go?

Review Article

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Summary

Several lines of researches have revealed that the women having Down Syndrome (DS) child are usually biologically older than the women of same chronological age with euploid baby. On other hand, Women having DS child often suffer from early onset of Alzheimer disease (AD). Frequent association between AD and DS in some families intuitively suggests sharing of some common genetic risk factors between maternal precocious aging and chromosomal nondisjunction. Subsequent molecular analyses have revealed polymorphisms of certain genes simultaneously associated with AD and DS birth. In this regard polymorphic alleles of APOE, Presinilin-1 and BubR1 are of particular interest. So, understanding the molecular relation between accelerated maternal aging and increased risk of DS conception will provide basis of future research that may have large medical applicability.

Keywords: Down syndrome; Maternal age; Accelerated aging; Nondisjunction; Telomere

Introduction

The aetiology of nondisjunction (NDJ) of Chromosome 21 (Ch21) that causes birth of baby with Down syndrome (DS) is an unsolved issue in the field of medical genetics for decades. DS represents the most frequent genetic form of intellectual disability in human. In overwhelming majority of live born DS cases NDJ errors originate in oocyte and the frequency of error increases with advancing chronological age of women [1,2]. The association between advanced maternal age of conception and elevated risk of DS birth was reported initially by Penrose [3] and subsequently confirmed in other studies [4-6]. On other hand, population based statistical analyses have revealed elevated risk of Alzheimer Disease (AD), (which is the expression of aging associated dementia) among some women who bear DS child before 35 years of age; but the mothers who have DS pregnancy beyond 35 years of their age do not exhibit such association [7]. Thus the relationship between maternal age and risk of Ch21 NDJ in oocyte is intriguing and can be viewed in two different but parallel ways; firstly, the gradual increase in the risk of NDJ with advancing maternal chronological age and secondly, stochastic risk among chronologically younger women who otherwise suffer from accelerated biological aging. This second notion is truly riddling as our current understanding of maternal biological aging and its relation with the risk of Ch21 NDJ at molecular level is surprisingly limited. The present review is focused to address the prospective genetic and epidemiological candidates that may relate accelerated aging and increased risk among women to conceive DS child.

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Chronological Aging and Increasing Risk of NDJ

The hypotheses that explain association of advancing maternal age with NDJ have generalized approach to accommodate all types of human aneuploidy involving autosomes and sex chromosome. Several hypotheses have been put forward to elucidate the link between advancing maternal age and higher incidence of aneuploid oocyte formation, though no one has proved to be completely satisfactory. The most popular hypothesis [8] holds that protracted tenure of oogenesis interrupted with meiotic halts probably makes the eggs more vulnerable to the aging effect than sperms (Text Box 1). This long period of oocyte maturation causes deteriorative changes to accrue over time either in the oocyte or its milieu. Examples of such factors are diminishing amount of a meiotic proteins, like those maintaining sister chromatid adhesion [9] or meiotic checkpoint components [10] or weakening of centromere cohesion due to age-related reduction in centromere associated proteins MCAK [11]. This list of age related risks may also include the accumulation of environmentally induced damages to the meiotic machinery over time or genetic changes such as mitochondrial deletions [12]. Among all these variables the spindle assembly check point (SAC) components and sister chromatid cohesion (SCC) were investigated thoroughly [13]. The SAC is a molecular machine that ensures proper chromosome separation in both mitosis and meiosis. In meiosis SAC prevents anaphase until all chromosomes get attached properly to the spindle. The SAC includes *MAD2L1*, *BUB1B*, and *TTK* [14,15], which show decline in concentration with age and causes misalignment of chromosomes on metaphase plate in mouse [16]. This observation suggests that errors in SAC function contribute to age-related aneuploidy. Consistent with this hypothesis, disrupted spindles, misaligned chromosomes and decreased expression of SAC components *MAD2L1* and *BUB1B* have evident in aged human oocytes [17,18]. On the other hand the SCC mediates physical pairing of duplicated chromosome which is essential for their appropriate distribution in daughter cells. The cohesion along chromosome arms keeps the bivalent intact in meiosis I (MI), and centromere cohesion holds sister chromatids together in MII. Defect in cohesion distal to crossover sites may result in a shift of chiasmata placement (chiasmata slippage) or even premature bivalent separation in MI, whereas reduced centromere cohesion may result in premature separation of sister chromatids in MII [18]. The loss of cohesion with maternal age for distally placed chisama [19] is consistent with the idea that cohesion defects may contribute to age related aneuploidy [20]. More specifically the meiotic cohesin proteins Smc1β and Rec8 exhibit age related reduction in mouse oocyte resulting in misaligned chromosomes and aneuploidy [20,21].

Another component that is supposed to decline with age and contributes significantly to the maternal aging effect on DS birth is the surveillance system of ovary that ensures segregation of achiasmate chromosomes at meiotic anaphase [1]. Chiasma formation and subsequent recombination are prerequisite of faithful separation of homologous chromosomes at meiotic anaphase (Text Box 2). Absence of chiasma, faulty chiasma configurations and reduction in chiasma frequency result in NDJ of Ch21 and subsequent DS birth [22]. A high proportion of achiasmate Ch21 tetrad was reported among the mothers of DS having age >35 year [1]. As the decision regarding chiasma formation is taken in foetal ovary, high frequency of achisamate nondisjoined Ch21 in older oocyte can only be explained by down regulation of surveillance system. Human proteins involved in proper segregation of nonexchange chromosome show down regulation with increasing ovarian age [18,23].

Advanced Biological Aging among DS bearing Women

All the above mentioned hypotheses that incriminate decay in subcellular protein components in oocyte for age-related increase of trisomy 21(T21) conception do consider the maternal chronological age, although individual variation in the extent of these changes could occur [5]. A new idea regarding maternal age effect on meiotic errors was proposed by Warburton, [24,25] and the hypothesis states that the "biological aging" or "ovarian aging" is the cause of increasing rate of meiotic errors. The central theme of this hypothesis is the prediction that biological aging is different among women of the same chronological age, and that the frequency of trisomic conceptions depends upon the biological age of the woman rather than their chronological age [25]. The biological age of women can usually be assessed by counting the falling number of antral follicles with chronological age together with decrease in total oocyte pool size [26,27]. These altogether alter the optimum hormonal balance in ovary, which is marked by falling concentration of serum inhibin A and B, decline in estrogens surge and elevated level of FSH [25]. This change in hormone balance is related to increased rate of aneuploidy at advanced maternal age. Support to this prediction is available from the experiment in mouse model [28].

The "biological aging" hypothesis predicts that women with a trisomic conception should on the average have an older "ovarian age" than women of the same chronological age with normal euploid conception [25] and women having T21 pregnancy have average earlier (~1 year) age of menopause [29] than the women with chromosomally normal conception. If this were the case, one would expect that after a trisomic conception, the risk of a subsequent trisomy birth for any chromosome should be higher than the maternal age-related risk. Support to this prediction has been provided from the observation that risk of trisomic pregnancy after a previous trisomic conception is about 1.7 times the maternal age-related risk [30]. Mathematic model proposed by Kline and Levin [31] estimated that women with trisomy pregnancy experience 0.9 years early menopause which suggests women with trisomy pregnancy suffer from advanced ovarian age than the women with chromosomally normal pregnancies. Population sample survey for estimating median age of menopause among the women with trisomic pregnancy also suggested an early cessation of menstrual cycle among them than the mothers with chromosomally normal foetus [29]. Elevated level of FSH has been reported among the women with DS pregnancy [32,33], which suggests precocious aging among them.

Owing to lack of conclusive evidence in favour of the 'biological aging, Warburton [25] proposed an alternative notion, namely 'limited oocyte pool hypothesis' which stated that with increasing biological age gradual decrease in the number of antral follicle leaves only the premature or post mature oocyte to ovulate and that inevitably leads to aneuploid conception. Recently Kline et al. [34] conducted a survey on hormonal level of women with trisomic pregnancy and the outcome of the study supported the "reduced

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oocyte pool hypothesis". The authors inferred that some women have smaller follicle content than the others of same chronological age and the former group are susceptible for rapid ovarian aging and associated trisomic conceptions. All these findings imply an intuitive existence of predisposing factors that make some women susceptible for both the accelerated aging and to have trisomic conception.

Accelerated Genetic Aging among DS bearing Women

If the biological aging hypothesis holds true, the question that obviously comes in mind whether, any genetic factor underlies the cause of biological aging or not. In others words, some women may be genetically predisposed to rapid molecular aging and therefore experience advanced biological and ovarian aging, which increases the chance of trisomic conception. Attempt to resolve this issue was started by measuring the telomere length (TL) of women having trisomic pregnancy as the telomeric repeat attrition is an authentic marker of molecular aging in somatic tissue [35,36]. The initial study for determining the maternal molecular age for DS was carried by Dorland et al. [37] who estimated the TL of peripheral blood lymphocytes from women having DS baby and compared the TL with that of women having euploid child. This study included women of <35 years age and did not achieve statistically significant difference between cases and controls. The outcome of this study suggested that the younger women who have DS baby do not differ in their genetic or molecular age from the women of similar chronological age having euploid baby. A positive correlation between loss of TL in somatic tissue and shorter reproductive life span due to ovarian aging was reported in other studies [38,39]. The study on the women with history of recurrent miscarriages of trisomic foetus conducted by Hanna et al. [40] revealed no difference in TL of lymphocytes taken from cases and controls. In contrast to this report, a very recent study on DS bearing mothers [41] have demonstrated a significant difference in TL among the case and control women of older age (>34 years). In this cross sectional study the participating women were stratified initially by age of conception (young :< 29 years, middle: 29-34 and old >34 years) and then by meiotic origin of NDJ of Ch21 (MI NDJ or MII NDJ for DS case category). The TL of lymphocytes was estimated by restriction digestion-Southern blot approach. The result shows much faster rate of TL shortening among mothers of DS child and the rate of shortening is significantly different from the estimated TL attrition rate of controls (61 bp/years in control; 111 bp/year in MI NDJ group; 230 bp/year in MII NDJ group) (Figure 1). Moreover, authors found significant difference in mean TL among the controls, MI and MII (p = 0.004 for MI-NDJ vs. MII-NDJ, p < 0.001 for MI-NDJ vs. control and p < 0.001 for MII-NDJ vs. control) with shortest TL recorded in older MII group (Figure 2). The authors proposed 'genetic aging hypothesis' which holds the notion that some women are predisposed to rapid genetic and molecular aging and its effect is exacerbated at advance age when age-related natural deteriorative changes also affect the chromosome separation system leading to NDJ. The notion suggested some intuitive link between telomere maintenance system (i.e., system of molecular aging) and chromosome segregating apparatus at molecular level possibly in sharing one or more molecular components. Some polymorphisms of telomere maintenance components *TERC* and *TERT* are reported [42-44] to associate the rapid telomere attrition and some cardiovascular and cerebro-vascular phenotypes resembling aging [45], but their role have not been evaluated as risk factors for Ch21 NDJ and DS birth.

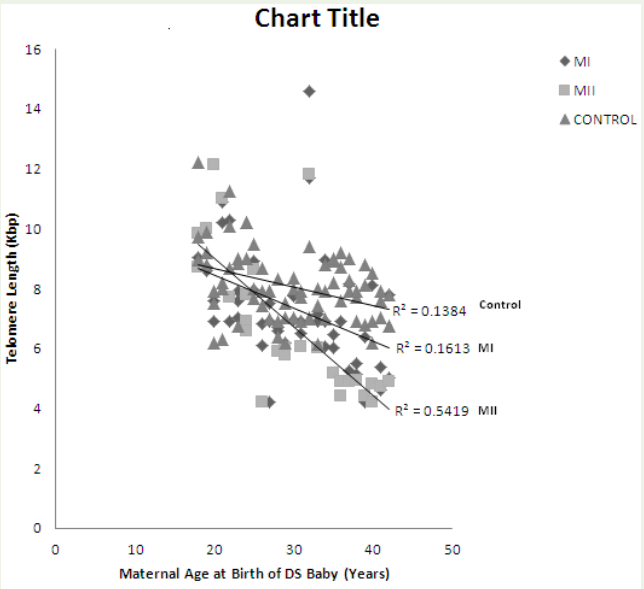

Figure 1: Figure showing telomere shortening over the age among control, MI nondisjoined and MII nondisjoined DS bearing women. The MII mothers show highest shortening rate than other categories (p<0.001 for MI vs MII, Control vs MI and Control vs MII). (The figure is from unpublished data of the study by Prof. P. Ghosh & S. Ghosh Kolkata, India, Study period: 2005-2013).

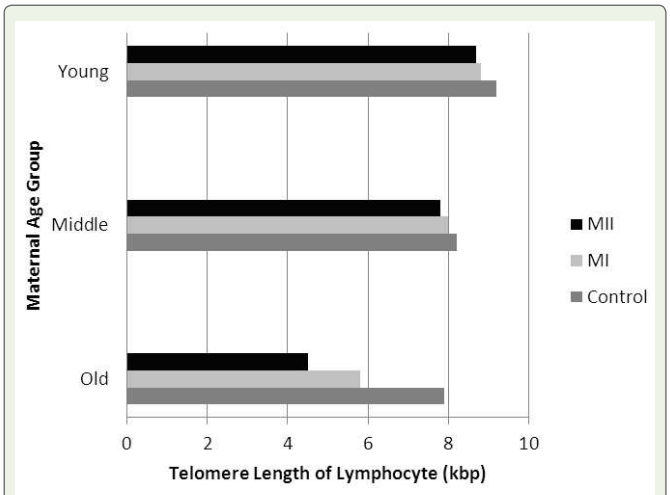

Figure 2: Figure showing mean telomere length of different maternal age categories (young: <29 years, middle:29-34 years, old: >34years) with highest difference in old age group ((p<0.001 for both Control vs MI and Control vs MII in older age group). (The figure is from unpublished data of the study by Prof. P. Ghosh & S. Ghosh Kolkata, India, Study period: 2005-2013).

Signature for Accelerated Aging: Early onset of AD among DS bearing women

Probably the most convincing evidence for accelerated aging among women having DS child is the early onset Alzheimer disease

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(AD) among them. Several studies have suggested the possibility of shared risk of AD and DS among women. In their study on DS families, Heston et al. [46] noted an association of early age at onset of AD among the family members and inheritance was through maternal line. The study by Schupf et al. [7] revealed that women having DS baby at <35 years age suffered from early onset of AD and they hypothesized that DS and AD shared a genetic susceptibility through accelerated aging of mothers. The authors estimated the relative risk of developing symptoms of dementia among women of age <35 years bearing DS child and it were about five times than for controls. In search of putative candidates that link the early onset of AD phenotypes among women and their DS conception, different groups of workers have reported the allelic variants of two genes. The first of them is ε4 allele of *APOE* gene (located on Chromosome19) and the other one is intronic polymorphism of the gene *Presenilin-1*(located on Chromosome14). The study by Hofman et al. [47] suggested an association between meiotic stage of NDJ and the *APOE* ε4 allele among mothers who gave birth to a DS child when 32 years of age and the authors inferred that the shared susceptibility to DS and AD might be mediated by an increased frequency of the ε4 allele. The study revealed that frequency of the ε4 allele was greater in young mothers with MII-NDJ than in young mothers with a MI-NDJ (30% versus 19%), but did not differ between young mothers with meiosis I error and control mothers (19% versus 17%). This observation was in agreement with the findings of Avramopoulos et al. [48] who hypothesized that APOE allele ε4 could be a risk factor for chromosomal NDJ and probably links the meiotic error with early onset of aging phenotypes among chronologically younger women. Beside APOE/ ε4 analyses, Petersen et al. [49] reported an association among MII-NDJ, Down syndrome conception and preferential occurrence of intron 8 polymorphism of *Presenilin 1* gene. The Presenilin-1 is a candidate for kinetochore functioning complex, involved in chromosome segregation and mutant form of this gene is associated with early onset of autosomal dominant AD phenotype [49]. The study of Petersen et al. [49] included 168 families each with free trisomy 21 child and the authors found a higher frequency of susceptible *Presinilin-1* intronic polymorphism (allele 1) in homozygous state among the mothers experienced MII error (nearly 53%, P<0.05). More interestingly, the authors reported significant co-segregation of *Presenilin-1* intronic allele 1 and *APOE* allele ε4 allele among the DS child bearing mothers (68%) when compared with non- ε4 allele bearing mothers (P<0.01). The AD susceptible polymorphic alleles of *Presenilin-1* and *APOE* exhibited increased frequency of occurrence among young mothers (<32 years age of DS conception) with MII errors [48,49]. To refute this finding Bhowmik et al. [50] have conducted analyses on Indian women and confirmed that Presenilin-1 polymorphism is associated with MII NDJ among the young mother. This study included 96 probable Alzheimer's patients (mean age 62.26 ± 11.93 years with 70.48% male and 29.52% female subjects), 173 age matched healthy controls and 136 DS families. The authors reported a rare polymorphism rs201992645 [(NG_007386.2:g.66696T>A or NM_000021.3:c.868+37T>A) ss515119316] within the intron 8 of PSEN-1 gene at the 73664874th nucleotide position on chromosome 14 (GRCh37.p5 Assembly). The change involves nucleotide transition T>A. The mutant 'A' allele exists only as heterozygous condition (T/A) with genotype and allele frequencies of 0.031 and 0.02 respectively for AD cases and 0.029 and 0.01 respectively for DS. Within the parents of DS, the mutant allele was recorded only among the mother with genotypic and allelic frequencies of 0.029 and 0.01 respectively. To anticipate the probable damaging effect of the detected intronic mutation on PSEN-1 expression and functions, the authors employed bioinformatics software which identified said polymorphic site caused alternation in splice site at intron exon junction that in turn may result into change in protein structure and functions. Result of this study inferred Presenilin-1 as prospective molecular link between AD and DS birth and it predisposes the women simultaneously for Ch21 NDJ and AD irrespective of maternal age of conception.

To explain the familial segregation of AD associated geriatric phenotypes and trisomy 21 birth, an alternative hypothesis has been put forward and the central idea of this notion is Ch21 mosaicism in the germ cells and brain accounts for familial segregation of AD and trisomy 21, [51]. Recently proposed 'oocyte mosaicism selection model' [52] provides the evidence of presence of Ch21 disomic mosaic cells in the germinal epithelium of ovary and suggest is may be the underlying cause of DS birth. But presence of chromosomally mosaic germinal cell line may not an inevitable evidence of existence of such aneuploid cells in neuronal tissue. Therefore, the common genetic origin risk of trisomy 21 conception and early onset of AD phenotype remain inexplicable.

Conclusion and Future Research

Understanding the cause of frequent co-occurrence of accelerated genetic aging and risk to conceive TS21 foetus among some women is difficult. Several apparent conflicting evidences have made the picture messy. It is now known that the cause of DS birth is multifactorial, includes both maternal age-dependent and age-independent risk [53] and there are several tiers of interactions among genetic factors, environmental agents and maternal age. But the efforts for finding out the origin of accelerated molecular aging and its connection with chromosomal NDJ is tantalizingly low. Sincere research works have identified some potential candidate genes that may be the 'missing link' between the molecular aging mechanism and chromosome separation system and act as maternal age independent risk factor for DS birth. The *BubR1* is of particular interest as available evidence [23] suggests its role for aging and associated chromosomal missegregation. Moreover, the co-segregation of *APOE* allele ε4 and *Presinilin-1* intronic polymorphism allele-1 and their role in origin of trisomy21 may be the subject of future research. The discovery of rapid shortening of TL among DS bearing mothers opens another line of thinking. Further researches are needed to explore the genetic polymorphism of the molecular components of telomere that might predispose TL attrition on one hand and NDJ on the other. There are several cross-talks among different genetic circuits and a sharing of genetic components between molecular aging process and chromosome segregation apparatus may not be overruled. Although the possibilities are speculative, nevertheless, the available evidences are suggestive of common shared genetics of accelerated biological and molecular aging of women and their risk to conceive trisomy 21 foetus. Future researches are needed to realize explicitly what is going exactly at subcellular level in the oocyte.

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Text Box 1

Meiosis is initiated in the human fetal ovary at 11–12 weeks of gestation, 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 onset of puberty. Then the oocyte completes meiosis I and enters meiosis II 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 menarchy, 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 at advanced age of women. Moreover, each menstrual cycle recruits several follicles to initiates growth. Subsequently, all follicles degenerate except one which becomes the Graafian follicle. The follicular atresia reduces the follicular pool in ovary and left more defective oocyte to ovulate stochastically in more advancing age of women. This explains why increased rate of Down syndrome birth is associated with advancing maternal age.

Text Box 2

Recombination between homologous chromosomes is an essential criterion for their proper segregation towards opposite pole. A chiasma at the middle of chromosome arms maintains and balances the pull of spindle fibre from the opposite poles which ensures proper chromosome movement at anaphase. So, any deviation in chiasma placement on chromosome arm inevitably leads to malsegregation of chromosomes. For chromosome 21 three defective exchange patterns have been observed. These include chiasma too close to centromere, too close to telomere and no chiasma formation. The peri-centromeric chiasma cause chromosomal entanglement and oocyte compromises this configuration with increasing maternal age and ovulates with this defect. So this configuration is maternal age dependent risk factor for DS birth. On the other hand, telomeric chiasma formation involves very little sister chromatid adhesion protein recruitment leading to premature sister chromatid separation and this is maternal age independent risk for DS birth. The chromosome 21 that does not experience any chiasma formation segregates randomly and imparts risk in maternal age independent manner.

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