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A Cytogenetic Study of Heavy Mental Retardates
II. A study on heavy mental retardates with behavior disorders

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ABSTRACT

A cytogenetic study was made on heavy mentally retarded patients with behavior disorders. The purpose of this study was to explore the causes of mental retardation and behavior disorders. As the results, chromosome abnormalities were found in 16,1% of the patients. This study revealed that, in the mental retardates with behavior disorders, although they were not associated with gross malformations, the chromosome abnormalities were detected with a relatively high incidence as compared with the normal population.

The 56 cases examined in this study were admitted to National Sanatorium Kamo Hospital. Their common clinical signs were heavy mental retardation and behavior disorders.

Chromosome slides were prepared in accordance with the standard blood culture procedure. Karyotype analyses were made with the application of the conventional Giemsa staining and G-, C-, and Q-banding differential staining.

Of these 56 cases, 9 cases had abnormal karyotypes, showing an incidence of 16,1%. All the abnormal karyotype cases were autosomal abnormalities. And additional 6 cases had normal variations of no.1, 9, and Y chromosomes. The clinical and cytogenetic findings of these patients were presented.

A chromosome study was conducted on 56 cases of heavy mental retardation with behavior disorders. The patients under investigation were admitted to National Sanatorium Kamo Hospital.

For long time, one of the primary concerns of chromosome studies was the relationship between multiple malformations and chromosome abnormalities. And, to date, the chromosome studies on behavior disorders are still meager.

The purpose of this study was to explore the causes of mental retardation and behavior disoredrs.

In order to detect even minor chromosome abnormalities, the banding techniques were employed routinely on all the cases.

PATIENTS

All the 56 cases examined in this study were admitted to National Sanatorium Kamo Hospital. Their common clinical signs were heavy mental retardation, speech disorder, and various behavior disorders; hyperactivity, aggressiveness, excitement, wandering, violence, stereotypic movement, autistic tendency, obstinacy, self-injury, paraphagia, aerophagia, and others. And not all the patients were associated with multiple malformations. The mental retardation of the patients ranged from severe in 2 cases being 35-20 in IQ score to profound in 54 cases being under 20 in IQ score.

The chromosomal examinations were also per-

formed on available relatives of karyotypically abnormal patients.

METHODS

The chromosomal preparations were made by the standard leucocyte culture procedure. Phytohemagglutin-stimulated peripheral blood was cultured in Eagle EME medium for 72 hr, and slides were made by means of the air-drying technique.

The conventional Giemsa staining and G-banding differential staining were routinely employed for chromosome identification.

Chromosome counts were made with about 25 well delineated metaphases. The karyotype was analysed in 6 cells by the conventional Giemsa staining and G-banding staining respectively.

In abnormal or ambiguous cases, C-, or Q-banding staining were also employed as necessary, and the number of chromosome counts and

Table 1. Clinical and cytogenetic findings in 56 cases of heavy mental retardation with behavior disorders

Case no.	Age	Sex	Karyotype	Clinical features
1	18 y.	M	46,XY	seizure, autistic tendency, excitement
2	12 y.	M	46,XY	seizure, small penis, autistic tendency stereotypic movement
3	15 y.	M	46,XY	flat occiput, hypoplastic external genitalia, funnel breast, autistic tendency
4	17 y.	M	46,XY	flat occiput, kyphosis, hypoplastic external genitalia, blepharophimosis, stereotypic movement
5	14 y.	F	46,XX	short stature, hypertelorism, ptosis of eyelid, impaired vision, saddle nose, syndactyly of the index finger and the middle finger on the left, moodiness, hot temper, obstinacy
6	14 y.	M	46,XY	seizure, sparse hair, saddle nose, dysplasia and malimplantation in teeth, hypoplastic external genitalia, aggressiveness, impulsiveness
7	27 y.	F	46,XX	obstinacy, impulsiveness, moodiness
8	16 y.	F	46,XX	seizure, sparse hair, hypertelorism, upward slanted palpebral fissure, moodiness, hot temper, obstinacy
9	17 y.	M	46,XY	hyperactivity, tenseness
10	19 y.	M	46,XY	excitability, hyperactivity
11	23 y.	F	46,XX	seizure, hypertelorism, saddle nose, bird-like facies, kyphosis, stereotypic movement, obstinacy, monologue
12	16 y.	M	46,XY,5p+	head deformity, torticollis, impulsiveness, obstinacy
13	28 y.	F	46,XX	seizure, short stature, excitability, impulsiveness
14	27 y.	M	46,XY,5q-	head deformity, aged facies, microphthalmus, impaired vision, kyphosis, hypoplastic external genitalia, aerophagia, burxism, finger suck
15	15 y.	M	46,XY,1qh+, rcp t(3;4)	short stature, ptosis of eyelid, epicanthal fold, strabismus, malformed auricle, dysplasia and malimplantation in teeth, asthma, kyphosis, tenseness, obstinacy, repetitive behavior
16	10 y.	M	46,XY,ins(Y;15)	deafness, flat occiput, low set ears, hyperactivity, stereotypic movement
17	24 y.	M	46,XY	seizure, frontal bossing, aged facies, hypertelorism, downward slanted palpebral fissure, saddle nose, prognathism, dysplasia and malimplantation in teeth, ataxia, tenacity, wandering
18	31 y.	M	46,XY,1qh+	seizure, congenital cataract, blindness, frontal bossing, aged facies, hypertelorism, prominant nasal bridge, dysplasia and malimplantation in teeth, stereotypic movement, wandering
19	12 y.	M	46,XY	blepharophimosis, downward slanted palpebral fissure, dysplasia and malimplantation in teeth, hyperactivity, impulsiveness
20	9 y.	F	46,XX	short stature, macrocephalus, macroglossia, hyperplastic clitoris, seizure, stereotypic movement, bite
21	19 y.	M	46,XY	seizure, flat occiput, aged facies, blepharophimosis, hypoplastic external genitalia, hyperactivity
22	15 y.	M	46,XY	nevus, aggressiveness, moodiness, polyphagia, hyperactivity, autistic tendency
23	16 y.	M	46,XY	flat occiput, hypoplastic external genitalia, seizure, paraphagia, coprophagia, hyperactivity, merycism, autistic tendency
24	12 y.	M	46,XY	flat occiput, hypoplastic external genitalia stereotypic movement, merycism
25	10 y.	F	46,XX	congenital heart failure(VSD), stereotypic movement, autistic tendency

Case no.	Age	Sex	Karyotype	Clinical features
26	24 y.	M	46,XY	hypoplastic external genitalia, stereotypic movement, obstinacy
27	13 y.	M	46,XY	strabismus, prominant nasal bridge, hypoplastic external genitalia, seizure, hyperactivity, impulsiveness
28	15 y.	M	46,XYq+	hypoplastic external genitalia, seizure, obstinacy, wandering
29	16 y.	M	46,XY	impulsiveness, obstinacy, violence, autistic tendency
30	13 y.	M	46,XY	flat occiput, saddle nose, dysplasia and malimplantation in teeth, aerophagia, wandering, autistic tendency
31	7 y.	F	46,XX	Cornelia dé Lange's syndrome, saddle nose, short legs, hirstism, impaired vision, self injury, hyperactiyity
32	15 y.	M	46,XY	Bloch-Sulzberger's syndrome, hyperpigmentation, microcephalus, ptosis of eyelid, hypoplastic external genitalia, Perthes' disease, seizure, hyperactivity
33	10 y.	M	46,XY	seizure, hyperactivity
34	13 y.	M	46,XY	epicanthal fold, malformed auricle, saddle nose, kyphosis, self-injury, wandering, monologue
35	14 y.	M	46,XY,9q-	seizure, asthma, stereotypic movement, hyperactivity, autistic tendency
36	19 y.	M	46,XY	Cornelia dé Lange's syndrome, short legs, hirstism, cataract, impaired vision, hyperactivity, impulsiveness
37	17 y.	F	47,XX,+21	Down's syndrome, short stature, microcephalus, deformed head, upward slanted palpebral fissure, epicanthal fold, exophthalmus, keratitis and blepharoptosis of the left eye, trichiasis, impaired vision, low and broad nasal bridge, malformed auricle, dysplasia and malimplantation in teeth, kyphosis, aplasia of pubic hair, obstinacy, hypothyroidism
38	18 y.	M	46,XY	flat occiput, seizure, encopresis, wandering
39	9 y.	M	46,XY	Lennox's syndrome, hyperactivity
40	7y.	F	47,XX,+21	Down's syndrome, epicanthal fold, upward slanted palpebral fissure, short extremities, kyphosis, congenital heart failure (VSD), saddle nose, hyperactivity, obstinacy
41	25 y.	M	46,XY	short stature, seizure, paraphagia, wandering
42	14 y.	M	46,XY	congenital cataract, short stature, stereotypic movement, obstinacy
43	17 y.	M	47,XY,+del(15)	downward slanted palpebral fissure, malformed auricle, prominant nasal bridge, kyphosis, seizure, hyperactivity, wandering
44	19 y.	M	46,XY	Lennox's syndrome, strabismus, malformed auricle, hypoplastic external genitalia, hyperactivity, impulsiveness
45	17 y.	F	46,XX	flat occiput, incurved fingers (left middle and ring finger), hyperactivity, finger suck
46	11 y.	F	46,XX,9qh+	prominent nasal bridge, seizure, self-injury, hyperactivity
47	11 y.	M	46,XY,inv(9)	large mouth, seizure, hyperactivity
48	7 y.	F	46,XX	blindness(retinopathy of prematurity), short stature, flat occiput, strabismus, nystagmus, saddle nose, seizure, wandering
49	12 y.	M	46,XYq+	congenital cataract, flat occiput, malformed auricles, dysplasia and malimplantation in teeth, self-injury, stereotypic movement
50	8 y.	F	46,XX	seizure, impaired hearing, wandering, autistic tendency
51	22 y.	M	46,XY	short stature, wandering
52	15 y.	F	46,XX	microcephalus, prominent nasal bridge, impulsiveness, hyperactivity, violence
53	31 y.	M	46,XYq+,1qh+	short stature, flat occiput, head deformity, dysplasia and malimplantation in teeth, excitement, obstinacy, monologue
54	17 y.	M	46,XY	seizure, ataxia, wandering
55	18 y.	M	46,XY,9qh+	slight oxycephalus, large nose, autistic tendency, wandering
56	16 y.	M	46,XY	macrocephalus, oxycephalus, short neck, flat facies, hypotelorism, epicanthal fold, short and coarse eyelashes, blepharitis, low set ears, malformed auricle, low nasal bridge, depressed nose, saddle nose, flat nasal base, large nose, protruding tongue, polydactyly, wandering, bite, hypothyroidism

All the patients had heavy mental retardation, behavior disorders, and speech disorders.

of karyotyped cells was increased.

RESULTS

The clinical and cytogenetic findings of all the patients are presented in Table 1. The abnormal karyotypes were found in 9 cases out of 56 cases, showing an incidence of 16,1%. All the abnormal cases were autosomal abnormalities. And additional 6 cases showed normal variations on the long arm of no.1, 9, and Y chromosomes.

As the results of chromosomal examinations on relatives of karyotypically abnormal patients, it was revealed that one case of partial trisomy of no.15 derived from the paternal balanced translocation, and two cases of normal variation on the long arm of no.1 also derived from their fathers.

Abnormal karyotypes were seen in one case of an elongated long arm of no.1 and reciprocal translocation between no.3 and no.4, one case of an elongated short arm of no.5, one case of a delated long arm of no.5, one case of a deleted long arm of no.9, one case of a pericentric inversion on on.9, two cases of partial trisomy of no.15, and two cases of trisomy 21.

Normal variations were seen in two cases of a long arm of no.1 (including one abnormal case of 1qh+, rcp t(3;4)), two cases of no.9, one case of Y chromosome, and one case of the coincidence of a long arm of no.1 and Y chromosome.

Details are given as follows.

CASE REPORTS

Cases of chromosome abnormalities

Case 1. (1qh+, rcp t(3;4))[51] The patient was a 15-year-old boy. He was born to a 25-year-old mother and a 37-year-old father as the first child. There was no history of abortion, stillbirth, congenital malformations, mental retardation, exposure to the atomic bomb, and consanguinity in this couple. Clinical examinations revealed that his parents and his brother were phenotypically normal.

The birth weight of this patient was 2950 g at 42 weeks of gestation with the Caesarian operation. The remarkable clinical signs of this patient were growth retardation, malnutrition, hypertelorism, epicanthal fold, downward slanted palpebral fissure, ptosis of eyelid, blepharophimosis at left eye, strabismus, low-set and malformed auricles, dysplasia and malimplantation in teeth, kyphosis, speech disorder, and behabior disorders; tenseness, obstinacy, repetitive behavior. He had also asthma and nephrosis (Fig. 1).

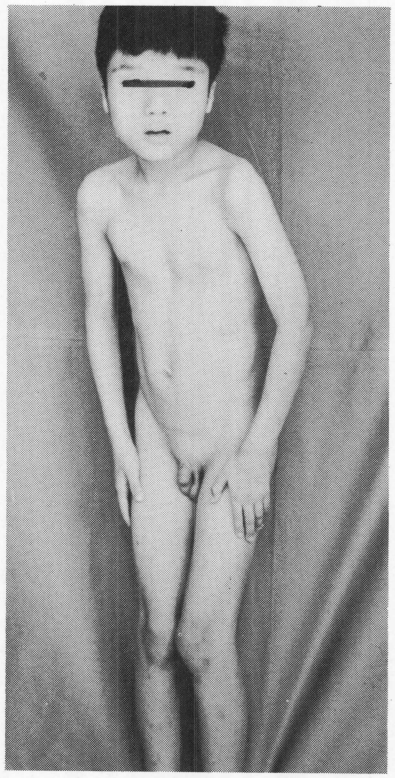

Fig. 1. External picture of the patient (Case 1).

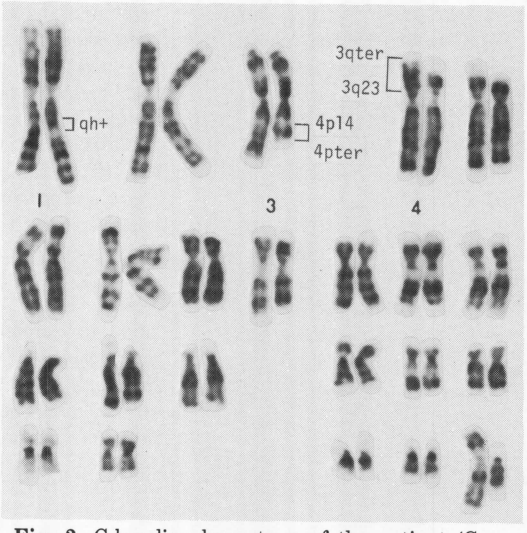

Fig. 2. G-banding karyotype of the patient (Case 1), showing 46,XY,1qh+,rcp t(3;4)(q23;p14).

The chromosome constitution of the patient based on the conventional Giemsa specimen showed 46 chromosomes which included a no.1 chromosome having an unusually elongated long arm and a reciprocal translocation between chromosome nos.3 and 4. The G-banding analyses revealed that an unusually elongated element of the long arm of a chromosome no.1 corresponded to the secondary constriction (constitutive heterochromatin), and that a reciprocal translocation between the segments of 3q23 → 3qter and 4p14 → 4pter (Fig. 2). His father's chromosome constitution showed 46 chromosomes including an elongated no.1. The G-banding analyses for his father's chromosome revealed that an unusually elongated element of the long arm of no.1 corresponded to the secondary constriction. Then the chromosome formula of his father was given as 46,XY,1qh+. His mother was chromosomally normal with no slight evidence for the abberation. Then the chromosome formula of the patient was given as 46,XY,1qh+,rcp t(3;4) (q23;P14).

Case 2. (5p+) The patient was a 16-year-old boy, 45,7 kg in weight, 158,5 cm in length. He was born to a 28-year-old mother and a 30-year-old father as the second child. There was no history of abortion, stillbirth, congenital malformations, mental retardation, exposure to atomic bomb, and consanguinity in this couple. His mother suffered from schizophrenia, and it was uncertain whether she took tranquilizer during the gestation. His father had been an alcoholism, and suffered from liver cirrhosis. He was already dead. The elder sister was phenotypically normal.

When, after 40 weeks of troubleless gestation, the patient was born with the Caesarean operation, he showed the condition of asphyxia. At birth he was 3150 g in weight. And the development of the patient was generally retarded.

The remarkable clinical signs of this patient were head deformity, torticollis, strabismus, behavior disorders; impulsiveness, obstinacy, self-injury, and speech disorder (Fig. 3).

The chromosome constitution of the patient based on the conventional Giemsa specimen showed 46 chromosomes which included a B-chromosome having an unusually elongated short arm. The G-banding analyses revealed that the abnormal chromosome was a no.5. Then the chromosome formula of the patient was given as 46,XY,5p+. Her mother was chromosomally normal with no evidence for the aberration. The chromosomal examinations of her elder sister was not cooperated (Fig. 4).

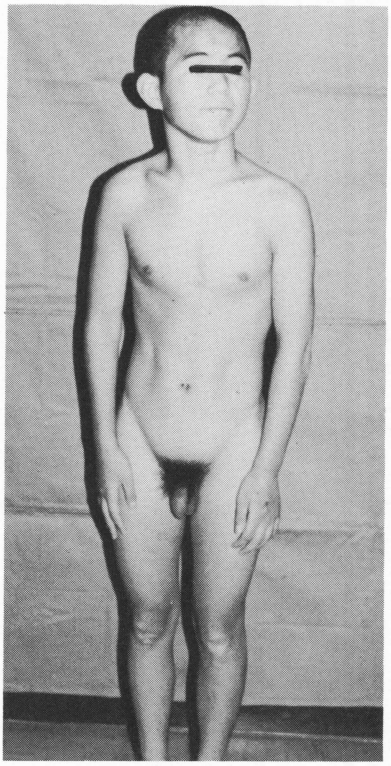

Fig. 3. External picture of the patient (Case 2).

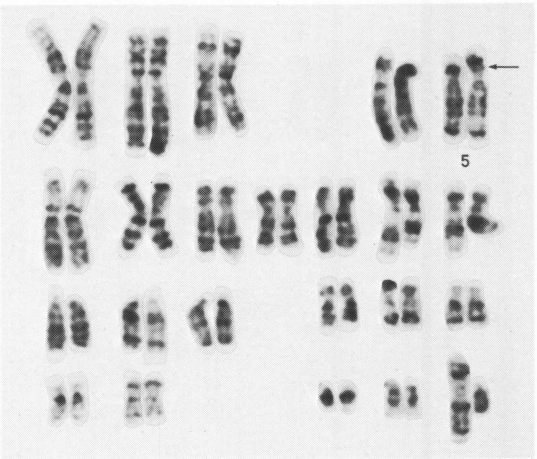

Fig. 4. G-banding karyotype of the patient (Case 2), showing 46,XY,5p+.

Case 3. (5q-)[50,59] The patient was a 27-year-old man. He was born to a 32-year-old mother and a 33-year-old father as the youngest child of four sibs. Although his parents were distantly consanguineous, there was no history of spontaneous abortion, stillbirth, congenital malformations, and the atomic bomb exposure, in this couple. His elder sister was born in a state of asphyxia, and died from pneumonia at neonatal period. His father was already dead. His mother and two elder brothers were phenotypically normal showing no evidence for the mental deficiency.

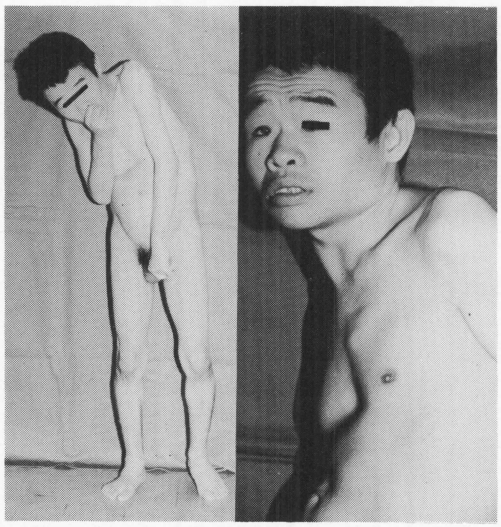

Fig. 5. External pictures of the patient (Case 3).

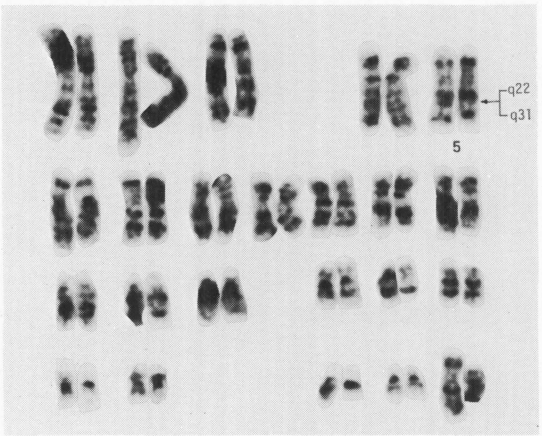

Fig. 6. G-banding karyotype of the patient (Case 3), showing 46,XY,del(5)(q22q31).

The birth weight of the patient was 3100 g at 40 weeks of gestation. The remarkable clinical signs of the patient were short stature, square head, low set hair line, aged facies, blepharophimosis, downward slanted palpebral fissure, hypertelorism, flat nasal bridge, broad nose, impaired vision, short webbed neck, funnel breast, kyphosis, incomplate development of the external genitalia with a small penis, speech disorder, and behavior disorders; burxism, aerophagia, finger suck (Fig. 5).

The chromosome constitution of the patient based on the conventional Giemsa specimen showed 46 chromosomes including a no.5 chromosome having an unusually shortened long arm. The G-banding analyses revealed that an unusual element corresponded to the interstitial deletion of the segment q22 → q31 of no.5 chromosome. Then the chromosome formula of the patient was given as 46,XY,del(5)(q22q31)(Fig. 6). His mother and second brother were chromosomally normal with no slight evidence for the aberration. The chromosomal examinations of his first brother were not cooperated.

Case 4. (9q-)[49,55] The patient was 14-year-old boy. he was born to a 34-year-old mother and 29-year-old father as the first child. There was no history of spontaneous abortion, stillbirth, congenital malformations, consanguinity, and the atomic bomb exposure in this couple. Clinical examinations revealed that his parents were phenotypically normal with no evidence for mental deficiency.

The birth weight of the patient was 3400 g at 40 weeks of gestation with the Caesarian operation. The remarkable clinical signs of the patient were growth retardation, seizure, bronchial asthma, atopic dermatitis, allergic rhinitis, speech disorder, behavior disorders; hyperactivity, stereotypic movement, impulsiveness, autistic tendency, and had no malformation.

The chromosome constitution of the patient based on the conventional Giemsa specimen showed 46 chromosomes which included a no.9 chromosome having an unusually shortened long arm. The G-banding analyses revealed that an unusually shortened element corresponded to the interstitial deletion of the segment q11 → q13 of no.9 chromosome. Then the chromosome formula of the patient was given as 46,XY,del(9)(q11q13)(Fig. 7 and Fig. 8). The

chromosomal examinations of his parents were not cooperated.

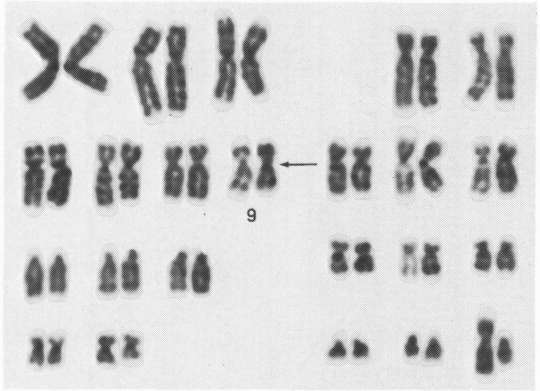

Fig. 7. G-banding karyotype of the patient (Case 4), showing 46,XY,del(9)(q11q13).

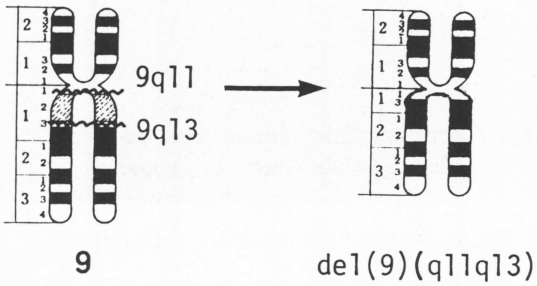

Fig. 8. Diagram showing the position of the interstitial deletion of no.9 chromosome.

Case 5. (inv(9))[56] The patient was an 11-year-old boy. He was born to a 26-year-old mother and a 24-year-old father as the second child. There was no history of spontaneous abortion, stillbirth, congenital malformations, the exposure to the atomic bomb, and consanguinity in this couple. His parents and elder brother were phenotypically normal with no evidence for the mental deficiency.

At birth, after 39 weeks of normal gestation, he was 3200 g in weight and 50 cm in length. At the beginning of his postnatal course, it seemed that he was growing and developing normally. His developmental disorders became clear at 3 years of age.

The remarkable clinical signs of the patient were growth retardation; 26,2 kg (–1,8 SD) in weight, 132 cm (–2,0 SD) in length, large mouth, slight kyphosis, speech disorder, and behavior disorders; hyperactivity, stereotypic movement, finger such (Fig. 9).

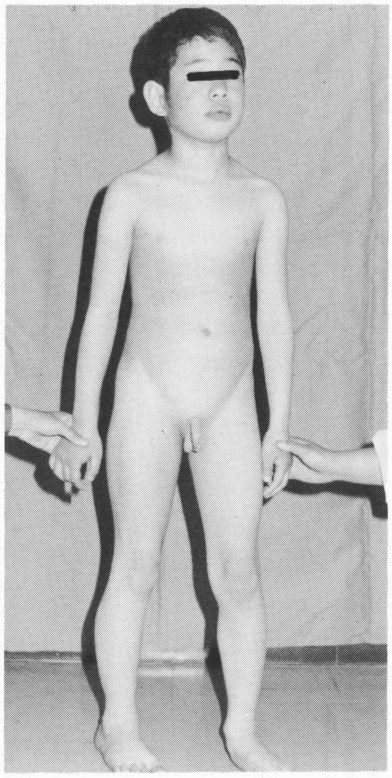

Fig. 9. External picture of the patient (Case 5).

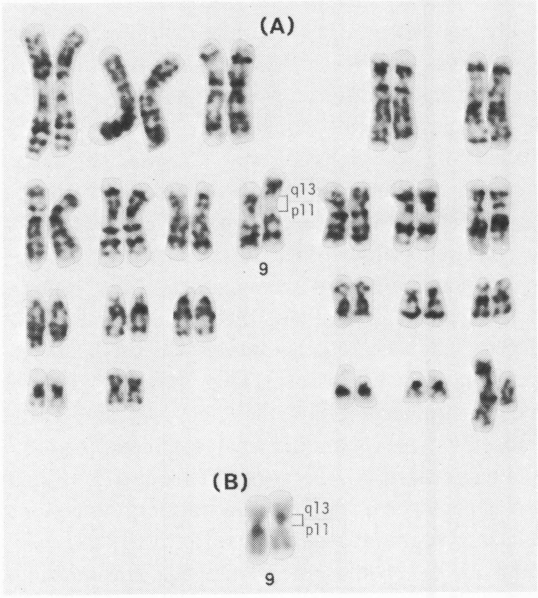

Fig. 10. G-banding karyotype (A) and partial C-banding karyotype (B) of the patient (Case 5), showing 46,XY,inv(9)(p11q13).

The chromosome constitution of the patient based on the conventional Giemsa specimen showed 46 chromosomes which included a no.9 chromosome having an unusually elongated short and shortened long arm. The G- and C-banding analyses revealed that one of no.9 chromosomes showed the pericentric inversion at p11 → q13. Then the chromosomal formula of the patient was given as 46,XY,inv(9)(p11q13)(Fig. 10). The karyotype of his mother was normal with no evidence for the aberration. The chromosomal examinations of his father and elder brother were not cooperated.

Case 6. (der(Y) ins (Y;15))[46,64] The patient was an 11-year-old boy. He was born to 21-year-old mother and 27-year-old father as the first child. There was no history of spontaneous abortion, stillbirth, congenital malformations, exposure to the atomic bomb, and consanguinity in this couple. Clinical examinations revealed that his parents were phenotypically normal with no evidence for mental deficiency.

The birth weight of the patient was 3100 g at 40 weeks of normal gestation. He had experienced in purulent meningitis at 4 months of age, in hepatitis at 2 years of age, and in chronic middle otitis.

The remarkable clinical signs of the patient were low set ears, perceptible deafness, flat occiput, seizure, speech disorder, and behavior disorders; hyperactivity, paraphagia (Fig. 11).

The chromosome constitution of the patient based on the conventional Giemsa specimen showed 46 chromosomes which included the Y chromosome having an unusually elongated short arm. The assessment of the unusual element became possible by the examinations of his father's karyotype. The results of the examinations in his father indicated that his father was the balanced carrier of insertion of a long arm segment of no.15 chromosome into the short arm of Y chromosome. The G-banding analyses made it possible to reveal that the segment from q11 → q13 of chromosome no.15 was missing, and that missing segment was inserted into the p11 portion of Y chromosome. Then the chromosome formula of his father was given as 46,XY,ins(Y;15)(p11;q11q13)(Fig. 12 and Fig. 13).

On the base of the findings of paternal translocation, it became evident that the aberration occurring in the patient corresponded to partial

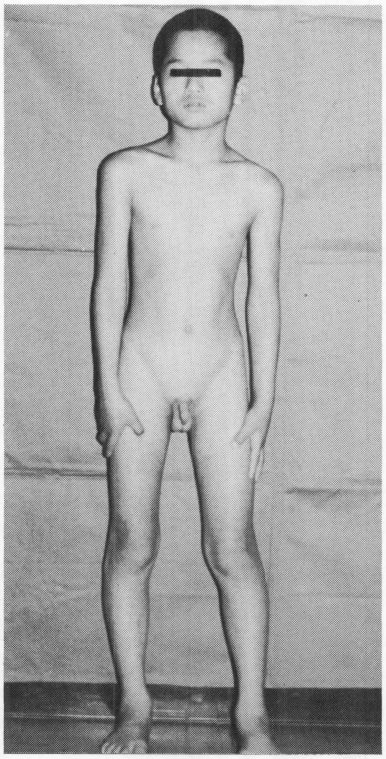

Fig. 11. External picture of the patient (Case 6).

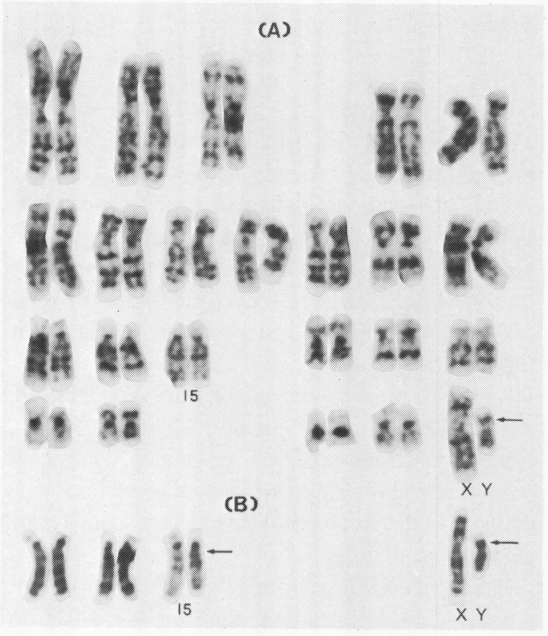

Fig. 12. G-banding karyotype of the patient (Case 6), 46,XY,der(Y), ins(Y;15)(p11;q11q13)(A), and Partial G-banding karyotype of the father, 46,XY,ins(Y;15)(p11;q11q13)(B).

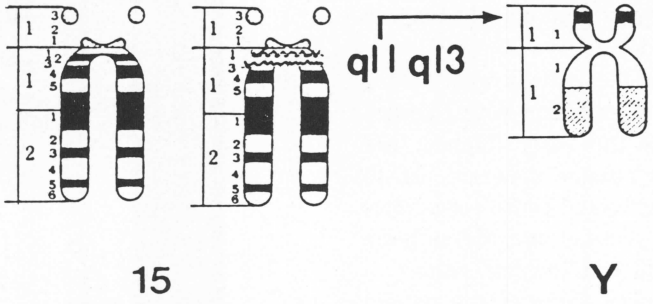

Fig. 13. Diagram showing direct insertion of a segment of Y chromosome (Yp11). Balanced condition in father.

trisomy for the long arm of no.15 chromosome. Then his chromosomal formula was represented by 46,XY,der(Y),ins(Y;15)(p11;q11q;13)pat(Fig. 12).

Case 7. (+15q-)[48] The patient was a 17-year-old boy, 43,5 kg in weight, 160,2 cm in length. He was born to a 37-year-old mother and a 38-year-old father as the third child. There was no history of spontaneous abortion, stillbirth, congenital malformations, exposure to the atomic bomb, and consanguinity in this couple. Clinical examination revealed that his parents and elder sister and brother were phenotypically normal with no evidence for the mental deficiency.

The birth weight of the patient was 3000 g at 40 weeks of normal gestation. The remarkable clinical signs of the patient were antimongoloid slant, hypertelorism, malformed auricle at the left side prominent nasal bridge, micrognathia, dorsal kyphosis, seizure, speech disorder, and behavior disorders; hyperactivity, wandering (Fig. 14).

The chromosome constitution of the patient based on the conventional Giemsa specimen showed 47 chromosomes including an additional element showing a little larger than the G group chromosomes. The result of the examinations with G-banding analyses, it was revealed that an additional element corresponded to a partial trisomy for 15(pter → q15). Then his chromosomal formula was given as 47,XY,+del(15)(q15qter)(Fig. 15). The karyotype of his mother was normal with no evidence for the aberration. The chromosomal examinations of his father and his elder sister and brother were not cooperated.

Case 8. (+21)[58] The patient was a 17-year-old girl, 38 kg in weight, 134,0 cm in length. She

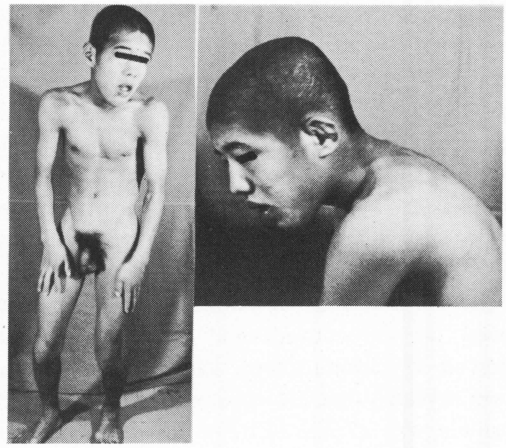

Fig. 14. External pictures of the patient (Case 7).

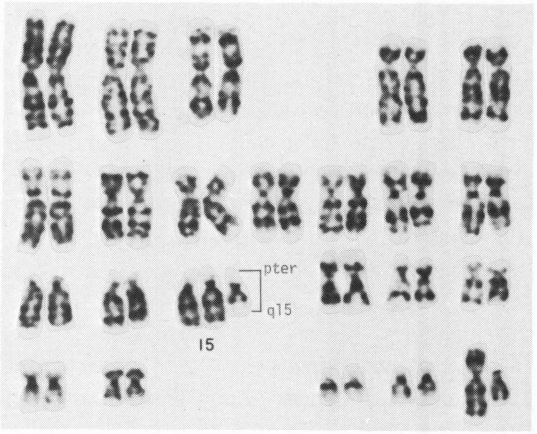

Fig. 15. G-banding karyotype of the patient (Case 7), showing 46,XY,+del(15)(q15qter).

was born to a 35-year-old mother and a 37-year-old father as the second child. There was no history of spontaneous abortion, stillbirth, congenital malformations, exposure to the atomic bomb, and consanguinity in this couple. Clinical exami-

nations revealed that her parents and her elder brother were phenotypically normal showing no evidence for mental deficiency.

The birth weight of the patient was 2900 g at 39 weeks of normal gestation with Caesarian operation. During the early infancy, her retarded development became apparent. At 10 months of age the diagnosis of Down's syndrome was established. At 3 years of age, she suffered from left keratitis and lost the left vision.

The remarkable clinical signs of the patient were short stature; 134 cm in length and 38 kg in weight, corresponding to 9 years of hight age and 11 years of weight age, microcephalus (49,0 cm in head circumference), deformed head, upward slanted palpebral fissure, epicanthal fold, exophthalmus, Keratitis and blepharoptosis of the left eye, trichiasis, loss of left vision, low and broad nasal bridge, malformed auricles, dysplasia and malimplantation in teeth, short and broad neck, kyphosis, aplasia of pubic hair, behavior disorders; obstinacy, and hypothyroidism (Fig. 16).

The chromosome constitution of the patient based on the conventional Giemsa specimen showed 47 chromosomes. The G-banding analyses revealed that her chromosome complement formula was 47,XX,+21(Fig. 17). Her parents were chromosomally normal with no evidence for the aberration. The chromosomal examination of her brother was not cooperated.

Case 9. (+21) The patient was a 7-year-old girl, 23,4 kg in weight, 105,5 cm in length. She was born to a 42-year-old mother and a 44-year-old father as the third child. There was no history of spontaneous abortion, stillbirth, congenital malformations, exposure to the atomic bomb, and consanguinity in this couple. The parents of the patient and her elder sisters were phenotypically normal with no evidence for the mental deficiency.

The birth weight was 2650 g at 38 weeks of gestation. At 3 months of age she was pointed out the congenital heart failure, and was diagnosed as Down's syndrome.

The remarkable clinical signs of the patient were epicanthal fold, upward slanted palpebral fissure, saddle nose, short extremities, kyphosis, congenital heart failure (VSD), speech disorder, and behavior disorders; hyperactivity, obstinacy, self-injury.

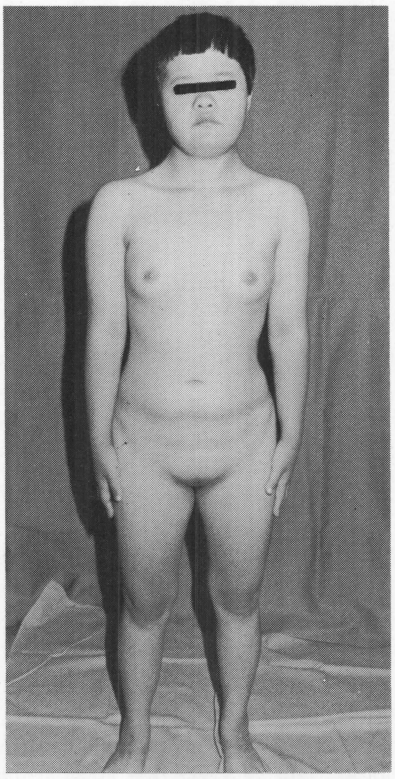

Fig. 16. External picture of the patient (Case 8).

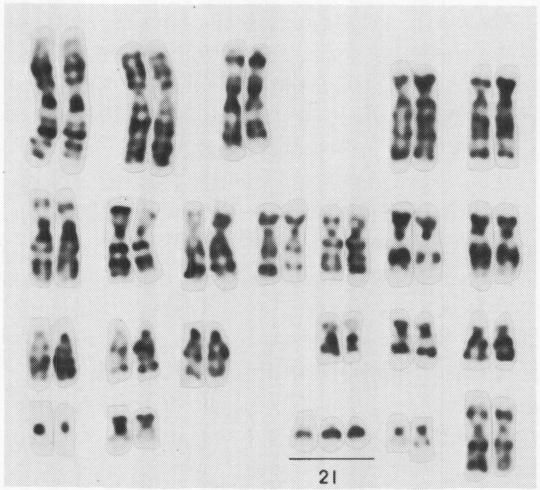

Fig. 17. G-banding karyotype of the patient (Case 8), showing 47,XX,+21.

The chromosome constitution of the patient based on the conventional Giemsa specimen showed 47 chromosomes. The G-banding analyses revealed that her chromosome complement formula was 47,XX,+21(Fig. 18). Her parents

were chromosomally normal with no evidence for the aberration. The chromosomal examinations of her elder sisters were not cooperated.

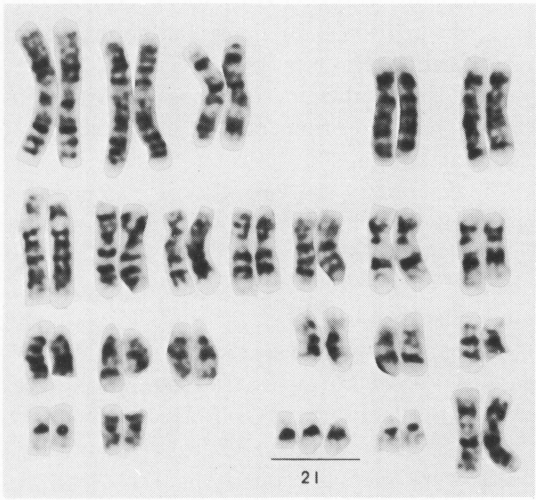

Fig. 18. G-banding karyotype of the patient (Case 9), showing 47,XX,+21.

Cases of normal variations

Case 1. (1qh+) The patient was a 31-year-old man. His remarkable clinical signs were frontal bossing, aged facies, hypertelorism, prominent nasal bridge, dysplasia and malimplantation in teeth, congenital cataract, blindness, seizure, speech disorder, and behavior disorders; wandering, stereotypic movement. His karyotype was given as 46,XY,1qh+. His father's karyotype was 46,XY,1qh+. And it was revealed that an elongated long arm of no.1 chromosome, at the constitutive heterochromatin area, of the patient was transmitted through the paternal line. The chromosomal examination of his mother was not cooperated.

Case 2. (9qh+) The patient was an 11-year-old girl. Her remarkable clinical signs were prominent nasal bridge, seizure, speech disorder, and behavior disorders; self-injury, hyperactivity, impulsiveness. Her karyotype was given as 46,XX,9qh+. Her parents, who had been phenotypically normal, were already dead. The karyotype of her grandmother was normal.

Case 3. (9qh+) The patient was an 18-year-old boy. His remarkable clinical signs were slight oxycephalus, speech disorder, and behavior disorders; autistic tendency, wandering. His karyotype was given as 46,XY,9qh+. His parents were phenotypically normal. But the chromosomal examinations of them were not cooperated.

Case 4. (Yq+) The patient was a 15-year-old boy. His remarkable clinical signs were seizure, hypoplastic external genitalia, speech disorder, and behavior disorders; obstinacy, wandering. His karyotype was given as 46,XYq+. His father was phenotypically normal, but the chromosomal examination of him was not cooperated.

Case 5. (Yq+) The patient was a 12-year-old boy. His remarkable clinical signs were congenital cataract, flat occiput, malformed auricles, dysplasia and malimplantation in teeth, speech disorder, and behavior disorders; self-injury, stereotypic movement. His karyotype was given as 46,XYq+. His father was phenotypically nor-

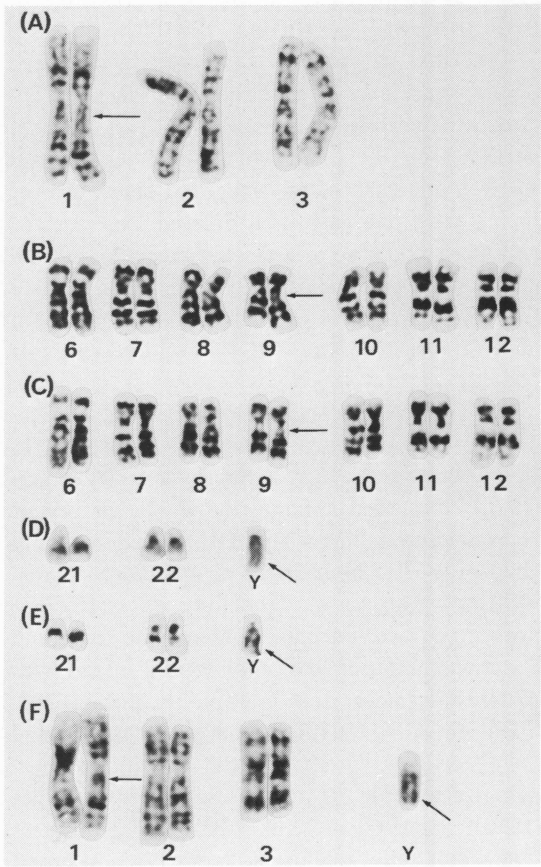

Fig. 19. Partial G-banding karyotypes of the patients having normal variations, (A) Case 1;46,XY,1qh+, (B) Case 2; 46,XY,9qh+, (C) Case 3; 46,XX,9qh+, (D) Case 4; 46,XYq+, (E) Case 5; 46,XYq+, (F) Case 6; 46,XYq+,1qh+.

mal, but the chromosomal examination of him was not cooperated.

Case 6. (1qh+, Yq+) The patient was a 31-year-old man. His remarkable clinical signs were short stature, flat occiput, head deformity, dysplasia and malimplantation in teeth, speech disorder, and behavior disorders; excitement, obstinacy, monologue. The karyotype analyses of the patient showed the elongation of a long arm of no.1 and Y chromosomes coincidently. Then his karyotype was given as 46,XYq+,1qh+. His parents had been phenotypically normal, but they were already dead (Fig. 19).

DISCUSSION

In this study, the incidence of chromosome abnormalities was 16,1%, indicating higher incidence as compared to normal population: 0,3 — 0,5% (reviewed by Makino, 1975)[74].

Abnormal karyotypes were seen in one case of the coincidence of reciprocal translocation between the chromosome nos.3 and 4, and normal variation on the long arm of no.1 (1qh+, rcp t(3;4)), one case of an elongated short arm of no.5 (5p+), one case of a deleted long arm of no.5 (5q-), one case of a deleted long arm of no.9 (9qh-), one case of a pericentric inversion of no.9 (inv (9)), two cases of partial trisomy of no.15 (der(Y), ins(Y;15) and +15q-), and two cases of trisomy 21 (+21).

The reciprocal translocation between chromosome nos.3 and 4 are rather rare at present in the literature [4,94,96,108]. Sarto and Therman (1976)[44] reported a family having a history of reproductive failure. The father and his only child proved to be carriers of a balanced translocation, t(3q-;4p+). Tenchini et al(1977)[108] presented two normal women, one repeated abortions, another had an abnormal infant with 47 chromosomes and multiple malformations. Schinzel et al (1978)[46] reported a malformed male newborn with trisomy 3 and his mother, being a carrier of t(3;4). Balíček and Zižka (1979)[4] reported a familial balanced translocation, t(3;4) and a malformed boy with unbalanced form of the same translocation. The variation on a long arm of no.1 have been known in both normal and abnormal individuals. It is then apparent that there is no concistency in clinical signs of Case 1 in relation to the chromosomal condition. The etiology of his clinical signs remains still unknown.

Case 2 had an elongated short arm of no.5 chromosome. Unfortunately the abnormal portion was too small to make the chromosomal identification. His relatives, except his mother, were not available for chromosomal examinations. Then the origin of this abnormality remains unknown.

The deletion of the long arm of no.5 chromosome has been described to occur very frequently in hematologic disorders such as refractory anemia[20,34,43,53,67,73,77,98,101,111,113,115], and preleukaemia and/or leukaemia [1,13,83,86,92,93,105,107,109,112,115]. On the other hand, only 10 cases without hematological disorders were reported on interstitial deletion of the long arm of no.5 chromosome[15,23,27,33,81,85,91,98,103]. The common clinical signs of these cases were mental retardation, short stature, frontal bossing, flat nasal bridge, saddle nose, hypertelorism, epicanthal fold, short neck, malformed ears and others. The deletion found in Case 3 without hematological disorder was also interstitial by showing the band q23, and he showed also heavy mental retardation, short stature, hypertelorism, flat nasal bridge, and short webbed neck. The relationship between clinical signs and breakpoint of the chromosome was, however, remains obscure.

The no.9 chromosome shows a high suspectibility for the structural rearrangement. In this study also, two cases showed the abnormalities of no.9 chromosome, one case was a partial monosomy (Case 4) and another case was a pericentric inversion (Case 5). The cases with partial monosomy for a long arm of no.9 chromosome were rather rare at present. In the literature, since Newton et al (1972)[80] reported the first case, as far as the author is aware of, only 7 cases were reported on the partial deletions of the long arm of the no.9 chromosome[12,35,80,99,110,119]. In those 6 cases out of 7 cases, the deleted segments included the area of secondary constitution composed of constitutive heterochromatin. Three cases (Newton et al, 1972; Buys et al, 1979; He et al, 1982) had a deficiency of secondary constriction. Two cases (Wisniewski et al, 1977, Turléau et al, 1978) had a deficiency of secondary constriction and its adjacent area. He et al (1972) noted a case with the complete deletion of the secondary constric-

tion of two chromosomes of no.9. In the previous reports on the monosomy of the long arm of no.9, the cases with the deletion of the secondary constriction alone had few malformations, and the cases including the enchromatin region had multiple congenital malformations. Case 4 was deleted at q11q13 corresponding to the secondary constriction alone, and showed no phenotypical abnormality. Wisniewski mentioned that the secondary constriction contributes little if any information necessary to normal development, deletion of the euchromatin alone is most probably responsible for the clinical findings. No significant relation between the secondary constriction and normal development, however, is yet established.

The pericentric inversion on no.9 chromosome have been reported in a number of papers. The incidence of inversions on no.9 depends on the methods used and population studied. Cytogenetic investigations of newborn populations with the conventional Giemsa staining yieled a low incidence, Gerald and Waltzer (1970)[29]; 1 among 3543, Lubs and Ruddle (1971)[70]; 2 among 3476. Fergson-Smith (1974)[24] showed, however, that after the application of banding techniques a much higher incidence, 4 among 367, was detected than after the conventional Giemsa staining, 1 among 2291. De la Chapelle et al (1974)[19] and Madan and Bobrow (1974)[71] observed incidence of about 1% in a Finnish and a British population respectively. Hansmann (1976)[32] reported the still higher incidence, 16 among 93, in German patients. Through the application of G- and C-banding techniques made it possible to reveal the exact points of breakage, the features of the cases with pericentric inv(9) were variable from the normal to the multiple malformations. According to Howard-Peebles and stoddard (1979)[38], the cases of inv(9), previously reported, were classified into four major groups: (1) phenotypically normal[19,36,38,47,68,84], (2) phenotypically normal but with reproduction failure or at least reduced fertility[19,38,68], (3) phenotypically abnormal due to another chromosome abnormalities[19,22,36,38,78,84,95,104], and (4) phenotypically abnormal with multiple malformations[3,19,38,45,47,52,56,57,62,65,66,68,79,84]. To date, the relationship between the inverted segment and the clinical features was yet in the dark.

The partial trisomy for the long arm of no.15 chromosome was detected in 2 cases in this study. One case (Case 6) had a duplicated segment of q11 → q13, and another case (Case 7) had a duplicated segment of pter → q15. The partial trisomy for a long arm of no.15 chromosome has been described by several authors. Sixteen cases from 13 reports were trisomic for the pter → q22 segment[5,8,9,14,16,18,37,72,82,88,106,117,118], one for the pter → q15 (Mankinen et al, 1976)[75], and two for the pter → q13 segment (Rethoré et al, 1973)[90]. As, in Case 6, the duplicated segment was very small (15q11 → q13), the chromosome identification was difficult. The result of the examination of his father that his father was a carrier of the direct insertion of a long arm of no.15 (q11 → q13) into a short arm of Y chromosome made it possible to reveal that this chromosome abnormality was identified as the partial trisomy for 15q transmitted from his father. The report of Case 7 also illuastrated the difficulty encountered in the identification of a small extra chromosome with few landmarks, in the absence of a paternal chromosome examination. The proper diagnosis of the extra chromosome was achieved after the employment of the clinical features which were differed from the 21- and also 22-trisomy (Kadotani et al, 1978)[40-42] and of G-banding technique. In reference to the reported cases, their common clinical features seemed to be mental and motor retardation, slow development, abnormalities of eye, ear, head and extremities, seizure, and behavior disorders. Case 6 and Case 7 corresponded to most of these findings, Case 6 had mental and developmental retardation, low set ears, deafness, seizure, and behavior disorders, and Case 7 had mental retardation, antimongoloid slant, malformations of auricles, nasal bridge and vertebra, seizure and behavior disorders. The clinical features of these cases, however, were rather variable by case.

The trisomy 21 was found in 2 cases (Case 8 and Case 9) in this study. The facial features of both cases were quite clearly those of Down's syndrome. Case 8 was found to have the association between trisomy 21 and primary hypothyroidism. Since Gilchirist (1946)[31] reported the first case of thyrotoxicosis in a child with Down's syndrome, the thyroid function among

patients with Down's syndrome has attracted the attention of investigators. Down's syndrome has been found with a frequency of 1/700 — 1/1000 in the human population, on the other hand a frequency of primary hypothyroidism 1/5000 — 1/8000 (Arita and Watanabe, 1981)[2], therefore the complication of Down's syndrome and hypothyroidism was very rare. Since Maranõn et al (1951)[76] reported the first case, several authors have reported on the hypothyroidism in children with Down's syndrome. It had been considered that the association between Down's syndrome and thyroid disease is rare. In contrast to the previous reports, Baxter et al (1975)[6] pointed out a high frequency of the association. In reported cases of Down's syndrome, the frequency of the hypothyroidism was lower than that of the hyperthyroidism. Because of the clinical features of Down's syndrome, the diagnosis of the hypothyroidism may be difficult to be made on clinical evidence alone. By using systematic investigations on autoimmunity, it was revealed that the thyroid autoantibody was associated with a high frequency of the thyroid dysfunction (Burgio et al, 1965[11]; Fialkow et al, 1965[25]; Shiono et al, 1973)[97]. Fialkow et al (1965)[25] reported, the frequency of the thyroid autoantibody was higher among mothers of children with Down's syndrome than among control females, and the age specific prevalence of seropositivity in mothers did not differ significantly throughout the age range. In some way the autoimmune reactions in women appear to be associated with a higher risk of Down's syndrome in the offspring. Concerning the prenatal maternal factors, previously Benda (1949)[7] suggested that the age alone couldn't be the decisive factor. Up to now, there has been no evidence that the autoimmune reactions played a role in the clinical manifestation of Down's syndrome. The pathogenetic mechanism has also remained unknown.

Seven cases, including one abnormal case of 1qh+, rcp t(3;4), showed normal variations on the long arm of no.1, 9, and Y chromosome. In all of those cases, it was found that the elongation occured at the area of constitutive heterochromatin. Although the elongated long arm of no.1, 9, and Y chromosome has been found in both normal persons and subjects with congenital abnormalities[10,11,21,39,44,54,69,87,89,100,120,121], more morphological variations of those chromosomes were found in abnormal population that in normal (Gardner et al, 1974; Ghosh, 1979). Further Soudek and Sroka (1979) mentioned in the report of chromosomal variations in mentally retarded and normal men that increased size of 9qh+ seemed to be a facter with possible negative effect. Up to date, however, the significance of the variation of constitutive heterochromatin in relation to mental retardation and behavior disorders is remained to be elucidated.

As a result of the chromosomal examinations of relatives of karyotypically abnormal patients, one case of the partial trisomy of no.15 and 2 cases of normal variation on the long arm of no.1 chromosome were found to be transmitted through the paternal line.

All the patients examined in this study had heavy mental retardation and behavior disorders, and not all the patients, however, had multiple malformations. In spite of those clinical features, the chromosome abnormalities were found in a high incidence of 16,1%.

As a result of this study, it was confirmed that chromosome abnormalities contribute significantly to the causes of mental retardation with behavior disorders, and that the chromosome analyses are important to any mental retardates with behavior disorders, even if the patient hasn't phenotypically manifest abnormalities.

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