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Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National Down Syndrome Projects

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Abstract

We examined the association between maternal age and chromosome 21 nondisjunction by origin of the meiotic error. We analyzed data from two population-based, case–control studies: Atlanta Down Syndrome Project (1989–1999) and National Down Syndrome Project (2001–2004). Cases were live born infants with trisomy 21 and controls were infants without trisomy 21 delivered in the same geographical regions. We enrolled 1,215 of 1,881 eligible case families and 1,375 of 2,293 controls. We report four primary findings. First, the significant association between advanced maternal age and chromosome 21 nondisjunction was restricted to meiotic errors in the egg; the

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association was not observed in sperm or in post-zygotic mitotic errors. Second, advanced maternal age was significantly associated with both meiosis I (MI) and meiosis II (MII). For example, compared to mothers of controls, mothers of infants with trisomy 21 due to MI nondisjunction were 8.5 times more likely to be ≥40 years old than 20–24 years old at the birth of the index case (95% CI = 5.6–12.9). Where nondisjunction occurred in MII, mothers were 15.1 times more likely to be ≥40 years (95% CI = 8.4–27.3). Third, the ratio of MI to MII errors differed by maternal age. The ratio was lower among women <19 years of age and those ≥40 years (2.1, 2.3, respectively) and higher in the middle age group (3.6). Lastly, we found no effect of grand-maternal age on the risk for maternal nondisjunction. This study emphasizes the complex association between advanced maternal age and nondisjunction of chromosome 21 during oogenesis.

Introduction

The chromosomal basis of Down syndrome, trisomy 21, has been recognized for nearly half a century (Book et al. 1959; Ford et al. 1959; Jacobs et al. 1959; Lejeune 1959), and the link between Down syndrome and advanced maternal age predates that discovery by at least another half century (Penrose 1933; Penrose 1934). In the United States, over 5,000 infants are born with Down syndrome (DS) each year with an estimated prevalence of 13.65/10,000 births (1 in 733) (Canfield et al. 2006). We now know that the extra chromosome 21 is the result of nondisjunction during meiosis in either the egg or the sperm (standard trisomy 21) in approximately 95% of individuals (e.g., Mutton et al. 1996).

In addition to Down syndrome and other trisomic live births, the impact of maternal-age-related chromosome nondisjunction on human reproductive health is evident from studies of spontaneous pregnancy losses and human oocytes. A recent investigation of over 1,700 karyotyped products of conception found that 14% of pregnancy losses in women <24 years of age were due to a trisomy, and that proportion rose to approximately 38% in women 40–44 years of age (Yusuf and Naeem 2004). Pellestor et al. (2003) found similar rates of aneuploidy among 1,367 karyotyped oocytes from 520 women: 8.5% of oocytes from women <24 years had aneuploidy compared with 39.5% of those from women between the ages of 40–44. Thus, it is thought that an increase in aneuploidy is the major underlying factor responsible for the increased infertility observed among women with advancing age (Hassold and Chiu 1985; Hassold and Hunt 2001; Pellestor et al. 2002).

The basis of the maternal age effect on aneuploidy remains one of the most important questions in medical genetics. A number of hypotheses center on general aspects of ovarian function such as maternal age-related changes associated with oocyte pool size or hormone function (e.g., Eichenlaub-Ritter and Boll 1989; Gaulden 1992; Warburton 2005). These general hypotheses have encouraged researchers to seek underlying mechanisms by assessing specific oocyte components for their vulnerability to maternal aging including mitochondria, the spindle apparatus, and sister cohesion protein complexes (e.g., de Bruin et al. 2004; Eichenlaub-Ritter et al. 2004; Hodges et al. 2005; Schon et al. 2000; Steuerwald et al. 2005). Others have investigated indicators of oocyte pool size, such as hormone profiles or antral follicle counts, to determine if women who have had a nondisjunction event have smaller oocyte reserves than do controls (e.g., Freeman et al. 2000; van Montfrans et al. 2002; Warburton 2005). In addition, we have recently examined recombination patterns known to be more common among nondisjoined chromosomes 21 within the context of maternal age in order to shed light on the interaction between these two established risk factors (Lamb et al. 2005; Oliver et al. 2008).

Historically, interest in the relationship between maternal age and chromosome nondisjunction has led investigators to examine the effect of grand-maternal age (Aagesen et al. 1984; Greenberg 1963; Malini and Ramachandra 2006; Papp et al. 1977; Penrose 1964; Richards

1970; Stoller and Collmann 1969). The most commonly proposed mechanism for a grand-maternal age effect involves nondisjunction in a grand-maternal oocyte leading to a trisomic embryo. Loss of the extra chromosome in a proportion of cells in that embryo would result in a mosaic offspring (the mother) without the DS phenotype, but with the capability of producing a trisomic child, assuming trisomic cells remained in her gonads. Thus, risk factors associated with nondisjunction would apply to the grandmother of the proband with trisomy as well as to the mother. These factors could be maternal-age related or not.

The use of chromosome 21-specific DNA markers to determine the parental origin of the extra chromosome has enabled investigators to refine studies of the maternal age effect by including only cases of maternal origin. Such population-based studies have reported that approximately 90% of errors are maternal (e.g., Gomez et al. 2000; Mikkelsen et al. 1995; Sherman et al. 2005; Yoon et al. 1996). In addition, specific pericentromeric chromosome 21 markers allow cases to be categorized as the result of an error in either meiosis I or meiosis II. Early on, investigators expected the maternal age effect to be limited to maternal meiosis I (MMI) cases because MMI begins during the fetal life of the mother and is completed decades later at the time of ovulation. In contrast, maternal meiosis II (MMII) is initiated and completed in 3–4 days at the time of ovulation. If true, the ratio of MMI to MMII would be predicted to increase with increasing maternal age. Although both MMI and MMII errors are observed in trisomies of mothers of all ages and overall show an average 3:1 ratio (Antonarakis et al. 1992; Muller et al. 2000; Sherman et al. 2005; Yoon et al. 1996), this specific hypothesis has not been addressed. In this study, we were able to examine pattern of MMI to MMII errors among trisomic outcomes to shed light on the influence of maternal age. Interestingly, Lamb et al. (1996) found specific differences in recombination patterns between MMI and MMII errors. They suggested that some MMII errors may not be the “classical” malsegregation of sister chromatids during meiosis II, but instead may be caused by errors initiated in meiosis I. Thus, as is true for most other autosomal chromosomes (Hassold and Hunt 2001) the majority of chromosome 21 maternal meiotic errors may begin during meiosis I,.

To better understand the effect of maternal age on nondisjunction of chromosome 21 over the entire reproductive life span of a woman, we have conducted a multi-year, multi-site case–control study (Freeman et al. 2007). Representing six sites nation-wide and 16 years of recruitment, this population-based, case–control study is the largest compilation of molecular, clinical, and epidemiological data on trisomy 21 characterized by the origin of the chromosomal error. Evidence from this data set sheds additional light on the relationship between maternal age and meiotic nondisjunction.

Subjects and methods

Subjects

Data from two population-based, case–control studies are presented here. The studies differ from each other with respect to the time frame of data collection and the geographic areas covered, but are otherwise nearly identical in methodology. Both projects were based at Emory University in Atlanta, Georgia and were approved by the appropriate Institutional Review Boards at all participating sites. Study personnel obtained informed consent from all participating families. From 1989 to 1999, investigators at Emory University directed the Atlanta Down Syndrome Project (ADSP) in cooperation with the Centers for Disease Control and Prevention (CDC). Eligible cases were identified through a birth defect surveillance system, the Metropolitan Atlanta Congenital Defects Program (MACDP) (Correa-Villasenor et al. 2003), and included all live born infants with documented trisomy 21 or mosaic trisomy 21 born in the five-county Atlanta metropolitan area. Controls were identified through hospital records and randomly selected from among newborns without birth defects from the same geographical population. Trained interviewers administered questionnaires by telephone or in

person to mothers of cases and controls and obtained blood samples from case infants, their mothers, and their fathers when available. The ADSP completed enrollment in 2000. Further details of the ADSP are available in earlier publications (Yang et al. 1999; Yoon et al. 1996).

Between 2001 and 2004, Emory expanded the study to include five other sites nationwide, all of which had well established birth defect surveillance systems. These sites ascertained cases and controls either statewide (Arkansas, Iowa, New Jersey) or within defined geographic areas within the state (California, New York). Together, the six sites represented approximately 11% of annual births in the US. As with the ADSP, the National Down Syndrome Project (NDSP) enrolled cases and controls on a population basis and collected both questionnaire data and biological samples. All six NDSP sites finished their recruitment efforts by May 2005. A detailed description of the design and implementation of the NDSP is available (Freeman et al. 2007).

In both studies an eligible case was defined as a live born infant with standard trisomy 21 or mosaic trisomy 21 born to a mother living in one of the study areas at the time of the birth. For practical reasons, NDSP-eligible cases were further limited by their “recruitability”. Recruitable families were those in which the mother spoke either English or Spanish and the infant was alive and available so that a biological sample could be collected at enrollment. For the present report, eligible and recruitable NDSP cases are simply referred to as eligible. Combining all sites and all birth years, the ADSP and NDSP identified 1,881 eligible live born cases of trisomy 21 or mosaic trisomy 21 and 2,293 controls (Table 1). As in ADSP, study personnel interviewed mothers of cases and controls by telephone or in person to obtain information on maternal age, grand-maternal age, and ethnicity (race/ethnicity). In addition, for both participating and non-participating mothers, independent information regarding maternal age and ethnicity was available from birth records. Coding of ethnicity varied somewhat from site to site, but for this report we reduced the groups to (1) white non-Hispanic, (2) black non-Hispanic, (3) Hispanic, (4) American Indian/Alaskan Native, (5) Asian, (6) other, and (7) unknown. Among participating mothers, we found good agreement between self-reported ethnicity and ethnicity from birth records (white 96%, black 95%, Hispanic 98%). In order to be able to include our entire sample of eligible families for these analyses, we used ethnicity from birth records. For the general population, maternal age at the birth of the infant came from vital statistics obtained from the same geographic areas of surveillance during the same years of data collection.

For both studies, the minimum requirements for a case family to be defined as “enrolled” were a completed maternal questionnaire and biological samples from at least the mother and the infant with DS. The minimum requirement for a control family was the completion of a maternal questionnaire. In total, 1,215 case families and 1,375 control families successfully enrolled in the ADSP and NDSP (participation rates: cases 64.6%; controls 60.0%). Table 1 presents total population data and a breakdown of these numbers by study (ADSP or NDSP) and by NDSP site and includes mean maternal age at the birth of the child for cases and controls.

Laboratory methods

Each participating family was genotyped for a panel of chromosome 21-specific polymorphic markers (primarily small tandem repeat polymorphisms, STRPs) that span 21q (Freeman et al. 2007). The contribution of parental marker alleles to the infant with DS was used to establish the parental origin of the nondisjunction error and was based on at least one informative marker. In a minority of cases, the father was unavailable and the origin of the error was based on information from the mother and infant only. In these cases, at least eight markers had to be informative. We inferred that an error was maternal when all markers were consistent with a maternal origin. A paternal error was inferred when at least two markers were inconsistent with a maternal origin. There were 20 ADSP cases and 125 NDSP cases for whom we could not

determine the parental origin. Probands who were determined to be mosaic trisomy 21 by cytogenetic analysis were not analyzed using genetic markers, as dosage cannot be accurately determined. Thus, data on mosaics are only included among "eligible" cases.

Once parental origin was established, a core set of markers located in the pericentromeric region was used to infer the type of nondisjunction error (MI or MII). Specifically, if parental heterozygosity was retained in the trisomic offspring ("nonreduction"), we concluded that nondisjunction occurred during meiosis I with failure of homologs to separate properly. If parental heterozygosity was reduced to homozygosity ("reduction"), we inferred an MII error. As noted in the Introduction, there is evidence to suggest some portion of the MII errors may actually originate during meiosis I in which homologs fail to segregate properly followed by an error in meiosis II in which sister chromatids fail to separate; hence, our assay based on pericentromeric alleles in the offspring will only identify the contribution from one parental allele. Thus, we define MMII cases as maternally-derived cases in which chromosome 21-specific pericentromeric markers from the mother are identical by descent.

The last category of errors includes post-zygotic mitotic errors. These are characterized as such when all informative markers in the parent of origin are reduced to homozygosity along the entire chromosome. The criterion to establish an error as mitotic included having at least eight informative homozygous markers spanning the length of 21q. Such cases could also be inferred to be MII errors with no recombination. We do not have a method to accurately distinguish these two types of errors. We expected these cases to be maternal-age independent and, in fact, found this to be the case: the mean maternal age of so-called mitotic cases did not differ from that of controls (Table 2). However, we also expected that there should be equal numbers of "maternal" and "paternal" errors among such cases. Instead, we observed about three times as many "maternal" cases as paternal cases (26 maternal and 8 paternal cases). Thus, some cases that we classified as being due to mitotic errors actually may be due to meiotic errors. Nevertheless, if a case was determined to be a mitotic error using the criteria above, it was not included in any analyses of meiotic errors.

Statistical analysis

In order to test the validity of combining the ADSP and NDSP populations, we investigated differences in maternal age using *t* tests and in ethnicity using analysis of variance adjusting for covariates (ANCOVA). Significant results from ANOVAs were follow-up by post-hoc pairwise comparisons using Tukey's Studentized range test. Linear regression was used to test for an association between maternal age and birth year. Logistic regression was used to determine if there was an association between the type of nondisjunction error and ethnicity.

After establishing that our two study populations could be combined when adjustments for ethnicity and year of birth were made (see "Results"), our objective was to investigate the maternal age effect on each type of nondisjunction error, similar to our previous study on a significantly smaller data set (Yoon et al. 1996). Our basic approach was logistic regression for comparison of DS case and control groups as well as for comparison of MMI and MMII groups. First, we compared mothers with each specific nondisjunction error (i.e., MMI or MMII error) to control mothers to obtain odds ratios (ORs) for being in a specific maternal age group adjusting for ethnicity and birth year of the infant. Case-population analysis, adjusting for birth year only, was done to obtain rate ratios (RRs). Maternal ages were divided into six groups: ≤19, 20–24, 25–29, 30–34, 35–39, and ≥40 years of age and age 20–24 was used as the referent group. Second, to ask if maternal ages differed by origin of the error, we compared MMI and MMII groups and included maternal age as a continuous variable and its square to account for non-linear effects as predictors. All models were adjusted for maternal ethnicity (white, black, Hispanic and other) and birth year (continuous variable).

We also investigated grand-maternal age as a risk factor for nondisjunction. For these analyses, we used enrolled cases and controls. Similar to others, we hypothesized that the grand-maternal age effect may be more detectable among younger mothers who had a nondisjunction error compared with older mothers, as the younger mother's own maternal age-related factors would be minimized. Thus, we stratified enrolled cases and controls by maternal age (<30 and ≥30 years) and conducted logistic regression using grand-maternal age as a continuous variable and maternal race and maternal age as covariates in the model.

All analyses were done using SAS V9.

Results

Study sample characteristics

Before investigating the specific effect of maternal age on nondisjunction, we first examined the mean maternal age and ethnic composition of the ADSP, NDSP, and the combined study samples for their potential confounding effects. For these analyses, we used all eligible cases and controls to get the most accurate population-based estimates. We found that the mean maternal age overall increased from the ADSP (1989–2000) to the NDSP (2001–2004) for both cases and controls (Table 1). Adjusting for case/control status, there was a statistically significant increase in maternal age for each unit increase in birth year ($p < 0.0001$; partial $r^2 = 0.02$) Interestingly, there was a significant interaction between case/control status and birth year ($p = 0.0012$; partial $r^2 = 0.002$) which indicates a steeper increase over time in mean maternal age among cases than among controls (Fig. 1). The increase for controls across the two studies was approximately one-half that observed in cases.

It was also evident from the changing demographics of Atlanta over time and the different demographics at each NDSP site that ethnicity would vary between the ADSP and NDSP. The ADSP had a higher proportion of cases and controls who were black and a significantly smaller proportion of Hispanics than did the NDSP. Comparison of mean maternal ages indicated variation by ethnic group (Table 3). In both the ADSP and NDSP, white mothers tended to be older than their black or Hispanic counterparts. Specifically, for both cases and controls, white mothers were found to be significantly older than black mothers ($p < 0.01$) and Hispanic mothers ($p < 0.01$); blacks and Hispanics were not significantly different from each other ($p > 0.05$). These results were the same if all eligible subjects or if only enrolled subjects were used.

We also tested ethnicity as a predictor variable for case/control status when the model was adjusted for maternal age and birth year. The combined data set of all eligible cases and controls was used for this analysis. The case mothers more often self-reported as Hispanics than as whites compared to control mothers (adjusted OR = 1.3; 95% CI = 1.1–1.6). In addition, the case mothers less often self-reported as blacks than whites compared to control mothers, although this reduction was not statistically significant (adjusted OR = 0.9; 95% CI = 0.7–1.1).

Maternal age by type of nondisjunction error

Parental origin—We examined parental origin of the nondisjunction error and its relationship to maternal age. As we required biological samples to determine parental origin, we compared mean maternal ages among enrolled cases to mean maternal ages of enrolled controls. After adjusting for birth year and ethnicity, we found that the association between advanced maternal age and DS was only present in cases of DS of maternal origin ($p < 0.0001$ in each study sample) and was not observed in meiotic errors of paternal origin or in post-zygotic mitotic errors ($p > 0.10$ for each study sample) (Table 2). As advanced maternal age was restricted to cases that were due to maternal nondisjunction, we hypothesized that the proportion of maternal versus paternal and mitotic errors would differ between the two study

periods. This would be expected, as we established that the mean maternal age increased from the earlier to the later study periods (Fig. 1). Indeed, we found a significantly increased proportion of cases of maternal origin in NDSP compared to ADSP (93.2% vs. 88.5%, $p = 0.01$; Table 2).

Because the proportions of ethnic groups in the ADSP/NDSP also varied over time, we examined the association between ethnicity and origin of the meiotic error. We hypothesized that any difference in the proportions of maternal errors compared to other errors could be explained by the overall increase in the age of mothers over time, not by the changing proportions of ethnic groups. To test this, we modeled origin of the error (maternal vs. other errors) as the outcome variable and ethnicity and maternal age as the independent variables and found no significant difference in the proportion of maternal errors by ethnic group ($p > 0.10$).

Stage of origin of maternal meiotic error—Our next objective was to examine the effect of maternal age on the risk for MMI and MMII errors using two different approaches. First, using logistic regression (see "Statistical analysis"), we found a statistically significant increase in maternal age for both MMI and MMII cases compared to controls (Table 4). For example, compared to mothers of controls, mothers of infants with trisomy 21 due to MMI nondisjunction were four times more likely to be 35–39 years old than 20–24 years old at the birth of the index case. Similarly, mothers of infants with trisomy 21 due to MMII nondisjunction were five times more likely to be 35–39 years old than 20–24 years old at the birth of the index case. The ORs for being in the oldest age group, ≥40, were 8.5 and 15.1 for MMI and MMII errors, respectively. In general, the RRs tended to show a similar maternal age effect, although they were somewhat greater than the ORs in the older age groups.

Because the ORs and RRs indicated that the frequency distribution of maternal ages may differ between mothers with an MMI error and those with an MMII error, our second approach was to directly compare the frequency distribution of maternal age for these two groups (Fig. 2). Although mean maternal age did not differ between error types (Table 2), the frequency distribution did differ significantly ($X^2_7 = 16.6$, $p = 0.01$; Fig. 2). By observation (Fig. 2) and by comparison of OR/RRs (Table 4), we found there was an increased proportion of MMII cases compared to MMI cases among both women <15 and those 40–45 years of age. Furthermore, by simply calculating the MMI to MMII ratio in each age group without covariate adjustment, the same pattern emerged: for the six maternal age groups, ≤19, 20–24, 25–29, 30–34, 35–39, and ≥40 years, the ratio was 2.1, 3.8, 3.5, 4.7, 2.9, and 2.3, respectively (taken from Table 4).

Grand-maternal age effect

We investigated grand-maternal age as a risk factor for nondisjunction using methods comparable to those in other reports (see "Laboratory methods") while taking advantage of our ability to categorize cases with respect to the origin of the nondisjunction error. We did not find a significant effect of grand-maternal age among younger case mothers (age <30 years) or among older mothers (age ≥30 years). This finding was the same when all enrolled mothers were included in the analysis or when categorized by stage of error: all maternal cases, MMI cases, or MMII cases (Table 5). The findings did not change when we grouped cases and controls at an older maternal age threshold (<35 and ≥35 years) (data not shown).

Discussion

To date, the combined ADSP/NDSP is the largest population-based study of DS to determine the origin of the chromosomal error and collect demographic information including parental ages and ethnicity. Overall, the proportion of maternal cases (92.0%) was similar to that of

other population-based studies (e.g., Gomez et al. 2000; Mikkelsen et al. 1995). However, we noted a significant change in the percentage of maternal meiotic errors over time: a greater proportion of errors were maternal in the NDSP (93.2%) than in the ADSP sample (88.5%) ($p = 0.01$, Table 2). This pattern can be explained by two important study observations. First, we found that the association between advanced maternal age and the increased occurrence of DS existed only for cases resulting from maternally-derived errors, not from paternally-derived or inferred post-zygotic mitotic errors. This confirms other studies (Antonarakis et al. 1993; Carothers et al. 2001; Petersen et al. 1993). Second, there was a significant increase in maternal age over time between the ADSP and NDSP samples (Fig. 1). Thus, as the maternal age increased, there was a consequent increase in the proportion of maternal age-dependent nondisjunction errors. This implies that the percentage of cases due to specific nondisjunction errors will vary with the maternal age structure of a population, and comparisons from one study to another need to be interpreted carefully.

The documented association between advanced maternal age and both MMI and MMII cases confirms our previous work (Yoon et al. 1996) and that of others (Antonarakis et al. 1992; Muller et al. 2000). Thus, the arrest of meiosis and its resumption after many years may compromise the ability of the oocyte to complete both stages of meiosis properly. Many hypotheses have been suggested to explain the maternal age effect and most imply an age-related degradation of the meiotic machinery. Recent studies have indicated changes in gene expression in younger compared with older oocytes in both mouse (Hamatani et al. 2004; Pan et al. 2008) and human studies (Steuerwald et al. 2007). Gene profiles that were altered by age included those involved in cell cycle regulation, cytoskeletal structure, energy pathways, transcription control, and stress responses. Such changes could play a role in the meiotic spindle abnormalities observed frequently in oocytes of older mothers (Battaglia et al. 1996; Eichenlaub-Ritter et al. 2004) and/or in the deterioration of sister chromatid or centromere cohesion complexes as seen in mice by Hodges et al. (2005). Further, checkpoint systems that monitor spindle assembly and chromosome movement may not be effective in older oocytes (e.g., Hodges et al. 2002; LeMaire-Adkins et al. 1997; Vogt et al. 2008).

With this large ADSP/NDSP data set, we dissected the maternal age influence further and found differences in the ratio of MMI to MMII cases across the maternal age continuum. At all ages, MMI errors exceeded MMII errors. However, the ratio of MMI to MMII was less in the youngest and the oldest maternal age groups compared with that in the other maternal age groups. This decreased MMI to MMII ratio was particularly noticeable for women ≥40. Thus, although there are more MMI than MMII errors across all maternal age groups, perhaps additional factors more often present at the beginning and/or the end of reproductive life lead to an increase in meiotic errors in which sister chromatids fail to separate properly. Hodges et al. (2002) provide strong evidence from the mouse model that oocyte growth in an altered environment leads to an increase in the failure of chromosomes to move toward the equator during MI (congression failure). They further show that congression failure at MI can increase the risk for premature sister chromatid segregation (PSCS) in both MI and MII. There are many factors that may be involved in the control of oocyte growth. These could include the complex orchestration of signaling from the hypothalamic-pituitary-ovarian (HPO) axis as well as others involved in folliculogenesis. Factors common to both early and late reproductive life may involve altered hormone profiles (e.g., increased FSH, cycle variability). Results from Hodges et al. (2002) implicated both oocyte-somatic cell communication and an altered endocrine environment as factors that increase congression failure.

Studies of human oocytes are also consistent with an increased maternal age being associated with both MMI and MMII errors (for review, see Pellestor et al. 2005). In a study of 309 karyotypically abnormal human oocytes observed at meiosis II metaphase, Pellestor et al. (2003) identified both whole chromosome nondisjunction and PSCS. Interestingly, they found

that, during meiosis I, single chromatid aneuploidy occurred more frequently than did whole chromosome aneuploidy among the 309 oocytes and had a stronger correlation with maternal age. PSCS at meiosis I could lead to the error being classified as MMI or MMII depending on the action of the chromatids. From our analyses, we cannot determine the underlying mechanism for meiosis II errors. That is, we cannot distinguish MII errors that result from PSCS at meiosis I, whole chromosome nondisjunction at meiosis I followed by a reductional division at meiosis II or a "classical" meiosis II error in which chromatids fail to separate properly after completing a successful meiosis I division. Maternal-age risk factors are most likely associated with one or more of these mechanisms.

Our recent data that examined recombination profiles along nondisjoined chromosomes 21 by type of nondisjunction error and maternal age provide additional insight into mechanisms underlying nondisjunction. These studies were performed on a subset of cases from the population-based studies presented here (Lamb et al. 2005; Oliver et al. 2008). Among MMI cases, we found that the majority of nondisjoined chromosomes 21 were associated with either a lack of an exchange or a telomeric exchange and that these patterns influenced the risk for nondisjunction irrespective of maternal age. In contrast, we found that the nondisjoined chromosomes 21 that were categorized as MMII errors and had a pericentromeric exchange were enriched among older women with this type of error. These data suggested a maternal age-dependent mechanism (Oliver et al. 2008). In Oliver et al., we offered two alternative explanations for this observation: (1) a pericentromeric exchange initiates or exacerbates the susceptibility to maternal age risk factors, perhaps leading to an increase in PSCS, or (2) a pericentromeric exchange protects the bivalent against age-related risk factors allowing proper segregation of homologues at meiosis I, but not segregation of sisters at meiosis II. The former explanation would represent a two-hit model: the first hit being the pericentromeric recombinant event and the second hit would involve any number of meiotic-related structures or proteins that degrade with oocyte age (Lamb et al. 1996). The latter explanation implies that true MII errors may occur among older women only if bivalents are protected from age-related factors in some way. This protective factor could be a proximal recombinant event which then allows the sister cohesion complex to remain intact along most of the chromosome arm. Other protective factors could include genetic variants that reduce age-related degradation of meiotic structures or environmental factors that create an optimal environment during the arrested state of the oocyte, to name a few.

Lastly, we tested the hypothesis that the age of the maternal grandmother of the child with trisomy 21 affects the risk for a nondisjunction error. Results from past studies are conflicting, potentially due to differences in design and sampling strategies (Aagesen et al. 1984; Greenberg 1963; Malini and Ramachandra 2006; Papp et al. 1977; Penrose 1964; Richards 1970; Stoller and Collmann 1969). However our failure to find a relationship between nondisjunction and grand-maternal age is strong evidence against such an effect for the following reasons: we had adequate numbers of cases and controls representing the same populations in the same time frames, we documented standard trisomy 21 by karyotype and included only maternally-derived cases in the comparison.

Although this study has many strengths, it is important to outline its limitations. First, due to limited resources, the NDSP could only recruit mothers who spoke either English or Spanish. Further, case and control families whose infant died or was placed for adoption prior to enrollment were not recruited. These factors probably have limited impact on the results of this study. The most important limitation was that we were not able to include pregnancies with trisomy 21 that were either spontaneously lost or terminated. We included only live births which represent no more than 10–20% of conceptions with trisomy 21(for review, see Hassold and Hunt 2001), thus, our results must be interpreted with this in mind. For example, we discovered that the mean age of mothers at the time of birth increased over the time period of

the study. Martin et al. (2005) presented a similar increase in mean maternal age based on National Vital Statistics data. We found this increase occurred in mothers of both cases and controls; although the slope of the increase for cases was steeper than that for controls. The steeper increase in maternal age of infants with trisomy 21 from 1989–2004 could be due to increased prenatal screening being offered to younger women (maternal serum screening) beginning in the mid 1990s. It is possible that positive screens among these women led to confirmatory testing and pregnancy termination, thus reducing the proportion of mothers eligible for our study. Although only speculation, there may have been increased acceptance of an infant with trisomy 21, perhaps more often among older women. Potentially, this could also influence this increased slope. Nevertheless, these influences should not affect our interpretation of the comparison of MI to MII errors, as women are blind to the type of nondisjunction error. The participation rates varied by study site; however, there were no significant differences in mean maternal age for enrolled and non-enrolled cases or controls. Thus, the associations with maternal age should be representative of the population of eligible live-born cases.

In summary, in this large population-based study, we have confirmed our previous findings (Yoon et al. 1996). Specifically, the significant association between advanced maternal age and chromosome 21 nondisjunction was restricted to errors in the egg; the association was not observed in paternal or in post-zygotic mitotic errors. Further, an almost three-fold higher proportion of MMI errors over MMII errors is present at all maternal ages; however, we note that this ratio decreases for mothers <19 years and those ≥40 years at the time of their infant's birth. The next logical step will be to use both origin of the meiotic error and recombination profiles along the nondisjoined chromosomes 21 to classify types of nondisjunction errors. Although such parameters are still only surrogates for the exact type of error, they will provide more homogeneous groups in which to detect maternal-age associated risk factors.

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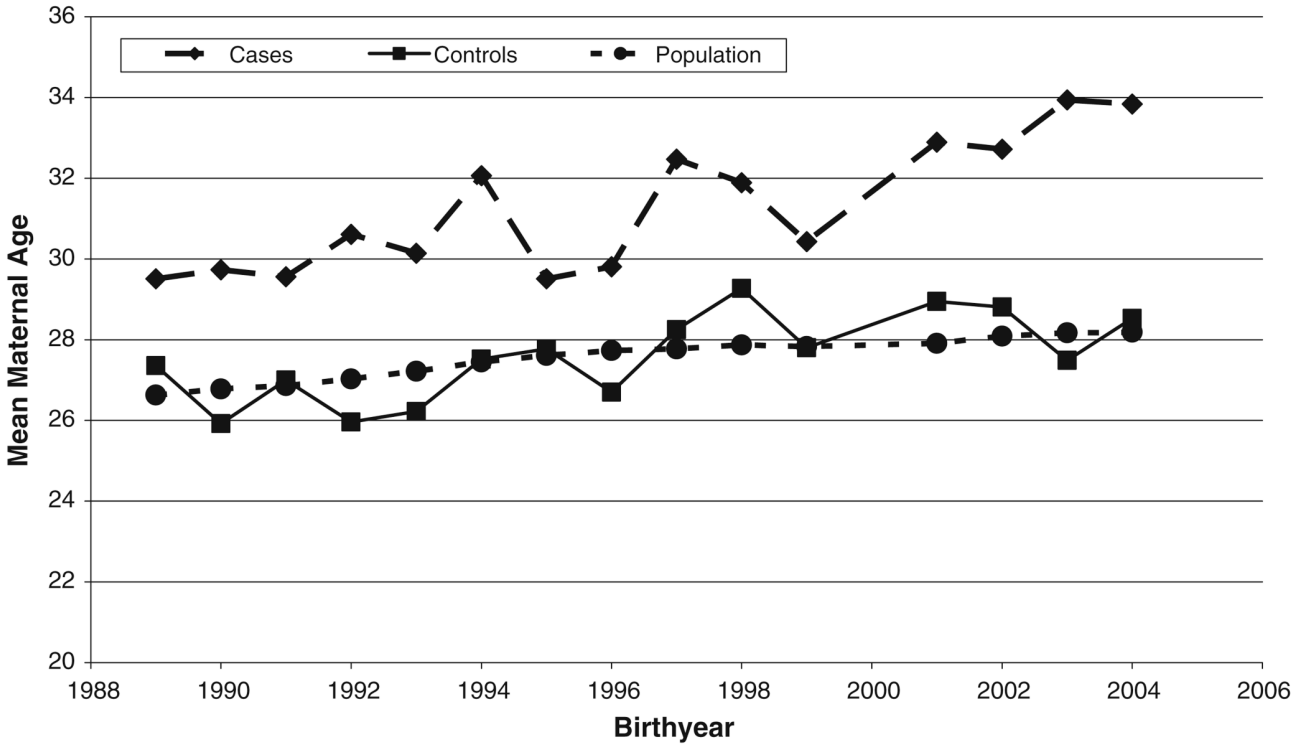

Fig. 1.
Comparison of mean maternal ages at the time of birth by the infant's birth year. *Case* maternal age at birth of infant with trisomy 21, *Control* maternal age at birth of infant without trisomy 21, *Population* maternal ages at birth of infants in the population from with cases and controls were drawn

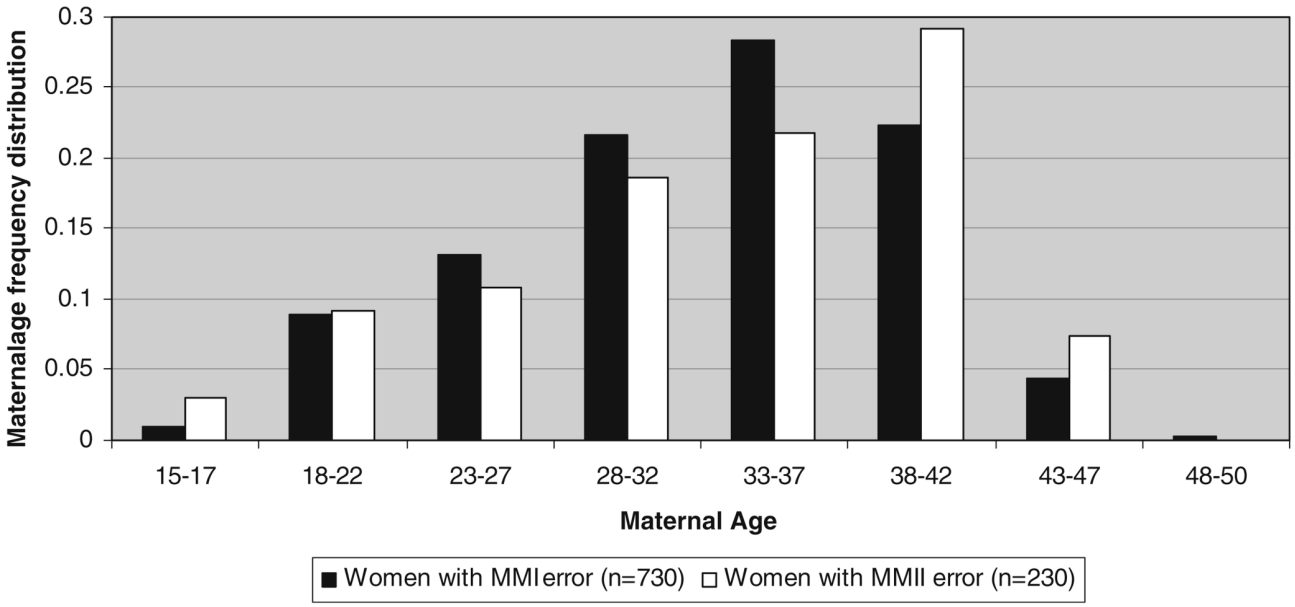

Fig. 2.
Maternal age frequency distribution of women at the time of birth of an infant with trisomy 21 due to a maternal meiosis I (MMI) error or a maternal meiosis II (MMII) error

Table 1

Sample size, mean maternal age and standard deviation (SD) for the Atlanta Down Syndrome Project (ADSP), National Down Syndrome Project (NDSP) and for total birth population during the study period

Study site (years of enrollment)	Study sample	Eligible		Enrolled		Participation rate (%)
		N	Maternal age (mean ± SD)	*N*	Maternal age (mean ± SD)	
ADSP–GA 1/89–12/99	Case	400	30.5 ± 7.2	308	30.0 ± 7.0	77.0
	Control	577	27.2 ± 6.2	398	27.2 ± 6.2	69.0
	Population	*N* = 447,436; maternal age = 27.4 ± 6.1				
NDSP Total	Case	1,481	33.2 ± 7.2	907	33.1 ± 7.1	61.4
	Control	1,716	28.1 ± 6.2	977	28.8 ± 6.2	56.9
	Population	*N* = 1,460,083; maternal age = 28.3 ± 6.2				
NDSP–GA 1/01–9/04	Case	206	33.5 ± 6.7	154	33.4 ± 6.6	74.8
	Control	239	28.3 ± 5.8	170	28.9 ± 5.8	71.1
	Population	*N* = 204,696; maternal age = 28.1 ± 6.2				
NDSP–AR 10/00–9/03	Case	96	30.1 ± 8.6	68	30.0 ± 8.5	70.8
	Control	117	25.2 ± 6.1	75	26.3 ± 6.2	64.1
	Population	*N* = 110,007; maternal age = 25.3 ± 5.7				
NDSP–CA 1/01–6/03	Case	498	33.3 ± 7.4	267	33.0 ± 7.4	53.6
	Control	604	27.7 ± 6.4	261	28.1 ± 6.5	43.2
	Population	*N* = 563,211; maternal age = 28.3 ± 6.3				
NDSP–IA 1/01–12/03	Case	126	31.7 ± 6.8	75	31.8 ± 6.7	59.5
	Control	150	27.2 ± 5.4	81	28.0 ± 5.0	54.0
	Population	*N* = 113,295; maternal age = 27.1 ± 5.7				
NDSP–NJ 1/01–6/04	Case	400	34.2 ± 6.8	252	34.2 ± 6.6	63.0
	Control	457	29.3 ± 6.0	299	30.0 ± 6.1	65.4
	Population	*N* = 329,587; maternal age = 29.4 ± 6.				
NDSP–NY 10/00–9/03	Case	155	33.4 ± 7.1	91	33.1 ± 6.6	58.7
	Control	149	29.2 ± 6.2	91	29.2 ± 6.2	61.1
	Population	*N* = 139,287; maternal age = 29.1 ± 6.2				
ADSP + NDSP Total	Case	1,881	32.7 ± 7.3	1,215	32.3 ± 7.2	64.6
	Control	2,293	27.9 ± 6.2	1,375	28.3 ± 6.2	60.0

Study site (years of enrollment)	Study sample	Eligible		Enrolled		Participation rate (%)
		N	Maternal age (mean ± SD)	*N*	Maternal age (mean ± SD)	
	Population	*N* = 1,907,519; maternal age = 28.1 ± 6.2				

Maternal age was missing for 20 cases and 1 control

Table 2

Origin of chromosome error, mean maternal age and standard deviation (SD) for enrolled participants in ADSP, NDSP, and control populations

Origin	ADSP			NDSP			ADSP + NDSP		
	N	%	Maternal age	*N*	%	Maternal age	*N*	%	Maternal age
Maternal	255	88.5	30.5 ± 7.0	729	93.2	33.6 ± 6.8	984	92.0	32.8 ± 7.0
MI	201	79.8	30.6 ± 6.8	529	74.7	33.4 ± 6.6	730	76.0	32.6 ± 6.8
MII	51	20.2	30.3 ± 7.8	179	25.3	34.2 ± 7.3	230	24.0	33.3 ± 7.6
Paternal	20	6.9	25.8 ± 5.2	32	4.1	29.7 ± 6.6	52	4.9	28.2 ± 6.3
MI	9	45.0	25.6 ± 5.6	13	41.9	30.3 ± 7.0	22	42.3	28.4 ± 6.7
MII	11	55.0	25.9 ± 5.1	18	58.1	28.9 ± 6.3	29	55.8	27.8 ± 6.0
Mitotic	13	4.5	30.0 ± 5.6	21	2.7	26.9 ± 6.0	34	3.2	28.1 ± 5.9
Total of cases	288		30.1 ± 6.9	782		33.3 ± 6.9	1,070		32.4 ± 7.0
Controls	398		27.2 ± 6.2	977		28.8 ± 6.2	1,375		28.3 ± 6.2
Population	447,436		27.4 ± 6.1	1,460,083		28.3 ± 6.2	1,907,519		28.1 ± 6.2

Totals may be greater than the sum of sum categories because the origin of the nondisjunction error could not be determined in all cases. The proportion of MI and MII are among the parental subtypes

Table 3

Maternal race/ethnicity, mean maternal age and standard deviation (SD) for all eligible cases and controls

Study sample	White			Black			Hispanic			Other		
	N	%	Maternal age	*N*	%	Maternal age	*N*	%	Maternal age	*N*	%	Maternal age
ADSP												
Cases	199	49.7	31.8 ± 6.2	153	38.2	29.1 ± 8.1	27	6.7	27.2 ± 7.3	21	5.2	32.3 ± 6.2
Controls	269	46.6	29.4 ± 5.5	253	43.8	24.7 ± 6.2	34	5.9	26.4 ± 5.7	21	3.6	29.3 ± 5.5
NDSP												
Cases	636	42.9	34.0 ± 6.4	185	12.5	32.3 ± 8.1	574	38.8	32.8 ± 7.8	86	5.8	32.9 ± 6.4
Controls	772	45.0	29.7 ± 5.8	258	15.0	26.8 ± 6.6	559	32.6	26.2 ± 6.0	127	7.4	29.6 ± 5.2
Total												
Cases	835	44.4	33.5 ± 6.4	338	18.0	30.8 ± 8.3	601	31.9	32.5 ± 7.8	107	5.7	32.8 ± 6.4
Controls	1,041	45.4	29.6 ± 5.8	511	22.3	25.7 ± 6.5	593	25.9	26.2 ± 5.9	148	6.4	29.6 ± 5.2

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Table 4

Estimated adjusted odds ratio (OR) and rate ratio (RR) for mothers of infants with trisomy 21(MMI or MMII errors) being in a specific age group compared to mothers of controls and the general population

Maternal cases	Age group	N of cases	N of controls	Case–control analysis		Case-population analysis	
				OR[a]	95% CI	RR[b]	95% CI
MI	≤19	31	122	0.9	0.5–1.4	0.8	0.5–1.3
	20–24	84	281	Ref.	–	Ref.	–
	25–29	106	355	1.0	0.7–1.4	1.0	0.8–1.4
	30–34	189	396	1.6	1.2–2.2	1.9	1.4–2.4
	35–39	193	170	4.0	2.8–5.5	3.8	2.9–4.9
	≥40	127	51	8.5	5.6–12.9	11.6	8.8–15.3
MII	≤19	15	122	1.7	0.8–3.4	1.6	0.8–3.0
	20–24	22	281	Ref.	–	Ref.	–
	25–29	30	355	1.1	0.6–1.9	1.1	0.6–1.9
	30–34	40	396	1.4	0.8–2.4	1.5	0.9–2.5
	35–39	67	170	5.4	3.2–9.3	5.0	3.1–8.1
	≥40	56	51	15.1	8.4–27.3	19.2	11.7–31.5

Referent group are mothers age 20–24 years. Enrolled participants in ADSP and NDSP were used

[a]Odds ratio adjusted for ethnicity/race of mother and for birth year of infant

[b]Rate ratio adjusted for birth year of infant

Table 5

Estimated odds ratio and 95% confidence interval (CI) (adjusted for maternal age and race) for age of maternal grandmother at birth of mother using enrolled mothers from ADSP and NDSP

	All mothers			Dichotomized by mother's age			
				<30 years		≥30 years	
	N	Mean grand-maternal age (SD)	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)
Controls	1,325	25.7 (6.3)	Referent	728	Referent	597	Referent
Cases							
All	1,176	25.5 (5.8)	0.98 (0.97–1.00)	388	0.98 (0.95–1.00)	788	0.99 (0.98–1.01)
Maternal errors	970	25.7 (6.2)	0.98 (0.97–1.00)	294	0.97 (0.95–1.00)	676	0.99 (0.97–1.01)
MI	727	25.7 (6.3)	0.98 (0.97–1.00)	221	0.97 (0.95–1.00)	506	0.99 (0.97–1.01)
MII	222	25.7 (6.5)	0.98 (0.96–1.01)	67	0.96 (0.92–1.01)	155	0.99 (0.96–1.02)

The sample sizes vary slightly from Table 2 because of missing grand-maternal ages