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No significant relationship between age and frequency of chromosome lesions in mentally retarded individuals with or without the fragile X syndrome

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Fragile sites on chromosomes are locations prone to breakage. An example is the Xq27.3 fragile site, which is observed in cells grown in folate-deficient culture medium and associated with one form of X-linked mental retardation (Sutherland 1979; Chudley and Hagerman 1987). Folate-deficient culture conditions have been shown to increase chromosome breakage compared with folate-replete culture conditions (Zhou et al. 1982; Steinbach et al. 1982), although increased chromosomal instability apparently was not found in cells of patients with fragile X syndrome compared with cells from control subjects (Vekemans et al. 1983; Branda et al. 1984; Butler et al. 1988). Cells grown in fluorodeoxyuridine (FUdR), an inhibitor of thimidylate synthetase, also show increased chromosome breakage (Sutherland and Hecht 1985). A decline with age in fragile X chromosome expression has been reported (Chudley et al. 1983) but not confirmed by others (Jacobs et al. 1980; Turner and Jacobs 1983). Additionally, a negative correlation was suggested between the expression of chromosome fragile sites and age in control individuals without the fragile X syndrome (Murata et al. 1988). Hence, I report our experience with chromosome breakage in cells grown for 96 h in folate-deficient medium 199 from 105 individuals and in cells grown in RPMI medium and FUdR (10^{-7} *M*) from 54 of these individuals to specifically address whether chromosome fragile site expression decreases with age or if generalized chromosome instability exists in mentally retarded individuals with or without the fragile X syndrome.

We analyzed 7690 lymphocytes (grown in medium 199) from 24 fragile X syndrome individuals (average age of 20.9 years with a range of 2 to 75.6 years), 44 mentally retarded individuals without the fragile X syndrome or other causes of mental retardation (average age of 30.5 years with a range of 7.8 to 74.7 years), and 37 control individuals with normal intelligence (average age of 31.9 years with a range of 0.1 to 71 years). For the 1993 lymphocytes analyzed from the 24 fragile X syndrome individuals, the average fragile X chromosome (Xq27.3) expression was 15.3% while the average percentage of cells with chromosome lesions (e.g., breaks, gaps) other than the Xq27.3 was 6.9%. The 2329 lymphocytes analyzed from the 44 mentally retarded individuals without the fragile X syndrome showed an average 5.4% of cells with chromosome lesions. The 3368 lymphocytes analyzed from the 37 control individuals with normal intelligence gave an average 6.8% cells with chromosome lesions. Although the number of individuals studied with FUdR was smaller than with medium 199 for both the fragile X syndrome and normal control groups but comparable to the figure for the mentally retarded individuals without the

fragile X syndrome, the average percentage of non-Xq27 chromosome lesions was increased in the FUdR-treated cells compared with medium 199. Table 1 shows the chromosome breakage data from cells grown in medium 199 and cells grown in RPMI medium with FUdR.

No significant difference in the average number of chromosome lesions from cells grown in medium 199 was found between fragile X syndrome and mentally retarded individuals without the fragile X syndrome (independent t test = 0.66; $P = 0.52$) or between fragile X syndrome and control individuals with normal intelligence (independent t test = 0.04; $P = 0.97$). Furthermore, no significant difference in the average number of chromosome lesions was found between mentally retarded individuals without fragile X syndrome and control individuals (independent t test = 1.32; $P = 0.19$). Therefore, comparison of our chromosome breakage data among the three groups did not support increased chromosome instability in fragile X syndrome or other mentally retarded individuals.

In cells grown in medium 199 for the fragile X syndrome individuals, a correlation *(r)* of −0.002 ($P = 0.99$) was found for the fragile X chromosome (Xq27.3) expression and age while a negative correlation ($r = -0.12$; $P = 0.56$) of chromosome breakage (excluding the Xq27.3 site) and age was found but neither correlation was significant. For the mentally retarded individuals without the fragile X syndrome, the correlation between chromosome breakage and age was not significant ($r = -0.07$; $P = 0.63$). For the control individuals with normal intelligence, the correlation between chromosome breakage and age was also not significant ($r = -0.26$; $P = 0.13$). Similarly, no significant correlations were found between percentage of cells with chromosome lesions (Xq27 or non-Xq27) and age for any of the three groups of individuals studied with FUdR.

In summary, our chromosome breakage data confirm the absence of increased chromosome instability in cells from mentally retarded individuals with or without the fragile X syndrome and the absence of a significant correlation with the expression of Xq27.3 fragile site or other chromosome lesions and age in cells grown in either medium 199 or RPMI medium with FUdR from fragile X syndrome, mentally retarded, or normal control individuals. Significantly more chromosome lesions were seen in cells grown in RPMI medium with FUdR compared with medium 199 for the three groups of individuals in this study.

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Table 1

Chromosome breakage data in mentally retarded patients with or without fragile X syndrome and control individuals

Group	Cells grown in medium 199			Cells grown in RPMI medium with FUdR (10^{-7} *M*)		
	Total no. of cells analyzed	Percentage of cells with non-Xq27 chromosome lesions average ± SD (range)	Percentage of cells with Xq27 chromosome lesions average ± SD (range)	Total no. of cells analyzed	Percentage of cells with non-Xq27 chromosome lesions average ± SD (range)	Percentage of cells with Xq27 chromosome lesions average ± SD (range)
Mentally retarded fragile X syndrome patients (*n* = 24)	1993	6.9 ± 11.0 (0–44)	15.3 ± 12.9 (1–46)	402[a]	13.4 ± 10.3[b] (0–36)	27.1 ± 19.0[a] (2–60)
Mentally retarded non-fragile X syndrome patients (*n* = 44)	2329	5.4 ± 4.3 (0–20)		1090[c]	22.3 ± 10.7[c] (3–44)	
Control individuals (*n* = 37)	3368	6.8 ± 5.6 (0–21)		403[b]	10.0 ± 3.5[b] (4–14)	

[a]Based on *n* = 8 subjects

[b]Based on *n* = 6 subjects

[c]Based on *n* = 40 subjects