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A Clinical and Cytogenetic Study of Institutionalized Mental Retardates

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ABSTRACT

One hundred and four out of 110 patients in a residential institution for mental retardates were examined clinically and cytogenetically. Both conventional and folate deficient media were employed in order to detect both conventional chromosomal abnormalities and rare fragile sites. Conventional abnormalities were detected in 18 cases (17%). Rare folate sensitive fragile site at 2q13 was detected in one female patient. The same chromosomal aberration was also detected in the patient's mother who had a normal phenotype. Spontaneous expression of the rare fragile site at 2q13 was also observed.

Key words: *Chromosome abnormality, Mental retardation, Fragile site*

Chromosomal abnormality has been considered one of the causes of mental retardation as well as congenital anomaly, growth retardation, reproductive failure, and so on. Many chromosomal surveys of mental retardates have been carried out mostly in a hospital or in an institution, and the cytogenetic aspect of the mental retardation has gradually become clear. With regard to the methodology, in early surveys[19,25,78,102,103,122-124], chromosomes were screened initially by non-banding techniques and then only in abnormal cases bandings were used to characterize the abnormalities. There is a possibility that some minor abnormalities which could have been detected by a banding technique, might have been overlooked by a non-banding technique. In later years, such surveys employed a banding technique in all cases for initial screening[1,39,54,69,84,89,106,112].

Recently, chromosomal fragile sites have drawn considerable attention. Fragile sites are heritable points at which gaps, breaks, and rearrangements nonrandomly occur[47]. These aberrations are induced under special culture conditions[125,126]. The rare folate sensitive fragile site, a class of fragile sites, shows a low prevalence in the population, and is revealed under a folate deficient medium of culture[17]. Among all fragile sites, rare folate sensitive fragile site at Xq27.3 (FRAXA) has been studied most intensively by many cytogenetists. It was established that FRAXA is associated with mental retardation[31,90]. Many cytogenetic surveys for FRAXA have been performed on mental retardates[3,4,18,38,56,63,64,76,84,89]. However, the phenotypic effects of other fragile sites remain to be elucidated. There are few cytogenetic surveys of mental retardates for autosomal rare folate sensitive fragile sites[63,65,76,127,128]. Sutherland[124,127] and Käkönen et al[63] reported cytogenetic surveys of mental retardates for both conventional chromosomal abnormalities and folate sensitive fragile sites. Such studies have not been reported in Japan.

In the present study, the patients were not selected by phenotype. Both conventional and folate deficient media were employed in order to detect both conventional chromosomal abnormalities and rare folate sensitive fragile sites. Lymphocytes cultured in a conventional medium were analysed after both banding and non-banding staining. The purpose of this study was to investigate the clinical and cytogenetic aspects of mental retardation and to elucidate the etiological significance of rare folate sensitive fragile sites for mental retardation.

MATERIALS AND METHODS

During the survey period, from October 1986 until September 1988, out of 110 patients in the Chugoku Geinan Gakuen, which was a residential institution for mental retardates, 104 patients were examined. The 104 patients were not selected by phenotype. Their ages were distributed from 9 to 49. The mean age was 23 years. Fifty five were males, and forty nine were females. As Table 1 shows, their retardation ranged from mild (IQ

Table 1. The degree of retardation

Degree	Number of cases
Mild (IQ 67—52)	6
Moderate (IQ 51—36)	29
Severe (IQ 35—20)	60
Profound (IQ < 20)	9
Total	104

Table 2. Cytogenetic and clinical findings

Case no.	Age	Sex	Karyotype	Fragile site (frequency)	Level of M.R.	Other clinical findings
1	31y.	F	46,XX	—	severe (IQ = 27)	short stature
2	30y.	F	46,XX	—	severe (IQ = 28)	epicanthus, short stature, brachydactyly at both of the little fingers
3	22y.	F	46,XX	—	moderate	epilepsy, strabismus
4	29y.	F	46,XX	—	severe	short stature, brachydactyly at both of the little toes
5	26y.	F	46,XX	—	severe	normal figure
6	27y.	M	46,XY/47, XY,+mar	3p14 (26%) 16q23 (6%)	moderate (IQ = 38)	macrocephalus, deformed ears, coarse skin, pigmentation on the face and body, many verrucae, hypoplastic external genitalia, left hemiplegia, kyphoscoliosis, gait disturbance
7	24y.	M	46,XY	3p14 (10%)	moderate (IQ = 46)	dysplasia and malimplantation in teeth, epilepsy, behavior disorders
8	21y.	M	46,XY	3p14 (8%) 7q32 (4%)	severe	epicanthus, gait disturbance
9	33y.	M	46,XY	—	severe	torticollis, scoliosis, small penis, gait disturbance
10	29y.	M	46,XY	—	severe (IQ = 23)	normal figure
11	22y.	M	46,XY	—	severe	short limbs
12	29y.	M	46,XY,r(22) (p13q13)	1q13 (4%) 16q22 (6%)	severe (IQ = 22)	left hemiparesis, kyphosis, large deformed auricles, saddle nose, thick lips, pigmentation on the back, behavior disorders, speech disturbance, enlargement of lateral vetricle of the brain
13	29y.	M	46,XY	—	severe	microcephalus, behavior disorders, speech disturbance
14	20y.	M	46,XY	3p14 (16%)	severe	microcephalus,
15	32y.	M	46,XY	—	profound (IQ = 12)	pigmentation on the cervical region, speech disturbance
16	23y.	M	46,XY	3p14 (4%)	moderate (IQ = 37)	cerebral palsy, epilepsy,
17	23y.	M	46,XY	3p14 (24%)	moderate (IQ = 37)	cataracta, macular degeneration, simian crease at right hand
18	19y.	M	46,XY	1p22 (4%) 7q32 (4%)	severe	upward slanted palpebral fissure, behavior disorders, speech disturbance
19	27y.	M	46,XY	—	severe (IQ = 30)	normal figure
20	27y.	M	46,XY	3p14 (18%)	severe (IQ = 26)	simian crease at both hands
21	27y.	M	46,XY	—	severe	noamal figure
22	35y.	M	46,XY	—	severe	deformed face, dyskinesia
23	26y.	M	46,XY	—	moderate (IQ = 48)	epilepsy
24	19y.	M	46,XY	—	moderate (IQ = 47)	deformed face
25	25y.	M	46,XY	—	mild (IQ = 52)	epilepsy
26	18y.	M	46,XY	—	moderate (IQ = 42)	simian crease at both hands
27	23y.	M	46,XY	—	moderate	hypertelorism, deformed auricles
28	26y.	M	46,XY,inv (9)(p11q13)	—	severe (IQ = 35)	upward slanted palpebral fissure, simian crease at left hand, bilateral congenital cataracta, bronchial asthma, atopic dermatitis
29	31y.	M	46,XY	—	profound (IQ = 15)	speech disturbance
30	25y.	M	46,XY	—	moderate	normal figure
31	27y.	M	46,XY	—	severe	simian crease at right hand, epilepsy
32	33y.	F	46,XX	2q13 (8%)	severe	mild hypertrichosis, negativism, speech disturbance, bilateral polycystic ovaries
33	33y.	F	46,XX	—	profound (IQ = 13)	normal figure
34	30y.	F	46,XX/46,XX, r(22)(p11q13)	—	profound	speech disturbance, epilepsy, ataxic gait, kyphosis
35	20y.	M	46,XY	—	severe	epilepsy, behavior disorders, speech disturbance
36	21y.	F	46,XX	3p14 (12%)	moderate	behavior disorders, epilepsy
37	29y.	F	46,XX	—	severe	epilepsy
38	33y.	F	46,XX,del (18)(p11)	—	severe	left blephaloptosis, short neck
39	30y.	F	46,XX	—	severe (IQ = 30)	normal figure
40	27y.	F	46,XX,1qh+	—	moderate (IQ = 41)	hypertelorism, deformed auricles, gait disturbance
41	24y.	F	46,XX	—	severe (IQ = 28)	epilepsy
42	28y.	F	46,XX	—	severe (IQ = 33)	normal figure

Table 2. Continue

Case no.	Age	Sex	Karyotype	Fragile site (frequency)	Level of M.R.	Other clinical findings
43	25y.	F	46,XX	—	severe (IQ = 32)	cerebral palsy, strabismus, simian crease, gait disturbance
44	50y.	F	46,XX	—	profound (IQ = 13)	normal figure
45	25y.	F	46,XX	—	severe	cerebral palsy, strabismus
46	27y.	F	46,XX	—	severe	epilepsy
47	23y.	F	46,XX	—	moderate	simian crease at left hand
48	32y.	F	46,XX	—	moderate (IQ = 42)	normal figure
49	23y.	F	46,XX	—	severe	deformed face
50	22y.	F	46,XX	—	severe (IQ = 25)	normal figure
51	22y.	F	46,XX	3p14 (4%)	severe	upward slanted palpebral fissure, deformed left auricle, simian crease at right hand
52	28y.	M	46,XY	3p14 (4%)	moderate (IQ = 36)	normal figure
53	20y.	F	46,XX	—	severe	epilepsy
54	15y.	F	46,XX	—	mild (IQ = 55)	epilepsy, short stature, simian crease at both hands
55	17y.	M	46,XY	—	moderate (IQ = 40)	epilepsy, cataracta, arachnodactyly, juvenile diabetes mellitus
56	19y.	M	46,XY	—	severe	epilepsy, behavior disorders
57	19y.	M	46,XY	—	mild (IQ = 55)	cerebral palsy, epilepsy, microcephaly, deformed face
58	16y.	F	46,XX	—	mild (IQ = 53)	strabismus
59	19y.	F	46,XX	—	severe	short stature, simian crease at both hands, microcephaly
60	19y.	F	46,XX	—	severe	strabismus
61	33y.	F	46,XX	—	moderate (IQ = 40)	behavior disorders
62	19y.	F	46,XX	—	severe (IQ = 24)	normal figure
63	25y.	F	46,XX	—	severe	right blephaloptosis, gait disturbance
64	32y.	F	46,XX	—	severe (IQ = 27)	strabismus
65	33y.	F	47,XX,+21	—	severe (IQ = 31)	upward slanted palpebral fissure, epicanthus, simian crease at both hands
66	26y.	F	47,XX,+21	—	severe (IQ = 29)	upward slanted palpebral fissure, epicanthus, simian crease at both hands
67	11y.	M	46,XY	—	moderate (IQ = 43)	behavlor disorders
68	9y.	M	46,XY	—	mild (IQ = 65)	epilepsy, strabismus, behavlor disorders
69	12y.	F	46,XY	—	mild (IQ = 59)	normal figure
70	14y.	M	47,XY,+21	—	moderate (IQ = 39)	epicanthus, simian crease at right hand
71	14y.	M	46,XY	—	severe (IQ = 30)	normal figure
72	25y.	M	47,XY,+21	—	severe (IQ = 31)	short stature, hyperuricemia, epicanthus,
73	30y.	M	47,XY,+21	—	profound (IQ = 16)	short stature, epicanthus, congenital heart disease, simian crease at left hand, hyperuricemia
74	42y.	M	47,XY,+21	—	profound (IQ = 11)	eqicanthus, hyperuricemia
75	26y.	M	47,XY,+21	—	moderate (IQ = 42)	epicanthus, hyperuricemia
76	30y.	M	47,XY,+21	—	severe (IQ = 25)	short stature, epicanthus, strabismus, simian crease at right hand
77	30y.	M	47,XY,+21	—	moderate (IQ = 38)	short stature, epicanthus, large tongue, congenital heart disease, gout, dacryostenosis
78	25y.	F	47,XX,+21	—	severe (IQ = 35)	upward slanted palpebral fissure, epicanthus,
79	21y.	F	47,XX,+21	—	moderate (IQ = 39)	upward slanted palpebral fissure, epicanthus,
80	24y.	F	47,XX,+21	—	moderate (IQ = 41)	upward slanted palpebral fissure, hypoplasia in teeth
81	27y.	F	47,XX,+21	—	severe	upward slanted palpebral fissure, epicanthus, strabismus, simian crease at right hand, congenital heart disease
82	21y.	F	46,XX	—	severe	strabismus, kyphosis, simian crease at right hand, congenital heart disease
83	28y.	F	46,XX	—	severe (IQ = 21)	behavior disorders
84	12y.	M	46,XY,1qh+	—	profound	normal figure
85	12y.	M	46,XY	—	moderate	hypertelorism, congenital heart disease
86	12y.	F	46,XX	—	severe	normal figure
87	17y.	M	46,XY	—	severe	strabismus, hypoplasia of carpales
88	13y.	M	46,XY	—	severe	microcephaly, epilepsy, cerebral palsy

Table 2. Continue

Case no.	Age	Sex	Karyotype	Fragile site (frequency)	Level of M.R.	Other clinical findings
89	32y.	F	46,XX	—	moderate (IQ = 43)	short stature
90	26y.	F	46,XX,+21	—	severe (IQ = 34)	epicanthus, simian crease at right hand
91	16y.	F	46,XX	—	moderate (IQ = 41)	behavior disorders
92	12y.	M	46,XY	—	moderate	normal figure
93	16y.	F	46,XX	—	profound	cerebral plasy
94	11y.	M	46,XY	—	severe	normal figure
95	13y.	M	46,XY	—	moderate	simian crease at left hand
96	13y.	M	46,XY	—	severe	behavior disorders
97	12y.	M	46,XY	—	severe	behavior disorders, epilepsy
98	12y.	M	46,XY	—	severe	epilepsy
99	17y.	F	46,XX	—	severe	epilepsy
100	17y.	F	46,XX	—	severe	normal figure
101	13y.	M	46,XY	—	moderate	behavior disorders
102	19y.	M	46,XY	—	severe	behavior disorders
103	14y.	M	46,XY	—	severe	behavior disorders
104	17y.	M	46,XY	—	severe	normal figure

Table 3. Karyotypes of the patients

Karyotype		Number of cases
Normal	46,XY	44
	46,XX	40
	46,XX,1qh+	1
	46,XY,1qh+	1
Abnormal	47,XY,+21	7
	47,XX,+21	6
	46,XY,r(22)(p13q13)	1
	46,XX/46,XX,r(22)(p11q13)	1
	46,XY/47,XY,+mar	1
	46,XX,del(18)(p11)	1
	46,XY,inv(9)(p11q13)	1

Table 4. Fragile sites of the patients

	Location	Number of cases
Rare fragile sites	2q13	1
Common fragile sites	1p22	1
	1q13	1
	3p14	10
	7q32	2
	16q22	1
	16q23	1

67—52) to profound (IQ < 20), most of them from moderate (IQ 51—36) to severe (IQ 35—20)[106] (Table 1).

The peripheral blood lymphocytes were cultured for 72 hours in complete Minimal Essential Medium (MEM) and MEM without folic acid (MEM-FA). 0.04 mg/ml of colchicine was added 2 hours before harvesting. The slides were made by flame-drying technique[94].

1) The lymphocytes cultured in MEM were observed under Giemsa technique and G-banding[94]. At least 40 cells were counted. Six cells stained by G-banding technique were photographed for analysis.

2) The lymphocytes cultured in MEM-FA were stained with Giema technique. At least 50 cells were observed for the break, gap, and/or triradials. The locations of these aberrations were identified after G-banding[73]. A case was considered positive for the fragile site, only if 4% or more cells expressed these aberrations at the same point of the chromosomes[55,62]. When a conventional chromosomal abnormality or a rare folate sensitive fragile site was detected, further examinations were carried out.

RESULTS

The cytogenetic and clinical findings of all the cases are shown in Table 2. By the method with MEM, 18 (17%) out of 104 cases revealed a conventional chromosomal abnormality. Among them, 13 cases (13% of all the cases) had trisomy 21. All of these 13 cases had already been diagnosed clinically as Down syndrome. No cases had s sex chromosome abnormality. There were 5 cases (4.8%) with the other chromosomal abnormality. One case had a ring chromosome 22, one case a mosaic ring chromosome 22, one case a pericentric inversion of no. 9, and one case a mosaic marker chromosome. There were 2 cases with the elongated long arm of no. 1, a chromosomal heteromorphism. These results are summarized in Table 3. These results have been previously reported by the author in Kanata et al[71,78,74].

Concerning fragile sites, 10 cases showed a common aphidicolin inducible fragile site at 3p14, 2 cases showed that at 7q32, each one case showed that at 1p22, 1q13, 16q22, or 16q23, and one case had a rare folate sensitive fragile site at 2q13. These results are summarized in Table 4.

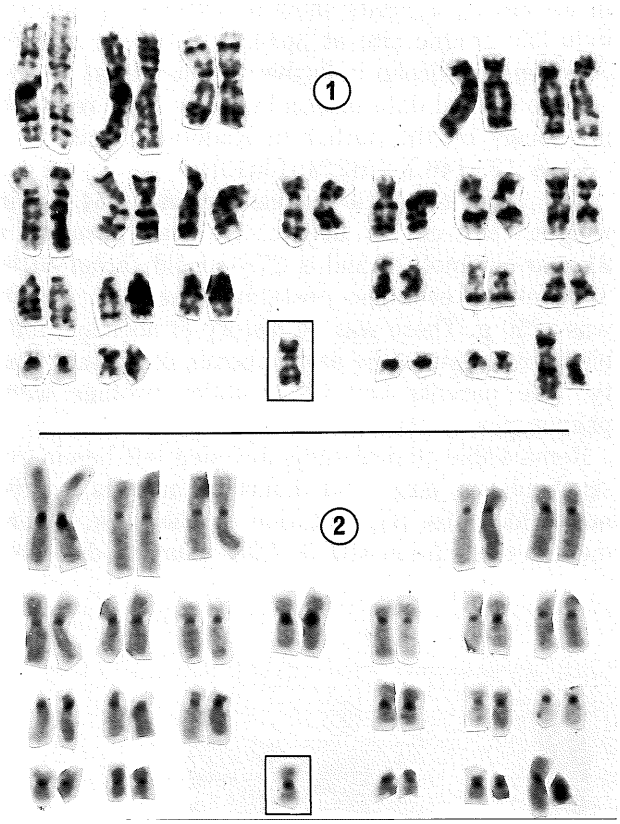

Fig. 1. G-banding, and C-banding karyotypes of the case 6, showing 47, XY, +mar.

CASE REPORTS

Case 6. (46,XY/47,XY,+mar)

The patient was a 27-year-old man, 52 kg in weight, 163.6 cm in height. He was born to a 30-year-old mother and a 39-year-old father after a full term of eventless gestation. The birth weight was 2850 g. There was no history of abortion, stillbirth, exposure to the atomic bomb, or consanguinity. The parents and his 2 siblings were phenotypically normal.

At 6 months, he was diagnosed as congenital hydrocephalus, and some years later a shunt operation was performed. Remarkable clinical signs included macrocephalus, deformed ears, coarse skin, pigmentation on the face and body, many verrucae, hypoplastic external genitalia, left hemiplegia, kyphoscoliosis, gait disturbance, and moderate mental retardation (IQ = 38).

Out of 183 cells cultured in MEM and stained with Giemsa, 92 cells showed 46 chromosomes, and 99 cells showed 47 chromosomes. The extra chromosome was metacentric, larger than E chromosomes, and smaller than C chromosomes. The G- and C-banding analysis revealed that this chromosome was neither a no. 16 chromosome nor a deleted C chromosome (Fig. 1). The C-band on this chromosome was positive and its origin remained unclear. The karyotype of the case was given, therefore, as 46,XY/47,XY,+mar.

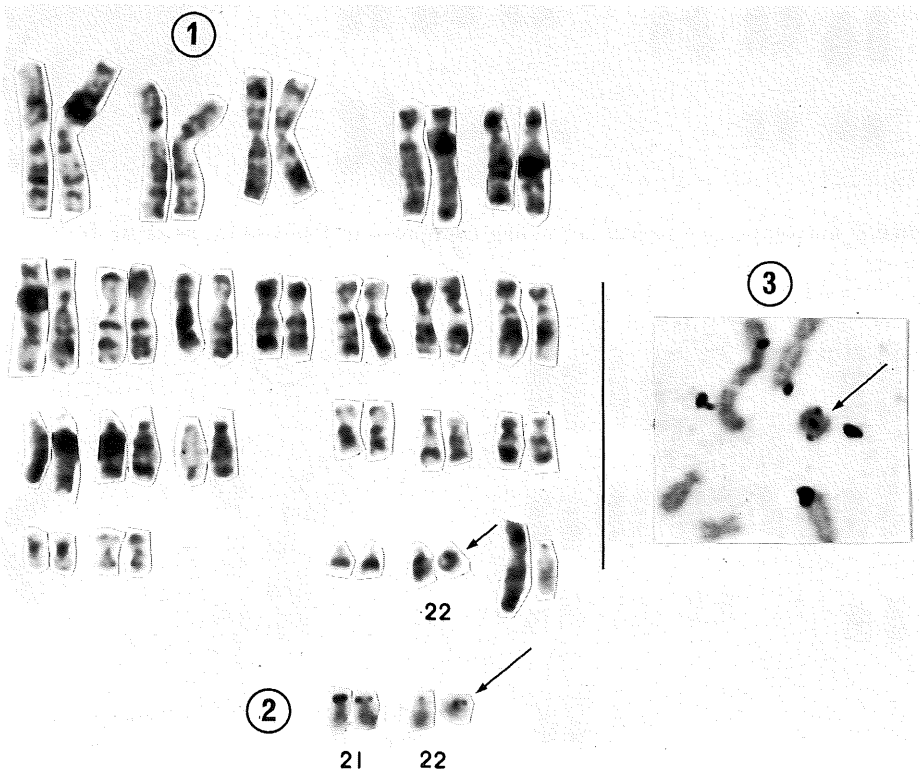

Fig. 2. G-banding karyotype, and patial N-banding karyotypes of the case 12, showing 46, XY, r(22)(p13q13). partial N-banding metaphase of the case 12, showing the double sized ring 22.

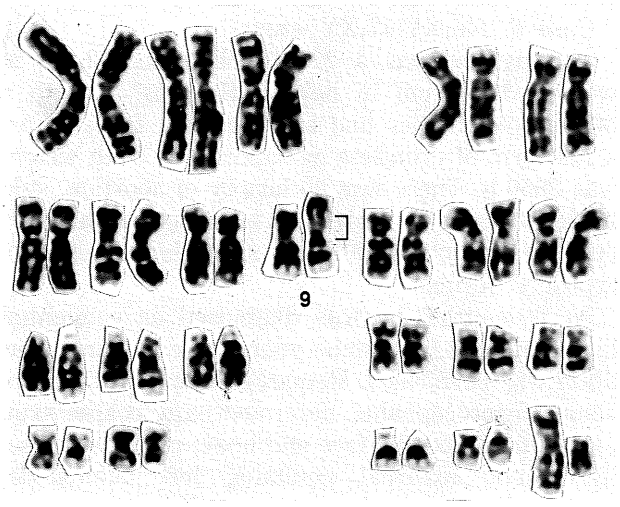

Fig. 3. G-banding karyotype of the case 28, showing 46, XY, inv(9)(p11q13).

Regarding the fragile site, out of 50 cells cultured in MEM-FA, 13 cells showed common aphidicolin inducible fragile site at 3p14, and 3 cells showed common aphidicolin inducible fragile site at 16q23.

More critical data of this case has been reported previously by the author in Kadotani et al[59].

Case 12. {46,XY,r(22)(p13q13)}

The patient was a 29-year-old man, 54 kg in weight, 157 cm in height. He was born to a 21-year-old mother and a 27-year-old father after 38 weeks of eventless gestation. The birth weight was 2250 g. There was no history of abortion, stillbirth, exposure to the atomic bomb, or consanguinity. The parents and his younger brother were phenotypically normal.

Remarkable clinical signs included left hemiparesis, kyphosis, large and deformed auricles, saddle nose, thick lips, pigmentation on the back, severe mental retardation (IQ = 22), behavior disorder,

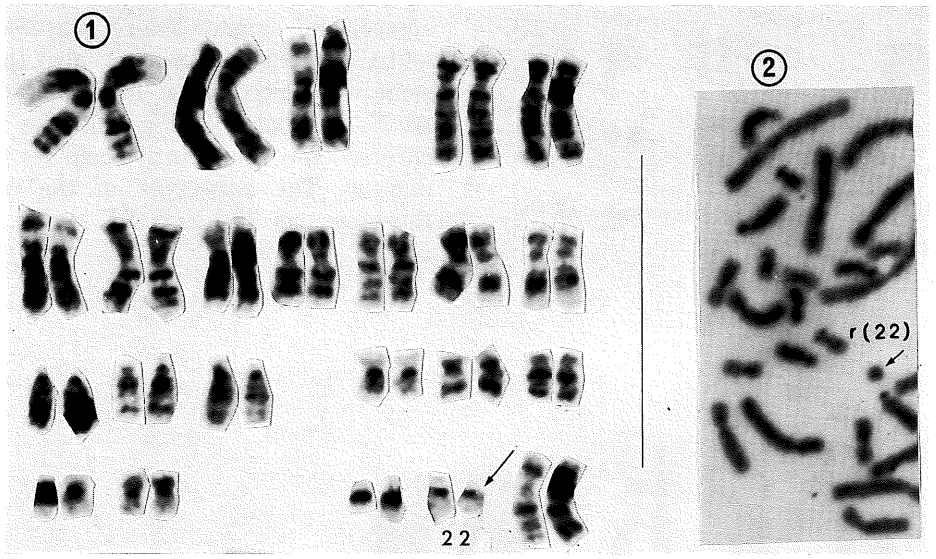

Fig. 4. G-banding karyotype, and partial N-banding metaphase of the case 34, showing 46, XX, r(22)(p11q13).

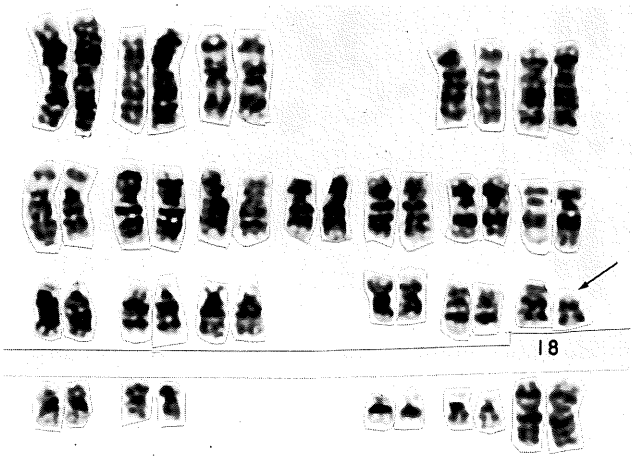

Fig. 5. G-banding karyotype of the case 39, showing 46, XX, del(18)(p11).

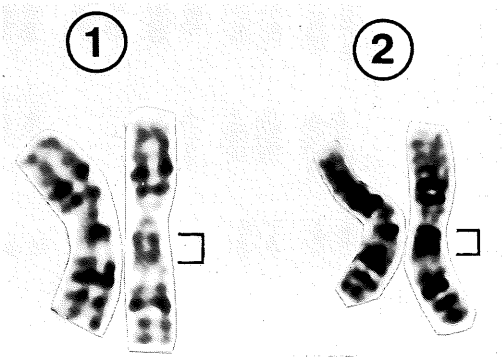

Fig. 6. Partial G-banding karyotypes of the case 40 and the case 84, showing 1qh+.

and verbal disability. Brain CT-scan revealed a enlargement of lateral ventricle. The cells cultured in MEM and stained with Giemsa showed 46 chromosomes including one ring chromosome in place of one normal G chromosome. By G-banding, the ring chromosome was revealed to be a chromosome 22 (Fig. 2). Silver staining showed the presence of a nucleolar organizing region on the ring (Fig. 2). The findings of the silver staining and the G-banding suggested that the breaks occured at p13 and q13. The karyotype of the patient was given, therefore, as 46,XY,r(22)(p13q13). The parents showed normal karyotype.

Out of 50 cells cultured in MEM—FA, 2 cells showed common aphidicolin inducible fragile site at 1q13 and 3 cells showed common aphidicolin inducible fragile site at 16q22.

More critical data of this case has been reported by the author in Kadotani et al[60] and Kanata et al[72].

Case 28. {46,XY,inv(9)(p11q13)}

The patient was 26-year-old man, 53 kg in weight, 160 cm in height. He was born to a 29-year-old mother and a 31-year-old father after a full term of eventless gestation. The birth weight was 3375 g. There was no history of abortion, stillbirth, exposure to the atomic bomb, or consanguinity. The parents and his elder sister were phenotypically normal.

Remarkable clinical signs included severe mental retardation (IQ = 35), bilateral congenital cataracta, upward slanted palpebral fissure, simian crease at left hand, bronchial asthma, and atopic dermatitis.

The cells cultured in MEM and stained with Giemsa showed 46 chromosomes including one abnormal metacentric chromosome in place of one normal C chromosome. By G-banding, the abnormal chromosome was revealed to be a inverted chromosome 9 (Fig. 3). The breaks occured at p11 and q13. The karyotype of the patient was given, therefore, as 46,XY,inv(9)(p11q13). Based on the 50 cells cultured in MEM-FA, the patient was considered negative for fragile sites.

Case 34. {46,XX/46,XX,r(22)(p11q13)}

The patient was a 30-year-old woman, 41 kg in weight, 150 cm in height. She was born to a 34-year-old mother and a 31-year-old father. At birth, she was in the state of asphyxia after seven months of the eventless gestation. Her birth weight was 1900 g. There was no history of abortion, stillbirth, exposure to the atomic bomb, or consanguinity. The parents and her two siblings were phenotypically normal. Remarkable clinical signs included profound mental retardation, speech disturbance, epilepsy, ataxic gait, and kyphosis.

Out of 78 cells cultured in MEM and stained with Giemsa, 69 cells showed 46 chromosomes including one small ring chromosome in place of one normal G chromosome. Other 9 cells showed 46 chromosomes without any abnormalities. By G-banding, the ring was revealed to be a chromosome 22 (Fig. 4). Silver staining showed the absence of a nucleolar organizing region on the ring (Fig. 4). The findings of the G-banding and the silver staining suggested that the breaks occured at p11 and q13. The karyotype of the patient was given, therefore, as 46,XX,/46,XX,r(22)(p11q13). Based on the 50 cells cultured in MEM-FA, the patient was considered negative for fragile sites.

More critical data of this case has been reported by the author in Kanata et al[70].

Case 38. {46,XX,del(18)(p11)}

The patient was a 33-year-old woman, 46 kg in weight, 141 cm in height. She was born to a 24-year-old mother and a 28-year-old father. There was no history of abortion, stillbirth, exposure to the atomic bomb, or consanguinity. The parents and her 5 siblings were phenotypically normal. Remarkable clinical signs of the patient included severe mental retardation, short neck, and left blephaloptosis.

The cells cultured in MEM and stained with Giemsa showed 46 chromosomes including one abnormal acrocentric chromosomes in place of one normal E chromosome. The G-banding suggested that the abnormal chromosome was a deleted chromosome 18 and the break occured at p11 (Fig. 5). The karyotype of the patient was given, therefore, as 46,XX,del(18)(p11). Based on the 50 cells cultured in MEM-FA, the patient was considered negative for fragile sites.

Case 40. (46,XX,1qh+)

The patients was a 27-year-old woman, 50 kg in weight, 148 cm in height. She was born to a 32-year-old mother and a 43-year-old father. There was no history of abortion, stillbirth, exposure to the atomic bomb, or consanguinity. The parents and her brother were phenotypically normal. Her remarkable clinical signs included hypertelorism, asynmetrical face, thin and deformed auricles, many large and little café-au-lait spots, atrophyic skin, gait disturbance, and moderate mental retardation (IQ = 41). The karyotype of the patient was given as 46,XX,1qh+ (Fig. 6). The case was considered negative for fragile sites.

Case 84. (46,XY,1qh+)

The patient was a 12-year-old boy, 32 kg in weight, 149 cm in height. He was born to a 27-year-old mother and a 31-year-old father. There was no history of abortion, stillbirth, exposure to the atomic bomb, or consanguinity. The parents and his brother were phenotypically normal. His remarkable clinical signs included profound mental retardation and behavior disorders. The karyotype of the patient was given as 46,XY,1qh+ (Fig. 6). He was considered negative for fragile sites.

Case 32. {46,XX with fra(2)(q13)}

The patient was a 33-year-old woman, 84 kg in weight, 164 cm in height. She was the first child

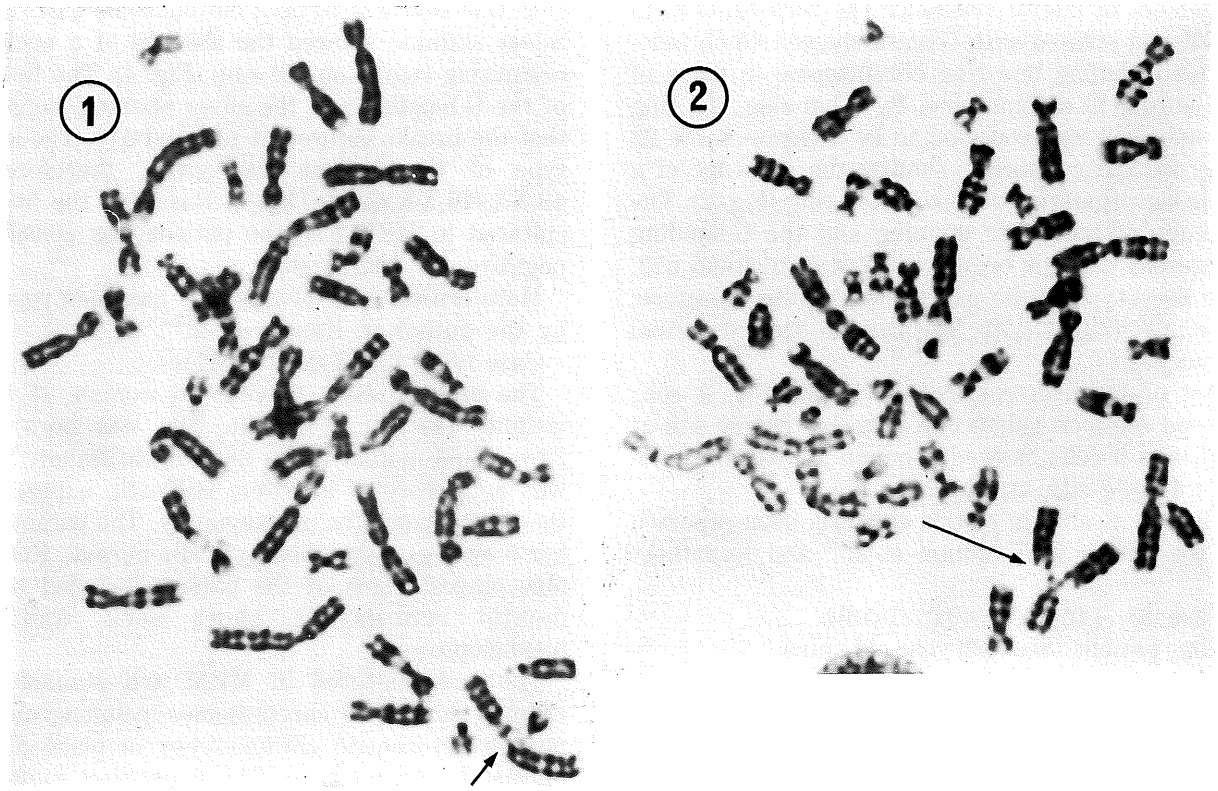

Fig. 7. Fra(2)(q13) in the lymphocytes f the case 32, cultured in MEM-FA: break, triradialis.

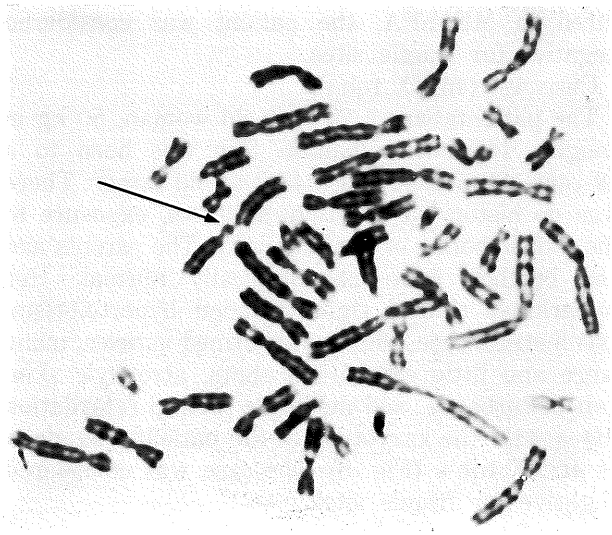

Fig. 8. Fra(2)(q13) in the lymphocyte of the mother of the case 32, clutured in MEM.

of a 30-year-old mother and a 37-year-old father. She was born with forceps operation at overterm, without asphyxia or other clinical problems. Her infancy is unclear. At the age of 10, she appeared to have behavioral problems. She graduated from a special class of junior high school, and was soon institutionalized. She underwent bilateral ovphorectomy for polycystic ovaries at the age of 33. At the present time, remarkable clinical signs included mild hypertrichosis, negativism, speech disorder, and severe mental retardation (IQ = 35—20). The parents were phenotypically normal and have no history of abortion, stillbirth, exposure to the atomic bomb, or consanguinity. The mother was 63 years old, and had undergone an operation for ploy p of the colon. Two siblings of the patient were phenotypically normal.

Regarding the patient, in the cells cultured in MEM, no remarkable findings were observed. On the other hand, in 9 cells out f 110 cells cultured in MEM-FA, fragility at 2q13 was observed (Fig. 7). In one cell out of 130 cells cultured in MEM, the same breakage was also detected. The karyotype was given, therefore, as 46, XX with fra (2)(q13).

About the mother, in 7 cells out of 100 cells cultured in MEM-FA, fragility at 2q13 was observed. In 5 cells out of 100 cells cultured in MEM, the same breakage was also detected (Fig. 8). The karyotype was given, therefore, as 46,XX with fra (2)(q13).

No chromosomal abnormalities were detected in the father of the patient.

This case has been reported by the author et al[81].

DISCUSSION

Kanata et al[69] studied hospitalized patients with heavy mental retardation. Most of their patients had profound mental retardation (IQ < 20) and half of them had cerebral palsy. In the present study,

the patients were institutionalized, most of them had moderate (IQ = 51—36) to severe (IQ = 35—20) mental retardation, and only 11 patients had cerebral palsy. The prevalence of chromosomal abnormalities (excluding rare fragile sites) among newborns is estimated to be 0.703 ± 0.091% ($p<0.01$, $n=57359$), based on the studies of consecutive newborns[8,13,41,53,83,91,93,104,114]. The same prevalence among mental retardates has been reported as 5—22%, in previous studies[1,19,25,39,54,69,78,84,89,102,103,106,112,122-124]. In the present investigation, chromosomal abnormalities (excluding rare fragile sites) were detected in 18 cases (17%). Based on previous and present studies, the prevalence of chromosomal abnormalities (excluding rare fragile sites) among mental retardates is estimated to be 13.29 ± 0.89% ($p<0.01$, $n=9733$), which is significantly higher than that of newborns ($p<0.01$). There seems to exist, therefore, a correlation between mental retardation and chromosomal abnormalities (excluding rare fragile sites).

Based on the studies of consecutive newborns[8,13,83,93,104,114], the prevalence of trisomy 21 and its variants among newborns is estimated to be 0.13 ± 0.06% ($p<0.01$, $n=27374$), and the prevalence of sex chromosome abnormalities (excluding FRAXA) among newborns 0.242 ± 0.053% ($p<0.01$, $n=57359$). In the previous studies of mental retardates[1,19,25,39,54,69,78,84,89,102,103,106,112,122-124], the prevalence of trisomy 21 and its variants among mental retardates has been reported as 1.2—19.3%. Kanata et al[69] found trisomy 21 and its variants in 1.65% of 121 hospitalized mental retardates. The relatively low rate of trisomy 21 and its variants compared with most other studies of mental retardates might reflect the particular features of the population. Sutherland et al[124] found similar results in the study of profound mental retardates (IQ < 20). In the present study, trisomy 21 or its variants was found in 13 cases (13%), sex chromosome abnormalities (excluding FRAXA) in no cases (0%), and other chromosomal abnormalities (excluding rare fragile sites) in 5 cases (5%). Based on previous and present studies, the prevalence of trisomy 21 and its variants among mental retardates is estimated to be 10.48 ± 0.81% ($p<0.01$, $n=9574$), the prevalence of sex chromosome abnormalities (excluding FRAXA) among mental retardates 1.16 ± 0.28% ($p<0.01$, $n=9733$). Both prevalences among mental retardates are significantly higher than those of consecutive newborns ($p<0.01$). These are summarized in Table 5. The rate of trisomy 21 and its variants among mental retardates is about 81 times as high as that of consecutive newborns. The cause of the remarkably high rate of trisomy 21 and its variants among mental retardates may be that almost all the cases with trisomy 21 or its variants develop mental retardation. The rate of sex chromosome abnormalities (excluding FRAXA) among mental retardates is about 5 times as high as that of consecutive newborns. The cause of the not so high rate of sex chromosome abnormalities (excluding FRAXA) among mental retardates may be that most of the cases with a sex chromosome abnormality (other than FRAXA) do not develop mental retardation.

Ring chromosomes are rare abnormalities. In 9 studies of consecutive newborns[8,13,41,53,83,91,93,104,114], only 1 case with a ring chromosome was reported. The prevalence of ring chromosome among newborns is estimated to be 0.002 ± 0.005% ($p<0.01$, $n=57359$). In the present study, ring chromosome 22 was detected in 2 cases (2%). Based on previous[1,19,25,39,54,69,78,84,89,102,103,106,112,122-124] and present studies the prevalence of ring chromosomes among mental retardates is estimated to be 0.11 ± 0.09% ($p<0.01$, $n=9733$), which is about 55 times as high as that of newborns and significantly higher than that of newborns ($p<0.01$). The cause of the remarkably high rate of ring chromosomes among mental retardates may be that almost all the cases with a ring chromosome develop mental retardation, when they survive. In previous publications [9,26,51], mental retardation, verbal delay, epilepsy, ataxic gait, hypotonia, reduced head circumference, spinal curvature, epicanthus, full eye brows, large ears, and thick lips have been reported as frequent symptoms of the ring chromosome 22. The cases with ring chromosome 22 in the present studies shared some of these symptoms. These symptoms may be chiefly due to a loss of material from the long arm of no. 22[22]. Based on previous[1,19,25,39,54,69,78,84,89,102,103,106,112,122-124] and present studies, the prevalence of the ring chromosome 22 among mental retardates is estimated to be 0.04 ± 0.05% ($p<0.01$, $n=9733$).

The prevalence of marker chromosome among newborns is estimated to be 0.030 ± 0.019% ($p<0.01$, $n=57359$), based on the studies of consecutive newborns[8,13,41,53,83,91,93,104,114]. In the present study, marker chromosome was detected in one case (1%). Based on previous[1,19,25,39,54,69,78,84,89,102,103,106,112,122-124] and present studies, the prevalence of marker chromosomes among mental retardates is estimated to be 0.32 ± 0.15% ($p<0.01$, $n=9733$), which is about 10 times as high as that of newborns and significantly higher than that of newborns ($p<0.01$).

The prevalence of chromosome deletions among newborns is estimated to be 0.01 ± 0.01% ($p<0.01$, $n=57359$), based on studies of consecutive newborns[8,13,41,53,83,91,93,104,114]. In the present study, a deleted short arm of chromosome 18 was detected in one case (1%). Based on previous[1,19,25,39,54,69,78,84,89,102,103,106,112,122-124] and present studies, the prevalence of deletions among mental retardates is estimated to be 0.48 ± 0.18% ($p<0.01$, $n=9733$), which is about 48 times as high as that of newborns and significantly higher than that of newborns ($p<0.01$). The cause of the remarkably high rate

Table 5. The prevalences of chromosomal abnormalities (excluding rare fragile sites)

Type of abnormalities	Among newborns, estimated ($p<0.01$)	Among mental retardates		
		In previous studies	In the present study	estimated on previous & present studies ($p<0.01$)
Trisomy 21 and its variants	0.13 ± 0.06 %** (n=27374)	1.2 – 19.3%****	13% (n=104)	10.48 ± 0.81% (n=9574)
Sex chromosome abnormalities	0.242 ± 0.053%* (n=57359)	0 – 3.6%***	0% (n=104)	1.16 ± 0.28% (n=9733)
Other abnormalities	0.453 ± 0.106%** (n=27374)	0.5 – 5.8%****	5% (n=104)	1.72 ± 0.35% (n=9574)
Total abnormalities	0.703 ± 0.091%* (n=57359)	5 – 22 %***	17% (n=104)	13.29 ± 0.89% (n=9733)

* 8,13,41,53,83,91,93,104,114)

** 8,13,83,93,104,114)

*** 1,19,25,39,54,69,78,84,89,102,103,106,112,122-124)

**** 1,19,25,39,54,69,78,84,89,102,103,106,112,122,123)

Table 6. The prevalence of chromosomal abnormalities

Type of abnormalities	Among newborns, estimated ($p<0.01$)	Among mental retardates		
		In previous studies***	In the present study	estimated on previous & present studies ($p<0.01$)
rings	0.002 ± 0.005%* (n=57359)	0 – 0.826%	2% (n=104)	0.11 ± 0.09% (n=9733)
ring 22	—	0 – 0.2 %	2% (n=104)	0.04 ± 0.05% (n=9733)
marker	0.030 ± 0.019%* (n=57359)	0 – 1.69 %	1% (n=104)	0.32 ± 0.15% (n=9733)
deletions	0.01 ± 0.01 %* (n=57359)	0 – 1.71 %	1% (n=104)	0.48 ± 0.18% (n=9733)
18p-	0.002 ± 0.006 ** (n=46221)	0 – 0.3 %	1% (n=104)	0.06 ± 0.07% (n=9733)

* 8,13,41,53,83,91,93,104,114)

** 8,13,41,53,83,91,93,114)

*** 1,19,25,39,54,69,78,84,89,102,103,106,112,122-124)

of deletions among mental retardates may be that almost all the cases with a deletion develop mental retardation, when they survive. In 8 studies of consecutive newborns[8,13,41,53,83,91,93,114], only 1 case with a deleted short arm of no. 18 was reported. The prevalence of the deleted short arm of no. 18 among newborns is estimated to be 0.002 ± 0.006% ($p<0.01$, n=46211). Based on previous[1,19,25,39,54,69,78,84,89,102,103,106,112,122-124] and present studies the prevalence of the deleted short arm of no. 18 among mental retardates is estimated to be 0.06 ± 0.07% ($p<0.01$, n=9733). These are summarized in Table 6. Mental retardation, short stature, short broad neck, round flat face, hypertelorism, blephaloptosis, epicanthus, and big ears have been reported as frequent symptoms of this abnormality[111]. The present case with deleted short arm of no. 18 shared some of these symptoms.

In previous studies, pericentric inversions have been detected in the cases with mental retardation, congenital malformation, and/or normal phenotype[52,68,82]. The direct etiological significance of pericentric inversions for mental retardation does not seem to be so high, if it exsists[77,121]. The association of inversions with neoplasia has been reported. Le Beau et al[85] reported that the lymphocytes of most of the patients with myelomonocytic leukemia and abnormal eosinophils showed pericentric inversion of no. 16. Miyamoto et al[100], Ueshima et al[139], and Zech et al[152] reported that the lymphocytes of some of the patients with chronic T-cell leukemia or adult T-cell leukemia showed paracentric inversion of no. 14. These may suggest the genetic effect of inversions. On the other hand, the correlation between pericentric inversions and reproductive failures has been studied[28,120]. These problems may be associated with the synaptic disturbance or the recombination syndrome, in part. Chromosome 9 shows a high susceptibility for structural rearrangements, and particularly pericentric inversions[50]. In the present

study, inv(9)(p11q13) was detected in one case. Inv(9)(p11q13) has been reported most frequently among pericentric inversions of no.9[68]. Elongated long arm of no. 1 has been detected in cases with mental retardation, congenital anomaly, reproductive failure, e.t.c., and/or normal phenotype, previously[30,67]. In the present study, elongated long arm of no. 1 was detected in 2 cases. The etiological significance of elongated long arm of no. 1 for mental retardation seems not to be so high, if it exsists[141].

According to the prevalence among the population, fragile sites can be divided into 2 major groups, namely rare fragile sites and common fragile sites[6,33]. According to the mode of induction, rare fragile sites can be subdivided into 3 groups, namely folate sensitive fragile sites, distamycin A inducible fragile sites, and bromodeoxyuridine requiring fragile sites[6]. Likewise, the common fragile sites can be subdivided into 3 groups, namely aphidicolin inducible fragile sites, 5-azacytidine inducible fragile sites, and bromodeoxyuridine inducible fragile sites[6]. In the present study, by MEM-FA, rare folate sensitive fragile site at 2q13 was induced in one case. Also, 10 cases were considered positive for common aphidicolin inducible fragile site at 3p14, 2 cases for that at 7q32, and each case for that at 1p22, 1q13, 16q22, or 16q23. Rare folate sensitive fragile sites can be induced *in vitro* by low folate and thymidine[126], by folate antagonist methotrexate[97,126], by thymidilate synthetase inhibitor 5-fluorodeoxyuridine[32,134], and by excessive thymidine[129]. Common aphidicolin inducible fragile sites can be induced *in vitro* by low folate and thymidine[88], by methotrexate[5,95], by 5-fluorodeoxyuridine[32,134], by excessive thymidine[147], and by DNA synthetase inhibitor arabinofuranosyl cytosine[87,151], arabinofuranosyl adenine[87], hydroxyurea[146,147], and aphidicolin[33]. The induction of the common aphidicolin inducible fragile sites under folate deficiency can be enhanced by caffeine[149], e.t.c..

The mechanism of the induction of fragile sites under folate deficiency can be explained as follows[36,126]. The conversion of deoxyuridine monophosphate to thymidine monophosphate requires 5,10-methylene-tetrahydrofolate, a metabolite of folate. Thymidine monophosphate is metabolized to thymidine triphosphate, which is used for DNA synthesis. Folate deficiency may be followed by 5,10-methylene-tetrahydrofolate deficiency, leading to the arrest of the conversion of deoxyuridine monophosphate to thymidine monophosphate. the arrest of the conversion may result in a decrease in thymidine monophosphate and an increase in deoxyuridine monophosphate. These results may lead to a decrease in thymidine triphosphate for DNA synthesis, and an increase in deoxyuridine triphosphate. Sutherland[126] suggested that the decrease in thymidine triphosphate for DNA synthesis may induce folate sensitive fragile sites. Sutherland et al[129] proposed the model for the DNA at folate sensitive fragile sites, composed of alternating repeating polypurine/polypirimidine sequences. Other authors[36,113] suggested that the increase in deoxyuridine triphosphate with or without the decrease in thymidine triphosphate may promote misincorporation into DNA of deoxyuridine triphosphate in place of thymidine triphosphate and so induce the expression of folate sensitive fragile sites. Krumdieck and Peebles[80] hypothesised that the misinocorporation of deoxyuridine triphosphate may preclude the interaction between DNA and folding protein especially at folate sensitive fragile sites, and so induce the expression of fragility. Rare folate sensitive fragile sites and common aphidicolin inducible fragile sites may share a common mechanism of expression[32,33].

The clinical significance of FRAXA has been established[12,14]. Males with typical fragile X syndrome show mild to severe mental retardation[42,90], macro-orchidism[125,135], and long face with big ears[31,136]. They tend to demonstrate autistic features[40] such as language disturbances including verbal delay, repetitive words or pharases, and echolalia[49,55,136] and behavior disturbances including hyperactivity, hand-flapping, hand-biting, desire for order and routine, and poor eye contact[10,23,136]. Some of them develop epilepsy[37,58,98]. Some of them are diagnosed as infantile autism[11,99]. Clinical features of the females with fragile X syndrome are similar to those of the males with fragile X syndrome[105,137]. Sherman et al[117] estimated the penetrance of mental impairment in hemizygous males at 79%, and the same in heterozygous females at 35%.

In 6 cytogenetic surveys of normal populations or consecutive newborns[61,64,127,128,131], FRAXA was not detected (n=4585 in total). The prevalence of FRAXA among autistic males is estimated to be 6.7 ± 2.6% ($p<0.01$, n=626), based on previous studies[7,21,35,48,92,96,107,140,143]. The same among male mental retardates has been reported as 0—13%, and the same among female mental retardates as 0—4%, in previous studies[3,4,18,38,56,63,64,76,84,89,125,127,137]. In the present study, FRAXA was not detected. Based on previous and present studies, the prevalence of FRAXA among male mental retardates is estimated to be 3.7 ± 0.9% ($p<0.01$, n=2721), and that among female mental retardates 1.7 ± 1.1% ($p<0.01$, n=879). These are summarized in Table 7.

The clinical significance of other fragile sites is unknown. Some authors suggested that breakages at fragile sites may occur *in vivo*, and may result in partial aneuploidy or rearrangement[66,145]. The correlation between fragile site and neoplasia has been studied intensively. Some fragile sites are located at or near the cellular oncogenes and/or breakpoints of aquired chromosome rearrangements characteristic of specific neoplasia[86,148]. Some

Table 7. The prevalences of FRAXA

	Among consecutive or normal population*	Among autistic patients, estimated** ($p<0.01$)	Among mental retardates		
			In previous studies***	In the present study	estimated on previous & present studies ($p<0.01$)
male	0%	6.7 ± 2.6% (n=626)	0 - 13%	0% (n=56)	3.7 ± 0.9% (n=2686)
female	0%	—	0 - 4%	0% (n=48)	1.7 ± 1.1% (n= 879)

* 61,64,127,128,131)

** 7,21,35,48,92,96,107,140,143)

*** 3,4,18,38,56,63,64,76,84,89,127,128,137)

Table 8. The prevalences of autosomal rare folate sensitive fragile sites

	Among healthy or consecutive population, estimate ($p<0.01$)*	Among mental retardates		
		In previous studies**	In the present study	estimated on previous & present studies ($p<0.01$)
Fra(2)(q13)	—	0%	1%	0.06 ± 0.15%
All autosomal rare folate sensitive fragile sites	0.2 ± 0.2% (n=4585)	0.39 - 1.1%	1% (n=104)	0.97 ± 0.61% (n=1759)

* 61,65,127,128)

** 65,76,127,128)

authors showed statistically that chromosome rearrangements in neoplasia tend to occur at or near the locations of fragile sites[16,43,46]. On the other hand, Sutherland and Simmers[130] cast serious doubt on such statistical studies. It was reported that some patients with neoplasia carried a rare fragile site at the chromosome region that was also involved in a rearrangement in their malignant cells[86,148,149]. However, some authors[109,118] found no correlation between chromosomal breakpoints of malignant cells in the patients with a rare fragile site and the fragile site. Tedeschi et al[132] reported significantly increased expression of common aphidicolin inducible fragile sites in lymphocytes from cancer patients. Also, the correlation between fragile site and constitutional partial aneuploidy or rearrangement has been studied. Some families of the cases with a constitutional chromosome rearrangement revealed a rare fragile site at the same region as the breakpoint involved in the rearrangement[29,116]. Fuster et al[27] and Hecht and Hecht[44,45] showed statistically that constitutional chromosome rearrangements tend to occur at or near the locations of fragile sites. However, Davis and Hagaman[15] and Porfirio et al[108] challenged such statistical studies.

Based on the previous studies of healthy populations or consecutive newborns[61,65,127,128], the prevalence of autosomal rare folate sensitive fragile sites among newborns or healthy population is estimated to be 0.2 ± 0.2% ($p<0.01$, n=4585). The same among mental retardates has been reported as 0.39—1.1% in previous studies[65,76,127,128]. In the present study, a rare folate sensitive fragile site at 2q13 was detected in one case (1%). Based on previous and present studies, the prevalence of autosomal rare folate sensitive fragile sites among mental retardates is estimated to be 0.97 ± 0.61% ($p<0.01$, n=1759), which is significantly higher than that among newborns ($p<0.01$). In the previous surveys of healthy or consecutive population[61,65,127,128], fra(2)(q13) was not detected. Also in the previous studies of mental retardates[65,76,127,128], fra(2)(q13) was not detected. Based on previous and present studies, the prevalence of fra(2)(q13) among mental retardates is estimated to be 0.06 ± 0.15% ($p<0.01$, n=1759). These are summarized in Table 8.

Fra(2)(q13) was detected in the patient with mild hypertrichosis, negativism, speech disorder, and severe mental retardation. The same aberration was also detected in her mother with normal phenotype. In several reports[2,20,115,145], fragile secondary constrictions close to the centromere on the long arm of chromosome no. 2 were detected in the cases with mental retardation, hyper-beta-lipoproteinemia, central nervous system malformation, cardiomyopathy, carcinoma, and/or Crohn's disease. These aberrations were also detected in normal cases[2,20]. It is not clear whether these aberrations are fra(2)(q13) or not. Recently, fra(2)(q13) has been detected in cases with autism, mental retardation, epilepsy, craniofacial dysmorphism, and/or cerebral hygroma[24,75]. Jayaker et al[57] reported that

fra(2)(q13) was found in 2 cases out of 20 autistic children and no cases out of 20 normal controls. In the present study, however, fra(2)(q13) was detected also in the normal case. This throws doubt on the clinical significance of fra(2)(q13). The normal carrier of fra(2)(q13) may constitute a similar existence to the normal carrier of fra(X)(q27). The clinical significance of fra(2)(q13) needs further study. Keshiaho et al[75] reported the absence of fra(2)(q13) in the parents of 3 unrelated children with fra(2)(q13) and Fryns and Van Den Berghe[24] reported the absence of fra(2)(q13) in the parents of the brothers with fra(2)(q13). These authors suspected that the expression of fra(2)(q13) may be age dependent. The suspicion was not supported in the present study. Fra(2)(q13) has been considered to be folate sensitive[6]. On the other hand, it was reported by Annerén and Gustavson[2] that the fragile secondary constriction on chromosome no. 2 was detected in the cells cultured in the medium Parker 199, which includes folic acid. In the present study, spontaneous breakage at 2q13 was observed in the cells cultured in MEM. However, this phenomena does not indicate that the breakage is not folate sensitive[131]. In the patient's cells, folate deficiency seems to have enhance the breakage at 2q13. Regarding the mother, the observed cells are too few to conclude that folate deficiency does not enhance the breakage at 2q13.

Common aphidicolin inducible fragile site at 3q14 is the most common of all fragile sites[119,153]. Fra(3)(p14) is close to the positions of rearrangement breakpoints frequently observed in small cell carcinoma of the lung[101,144] and renal cell carcinoma[142]. Glover et al[34] suggested that fra(3)(p14) is very close to the translocation breakpoint of renal cell carcinoma. However, Kovacs and Brusa[79] challenged such a suggestion.

To conclude the present study, etiological significance of chromosomal abnormalities for mental retardation seems apparent. The clinical significance of chromosome inversions and autosomal rare folate sensitive fragile sites remains unknown, and needs further study.

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