Maternal meiosis II nondisjunction in trisomy 21 is associated with maternal low socioeconomic status

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Purpose: We evaluated whether the association of socioeconomic risk factors for trisomy 21 differed by type of maternal meiotic error. **Methods:** We determined meiotic errors by DNA analysis for 150 trisomy 21 cases, and maternal lifetime exposures to low socioeconomic factors by questionnaire. **Results:** Mothers of meiosis II cases were significantly more likely to be exposed to four low socioeconomic factors than mothers of meiosis I cases (odds ratio = 9.50; 95% confidence interval = 1.8–49.8). **Conclusion:** Maternal lifetime exposure to poor socioeconomic environment is a risk factor for a trisomy 21, particularly if nondisjunction leads to a maternal meiosis II. *Genet Med* 2004:6(6):487–494.

Key Words: trisomy 21, meiosis I, meiosis II, socioeconomic status, risk factors

Down syndrome (DS) is a major cause of mental retardation in the United States and affects over 1 per 1000 births.[1] Individuals with Down syndrome often have additional severe birth defects, such as heart and intestinal defects.[2] The presence of three, instead of two, chromosomes 21 in each cell of the body is the cause of 95% of cases of Down syndrome then usually called free trisomy 21 and abbreviated for this report as DS.[3] The remaining cases result from translocations or partial duplications of the area of chromosome 21 that is critical for the expression of the syndrome.[4] DS results from nondisjunction (NDJ) of chromosome 21 during either of the two stages of meiosis, meiosis I (MI) or meiosis II (MII), or after the first few divisions (mitosis) of the embryo. Approximately 90% of meiotic errors are of maternal origin, the remainder being of paternal origin.[5–7] Of the maternal errors, about 75% are of meiosis I (MMI) and 25% of meiosis II (MMII) origin.[6,7] Previously it was thought that MMI errors were set up at the time of formation of the mother's reproductive cells, while she was still in her own mother's womb, but that MMII errors occurred at the time of ovulation. However, researchers have recently suggested that it is the number and location of the chiasmata between the chromosome 21 homologues that predispose to the specific type of meiotic error.[3] Consequently the predisposition for all chromosome 21 meiotic errors may be set during the prophase of the first meiotic division, during the mother's fetal development.

Maternal age is the most important known factor associated with the risk for trisomy 21.[8,9] One possible explanation for this strong effect is the limited oocyte pool hypothesis: as a woman ages and the number of her oocytes decreases, her probability for releasing immature or postmature follicles with a higher risk for NDJ increases.[10] However, this hypothesis has been recently challenged.[11] Additional factors, environmental, hormonal,[12,13] or genetic, might impact either the maturation, ovulation, fertilization, or viability of an aging oocyte with a susceptible chiasma.[14] In the female, such factors could presumably intervene at any time between the formation of the oocyte pool in fetal life and the ovulation and fertilization of the oocyte carrying a chiasma configuration susceptible to NDJ. Maternal factors that have been explored include smoking,[15] the intake of caffeine,[16] the use of contraceptive pills,[15] and socioeconomic status (SES).[17] However, in only one study[15] were environmental factors analyzed according to the parental origin and the type of meiotic NDJ, and no study has examined sociodemographic factors related to the type of meiotic error.

In an earlier study,[17] we found an approximate 2-fold increase in risk for a clinically recognized DS pregnancy, either a live birth or a fetus, associated with the presence of four factors indicative of the mother's low SES. In that study, we hypothesized that adverse SES exposures accumulated since conception of the mother would influence her risk for having a recognized DS pregnancy. Other researchers have used this life-course approach for other outcomes, such as chronic diseases[18] and low birth weight in offspring.[19] In the present study, we evaluated the cumulative effect of adverse socioeconomic factors in a subset of infants with DS whose type of meiotic NDJ, either MMI or MMII, was determined. We first compared infants in each maternal meiotic group to randomly selected controls. To remove biases associated with the selection of cases, we then compared DS infants with an MMII NDJ to those with an MMI NDJ for the risk associated with socioeconomic factors.

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MATERIALS AND METHODS

Cases and controls were ascertained by the California Birth Defects Monitoring Program (CBDMP), an active surveillance registry that monitors births in selected California counties, which, at the time of the study, represented over half the births occurring in the state. Information on infants or fetuses with birth defects is obtained from all hospitals, birthing centers, and genetic laboratories that serve these counties. From July 1991 through December 1993, CBDMP conducted a case-control study on Down syndrome. Cases included all ascertained fetuses or live births diagnosed with Down syndrome. Controls were infants without birth defects, randomly chosen in proportion to the expected total number of births at each hospital in the monitored area. Individuals who had been adopted or whose parents did not reside in the monitored counties were excluded. Participants had to speak English or Spanish. The mothers were administered a structured questionnaire by phone. The interview refusal rate was 6.4% for cases and 5.7% for controls, whereas the loss to follow up was 10.0% for cases and 16.3% for controls. In all, 998 mothers of Down syndrome infants or fetuses and 1007 control mothers were interviewed for the case control study. One case from the original cohort who completed DNA analysis was added to the study when the interview was received after the original cutoff date. Further details on this case-control study can be found in a previous publication.[17] The study was approved by the Committee for the Protection of Human Subjects of the California Department of Health and Human Services.

One of the aims of the study was to determine the parental origin and type of NDJ of chromosome 21 by obtaining blood or tissue samples from a subset of families whose three members—father, mother, and infant with DS—were available. Only families whose proband had a confirmed free trisomy 21 with a determined parental origin of NDJ were included in the final analyses. The families who participated were given a small stipend to offset travel expenses. The findings on this subset of our population are the basis of this study.

Laboratory methods

For each sample, an extensive set of small random tandem repeat (STR) DNA markers that are chromosome 21–specific were analyzed.[3] Parental origin of the extra chromosome was determined by examining the contribution of each parent's alleles to the offspring. Two markers had to be informative to conclude parental origin. To determine the type of meiotic NDJ, we compared the pericentromeric markers of the parents to that of the offspring. If a pericentric marker that was heterozygous in the parent with the chromosome 21 NDJ error maintained heterozygosity in the offspring, a MI error was concluded. If that marker was reduced to homozygosity, a so-called "MII" error was concluded. A mitotic error was indicated when all informative markers along the chromosome area were reduced to homozygosity. Cases with mitotic errors were excluded from the analysis of SES variables. Other details of the analysis are described elsewhere.[3]

Variable definitions

Five variables on the interview have a strong bearing on the lifetime SES of the mother. They include the occupation of the mother's own father at the time of her birth, the mother's educational level, the infant's father's occupation and educational level, and the family income at the time of the interview. Although the original interview asked for the actual occupation of both father and grandfather, occupations were classified for this study into three groups: (1) laborer or unemployed, (2) all other known occupations, and (3) unknown occupation; the first group represents the families with the lowest SES. The mother's educational level was originally subdivided into less than high school, high school graduation, some college, and college graduation. We collapsed the last three categories for this analysis into one labeled as greater than or equal to high school graduation. Family income was recorded as under $10,000, $10,000 to 19,999, $20,000 to 29,999, $30,000 to 39,999, $40,000 to $49,999, $50,000 and over, and unknown. Families with an income below $20,000, a value considered to be below the poverty line for a family of four, were grouped into the low income group. All other families were included in the high-income group. Unknown income was primarily correlated with the other low socioeconomic indicators. Nevertheless, by combining the unknown income group with the higher income group in the regression analyses, we handled the variable conservatively.

A previous analysis showed that all four SES variables, although somewhat correlated, independently increased the risk for a recognized pregnancy with DS.[17] To create a combined variable representing SES over the life of the mother, we generated a variable that added the number of low socioeconomic indicators that were present from her childhood up to the time of birth of the case. The variable was originally set to zero, and a value of 1 was added for each of the following variables: the maternal grandfather was a laborer or unemployed, the mother had less than a high school education, the father was a laborer or unemployed or had less than a high school education, and the family income was under $20,000.

Three additional variables known or suspected to be associated with the risk for a DS were included in this analysis: mother's age, ethnic background,[1] and gravidity[20] or parity.[21] The original interview classified ethnic background into non-Hispanic white, Hispanic, African American, Asian, and Other. This classification was reduced to Hispanic and non-Hispanic for the regression because Hispanics differed significantly from other ethnic groups in their risk for DS.[16] Gravidity was entered in the analyses of MMI and MMII that included controls because that factor had shown a slight association with the risk for a pregnancy with DS for Hispanics only. However, the term was dropped in the analyses comparing MMI to MMII cases, where it was not a confounder. Mother's age at the birth of the index child was considered in both single years of age and in grouped categories. Because the risk for DS increases approximately exponentially with mother's age, a term representing mother's age squared was entered in regression analyses that included controls. Several additional variables, including mother's smoking and coffee consumption, were originally con-

sidered, but were dropped from the analyses when they showed no effect on the results.

Chi square tests for homogeneity were used to evaluate the differences between cases who did, and cases who did not, have the origin of meiosis determined, and to contrast MMI cases to MMII cases. Mean parental ages with standard deviations were given for each type of meiosis within parental origin of NDJ. Odds ratios (OR) with 95% confidence intervals were used to evaluate socioeconomic factors for cases of maternal origin. In all multivariate analyses comparing cases and controls, adjustments were made for maternal age, maternal age squared, and maternal ethnicity and gravidity. No adjustments were made in comparing MMI versus MMII DS cases because no factors differentiating the two groups were found or are otherwise known. For multiple logistic regression, we used Proc Logistic under SAS 6.12.[22]

RESULTS

Among the 998 DS cases included in the study, 688 were live born, 279 were elective terminations, and 31 were spontaneous fetal losses. To determine the origin of NDJ, blood samples or tissue samples were obtained from 172 families, three of them with an elective termination and 169 with a live birth. However, the DNA analysis was performed on only 167 families because five families did not provide a blood sample from the father and were thus excluded. Only 150 of the sampled families were informative with regard to the type of meiosis. Among the remaining ones, three cases had a translocation, eleven samples from the trisomic child failed to grow and consequently no DNA was available, one case was a nonpaternity, and two were excluded due to inconsistencies in the DNA analysis.

Table 1 presents the distributions of various family characteristics for the 1007 controls and for all DS cases grouped into four categories: total births, cases sampled, cases not sampled, and live born cases.

As expected from the population distribution of births from which the controls were randomly selected, and from the known maternal age–associated risk for DS, the age distribution differed substantially between case and control mothers. The differences between case and control mothers for gravidity and ethnicity were also significant.

Except for family income, the low categories of all SES variables were significantly more prevalent in families of DS cases than in families of controls, and more prevalent among the DS families that were sampled than among the DS families that were not sampled. Furthermore, the families that were sampled were more similar to the families of live born DS cases than to the families of all DS cases in the study. This may be attributable to the large proportion of the total DS cases that were elective terminations whose families were then less likely to be sampled and to have low SES. In summary, the distributions of SES variables in Table 1 show that the sampled DS families were more similar to the families of DS live births than to either the families of controls or to families of DS cases that included elective terminations.

Table 2 gives the distribution of the parental origin and type of meiotic NDJ for the 150 sampled cases with a free trisomy

21. Nearly 89% of cases were of maternal origin, of which approximately 77.4% were MMI and 21.8% were MMII errors. A paternal origin of NDJ was found in 7.3% of all cases, of which 81.8% were of meiosis II origin, whereas cases of mitotic origin accounted for 4.0% of all cases.

Table 3 shows the mean maternal and paternal ages by parental origin and type of meiotic NDJ. Mothers' mean age was not significantly different for MMI and MM II cases (32.9 and 32.8 years, respectively). However, mothers of meiotic cases were significantly older (32.8 years) than mothers of mitotic cases (23.8 years). Mean maternal age for trisomies of paternal origin (27.5 years) was close to the mean maternal age of mothers of controls (26.8 years), and lower than that of mothers of cases of meiotic origin (32.8 years). Mean father's age for cases of maternal meiotic origin was about 5 years older than that of control fathers (29.2 years), whereas mean father's age for cases of mitotic origin (28.2 years) was similar to that of control fathers. Mean father's age was lower for cases of paternal origin (29.5 years) than for cases of maternal origin (34 years), but similar to that of mitotic cases (28.2 years).

Table 4 contrasts the percent distribution of family characteristics for MMI and MMII cases. Each of the socioeconomic factors studied—maternal and paternal education, father's and grandfather's occupations, and family income—demonstrated strong differences by the type of meiotic error: variables associated with lower SES occurred more frequently among MMII than among MMI cases.

Table 5 shows the result of the logistic regression for the association of an increasing number of low SES risk factors with the occurrence of 103 MMI and of 29 MMII DS cases. These analyses were adjusted for variables shown in previous analyses to be associated with the risk for a DS pregnancy,[16] namely single year maternal age, maternal age squared, Hispanic ethnicity, and gravidity of four or more. Because the sampled group is biased toward low SES, the results in Table 5 are presented merely to contrast the findings between MMI and MMII cases compared with the same population-based controls. For each meiotic group, there was an increasing risk with an increasing number of low SES factors. The trend was significant for both the MMI and the MMII cases. However, the odds ratios was much larger for the MMII cases than for the MMI cases, but with much larger confidence intervals due to smaller numbers.

Table 6 contrasts MMII cases to MMI cases with respect to SES. The odds ratios associated with MMII compared to MMI cases increased from 5.94 for one low SES factor to 9.50 for all four SES factors. All comparisons are highly significant, although the wide confidence intervals indicate low precision. Additional analysis showed that the presence of one or more low SES factors compared to none was almost eight times more likely for MMII cases than for MMI cases (OR = 7.89; 95% CI = 1.78–35.05).

DISCUSSION

In a previous analysis of this population that includes live births, spontaneous fetal deaths, and elective terminations, we observed an increased risk for a recognized pregnancy with DS for

Table 1
Distribution (%) of family characteristics for controls and for Down syndrome cases, sampled and not sampled for the determination of the type of nondisjunction, and for live born cases only

| | Controls (%) | | Cases of Down syndrome (%) | | | | |
| | | | All outcomes | | | Group Comparisons | |
Characteristic		Total $N = 1007$	Not sampled $N = 998$	Sampled $N = 831$	Live Births $N = 167$	Total births vs. controls $N = 688$	Sampled vs. not-sampled cases
Mother's age							
<25	38.0	16.9	16.3	20.4	23.1		
25–34	51.4	33.6	32.0	41.3	41.6	$P < 0.001$	$P < 0.01$
≥35	10.5	49.5	51.7	38.3	35.3		
Mother's gravidity							
1–3	77.2	57.4	56.7	61.1	56.0	$P < 0.001$	$P < 0.29$
≥4	22.8	42.6	43.3	38.9	44.0		
Mother's ethnicity							
White	34.9	34.4	35.0	31.1	24.3		
Hispanic	47.3	51.7	50.4	58.1	62.4	$P < 0.03$	$P < 0.16$
Other	17.9	13.9	14.6	10.8	13.4		
Mother's education							
Less than high school	31.3	36.2	34.7	43.7	46.2		
High school or more	68.5	63.7	65.3	55.7	53.6	$P < 0.02$	$P < 0.02$
Unknown[a]	0.2	0.1	0.0	0.6	0.1		
Family income							
<$20,000	42.9	43.4	42.5	47.9	55.2		
≥$20,000	43.9	45.0	46.3	38.3	31.4	$P < 0.56$	$P < 0.19$
Unknown	13.2	11.6	11.2	13.8	13.4		
Father's education							
Less than high school	27.5	32.6	30.7	41.9	41.7		
High School or more	67.3	62.6	64.3	54.5	52.6	$P < 0.05$	$P < 0.02$
Unknown	5.2	4.8	5.1	3.6	5.7		
Father's occupation							
Laborer/unemployed	18.6	22.1	20.5	30.5	28.1		
Other occupation	76.9	74.8	76.2	67.7	68.2	$P < 0.04$	$P < 0.01$
Unknown	4.6	3.1	3.4	1.8	3.8		
Grandfather's occupation							
Laborer/unemployed	26.1	33.6	31.7	43.1	41.1		
Other occupation	65.4	60.8	62.3	53.3	52.5	$P < 0.001$	$P < 0.01$
Unknown	8.7	5.6	6.0	3.6	6.4		

[a] 3 mothers with unknown education status were not included in the Chi square computations because of low expected values.

mothers with a cumulative life-exposure to low SES factors.[17] In order to test the hypothesis that those SES risks would vary according to the type of NDJ, we evaluated in the present analysis the same factors in a subsample of cases whose type of NDJ had been determined. A concern would be that the sample used for the determination of the origin of NDJ would not be representative of DS cases in general. Because the inclusion of families in the subsample was not based on their type of NDJ, which was unknown at the time, there could not have been a selection bias favoring one

or the other type of NDJ. This is corroborated by the distribution of the types of NDJ among the sampled cases: 77.4% with MMI and 21.8% with MMII, which is similar to the proportions reported by other researchers.[7,23,24]

The inclusion of three pregnancy terminations in the sampled case group should not have changed the distribution of the meiotic origin of NDJ as others have found no differences between live births and pregnancy terminations in the distribution of MMI and MMII.[15]

Table 2
Percent distribution of 150 informative trisomy 21 cases, by parental origin and type of nondisjunction (NDJ) error

Parental origin	Type of NDJ	N	%
Maternal[a]	Meiosis I	103	68.7
	Meiosis II	29	19.3
	Unknown	1	0.7
	Subtotal	133	88.7
Paternal	Meiosis I	1	0.7
	Meiosis II	9	6.0
	Unknown	1	0.7
	Subtotal	11	7.3
Mitotic		6	4.0
Total		150	100

[a]77.4% of maternal meioses were of the MMI type.

In other respects, the sample of cases in this analysis resembles other DS samples from the literature. The distribution of cases by parental origin of the NDJ, 88.7% maternal and 7.3% paternal, fits the expected pattern,[5,15,25] as does the larger proportion of MII NDJ among cases of paternal origin.[5,7,15,26] Studies on the origin of NDJ in Down syndrome have reported that the age effect associated with DS is limited to cases of maternal origin[7] and that mothers of both MMI and MMII cases have similarly high mean maternal ages.[15] Our study supports these findings with very similar results in our sampled cases (Table 3).

Discussion of the association of low SES with DS

In the present study, which includes primarily a sample of live born infants with DS, we found an association of SES with the risk of having a DS that is similar to that found in our analysis of the group that includes all outcomes. However, because the possible effect of environmental factors on the risk of having a trisomy 21 may differ for cases with MMI and MMII errors,[15] we reexamined the association of SES with each of the two types of meiotic NDJ. Although our sample was not a random selection from all DS cases, but a selection based on the availability of the family for a blood draw, the type of NDJ was not known to us or to the families that participated. This precludes a selection bias for either cases of MMII origin or of MMI origin. The strong association of low SES factors with cases with an MMII error compared to cases with an MMI error was unexpected.

Choice of SES variables and correlation of variables

Our choice of variables captures the life-course SES of the case mother, from the time of formation of her oocyte pool and her youth, as represented by her father's occupation, to the time of conception of her offspring with DS, as represented by her education, the case father's occupation or education, and the family income. However, many young mothers did not know their family income. When considered separately, unknown income was strongly associated with MMII. With one exception, it was also correlated with low socioeconomic factors. By using the conservative approach of including unknown income with the high-income group, we biased the results toward the null hypothesis of no association between the type of meiotic NDJ and low SES. When the cases with an unknown income were included with the cases with low income, the odds ratios for trends were even higher, confirming that our measure of association was conservative.

Although the SES variables were highly correlated, in multivariate analysis they were individually associated with the risk for a pregnancy with a DS.[17] To evaluate the risk associated with the cumulative lifetime exposure of low SES of the mother, we consequently created the composite variable that

Table 3
Mean maternal and paternal age[a] for 150 trisomy 21 cases, by origin and type of meiotic nondisjunction (NDJ)

Origin of NDJ	Type of NDJ error	Maternal		Paternal	
		N	Age[a] (y) Mean ± SD	N	Age[c] (y) Mean ± SD
Maternal	Meiosis I	103	32.9 ± 6.6	101	34.3 ± 7.9
	Meiosis II	29	32.8 ± 8.2	27	33.2 ± 9.3
	All[d]	133	32.8 ± 7.0[b]	129	34.0 ± 8.3
Mitotic		6	23.8 ± 6.9[b]	6	28.2 ± 7.1
Paternal	Meiosis I	1	22.0	1	23.0
	Meiosis II	9	27.8 ± 6.3	9	29.7 ± 7.5
	All[d]	11	27.5 ± 5.9	11	29.5 ± 7.2
All trisomies 21		150	32.0 ± 7.2	146	33.4 ± 7.9

[a]1007 control mothers had a mean age of 26.8 ± 6.0 years; 916 control fathers with a known age had a mean age of 29.2 ± 6.9 years.
[b]$P < .002$ by t-test for comparison between all maternal meiotic cases and mitotic cases.
[c]Excludes 4 fathers with exact age unknown.
[d]Includes one case with unknown type of meiotic NDJ.

measures the number of low SES exposures, not their individual values. This precludes confounding that could have been introduced if all the SES variables had been included in the analysis as separate entities. The results show that the risk for a recognized pregnancy with DS increases with the number of low SES factors present in the mother's life, and that the association is strongest for mothers of a child with an MMII NDJ than for mothers with a child with an MMI NDJ.

The reason for an association of low SES with the risk for a live born with DS, independently of maternal age, ethnicity, and gravidity or parity, is not explained, but has been reported by others.[27,28] One hypothesis is that environmental risk factors that would predispose to an aneuploidy would be more likely to occur in lower socioeconomic groups. Because age is the most important risk factor for DS, one hypothesis would imply that environmental risk factors could modify the aging of the oocyte pool of the mother. Several authors have reported that women of lower SES have an earlier menopause.[29–31] As the risk for a DS birth increases most steeply close to the time of menopause, women with low SES would thus be at higher risk at an earlier age. Those risk factors could increase the level of

Table 4
Distribution (%) of socioeconomic characteristics for Down syndrome cases of maternal origin, by type of meiotic nondisjunction

Socioeconomic characteristic	Meiosis I (N = 103) (%)	Meiosis II (N = 29) (%)	Statistic[a] P value
Mother's education			
Less than high school	37.9	62.1	$\chi^2_{1df} = 5.40$
High school or better	61.2	37.9	$P = 0.02$
Unknown[a]	1.0		
Family income			
<$20,000	41.8	62.1	$\chi^2_{2df} = 19.6$
≥$20,000	51.5	10.3	$P = 0.001$
Unknown	6.8	27.6	
Father's education			
Less than high school	36.9	51.7	$\chi^2_{1df} = 3.28$
High school or better	60.2	37.9	$P = 0.07$
Unknown[a]	2.9	10.3	
Father's occupation			
Laborer/unemployed	26.2	48.3	$\chi^2_{1df} = 5.63$
Other occupation	72.8	48.3	$P = 0.02$
Unknown	1.0	3.5	
Grandfather's occupation			
Laborer/unemployed	38.8	58.6	$\chi^2_{1df} = 3.80$
Other occupation	58.3	37.9	$P = 0.051$
Unknown	2.9	3.5	

[a]The proportion of unknowns are shown for each variable, but with the exception of family income, they were excluded from Chi-square computations because of low expected values.

spontaneous deletions of mitochondrial DNA, which are known to increase exponentially at approximately the same age as the exponential risk for a DS birth.[32] However, this would not explain why mothers with a low SES would be more likely to have an offspring with DS with an MMII error, at all ages, unless one speculates on differential energy needs for the two meiotic NDJs.

Other researchers have suggested that genetic factors could influence the type of meiotic error contributed to the DS offspring. Petersen et al.[33] have reported that mothers of cases with an MMII error are more likely than mothers of cases with an MMI error to have a specific polymorphism in the presenilin-1 gene. The authors suggest a function of presenilin proteins in chromosome segregation because the expression of these proteins has been localized to the nuclear membrane, kinetochores, and centromeres. Avramopoulos et al.[34] have reported an increased prevalence of the epsilon 4 allele of the apolipoprotein E gene in mothers of DS offspring with an MMII error. To our knowledge, an interaction between potential genetic and environmental risk factors for NDJ has not been explored to date.

Yang et al.[15] have conjectured that the type of predisposing chromosomal recombination pattern associated with MMII may be more likely to require the addition of an environmental insult or second hit for the actual meiotic error to occur. Their study is the only one that has evaluated environmental factors that might influence differentially the susceptibility to one or the other meiotic error.[15] In that study, the interaction of the mother's use of contraceptive pills and smoking was associated with a higher risk of having an offspring with an MMII NDJ. In our study, none of the mothers of MMII cases both smoked and took contraceptive pills, and only 3 of the mothers of MMI cases did so. The large majority of mothers in our mostly Hispanic population did not smoke. Neither smoking nor use of oral contraceptive pills, either separately or together, had any association with DS in our analyses (results not shown); consequently these variables were not entered in subsequent analyses.

In contrast to Yang's study,[15] in which the association with environmental factors was seen mainly in a small number of women who were < 35 years of age, our results did not depend on the mother's age. Analysis of our data according to mothers' age groups corresponding to those of the Yang study showed results similar to those of our main analyses (data not shown). Furthermore, the increasing trend in risk with the increasing number of low SES factors and the high values of the ORs suggest that the association is real.

Recently, an environmental factor, bisphenol A, has been shown experimentally to cause meiotic aneuploidy in oocytes of exposed mice.[35] This is the first time that an environmental factor has been shown to produce meiotic aneuploidy even at low doses, and it suggests that the meiotic process may be sensitive to some environmental insults.

Although evidence is accumulating for a possible effect of deleterious environmental factors on the meiotic process, the mechanism by which this effect would be obtained has not

Table 5
Association of socioeconomic (SES) risk factors with the occurrence of DS in 103 MMI cases and 29 MMII cases compared to 1007 controls

Type of meiosis	Number of low SES factors[a]	OR[b]	95% confidence intervals
MMI[c]	≥1	1.25	0.72–2.22
	1	0.98	0.50–1.91
	2 or 3	1.52	0.77–3.02
	4	2.50	1.06–5.91
MMII[d]	≥1	12.20	2.26–66.02
	1	8.50	1.37–52.65
	2 or 3	15.65	2.55–95.97
	4	42.46	5.94–303.48

[a] Each of the following counted as one factor: mother had less than a high school education, father had less than a high school education or was a laborer or unemployed, maternal grandfather was a laborer or unemployed, family income was under $20,000.
[b] Adjusted for age, age squared, ethnicity, and gravidity.
[c] 65 of 103 families in the MMI group had one or more low SES factor.
[d] 27 of 29 families in the MMII group had one or more low SES factor.

been elucidated. As the process of maturation of the oocyte involves many pathways, different environmental factors may impact different pathways. Our study suggests that factors associated with a low SES may significantly increase the risk for a maternal MII type of NDJ error.

Clearly NDJ is a multifactorial disorder. The pattern of chiasmata along the chromosome established during the fetal life of a female is thought to predispose the bivalent to NDJ. Other genetic and/or environmental factors must influence the segregation of homologues and chromatids during the extended process of meiosis in a woman. Presumably "the second hit" by the environmental factors would occur at an as yet undetermined time period in the mother's life before conception of the proband with DS. Although intriguing, our results need confirmation. Further explorations of the interaction of environmental and genetic susceptibility factors for NDJ are warranted.

Table 6
Odds ratio that the maternal nondisjunction of chromosome 21 occurred in meiosis II vs. meiosis I, according to the number of low socioeconomic factors present in the proband's family

Number of factors[a]	Odds ratios[b]	95% CI
≥1	7.89	1.78–35.05
1	5.94	1.04–33.85
2 or 3	8.06	1.71–38.10
4	9.50	1.81–49.76

[a] Each of the following counted as one factor: mother had less than a high school education, father had less than a high school education or was a laborer or unemployed, maternal grandfather was a laborer or unemployed, family income was under $20,000.
[b] The test for trend of the number of factors was significant at $P = 0.02$.

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