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Increased Low-Level Chromosome 21 Mosaicism in Older Individuals With Down Syndrome

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During a study of the familial aggregation of Down syndrome (DS) and Alzheimer disease (AD), we observed an increase in mosaicism for disomy 21 in older individuals with DS. In a total of 213 DS subjects who were studied cytogenetically, only 1 of 121 (0.8%) under age 45 exhibited mosaicism, while 14 of 92 (15.2%) who were age 45 or older had mosaicism. Mosaicism in this report connotes "low-level" mosaicism, where all 15 individuals exhibited a modal chromosome number of 47 (i.e., trisomy 21), and at least two cells lacked one of the three chromosomes 21. The occurrence of aneuploidy for chromosomes 15, 17, and X increased with age, and an inverse correlation between chromosome loss and size was also observed. Because older individuals had not been karyotyped at birth, it was not possible to determine whether our observations were due to either increased survival of mosaic individuals or accumulation of disomy 21 cells via increased chromosome loss with aging of the trisomy 21 individual. Using a modeling approach involving life table methods, we obtained results that suggested acquired mosaicism as the predominant mechanism to explain our findings. These results support the hypothesis that as individuals with DS age, there is an increased loss of chromosome 21. Am. J. Med. Genet. 68:147–151, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: Down syndrome; trisomy 21; mosaicism; low-level mosaicism; disomy 21; aging; Alzheimer disease

INTRODUCTION

The loss of a chromosome 21 in older individuals with Down syndrome (DS) was reported recently by Percy et al. [1993]. In a study of 154 DS individuals, they observed that low-level mosaicism for disomy 21 in individuals over age 46 was more than twice as frequent as in individuals 16–45 years old, and over seven times as frequent as in individuals 0–15 years old. In a report by Lai and Williams [1989] on Alzheimer disease (AD) in DS, we observed that older individuals exhibited an apparent increase in mosaicism for chromosome 21. Among 33 individuals age 49–69 years, 8 (24.2%) were reported to be mosaic in contrast to the 1–3% incidence of mosaicism commonly reported among liveborn individuals with DS [Jorde et al., 1995].

During a collaborative study on familial aggregation of DS and AD [Schupf et al., 1994], we observed a striking increase in mosaicism in older individuals with DS. Individuals with DS who were age 50 years or older were nearly 10 times as likely to be mosaic as those under age 50 years [Jenkins et al., 1994]. This prompted us to review our experience with 213 cases of DS ranging in age from 1 day to 72 years. Our findings support the hypothesis that as individuals with DS age, there is an increased loss of chromosome 21.

SUBJECTS AND METHODS

Subjects

The subjects were 213 persons with DS (113 males and 100 females, ranging in age from 1 day to 72 years). Fifty-seven subjects were ascertained through our population-based study on familial aggregation of DS and AD [Schupf et al., 1994], 132 through the George A. Jervis Clinic of the New York State Institute for Basic Research in Developmental Disabilities where they had been referred for cytogenetic confirmation of trisomy 21, and 24 through a study on aging in individuals with DS and mild/moderate mental retardation [De-

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TABLE I. Demographic Characteristics of Subjects*

Age in years	Schupf et al. [1994]	Jervis Clinic	Devenny et al. [1996]	Total males	Total females	Total
0–44 (% males)	8 (37.5)	100 (58.0)	13 (61.5)	69 (57.0)	52	121
45–54 (% males)	28 (50.0)	23 (47.8)	7 (42.9)	28 (48.3)	30	58
55–64 (% males)	18 (44.4)	8 (62.5)	4 (0)	13 (43.3)	17	30
65–72 (% males)	3 (66.7)	1 (100)	0	3 (75.0)	1	4
Total (% males)	57 (50.9)	132 (56.8)	24 (45.8)	113 (53.1)	100	213

*Subjects grouped as to origin of ascertainment, i.e., 57 specimens from Schupf et al. [1994]; 132 specimen referrals from the Jervis Clinic; and 24 specimens via Devenny et al. [1996] (all results regarding chromosome 21 loss unpublished elsewhere, except partially in abstract form [Jenkins et al., 1994]).

venny et al., 1996]. Demographic characteristics of the study participants are shown in Table I.

Cytogenetic and Statistical Analyses

Trypsin-Giemsa-banded chromosome preparations from short-term phytohemagglutinin (PHA)-stimulated whole-blood cultures were utilized in this study. Chromosome loss or gain was noted for each cell examined, as well as any chromosomal abnormalities such as deletions or translocations. For most individuals, 20–30 cells were analyzed (x = 25.87; SD, 7.82). At a 95% confidence interval (CI), 10–14% mosaicism was excluded [Hsu, 1992]. When two or more cells with disomy 21 were observed, the analysis was increased to 100 cells. Mosaicism in this study is defined as the consistent loss or gain of a chromosome in two or more cells from a modal chromosome number of 47 due to trisomy 21. Individuals were classified as having low-level mosaicism for trisomy 21 when the predominant cell line exhibited 47 chromosomes and at least two cells had lost one chromosome 21 (i.e., was disomic for chromosome 21), in order to avoid artifacts due to random loss. Persons whose predominant cell line exhibited 46 chromosomes were excluded from our analysis, but information on them is included in the results. Mantel-Haenszel odds ratios (OR) and chi-square tests were used to compare frequency of mosaicism among individuals with DS at different ages [Rothman, 1986]. Life table methods were utilized in a modeling approach to estimate the proportion of mosaic individuals expected at age 70 [Colton, 1974; Kleinbaum et al., 1982].

RESULTS

Cytogenetic study of 213 individuals involved analyses of 9,163 cells. Table II demonstrates the age-related increase in the prevalence of disomy 21 among individuals with DS. Only 1 of 121 individuals with DS under age 45 exhibited mosaicism for trisomy 21 (0.8%), while 14 of 92 (15.2%) individuals with DS who were age 45 years or older exhibited mosaicism. Persons with DS who were age 45 years or older were approximately 20 times more likely to be classified as mosaic than those under 45 (OR = 21.9; 95% CI: 2.82, 169.9; $\chi^2 = 14.68$; $P < .001$). The single case of mosaicism in the younger group occurred in an individual who was age 33 years. In those individuals with mosaicism for disomy 21 (with a modal chromosome number of 47), the percentage of disomy 21 as well as age of individuals at time of study are given in Table III. In most persons, the degree of mosaicism was low. The percentage of cells with 46 chromosomes or disomy 21 ranged from 2–30% (x = 7.67; SD, 7.58).

Two individuals with DS were also observed whose predominant cell line in vitro had 46 chromosomes. In contrast to adults showing a predominant cell line of 47 chromosomes, the ages of these 2 persons were 4 and 22 years, with 6 of 100 and 7 of 50 cells having exhibited trisomy 21, respectively. As mentioned in Subjects and Methods, the data from these 2 individuals were not included in the present analysis, because the modal chromosome number was 46.

The age-related increase in the prevalence of mosaicism is shown in Table IV. There was a significant increase in prevalence of mosaicism with increasing age ($\chi^2_{trend} = 17.5$; $P < .001$). We observed mosaicism in 25% of individuals over age 60 years, compared to 0.8% in those under age 45 years, and they were 40 times more likely to be mosaic.

Since the older individuals were not karyotyped at birth, it was not possible to determine whether the observed prevalence was due to increased survival of mosaic individuals or was acquired through accumulation of chromosome loss. We used a modeling approach involving life table methods to estimate the proportion of mosaic individuals that would be expected at age 70 if the increased proportion were primarily due to increased survival. We assumed a 1% prevalence of mosaic DS at birth [Jorde et al., 1995], and assigned general population age-specific death rates to mosaic individuals to model the hypothesized improved survival of mosaic individuals. For the remaining 99% of individuals assumed to be trisomic at birth, we employed age-specific death rates based on the life expectancy of recent cohorts [Dupont et al., 1986].

Based on these assumptions, our analysis indicated that the expected proportion of mosaic individuals at age 70 would be 5%. Under a more conservative assumption of 3% birth prevalence of mosaic DS, the

TABLE II. Distribution of Mosaicism in DS Individuals Younger and Older Than 45 Years*

Years	<45	≥45	Total
Mosaic	1	14	15
+21	120	78	198
Total	121	92	213

*Odds ratio = 21.54 (2.78, 167.1); $\chi^2 = 14.41$; $P < .001$.

TABLE III. Level of Mosaicism for 15 Individuals With Down Syndrome*

Case	% Disomy 21	Total cells	Age (sex)
1	30	50	33 (M)
2	18	50	46 (M)
	4	100	52
3	7	100	48 (M)
4	4	100	48 (F)
5	6	100	49 (F)
6	4	100	52 (F)
7	4	100	54 (M)
8	7	100	54 (M)
9	14	100	57 (M)
	2	50	64
10	4	100	57 (F)
11	2	100	58 (F)
12	5	100	62 (F)
13	2.5	81	62 (F)
14	5	100	63 (M)
15	3	100	72 (F)

*Cases 2 and 9 were studied at two different times.

expected proportion of mosaic individuals at age 70 was 9%. These estimated proportions were approximately 1/3 to 1/2 of our empirical result, suggesting that acquired mosaicism was the predominant mechanism for our findings. However, it should be noted that in two instances of individuals with repeated tests (Table III, cases 2 and 9), we observed decreases in the level of mosaicism when tested several years apart.

Monosomies for chromosomes 13 (66M), 17 (56F), 18 (1F, 59F), 19 (57M), 20 (52F), and X (45F) were observed in two cells from cultures of 7 individuals. Only one of the 5 female individuals was less than 45 years. This 1-year-old girl (1F) exhibited two cells with monosomy 18, as did a 59-year-old woman (59F). Similarly, a 66-year-old man (66M) with Down syndrome exhibited two cells that lacked a chromosome 13. These 7 individuals had a total of 14 cells that lacked a chromosome. Finally, the first 20 cells of each subject were analyzed for chromosome loss or gain. In a total of 4,260 cells, 112 from 83 individuals exhibited chromosome loss or gain, including chromosome 21. This is shown in Table V. A few structural variations were also noted. For chromosome 1, there were none lost in any of the cells analyzed across all age groups, while chromosome 21 was lost more often than any other chromosome in all age groups. Pearson's χ^2 analyses showed that there were statistically significantly increased losses of chromosomes 15 ($\chi^2 = 6.32$; $P = .0425$), 17 ($\chi^2 = 6.05$; $P = .048$), and 21 ($\chi^2 = 30.49$; $P = .016$) as a function of increasing age, with the greatest amount of aneuploidy observed for chromosome 21. Increased aneuploidy for X chromosome loss or gain was also age-related ($\chi^2 = 6.4$; $P < .05$). When chromosomes 21 and X were excluded, a χ^2 analysis for trend showed that there was an inverse relationship between chromosome loss and size ($\chi^2_{\text{overall}} = 15.93$; $P < .02$; $\chi^2_{\text{trend}} = 3.86$; $P < .05$).

DISCUSSION

Older individuals with DS appear to have increased mosaicism for loss of a chromosome 21, since only 1 in 121 individuals was mosaic at age 0–44 years, while 14 instances of mosaicism were observed among 92 individuals between age 45–72. The established inverse correlation between chromosome size and loss [Brown et al., 1983; Nowinsky et al., 1990] is insufficient to account for the loss of a chromosome 21 in 2–30% of cells among 15 individuals observed with "low-level" or "occult" mosaicism [Percy et al., 1993] among a total of 213 studied. In our study, whole-blood cultures from 7 people exhibited loss of a specific chromosome, other than chromosome 21, in two cells per individual.

In a longitudinal study, Jarvik et al. [1976] observed that only women exhibited significant increases of hypodiploidy as a function of increasing age. In contrast, we found that the largest number of disomic or hypomodal cells occurred in males (Table III). Among the 15 mosaic individuals studied, disomic cells accounted for 8.1% (68/831 cells) for males and 4.2% (25/600 cells) for females. It is possible that the number of individuals with low-level mosaicism is "underreported" in our study because our initial cytogenetic analysis involved only 20–30 cells.

Richard et al. [1993] reported that the rate of sex-chromosome loss only was correlated with increased age, in agreement with previous reports [Court Brown et al., 1966; Jarvik et al., 1976; Ford and Russel, 1985; Nowinski et al., 1990]. Since then, increased numbers of micronuclei, indicating whole or partial autosomal loss, have been observed in lymphocyte cultures from older individuals [Guttenbach et al., 1994; Richard et al., 1994]. Therefore, it appears that both sex-chromosome and autosomal loss occur with increasing age in the non-DS population. Nielsen [1968] compared three groups: individuals with senile dementia (group 1), age-matched controls (group 2), and younger controls (group 3). He found increased C-group chromosome loss in group 1 vs. group 2, while both groups 1 and 2 exhibited more losses than group 3. When non-C-group chromosomes were evaluated for hypodiploidy, there was no difference between the two older groups, while

TABLE IV. Distribution of Individuals With Trisomy 21 and Mosaicism According to Increasing Age*

Age (years)	Mosaic	+21	% mosaic	OR[a]	95% CI[b]
0–44	1	120	0.8	1.0	Reference
45–54	7	51	12.1	16.5	1.8, 153.0
55–64	6	24	20.0	30.0	3.1, 290.5
65–72	1	3	25.0	40.0	1.3, 1,198

*$\chi^2_{\text{overall}} = 18.96$, $P < .001$; $\chi^2_{\text{trend}} = 17.21$, $P < .001$.
[a]Odds ratio.
[b]Confidence interval.

TABLE V. Distribution of Chromosome Aneuploidy Among First 20 Cells Analyzed From 213 Individuals With Down Syndrome

Chromosome	Age <45 years (n = 121)	Age 45–54 years (n = 58)	Age ≥55 years (n = 34)	Total (n = 213) People (83)	Total (n = 213) Cells (112)
1	0	0	0	0	0
2	0	1 (−1)*	0	1	1
3	0	2 (−1)	0	2	2
4	0	1 (−1)	0	1	1
5	1 (−1)	0	0	1	1
6	2 (−1)	0	0	2	2
7	0	2 (−1)	0	2	2
8	0	1 (+1)*	1 (−1)	2	2
9	2 (−1)	1 (−1)	0	3	3
10	1 (−1)	1 (−1)	0	2	2
11	0	0	0	0	0
12	0	0	0	0	0
13	0	1 (−1)	1 (−1)	2	2
14	1 (−1)	(DEL[1])*	0	1	1
15[a]	1 (−1)	2 (−1) (DEL[2])	3 (−1)	6	6
16	2 (−1)	1 (−1)	0	3	3
17[a]	0	2 (−1)	2 (−1)	4	4
18	2 (−1)	1 (−1)	2 (±1) (DEL[3])	5	5
19	1 (−1)	2 (−1)	1 (−2)	4	5
20	2 (±1)	4 (−1)	3 (−1)	9	9
21[a]	6 (−1),* 1 (−7)*	2 (−1), 2 (−2), 3 (−3), 1 (−4)	5 (−1), 1 (−3), 1 (−5), 1 (−1), 1 (−4)	24	50
22	3 (−1)	2 (−1)	0	5	5
X[a] Y	0	2 (−X), 1 (+X), 1 (+XX, +X, +X)	0	4	6
Total people (% of n)	25 (20.7)	36 (62.1)	22 (64.7)	83	
Total Cells	31	49	32		112

*1 (−1) = one person who exhibited one cell that was monosomic for chromosome 2 in the 45–54 age group; 1 (+1) = one person with one cell with trisomy 8; 6 (−1) = six people who exhibited one cell that was disomic for chromosome 21; 1 (−7) = one person who had seven cells that were disomic for chromosome 21. DEL[1], a 50-year-old male with DS exhibited one cell with a deletion in the short arm of a chromosome 14 in 1 of 20 cells. When additional cells (40 total) were analyzed, two others also exhibited deletion del(14)(p11.2). DEL[2], a 45-year-old female who exhibited one cell in the first 20 examined with a long-arm terminal deletion in a chromosome 15-del(15)(q15), as well as an unidentifiable marker or acentric chromosome described as 48,XX,del(15)(q15),+21,+?mar. DEL[3], a 55-year-old female with a deletion in one cell on the short arm of chromosome 18. This deletion, del(18)(p11.2), was not observed again in a total of 32 cells studied.

[a]Chromosomes 15, 17, and 21 have exhibited statistically significant chromosome loss with increasing age (P = .0425, .048, and .016 respectively); individuals exhibited X chromosome aneuploidy with increasing age ($P < .05$); also, when chromosome X and chromosome 21 were excluded from analysis, the prevalence of chromosome loss increased as the chromosome size decreased ($P < .05$).

both exhibited more chromosome loss than the younger group.

Although our study was primarily concerned with chromosome 21 loss, we did observe 4 individuals ranging from age 45–53 years, with one or more cells that exhibited X chromosome aneuploidy (Table V), thus indicating age-associated X chromosome aneuploidy ($\chi^2 = 6.40$; $P < .05$). As shown in Table V, statistically significant trends were observed for age-associated losses of chromosomes 15, 17, and 21. A similar trend was suggested for chromosome 20, but it just failed to reach statistical significance. Therefore, for individuals with Down syndrome, age-associated increased losses of X chromosomes and specific autosomes have been observed in this study. Also, it is likely some chromosome losses, including some of the low-level chromosome 21 mosaics, were random and/or related to decreasing size. Finally, it can be seen from Table V that the percentage of individuals who exhibited aneuploidy above age 45 years was three times the percentage of those below age 45 years.

Two of the 15 individuals in our study had a reduced level of mosaicism for disomy 21 when cultured several years later. It is suggested that these 2 individuals may have been mosaic since birth and were losing the line with 46 chromosomes. If the modal chromosome number had been 46 since birth, then it is possible that increased numbers of "normal" cells would have been observed over time [Gravholt et al., 1991].

The clinical significance of this age-related increase in low-level mosaicism is still unknown. Percy et al. [1993] suggested that uniparental disomy of an imprinted gene on chromosome 21 might be related to age-at-onset or other aspects of the development of AD in adults with DS. We did not find any relationship between mosaicism and clinical expression of AD among our sample of adults with DS ascertained in our study of familial aggregation of DS and AD [Schupf et al., 1994]. In the individuals reported here, 10 of 37 (27%) with free trisomy developed AD, while 3 of 10 (30%) with low-level mosaicism developed AD (OR = 1.2; 95% CI: 0.2, 6.4; $\chi^2 = 0.04$; $P = 0.83$). However, we did not relate risk of dementia to uniparental disomy, nor did

we relate it to the occurrence of dementia in the mothers of the mosaic individuals. Conversely, some investigators have suggested that mosaicism for chromosome 21 in the general population without DS may increase risk of AD [Rowe et al., 1989; Potter, 1991], while others have not confirmed this observation [Yao et al., 1995]. Such mosaicism is presumed to have existed undetected from birth [Rowe et al., 1989; Hardy et al., 1989], or to arise from the accumulation of chromosome 21 trisomy cells by somatic nondisjunction or anaphase lag, during the individual's lifetime [Potter, 1991]. Future studies may determine whether there is any relationship between: 1) chromosome loss and uniparental disomy and a phenotypic effect of these disomic cells relative to parental imprinting [Percy et al., 1993; Henderson et al., 1994]; and 2) the occurrence of mosaicism and maternal age at the birth of a child with DS [Schupf et al., 1994]. Finally, comparative genomic hybridization studies may also reveal cryptic changes in parts of the karyotype of these individuals [Kallioniemi et al., 1992; van Ommen et al., 1995], including telomeric shortening [Vaziri et al., 1993; Flint et al., 1995], that would help to explain our observations of low-level mosaicism.

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