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Analysis of Chromosome Breakage in the Prader-Labhart-Willi Syndrome

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Abstract

Analysis of chromosome breakage with mitomycin C (MMC) and folate-deficient culture conditions was undertaken on 18 Prader-Labhart-Willi syndrome (PLWS) patients (10 with 15q12 deletion [5 females, 5 males; $\bar{x}$ age = 17.9 yr, range of 0.3 to 40 yr] and 8 without deletion [2 females, 6 males; $\bar{x}$ age = 18.6 yr, range of 7 to 26 yr]), 21 PLWS parents with an average age of 39.2 yr and a range of 25 to 70 yr (12 fathers [8 fathers of PLWS children with the 15q12 deletion and 4 fathers of PLWS children with normal chromosomes] and 9 mothers [4 mothers of PLWS children with the 15q12 deletion and 5 mothers of PLWS children with normal chromosomes]), and age-matched control individuals. There was no difference between PLWS patients and control individuals in the number of chromosome and chromatid aberrations in cells grown at 48 and/or 96 hr in either 20 ng/ml or 50 ng/ml of MMC or between the PLWS parents and control individuals in cells grown in 50 ng/ml MMC for 96 hr, although a small increase ($P < 0.05$) in chromosome breakage was found in cells from the total PLWS parental group compared with control individuals exposed for 48 hr in 50 ng/ml MMC. There was also no significant difference in chromosome fragile site frequency in cells grown in folate-deficient culture conditions in PLWS patients, their parents, or controls. The average sister chromatid exchange (SCE) frequencies observed in PLWS subgroups (deletion vs. nondeletion), their parents or control individuals were not significantly different. No clustering of chromosome/chromatid breaks or SCEs identified in the proximal long arm was found when compared with the middle or distal long arm regions of the D group chromosomes.

Keywords

sister chromatid exchange; mitomycin C; folate deficient culture conditions

INTRODUCTION

Prader-Labhart-Willi syndrome (PLWS) is usually characterized by infantile hypotonia, early childhood obesity, mental deficiency, small hands and feet, hypogonadism and a characteristic combination of minor anomalies, and facial appearance. The cause of this syndrome is not clearly understood, although a chromosome deletion (15q12) has been

found in 50% to 70% of PLWS individuals [Ledbetter et al., 1982; Mattei et al., 1984; Butler et al., 1986].

Cytogenetic studies to explain the cause of the chromosome deletion are limited. However, Hummel et al. [1986] studied sister chromatid exchanges (SCEs) in 7 PLWS patients with the 15q12 deletion and 3 patients with normal chromosomes in order to determine if chromosome instability exists in PLWS and found an increased SCE frequency in cells from deletion PLWS patients when compared with control individuals. They suggested that this increase may lead to the chromosome deletion. SCE frequency was not increased in 16 PLWS individuals (8 with 15q12 deletion and 8 nondeletion) or in 18 PLWS parents when compared with age-matched control individuals reported by Butler and Jenkins [1987]. Wenger and Rauch [1988] found a significantly higher number of SCEs in the proximal long arm of chromosome 15 in 9 nondeletion PLWS individuals compared with 5 deletion PLWS patients and 7 control subjects. Their data suggested instability in the 15q11–13 region in PLWS subjects without a visible deletion and that the unstable region was missing in the PLWS patients with apparent deletions. High-resolution parental chromosomes were also studied in 15 PLWS families and found to be normal, although the parental origin of the chromosome 15 deletion showed that the chromosome donated by the father led to the deletion in the child [Butler et al., 1986]. Recently, a significantly higher frequency ($P < 0.001$; two-tailed chi-square test) of 652 PLWS fathers (21%) when compared with 334 fathers (12%) of children with Down or fra (X) syndromes were employed in hydrocarbon-related occupations at the time of conception [Strakowski and Butler, 1987]. Therefore, we report a chromosome breakage study in PLWS patients and in their parents, particularly fathers who were previously identified to have donated the chromosome with the deletion, to determine if fragile sites and/or chromosome instability detectable by stressing the chromosomes with mitomycin C or folate-deficient culture conditions play a role in the development of the chromosome 15 deletion. Particular attention was given to the location of chromosome and chromatid breaks in the proximal, middle, and distal one-third segments of the long arm of the D group chromosomes.

MATERIALS AND METHODS

Our study group consisted of 1) 18 patients with PLWS who had a previous high resolution chromosome analysis (10 with 15q12 deletion [5 females, 5 males; $\bar{x}$ age = 17.9 yr with age range of 0.3 to 40 yr]) and 8 without deletion [2 females, 6 males; $\bar{x}$ age = 18.6 yr with age range of 7 to 26 yr]); 2) 21 PLWS parents with an average age of 39.2 yr and age range of 25 to 70 yr (12 fathers [8 fathers of the PLWS children with the 15q12 deletion and 4 fathers of PLWS children with normal chromosomes] and 9 mothers [4 mothers of PLWS children with the 15q12 deletion and 5 mothers of PLWS children with normal chromosomes]); and 3) control individuals matched for age. The 8 fathers of the PLWS children with the 15q12 deletion were previously identified to have normal chromosomes but had donated the chromosome 15 with the deletion in the child.

None of the individuals had a history of chemotherapy or radiation exposure and each denied recent illnesses. Chi-square and t-tests were used throughout the study for statistical analysis.

Mitomycin C (MMC)

Blood samples from 18 PLWS patients, 21 PLWS parents, and age-matched (<5 yr) control individuals were grown in RPMI 1640 medium with 50 ng/ml MMC for 48 and 96 hr at 37°C following the protocol used in previous studies [Butler et al., 1987a,b]. Thirty minutes before harvest, colcemid (0.2 µg/ml final concentration) was added. Conventional air-dried slides were prepared and stained with Giemsa. Approximately 100 metaphase cells were scored at 96 hr and 50 cells from the 48 hr cultures. Only diploid cells were analyzed for chromosome breakage, paying particular attention to the location of the chromosome break in the proximal, middle, or distal one-third segments of the long arm of the D group chromosomes. The following aberrations were observed: 1) chromatid type, including chromatid breaks, gaps, and exchange figures (e.g., triradials and quadriradials), and 2) chromosome type (dicentrics, rings, double minutes, fragments, and markers). Cells with tetraploidy, micronuclei, and endoreduplication were also recorded.

Folate-Deficient Culture Conditions

Blood samples from 12 PLWS patients (6 deletion and 6 nondeletion), and 16 PLWS parents and age-matched control individuals were cultured for 96 hr at 37°C in folate-deficient medium 199. Colcemid (0.15 µg/ml) was added 30–45 min before harvesting. Conventional harvest methods were used and air-dried slides were stained with Giemsa. All fragile sites were judged as chromosome or chromatid aberrations and recorded in 100 metaphases, paying particular attention to the location of fragile sites on the proximal, middle, or distal one-third segments of the long arm of the D group chromosomes.

RESULTS

Mitomycin C (MMC)

Table I summarizes the results of the MMC study from 16 individuals with PLWS (9 deletion and 7 nondeletion) and 16 age-matched control subjects grown in 50 ng/ml MMC for 96 hr. The average frequency and standard deviation for total chromosome and chromatid aberrations per 100 cells was 31.2 ± 12.2 for the control individuals and 33.2 ± 18.8 for the PLWS patients. The average frequency and standard deviation for chromatid aberrations per 100 cells was 21.6 ± 9.8 for the control subjects and 24.4 ± 14.0 for the PLWS patients. The average frequency and standard deviation for total chromosome and chromatid aberrations for the deletion and non-deletion PLWS patients were 26.6 ± 16.9 and 39.7 ± 15.1 , respectively, which were not significantly different ($P > 0.05$).

Table II summarizes the results of the MMC studies from 17 individuals with PLWS (8 deletion and 9 non-deletion) and 17 age-matched control subjects grown in 50 ng/ml MMC for 48 hr. The average frequency and standard deviation for total chromosome and chromatid aberrations per 50 cells was 16.0 ± 12.9 for the control individuals and 19.5 ± 19.7 for the PLWS patients. The average frequency and standard deviation for chromatid aberrations per 50 cells was 14.6 ± 12.3 for the control subjects and 16.7 ± 17.0 for the PLWS patients. The average frequency and standard deviation for total chromosome and chromatid aberrations per 50 cells for the 8 deletion and 9 nondeletion PLWS patients was 10.5 ± 4 and 28.0 ± 24.7 , respectively, which is not significantly different ($P > 0.05$). Therefore, there was no

significant difference in the number of aberrations observed after MMC exposure for either 96 or 48 hr between deletion and nondeletion PLWS patients or between the total PLWS group and control subjects.

Table III summarizes the results of the MMC studies from 13 parents of 10 PLWS patients (7 deletion and 3 nondeletion) and 13 age-matched control subjects grown in 50 ng/ml MMC for 96 hr. The average frequency and standard deviation for total chromosome and chromatid aberrations per 100 cells was 18.4 ± 15.7 for the control individuals and 31.5 ± 18.0 for the PLWS parents, which were not significantly different ($P > 0.05$). The average frequency and standard deviation for chromatid aberrations was 14.3 ± 13.2 for the control subjects and 22.8 ± 11.2 for the PLWS parents, which were also not significantly different ($P > 0.05$). There was no difference in the number of total chromosome and chromatid aberrations in PLWS parents, including 8 fathers previously identified to have donated the chromosome with the deletion in the child, or control subjects.

Table IV summarizes the results of the MMC studies from 20 parents of 13 PLWS patients (8 deletions and 5 nondeletions) and 18 control subjects grown in 50 ng/ml MMC for 48 hr. The average frequency and standard deviation of total chromosome and chromatid aberrations per 50 cells was 8.2 ± 5.7 for the control individuals and 17.0 ± 12.1 for the PLWS parents, and 6.9 ± 5.4 for chromatid aberrations for the control subjects and 14.0 ± 11.6 for the PLWS parents. There was a significant difference ($P < 0.05$) in the number of total chromosome and chromatid aberrations observed at 48 hr, but not 96 hr among the total parents of PLWS patients with and without the deletion when compared with control individuals. Cells from several PLWS patients, parents, and control individuals were also grown in 20 ng/ml MMC for 48 and 96 hr, but again, no significant difference was found ($P > 0.05$) in the number of aberrations. There was no over-representation of chromosome or chromatid breakage in the proximal one-third long arm segment of the D group chromosomes compared with the middle or distal one-third long arm segments of the D group chromosomes. Tables V and VI summarize chromosome breakage data including D group aberrations induced by MMC for 96 and 48 hr, respectively, for all subject groups.

Folate-Deficient Culture Conditions

Table VII summarizes the results of folate-deficient cultured lymphocyte studies in 12 PLWS patients (6 deletion and 6 nondeletion) and 12 age-matched control individuals. The average frequency and standard deviation for total chromosome and chromatid aberrations per 100 cells was 8.6 ± 6.6 for the control individuals and 14.0 ± 12.9 for the PLWS patients. Therefore, there was no significant difference in the number of aberrations among the total PLWS group, deletion or nondeletion patients, or control subjects. There was also no consistent fragile site identified on the D group chromosomes of the PLWS patients.

Table VIII summarizes the results of folate-deficient cultured lymphocyte studies on 16 parents of 11 PLWS patients (7 deletion and 4 nondeletion) and control subjects. The average frequency and standard deviation for total chromosome and chromatid aberrations per 100 cells was 5.6 ± 4.2 for the controls and 10.3 ± 6.2 for the PLWS parents. Therefore, there was no significant difference in the number of aberrations observed between the parents, particularly the 8 fathers who were previously identified to have donated the

chromosome with the deletion, or control subjects. No fragile site was identified on the D group chromosomes of the PLWS parents. Table IX summarizes chromosome breakage data from folate-deficient cultured lymphocytes including D group aberrations for all subject groups.

The average number of SCE data in PLWS patients, their parents, and control individuals have previously been reported [Butler and Jenkins, 1987] with no difference in the average SCE frequency in PLWS patients and their parents when compared with control individuals. Table X shows the SCE data from three published PLWS surveys. Our SCE data of the D group chromosomes are presented in Table XI for all subject groups, and no significant differences in the number of SCEs were identified in the proximal, middle, or distal long arm regions of the D group chromosomes in PLWS patients or their parents when compared with control individuals.

DISCUSSION

Our chromosome breakage analysis of 1) patients with PLWS with and without the deletion, 2) fathers who donated the chromosome 15 with the deletion in the PLWS child, 3) total parent group, and 4) age-matched control individuals did not show a significant difference in chromosome breakage or SCEs in PLWS patients or their parents when compared with control individuals, although increased breakage ($P < 0.05$) was observed in cells grown in 50 ng/ml MMC for 48 hr from PLWS parents. Also, there was no increased chromosome breakage or folate-sensitive fragile site expression recognized on the D group chromosomes at the site of the chromosome deletion in PLWS patients when compared with control subjects. From our cytogenetic study, the cause of PLWS does not alter chromosome structure or produce chromosome breakage that can be detected by stressing the chromosomes with either an alkylating agent (mitomycin C) at 20 or 50 ng/ml for short-term (48 hr) or long-term (96 hr) exposures or folate-deficient culture conditions. SCE and replicative indices of PLWS patients and their parents [Butler and Jenkins, 1987] also did not identify differences in chromosome structure, function, or cell kinetics.

In summary, our chromosome breakage study including SCE did not indicate consistent chromosome instability, particularly with the D group chromosomes. Therefore, the cause of the chromosome 15 deletion seen in 50 to 70% of PLWS patients does not appear to be due to chromosome changes that can be detected by the chromosome breakage analysis described in this cytogenetic report. DNA and mutagenicity studies are underway with PLWS patients and their parents, particularly the fathers previously identified to have donated the chromosome 15 with the deletion in the PLWS child, in order to gain a better understanding of the cause of the chromosome deletion and to analyze for DNA evidence of genetic instability.

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TABLE I

Chromosome Breakage in Cells Treated With 50 ng/ml Mitomycin C for 96 Hr From Prader-Labhart-Willi Syndrome Patients and Control Individuals

Subject group	Percentage of cells with chromatid and chromosome aberrations	Average number of chromatid aberrations per 100 cells	Average number of chromosome aberrations per 100 cells
PLWS (n = 16)	24.0	24.4	7.9
Control (n = 16)	23.9	21.6	9.4
t-test	0.04 *	0.74 *	-0.77 *

* Not significant (matched two-tailed t-test; $P > 0.05$).

TABLE II

Chromosome Breakage in Cells Treated With 50 ng/ml Mitomycin C for 48 Hr From Prader-Labhart-Willi Syndrome Patients and Control Individuals

Subject group	Percentage of cells with chromatid and chromosome aberrations	Average number of chromatid aberrations per 50 cells	Average number of chromosome aberrations per 50 cells
PLWS (n = 17)	25.4	16.7	2.8
Control (n = 17)	23.8	14.6	1.5
t-test	0.29 [*]	0.37 [*]	1.56 [*]

^{*} Not significant (matched two-tailed t-test; $P > 0.05$).

TABLE III

Chromosome Breakage in Cells Treated With 50 ng/ml Mitomycin C for 96 Hr From Prader-Labhart-Willi Syndrome Parents and Control Individuals

Subject group	Percentage of cells with chromatid chromosome aberrations	Average number of chromatid aberrations per 100 cells	Average number of chromosome aberrations per 100 cells
PLWS parents (n = 13)	23.8	22.8	8.6
Control (n = 13)	16.1	14.3	4.2
t-test	1.49 [*]	1.54 [*]	2.02 [*]

^{*} Not significant (matched two-tailed t-test; $P > 0.05$).

TABLE IV

Chromosome Breakage in Cells Treated With 50 ng/ml Mitomycin C for 48 Hr From Prader-Labhart-Willi Syndrome Parents and Control Individuals

Subject group	Percentage of cells with chromatid and chromosome aberrations	Average number of chromatid aberrations per 50 cells	Average number of chromosome aberrations per 50 cells
PLWS parents (n = 20)	23.5	14.0	3.0
Control (n = 18)	14.5	6.9	1.2
t-test	2.38 **	2.31 **	1.35 *

* Not significant (independent two-tailed t-test; $P > 0.05$).

** $P < 0.05$ (independent two-tailed t-test).

TABLE V

Chromosome Breakage Data in Cells Treated With 50 ng/ml Mitomycin C for 96 Hr

Subject group	Number	Average number of total aberrations per cell	Average number of D group aberrations per cell	$\frac{\text{D group aberrations}}{\text{Total aberrations}} \times 100$	D group aberrations ^a		
					Prox 1/3 (%)	Mid 1/3 (%)	Distal 1/3 (%)
PLWS (all)	16	0.34	0.022	8.8	12/34 (35)	9/34 (27)	13/34 (38)
Del (15q)	9	0.26	0.016	8.4	5/14 (36)	4/14 (29)	5/14 (36)
Nondeletion	7	0.44	0.029	9.1	7/20 (35)	5/20 (25)	8/20 (40)
Fathers (all)	9	0.24	0.022	11.0	5/16 (31)	7/16 (44)	4/16 (25)
Fathers [del (15q)]	7	0.23	0.017	9.4	3/12 (25)	5/12 (42)	4/12 (33)
Fathers (nondeletion)	2	0.25	0.038	22.2	2/4 (50)	2/4 (50)	0/4 (0)
Mothers	7	0.51	0.026	8.0	3/14 (21)	8/14 (57)	3/14 (21)
Control individuals	10	0.32	0.019	7.6	3/14 (21)	4/14 (29)	7/14 (50)

^aNo significant difference in aberrations were noted among the proximal, middle, or distal one-third regions of the long arm of D group chromosomes.

TABLE VI

Chromosome Breakage Data in Cells Treated With 50 ng/ml Mitomycin C for 48 Hr

Subject group	Number	Average number of total aberrations per cell	Average number of D group aberrations per cell	$\frac{\text{D group aberrations}}{\text{Total aberrations}} \times 100$	D group aberrations ^a			
					Prox 1/3 (%)	Mid 1/3 (%)	Distal 1/3 (%)	
PLWS (all)	18	0.34	0.033	10.6	7/31 (23)	9/31 (29)	15/31 (48)	
Del (15q)	10	0.22	0.018	8.5	1/7 (14)	4/7 (57)	2/7 (29)	
Nondeletion	8	0.50	0.052	11.5	6/24 (25)	5/24 (21)	13/24 (54)	
Fathers (all)	12	0.29	0.014	5.4	4/6 (67)	0/6 (0)	2/6 (33)	
Fathers [del (15q)]	8	0.26	0.002	2.0	1/1 (100)	0/1 (0)	0/1 (0)	
Fathers (nondeletion)	4	0.35	0.038	8.5	3/5 (60)	0/5 (0)	2/5 (40)	
Mothers	8	0.41	0.030	7.8	3/11 (27)	3/11 (27)	5/11 (45)	
Control individuals	8	0.26	0.010	4.4	2/4 (50)	1/4 (25)	1/4 (25)	

^aNo significant difference in aberrations were noted among the proximal, middle, or distal one-third regions of the long arm of the D group chromosomes.

TABLE VII

Chromosome Breakage in Cells Grown in Folate-Deficient Culture Conditions From Prader-Labhart-Willi Syndrome Patients and Control Individuals

Subject group	Percentage of cells with chromatid and chromosome aberrations	Average number of chromatid aberrations per 100 cells	Average number of chromosome aberrations per 100 cells
PLWS (n = 12)	11.8	11.4	1.6
Control (n = 12)	8.3	7.9	0.7
t-test	1.04 *	1.18 *	2.20 *

* Not significant (matched two-tailed t-test; $P > 0.05$).

TABLE VIII

Chromosome Breakage in Cells Grown in Folate-Deficient Culture Conditions From Prader-Labhart-Willi Syndrome Parents and Control Individuals

Subject group	Percentage of cells with chromatid and chromosome aberrations	Average number of chromatid aberrations per 100 cells	Average number of chromosome aberrations per 100 cells
PLWS parents (n = 16)	9.4	9.6	0.8
Control (n = 16)	5.8	5.2	0.4
t-test	1.58 *	2.10 *	0.84 *

* Not significant (matched two-tailed t-test; $P > 0.05$).

TABLE IX

Chromosome Breakage Data in Cells Grown in Folate-Deficient Culture Conditions

Subject group	Number	Average number of aberrations per cell	Average number of D group aberrations per cell	$\frac{\text{D group aberrations}}{\text{Total aberrations}} \times 100$	D group aberrations ^d			
					Prox $\frac{1}{3}$ (%)	Mid $\frac{1}{3}$ (%)	Distal $\frac{1}{3}$ (%)	
PLWS (all)	13	0.12	0.0060	5.6	1/8 (13)	5/8 (63)	2/8 (25)	
Del (15q)	7	0.17	0.0098	7.2	1/7 (14)	5/7 (71)	1/7 (14)	
Nondeletion	6	0.07	0.0016	2.7	0/1 (0)	0/1 (0)	1/1 (100)	
Fathers (all)	10	0.11	0.0032	3.1	0/3 (0)	2/3 (67)	1/3 (33)	
Fathers [del (15q)]	6	0.10	0.0020	1.9	0/1 (0)	0/1 (0)	1/1 (100)	
Fathers (nondeletion)	4	0.13	0.0050	4.4	0/2 (0)	2/2 (100)	0/2 (0)	
Mothers	8	0.11	0.0087	10.7	0/6 (0)	3/6 (50)	3/6 (50)	
Control individuals	9	0.08	0.0044	6.0	1/4 (25)	0/4 (0)	3/4 (75)	

No significant difference in aberrations were noted among the proximal, middle, or distal one-third regions of the long arm of the D group chromosomes.

TABLE X

Summary of Sister Chromatid Exchange (SCE) Data in Prader-Labhart-Willi Syndrome *

Subject group	Number	Mean number of SCEs
PLWS (all)	40	6.7
Del (15q)	20	7.5
Nondeletion	20	6.0
Controls for PLWS	33	7.0
Parents (all)	18	7.4
Fathers [del (15q)]	8	7.5
Controls for parents	18	7.9

* Data from three surveys [Hummel et al., 1986; Butler and Jenkins, 1987; Wenger and Rauch, 1988].

TABLE XI

Sister Chromatid Exchange (SCE) Data From Prader-Labhart-Willi Syndrome Patients, Their Parents, and Control Individuals

Subject group	Number	Average number of SCEs	Average number of D group SCEs per cell	D group SCEs ^a			
				Prox 1/3 (%)	Mid 1/3 (%)	Distal 1/3 (%)	
PLWS (all)	14	6.5	0.37	42/144 (29)	56/144 (39)	46/144 (32)	
Del (15q)	8	6.6	0.37	23/83 (28)	38/83 (46)	22/83 (27)	
Nondeletion	6	6.3	0.37	19/61 (31)	18/61 (30)	24/61 (39)	
Fathers (all)	7	7.3	0.34	16/63 (25)	28/63 (44)	19/63 (30)	
Fathers [del (15q)]	6	7.5	0.35	16/55 (29)	21/55 (38)	18/55 (33)	
Fathers (nondeletion)	1	5.9	0.27	0/8 (0)	7/8 (88)	1/8 (13)	
Mothers	5	6.9	0.35	15/47 (32)	16/47 (34)	16/47 (34)	
Control individuals	10	6.2	0.34	20/66 (30)	29/66 (44)	17/66 (26)	

^aNo significant difference in SCEs were noted among the proximal, middle, or distal one-third regions of the long arm of the D group chromosomes.