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Trisomy Recurrence: A Reconsideration Based on North American Data

Dorothy Warburton,[1,2] Louis Dallaire,[6] Maya Thangavelu,[7] Lori Ross,[7] Bruce Levin,[3] and Jennie Kline[3,4,5]

Departments of [1]Genetics and Development and [2]Pediatrics, [3]Mailman School of Public Health, and [4]Gertrude H. Sergievsky Center, Columbia University, and [5]Epidemiology of Developmental Brain Disorders Department, New York State Psychiatric Institute, New York; [6]Service de Génétique Medicale, Centre de Recherche, Hôpital Sainte-Justine, Montreal; and [7]Genzyme Genetics, Orange, CA

Few reliable data exist concerning the recurrence risk for individual trisomies or the risk for recurrence of trisomy for a different chromosome. We collected records from two sources: (1) prenatal diagnoses performed at the Hôpital Sainte-Justine in Montreal and (2) karyotype analyses performed at Genzyme. Using the standardized morbidity ratio (SMR), we compared the observed number of trisomies at prenatal diagnosis with the expected numbers, given maternal age–specific rates (by single year). SMRs were calculated both for recurrence of the same trisomy (homotrisomy) and of a different trisomy (heterotrisomy). After all cases with an index trisomy 21 were combined, the SMR for homotrisomy was 2.4 (90% CI 1.6–3.4; $P = .0005$). For women with both the index trisomy and subsequent prenatal diagnosis at age <30 years, the SMR was 8.0; it was 2.1 for women with both pregnancies at age ⩾30 years. For the other index viable trisomies (13, 18, XXX, and XXY) combined, the SMR for homotrisomy was 2.5 (90% CI 0.7–8.0). For heterotrisomy, the SMR after an index trisomy 21 was 2.3 (90% CI 1.5–3.8, $P = .0007$); the SMR did not vary with maternal age at the first trisomy. When all cases with index viable trisomies were combined, the SMR for heterotrisomy was 1.6 (90% CI 1.1–2.4; $P = .04$). For prenatal diagnoses following a nonviable trisomy diagnosed in a spontaneous abortion (from Genzyme data only), the SMR for a viable trisomy was 1.8 (90% CI 1.1–3.0; $P = .04$). The significantly increased risk for heterotrisomy supports the hypothesis that some women have a risk for nondisjunction higher than do others of the same age.

Introduction

In spite of the large numbers of prenatal diagnoses performed for the detection of trisomy, there are few reliable data concerning the risk of recurrence for individual trisomies, and there are almost no data concerning whether a trisomic pregnancy is associated with an increased risk for trisomy of a different chromosome.

Recurrence of trisomy in the same couple could occur for several reasons: (1) chance alone, due to the maternal age–associated risk, (2) parental gonadal mosaicism for trisomy, or (3) factors associated with an increased risk of meiotic error. In population studies, comparison of the observed numbers of recurrences of the same or a different trisomy with that expected on the basis of maternal age can indicate whether chance alone can account for trisomy recurrences.

Trisomy mosaicism in a gonad may explain an increased recurrence risk for trisomies of the same chromosome (homotrisomy), producing a very high rate of recurrence in a small number of families (Sachs et al. 1990). Mosaicism will be underestimated by studies of parental lymphocytes (Uchida and Freeman 1985) or genetic markers (Pangalos et al. 1992; Bruyere et al. 2000), which have suggested rates of ~2% in cases of Down syndrome. In contrast, gonadal mosaicism cannot explain an increased recurrence risk for a different trisomy (heterotrisomy). Rather, such an increase would imply that some couples have a higher risk for meiotic nondisjunction than do others of the same age. Since most trisomy is of maternal origin (Hassold and Hunt 2001), maternal factors probably would be implicated.

Knowledge of whether some women are at increased risk for meiotic error has both practical and theoretical implications. From a practical standpoint, it influences whether young women with a pregnancy loss known to be trisomic should be offered prenatal diagnosis in future pregnancies. From a theoretical standpoint, an increased recurrence risk for meiotic nondisjunction in general is predicted by many hypotheses concerning the origins of the maternal-age association—for example, genetic variation in recombination frequency (Brown et al. 2000; Lynn et al. 2002), mutations in genes involved in the meiotic process (Zwick et al. 1999; Schon et al. 2000; Arbuzova et al. 2001; Balicky et al. 2002), or

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Address for correspondence and reprints: Dr. Dorothy Warburton, Columbia University Medical Center, Room CHC-406, 3959 Broadway, New York, NY 10032. E-mail: cuh@cancercenter.columbia.edu

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biological aging processes in the ovary, which might vary among women of the same chronological age (Kline et al. 2000; Hodges et al. 2002).

At present, genetic counseling concerning trisomy recurrence is most often based on the analysis of European amniocenteses collected in the 1980s (Stene et al. 1984; reanalyzed by Warburton et al. [1987]). For trisomy 21, these data showed that among women aged <30 years at the time of prenatal diagnosis, the risk of recurrence was ~8 times the maternal age–associated risk, whereas, for women who had their first trisomy at age ⩾30 years, the risk was not increased above that based on maternal age. Data on trisomy recurrence have also been reported from 273 women with two karyotyped spontaneous abortions (Warburton et al. 1987). After adjustment for maternal age, the odds ratio for a second trisomic pregnancy loss in women with a previous trisomic loss (compared with a woman with no previous karyotyped loss) was 1.3 (95% CI 0.7–2.1). These data suggested that women having one pregnancy loss with trisomy were not at increased risk for trisomy in a second pregnancy.

We collected data on trisomy recurrence from two sources: (1) records of prenatal diagnoses performed over a 20-year period in the Hôpital Sainte-Justine in Montreal and (2) records of karyotype analyses performed at Genzyme, based in Santa Fe, NM. These data confirm the large increase in risk for recurrence of trisomy 21 among young women, but they indicate that there is also a doubling of risk among older women. They also provide evidence of an increased risk for trisomy in general following either a live birth with trisomy or a pregnancy loss with trisomy.

Subjects and Methods

Subjects

Data on karyotypes from prenatal diagnoses (without identifiers) were obtained from two cytogenetic laboratories:

1. Service de Génétique Médicale, Hôpital Sainte-Justine, Montreal: At the Hôpital Sainte-Justine, all records were derived from prenatal diagnosis by amniocentesis performed between 1976 and 1999. Cases were women for whom a previous trisomy, monosomy X, or triploidy (the index case) was recorded as a reason for the prenatal diagnosis; there was laboratory documentation of this result; and the maternal age at both the previous index pregnancy and the prenatal diagnosis were recorded. Some women had more than one amniocentesis after the index pregnancy. The final sample consisted of 1,027 amniocenteses from 748 women with a history of a previous numerical chromosome abnormality (table 1).

Table 1

Number of Prenatal Diagnoses, by Karyotype, of the Index Pregnancy: Sainte-Justine 1976–1999

Karyotype of Index Pregnancy[a]	No. of Women	No. of Amniocenteses per Woman					Total No. of PND[b]
		1	2	3	4	5	
Trisomy 21	503	359	121	20	2	1	674
Trisomy 18	93	51	38	4	0	0	139
Trisomy 13	59	42	16	1	0	0	77
XXX/XXY	6	6	0	0	0	0	6
45,X	78	50	18	9	1	0	117
Triploidy	9	6	2	0	1	0	14
Total	748	514	195	34	4	1	1,027

[a] Excludes cases with "other anomalies," cases with two prior trisomies, and double trisomies.

[b] PND = prenatal diagnoses.

The source of these data has been described in a previous publication (Caron et al. 1999).

2. Genzyme Genetics, at various sites in the United States: At Genzyme Genetics, we used a computerized database to identify all women with two or more pregnancies karyotyped in Genzyme laboratories. These pregnancies included both prenatal diagnoses and spontaneous abortions. Cases were women for whom a first pregnancy with trisomy, monosomy X, or triploidy (the index pregnancy) was followed by a prenatal diagnosis, either by amniocentesis or chorionic villus sampling, during the years 1994–2001. Maternal age was available in all cases for both the index pregnancy and subsequent prenatal diagnoses. Some women had more than one subsequent prenatal diagnosis. The final sample consisted of 1,536 amniocenteses and 293 chorionic villus samples from 1,702 women with a history of a previous numerical chromosome abnormality (table 2).

In both samples, we excluded women with more than one trisomy prior to the prenatal diagnosis, as well as women whose index pregnancy had a double anomaly, a monosomy other than X, a mosaic other than a trisomy/normal mosaic, or was 47,XYY (always paternally derived). We included, as a comparison group, women whose index abnormality was 45,X or triploid. Since the mechanisms of origin of these anomalies are usually considered different from those of trisomy, we expect no increase in trisomy above the maternal age–related rate. Trisomy risk after these karyotypes is also sometimes an issue in genetic counseling.

We refer to trisomies 13, 18, 21, X, and Y as "viable" trisomies, since they can occur as nonmosaics at the time of prenatal diagnosis and in live births. We refer to all the other trisomies, which usually are found only in spontaneous abortions, as "nonviable" trisomies. We refer to trisomies XXX and XXY as "X-aneuploidy."

Table 2

Number of Prenatal Diagnoses, by Karyotype, of the Index Pregnancy: Genzyme 1994–2001

Karyotype of Index Case[a]	No. of Women	No. of Prenatal Diagnoses				Total PND[b]
		First Amniocentesis	First Chorionic Villus Sample	Second Amniocentesis	Second Chorionic Villus Sample	
Trisomy 21	657	518	139	46	8	711
Trisomy 18	235	198	37	15	2	252
Trisomy 13	132	113	19	6	0	138
XXX/XXY	48	40	8	2	4	54
POC[c] with trisomy 16	118	103	15	7	1	126
POC[c] with other trisomy	251	228	23	10	3	264
45,X	165	145	20	11	2	178
Triploid	96	83	13	10	0	106
Total	1,702	1,399	266	137	27	1,829

[a] Excludes double anomalies including hyper- and hypotriploids, mosaics except for trisomy/normal mosaics, and double trisomies. Includes prenatal diagnoses subsequent to a spontaneous abortion following the index pregnancy.
[b] PND = prenatal diagnoses.
[c] POC = product of conception (spontaneous abortion).

Statistical Analysis

Expected numbers of trisomies by single year of maternal age.—Ages of women at the time of prenatal diagnosis ranged from 16 to 50 years. For women aged ⩾33 years, age-specific (in single years) rates of trisomy 13, 18, 21, XXX, and XXY from amniocenteses and chorionic villus samples in the United States are available from data analyzed by Hook (1992) and Snijders (1994, 1999). We used the rates from Hook, but the two estimates are very similar.

For women aged <33 years, there are no good estimates of trisomy rates in prenatal diagnoses by single year of maternal age. For trisomy 21, we converted data on live-birth frequencies by single year (Hook 1992) into rates at the time of prenatal diagnosis by correcting for losses that occur between the time of prenatal diagnosis and birth. For trisomy 21, there have been various estimates of this loss rate, after both amniocentesis and chorionic villus biopsy (reviewed by Morris et al. 1999; Snijders et al. 1999; Spencer 2001). For loss rates after amniocentesis (15–29 wk) we used 23%, the rate estimated by Morris et al. (1999) from a meta-analysis of published studies, which is very similar to the latest figure derived by Snijders et al. (1999). For chorionic villus samples, we used 36%, the best estimate from the same sources. We also tested the robustness of our analysis, using higher and lower estimates of loss between prenatal diagnosis and birth: the expected values of trisomy changed very little, because trisomy rates are so low among young women. For example, changing the estimated rate of loss between amniocentesis and birth from 23% to 36% after amniocentesis changes the expected number of trisomy 21 cases in women aged <33 years only in the second decimal place.

For viable trisomies other than 21, there are no age-specific rates in single years for either live births or prenatal diagnoses for women younger than 33 years. For trisomy 13 and 18, we used the estimates of Snijders et al. (1999) for amniocenteses and chorionic villus samples. These estimates are based on the ratio of trisomy 13 and 18 to trisomy 21 in 5-year maternal-age categories. Hook et al. (1979) used the same method to estimate rates of trisomy 18 by single year of maternal age. Since X-aneuploidy is not associated with fetal loss, and there is little increase in the rate with age <33 years, we used live-birth rates for these trisomies in 5-year maternal-age categories (Hook 1992).

The validity of our estimates of expected values is supported by the good agreement between the observed and expected numbers of trisomies in the women with a previous 45,X or triploid pregnancy (see the "Results" section).

We performed the analyses both with and without the inclusion of repeat prenatal diagnoses. No woman had more than one trisomy in prenatal diagnoses subsequent to the index trisomy.

The standardized morbidity ratio: comparison of observed versus expected numbers of trisomies.—Cases were classified by age at the time of prenatal diagnosis and, for women with a previous trisomy 21, by age at the birth or prenatal diagnosis of the index (preceding) trisomy 21. Observed numbers were those recorded in the data. We estimated the expected number of trisomy 21, trisomy 13, trisomy 18, and X-aneuploid prenatal diagnoses at each age, using the single-year risks described above. The total numbers of observed and expected trisomies were then summed over all maternal-age categories. The recurrence risk, compared with the age-associated risk, was estimated as the ratio of observed to expected, which is equivalent to the standard-

Table 3

Distribution of Prenatal Diagnoses by Maternal Age

Maternal Age (years)	No. (%) of Prenatal Diagnoses from	
	Genzyme Sample	Sainte-Justine Sample
<20	6 (.3)	2 (.2)
20–24	40 (2.2)	105 (10.2)
25–29	163 (8.9)	366 (35.6)
30–34	386 (21.1)	332 (32.3)
35–39	854 (46.7)	194 (19.0)
40–44	370 (20.2)	26 (2.5)
⩾45	10 (.6)	2 (.2)
Total	1,829 (100)	1,027 (100)

ized morbidity ratio (SMR). Assuming a Poisson distribution for the counts with the age-adjusted expectations, we used an exact, one-tailed test of significance (at $\alpha = .05$) to test whether there was a significant excess of observed over expected trisomies. We also report the corresponding one-tailed exact *P* values and—consistent with one-tailed testing—exact, two-sided 90% CIs by use of the point-probability method (Fleiss et al. 2003, p. 37). We tested heterogeneity of the SMRs between data sets, among maternal-age classes, and among trisomy classes, using the χ^2 statistic for binomial or multinomial data, which is appropriate for independent Poisson variables conditional on their sum. The tests for heterogeneity were two-tailed, conducted at the .05 level of significance. We assessed the possibility of information loss by the use of repeat entries from some women by calculating the variance-inflation factor due to clustering of repeat entries within those women (Fleiss et al. 2003, pp. 213, 441). This factor was trivial in these data (<.0004). Therefore, the analyses reported here include both first and repeat prenatal diagnoses without adjustment for clustering.

Results

Distribution of Maternal Age

The mean maternal age is 30.1 years in the Sainte-Justine sample and 35.7 years in the Genzyme sample (table 3). This age disparity may partly reflect the earlier time period covered in the Sainte-Justine sample and the demographics of the catchment area. However, it is probably largely because index trisomies in the Sainte-Justine sample include live births, whereas the Genzyme sample comprises only prenatal diagnoses or pregnancy losses, which tend to occur at older maternal ages.

Homotrisomy

Data concerning recurrence of the same trisomy were analyzed for cases in which the index pregnancy was trisomy 21, trisomy 18, trisomy 13, or X-aneuploidy. Since previous analyses had indicated a difference in risk depending on the age at the first trisomy, we also assessed the effect of age at the first trisomy and age at the subsequent prenatal diagnoses for index trisomy 21 pregnancies. For other trisomies, the numbers were too small to stratify by maternal age at index trisomy.

Tables 4 and 5 show recurrence of trisomy 21 among women with an index trisomy 21, classified by age at the index trisomy and age at a subsequent prenatal diagnosis. For comparison with previous analyses and to ensure adequate sample size, we stratified cases dependent on whether the index trisomy occurred at age <30 years or ⩾30 years. Whereas there is no significant difference between the SMRs in the two age groups ($P = .15$), the SMR is twice as high (4.6 vs. 2.1) in the women who had their first trisomy at a younger age. For women with both index pregnancy and prenatal diagnosis at age <30 years, the recurrence risk is eight times that expected,

Table 4

Recurrence of Trisomy 21: Index Pregnancy at Maternal Age <30 Years

Maternal Age and Sample	No. of Prenatal Diagnoses	Expected No. of Trisomy 21	Observed No. of Trisomy 21	SMR[a]	90% CI	*P*[b]
Prenatal diagnosis at age <30 years:						
Genzyme	80	.094	2	21.3	5.7–68.9	.004
Sainte-Justine	342	.391	2	5.1	1.4–16.6	.059
Total prenatal diagnoses	422	.485	4	8.2	3.6–18.6	.002
Prenatal diagnosis at age ⩾30 years:						
Genzyme	23	.045	0	0	.0–66.5	1.0
Sainte-Justine	140	.344	0	0	.0–8.7	1.0
Total prenatal diagnoses	163	.389	0	0	.0–7.7	1.0
All prenatal diagnoses:						
Genzyme	103	.139	2	14.4	3.8–46.6	.009
Sainte-Justine	482	.735	2	2.7	.7–8.8	.168
Total prenatal diagnoses	585	.874	4	4.6	2.0–10.3	.012

[a] Observed/expected.
[b] One-tailed exact *P* value.

Table 5

Recurrence of Trisomy 21: Index Pregnancy at Maternal Age ⩾30 Years

Maternal Age and Sample	No. of Prenatal Diagnoses	Expected No. of Trisomy 21	Observed No. of Trisomy 21	SMR[a]	90% CI	P[b]
Prenatal diagnosis at age 30–34 years:						
Genzyme	126	.320	1	3.3	.3–15.5	.274
Sainte-Justine	71	.164	0	0	.0–18.2	1.0
Total prenatal diagnoses	197	.484	1	2.1	.2–10.2	.274
Prenatal diagnosis at age 35–39 years:						
Genzyme	337	2.458	2	.8	.2–2.6	.704
Sainte-Justine	101	.734	6	8.2	4.1–16.4	.0001
Total prenatal diagnoses	438	3.192	8	2.5	1.4–4.6	.017
Prenatal diagnosis at age 40–44 years:						
Genzyme	145	3.453	6	1.7	.9–3.5	.136
Sainte-Justine	20	.511	1	2.0	.2–9.7	.400
Total prenatal diagnoses	165	3.964	7	1.8	.9–3.3	.107
All prenatal diagnoses:						
Genzyme	608	6.231	9	1.4	.6–2.5	.178
Sainte-Justine	192	1.409	7	5.0	2.6–9.2	.001
Total prenatal diagnoses	800	7.640	16	2.1	1.4–3.2	.005

[a] Observed/expected.
[b] One-tailed exact P value.

given maternal age alone (90% CI 3.6–18.6), and significantly different from the SMR of 2.1 (90% CI 1.4–3.3) in women aged ⩾30 years at both pregnancies ($P = .01$).

Table 6 shows recurrence of the same trisomy for all types of potentially viable index trisomies. For each trisomy except X-aneuploidy, the number of observed trisomies exceeds that expected on the basis of age alone. For trisomy 21, the SMR is 2.4 (90% CI 1.6–3.4; $P = .0005$). For the other trisomies, small numbers of cases lead to very large CIs about the SMR. For trisomies 18, 13, and X-aneuploidy, SMRs are 1.7 (90% CI 0.2–8.6), 8.6 (90% CI 0.9–42.3), and 0 (90% CI 0–25.4), respectively. After combination of all viable trisomies except tri-

Table 6

Recurrence of the Same Trisomy (Homotrisomy): All Trisomies

Index Karyotype and Sample	No. of Prenatal Diagnoses	No. Expected with Same Trisomy	No. Observed with Same Trisomy	SMR[a]	90% CI	P[b]
Trisomy 21:						
Genzyme	711	6.370	11	1.7	1.0–2.8	.06
Sainte-Justine	674	2.144	9	4.2	2.3–7.2	.0004
Total Trisomy 21	1,385	8.514	20	2.4	1.6–3.4	.0005
Trisomy 18:						
Genzyme	252	.467	0	0.0	.0–6.4	1.00
Sainte-Justine	139	.109	1	9.2	1.0–45.4	.10
Total Trisomy 18	391	.576	1	1.7	.2–8.6	.43
Trisomy 13:						
Genzyme	138	.098	1	10.2	1.1–50.6	.09
Sainte-Justine	77	.019	0	0.0	.0–157.6	1.00
Total Trisomy 13	215	.117	1	8.6	.9–42.3	.11
XXX/XXY:						
Genzyme	42	.106	0	0		
Sainte-Justine	6	.012	0	0		
Total XXX/XXY	48	.118	0	0	.0–25.4	1.00
All non-21 trisomies	654	.811	2	2.5	.7–8.0	.20
All viable trisomies:						
Genzyme	1,143	7.041	12	1.7		
Sainte-Justine	896	2.272	10	4.4		
Total trisomies	2,039	9.313	22	2.4	1.7–3.4	.0003

[a] Observed/expected.
[b] One-tailed exact P value.

somy 21, the SMR is 2.5 (90% CI 0.7–78.0; $P = .20$). When all viable trisomies are included, the SMR is 2.4 (90% CI 1.7–33.4; $P = .0003$).

Heterotrisomy

Table 7 shows the observed and expected numbers of viable trisomies (13, 18, 21, and X-aneuploidy) that are different from the index case. When the index case is trisomy 21, the SMR is 2.3 (90% CI 1.5–3.8; $P = .007$). The SMRs are similar for women aged <30 years and ⩾30 years at the time of the index trisomy 21 (table 8). For index trisomy 13, trisomy 18, and X-aneuploidy, the SMRs are 0.6 (90% CI 0.1–2.4), 1.9 (90% CI 0.5–4.9), and 0 (90% CI 0–4.5), respectively. There is no significant heterogeneity in the SMRs among the four trisomy classes ($P = .15$). After combination of all cases with an index viable trisomy, the SMR for a different viable trisomy is 1.6 (90% CI 1.1–2.4; $P = .04$).

In the Genzyme sample, we could examine prenatal diagnoses subsequent to an index karyotyped spontaneous abortion with a trisomy other than 13, 18, 21, or X-aneuploidy. In this situation, the SMR for a subsequent viable trisomy is 1.8 (90% CI 1.1–3.0; $P = .04$) (table 7). Because trisomy 16, the most frequent trisomy in spontaneous abortions, may involve different mechanisms of origin than do other trisomies (Hassold and Hunt 2001), we examined trisomy 16 separately. For trisomy 16 index pregnancies, the SMR for a subsequent viable trisomy is 1.2 (90% CI 0.3–3.8; $P = .50$); it does not differ significantly from the SMR of 2.2 (90% CI 1.1–3.6) for all other index nonviable trisomies combined.

Since the estimates of the SMR for viable and nonviable trisomies are not significantly different, we combined the data to estimate that the overall SMR for heterotrisomy is 1.7 (90% CI 1.2–2.3; $P = .006$).

We also estimated the risk of a subsequent viable trisomy in 414 cases for which the index pregnancy was either 45,X or triploid (table 7). The SMR is 1.0 (90% CI 0.3–3.9; $P = .60$), indicating no increased risk over the age-related rate of trisomy.

Heterogeneity between Samples

For both homotrisomy and heterotrisomy recurrence, the SMR is usually greater in the Sainte-Justine sample than in the Genzyme sample. With the exception of the combined risk for recurrence of heterotrisomy, the dif-

Table 7

Recurrence of a Different Trisomy (Heterotrisomy)

Index Karyotype and Sample	No. of Prenatal Diagnoses	Expected No. with Other Viable Trisomy	Observed No. with Other Viable Trisomy	SMR[a]	90% CI	P[b]
Trisomy 21:						
Genzyme	711	3.671	7	1.9	1.0–3.6	.08
Sainte-Justine	674	1.448	5	3.4	1.7–7.3	.02
Total trisomy 21	1,385	5.119	12	2.3	1.5–3.8	.007
Trisomy 18:						
Genzyme	252	2.402	1	.4	.0–2.1	.91
Sainte-Justine	139	.672	1	1.5	.2–7.4	.49
Total trisomy 18	391	3.074	2	.6	.2–2.1	.81
Trisomy 13:						
Genzyme	138	1.752	1	.6	.1–2.8	.83
Sainte-Justine	77	.334	3	9.0	3.3–23.9	.005
Total trisomy 13	217	2.086	4	1.9	.8–4.3	.16
XXX/XXY:						
Genzyme	54	.828	0	0	.0–3.6	1.00
Sainte-Justine	6	.059	0	0	.0–5.7	
Total XXX/XXY	60	.887	0	0	.0–3.4	1.00
All viable trisomies						
Genzyme	1,155	8.653	9	1.0	.6–1.8	
Sainte-Justine	896	2.513	9	3.6	2.0–6.2	
Total viable trisomies	2,051	11.166	18	1.6	1.1–2.4	.04
Nonviable trisomies:						
Trisomy 16 (G)	125	1.682	2	1.2	.3–3.8	.50
Other trisomies	264	4.373	9	2.1	1.1–3.6	.03
All nonviable trisomies	389	6.055	11	1.8	1.1–3.0	.04
Total trisomies	2,442	17.221	29	1.7	1.2–2.3	.006
Triploidy and 45,X	414	3.124	3	1.0	.3–3.9	.60

[a] Observed/expected.
[b] One-tailed exact P value.

ferences between the samples are not statistically significant ($P > .05$). We have therefore presented the data for the two samples separately, but we have used the combined sample for our final estimation of the SMRs.

The observed trend may merely reflect random variation, given the small number of subsequent trisomies. Another possibility is that the disparities relate to different methods of ascertainment. In Sainte-Justine, the reason for testing was recorded before amniocentesis. However, a trisomic prenatal diagnosis could have triggered post hoc disclosure and recording of a previous trisomy. Differential disclosure would inflate the recurrence risk. In the Genzyme sample, data derive from linked laboratory records for which the information on a previous trisomy does not depend on the woman's report. A second possible source of difference between the samples is the nature of the index trisomies, which included live births in the Sainte-Justine but not in the Genzyme sample.

Although recurrence risks are generally higher in the Sainte-Justine sample, the Genzyme sample alone provides estimates of the SMRs of 1.7 for homotrisomy and 1.9 for heterotrisomy after trisomy 21. The statistically significant increase in risk (SMR = 1.8) for a viable trisomy following a nonviable trisomy in a spontaneous abortion derives only from the Genzyme sample.

Discussion

Homotrisomy

Our North American data from prenatal diagnoses show a significant increase in risk for trisomy 21 after a previous trisomy 21; the increase is greater for women with their first trisomy at age <30 years. These findings are, for the most part, compatible with those from one other large study, based on European amniocentesis data (Stene et al. 1984; Warburton et al. 1987).

Since our results for recurrence of trisomy 21 do not differ significantly from those from the European data, we have combined the two data sets in table 9 to provide the best estimates of risk. The highest SMR (8.2) is found for women with both their index trisomy 21 and their prenatal diagnosis at age <30 years. The increased risk is lower (SMR = 2.2) when the index trisomy occurs at age <30 years but the prenatal diagnosis occurs at age ⩾30 years. For women with both the index and prenatal diagnosis at age ⩾30 years, the SMR is 1.6 (90% CI 1.1–4.1). An increase in the maternal age–related risk for older women was not seen in the European data alone.

Although the smaller sample size limits conclusions, the data suggest a similarly increased risk for repeating viable trisomies other than 21. In our sample, the SMR for homotrisomy is 2.5 (90% CI 0.7–8.0) when trisomies 13 and 18 and the sex chromosome trisomies are combined. The European sample provided no data on this issue.

Heterotrisomy

Our data indicate an increased risk for recurrence of a different trisomy subsequent to a trisomic pregnancy. The SMR for heterotrisomy is 2.3 (90% CI 1.5–3.8) after an index trisomy 21 and is 1.6 (90% CI 1.1–2.4) when all types of index viable trisomies are combined. In addition, in the Genzyme sample, we could also examine prenatal diagnoses following a spontaneous abortion with a nonviable trisomy other than 13, 18, or 21. In this case, the SMR for a subsequent viable trisomy at prenatal diagnosis is 1.8 (90% CI 1.1–3.0; $P < .04$). The similarity of the SMRs after a previous viable trisomy and after a previous trisomic spontaneous abortion suggests that the increased risk relates to trisomies in general. Although the data raise the possibility that trisomy 16 is an exception, the sample size is not sufficient to allow this conclusion.

The European study provides data on heterotrisomy risk only after an index pregnancy with trisomy 21. In table 10, we combine the two data sets for the best estimate of the SMR. For women with an index trisomy 21 at age <30 years, the SMR for a different viable trisomy is 2.4 (90% CI 1.4–4.1). For women aged ⩾30 years at the index trisomy 21, the SMR in the combined data is 1.7 (90% CI 1.1–2.7). The risks do not differ significantly for the younger and older women.

Finally, the data do not indicate any increase in trisomy risk after a pregnancy with monosomy X or triploidy (SMR = 1.0; 90% CI 0.3–3.9; $P = .60$).

Implications for Theories Concerning Origins of Trisomy

The higher recurrence risk for trisomy 21 among younger mothers can be explained if gonadal trisomy mosaicism accounts for a larger proportion of recurrences in women whose maternal age–related risk is low. Existing data suggest this is so. Combining results of the studies of Pangalos et al. (1992) and James et al. (1998), parental mosaicism was demonstrable in six of nine sibships with multiple cases of trisomy 21 born to mothers aged <35 years and in only one of eight such sibships when the mother was aged >35 years. The existence of gonadal mosaicism also predicts a higher recurrence risk for homotrisomy than for heterotrisomy. Although the SMRs are not significantly different (2.4 for homotrisomy and 1.7 for heterotrisomy), the results are consistent with this prediction.

The significantly increased risk for heterotrisomy indicates that the risk of meiotic nondisjunction at a given maternal age varies among women, with some at a

Table 8

Recurrence of a Different Viable Trisomy after Index Trisomy 21, for Women Classified by Age at Index Trisomy

Maternal Age and Sample	No. of Prenatal Diagnoses	No. Expected with Other Viable Trisomy	No. Observed with Other Viable Trisomy	SMR[a]	90% CI	P[b]
Index trisomy 21 at age <30 years:						
Genzyme	103	.137	0	0	.0–21.8	1.0
Sainte-Justine	482	.651	2	3.1	.8–9.9	.139
Total prenatal diagnoses	585	.788	2	2.5	.7–8.2	.187
Index trisomy 21 at age ⩾30 years:						
Genzyme	608	3.534	7	2.0	1.0–3.7	.068
Sainte-Justine	192	.797	3	3.8	1.4–10.0	.047
Total prenatal diagnoses	800	4.331	10	2.3	1.4–3.9	.013

[a] Observed/expected.
[b] One-tailed exact P value.

higher risk for nondisjunction in general. This conclusion is compatible with most hypotheses concerning the mechanism of nondisjunction and the maternal-age association, including variation in biological aging of the ovary (Kline et al. 2000; Beever et al. 2003), genetic variation in rates of recombination or genes involved in oocyte maintenance or division (Zwick et al. 1999; Brown et al. 2000), and environmental exposures (Hunt et al. 2003),

Implications for Genetic Counseling

The expected rate of trisomy recurrence for a given woman should be calculated as the SMR multiplied by the age-related risk. The overall risk for recurrence of a viable trisomy includes both the risk of homotrisomy and the risk of heterotrisomy. In table 11, we summarize the SMRs for selected characteristics at the index pregnancy and at age of prenatal diagnosis. We include the actual rate of trisomy at prenatal diagnosis (per 1,000) observed in our data, to indicate the approximate magnitude of the risks involved. However, the actual rate of trisomy observed in any sample will depend on the maternal-age distribution and the gestational age of the pregnancies (i.e., whether amniocentesis, chorionic villus sampling, or live birth).

Two findings in our study indicate different risks for

Table 9

Comparison of European and North American Data: Recurrence of Trisomy 21

Category	North American Data (2003)	European Data (1987)	Combined Data
Index trisomy 21 at age <30 years, PND at age <30 years:			
No. of PND[a]	422	1,661	2,083
No. of expected trisomy 21	.48	1.6	2.08
No. of observed trisomy 21	4	13	17
SMR[b]	8.2	8.1	8.2
90% CI	3.6–18.8	5.0–12.8	5.4–12.3
Index trisomy 21 at age <30 years, PND at age ⩾30 years:			
No. of PND[a]	163	888	1051
No. of expected trisomy 21	.39	2.4	2.79
No. of observed trisomy 21	0	6	6
SMR[b]	.0	2.5	2.2
90% CI	0–7.7	1.2–5.0	1.1–4.3
Total with index trisomy 21 at maternal age <30 years:			
No. of PND[a]	585	2,549	3,134
No. of expected trisomy 21	.87	4.0	4.87
No. of observed trisomy 21	4	19	23
SMR[b]	4.6	4.8	4.7
90% CI	2.0–10.4	3.3–7.0	3.3–6.7
Index trisomy 21 at maternal age ⩾30 years:			
No. of PND[a]	800	922	1,722
No. of expected trisomy 21	7.64	6.7	14.34
No. of observed trisomy 21	16	7	23
SMR[b]	2.1	1.0	1.6
90% CI	1.4–3.2	.5–2.0	1.1–4.1

[a] PND = prenatal diagnosis.
[b] Observed/expected.

Table 10

Comparison of European and North American Data: Recurrence of Other Trisomies after Trisomy 21

Category	North American Data (2003)	European Data (1987)	Combined Data
<30 years:			
No. of PND[a]	585	2,549	3,184
No. of expected other trisomies	.79	3.4	4.19
No. of observed other trisomies	2	8	10
SMR[b]	2.5	2.4	2.4
90% CI	.7–8.2	1.3–4.3	1.4–4.1
⩾30 years:			
No. of PND[a]	800	922	1,722
No. of expected other trisomies	4.33	3.7	8.03
No. of observed other trisomies	10	4	14
SMR[b]	2.3	1.1	1.7
90% CI	1.4–3.9	.5–2.4	1.1–2.7
All maternal ages combined:			
No. of PND[a]	1,385	3,437	4,906
No. of expected other trisomies	5.12	7.1	12.22
No. of observed other trisomies	12	12	24
SMR[b]	2.3	1.7	2.0
90% CI	1.5–3.8	1.1–2.8	1.4–2.8

[a] PND = prenatal diagnosis.
[b] Observed/expected.

trisomy recurrence from those commonly used in genetic counseling. First, we conclude that, after a previous pregnancy with trisomy 21, the risk of a subsequent trisomy 21 is greater than the age-related risk for women whose first trisomy occurred at age ⩾30 years. In practice, this new information is likely to have few implications. Women aged ⩾35 years are offered prenatal diagnosis regardless of history. A previous trisomy 21 is likely to cause anxiety sufficient to lead younger women to seek prenatal diagnosis. However, a higher risk estimate might lead a woman to choose first-trimester screening and/or chorionic villus sampling rather than amniocentesis.

Second, our data suggest that there is a 1.6- to 1.8-fold increase in risk for a different viable trisomy, both after a previous trisomy 13, 18, or 21 and after a pre-

Table 11

Estimated Risks for Recurrence of Trisomy at Prenatal Diagnosis

Index Trisomy Type and Maternal Age	Risk of Recurrence for	
	Same Trisomy	Other Viable Trisomy
Trisomy 21 at <30 years, PND[a] at <30 years:[b]		
Multiple of age-related risk (SMR)	8.2	
Rate/1,000[c]	8	
Trisomy 21 at <30 years, PND[a] at >30 years:[b]		
Multiple of age-related risk (SMR)	2.2	
Rate /1,000[c]	6	
All, trisomy 21 at <30 years:[b]		
Multiple of age-related risk (SMR)	4.7	2.4
Rate/1,000[c]	7	3
Trisomy 21 at >30 years:[b]		
Multiple of age-related risk (SMR)	1.6	1.7
Rate/1,000, PND[a] at maternal age 30–34 years:[c]	5	8[d]
Rate/1,000, PND[a] at maternal age 35–39 years:[c]	18	
Rate/1,000, PND[a] at maternal age ⩾40 years:[c]	42	
Trisomies 13, 18, XXX, and XXY		
Multiple of age-related risk (SMR)	2.5	1.6
Rate/1,000[c]	3	9
Nonviable trisomy in spontaneous abortion:		
Multiple of age-related risk (SMR)		1.8
Rate/1,000[c]		6

[a] PND = prenatal diagnosis.
[b] Based on tables 9 and 10.
[c] Based on observed numbers in tables 7–10.
[d] Ages combined.

vious nonviable trisomy detected in a spontaneous abortion. This inference differs from our interpretation of previous data on heterotrisomy recurrence, derived from women with two karyotyped spontaneous abortions (Warburton et al. 1987). The increased risk may provide an indication for first-trimester screening or prenatal diagnosis among women aged <35 years known to have had a trisomic spontaneous abortion.

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