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A Cytogenetic Study of Heavy Mental Retardates
III. A study on 114 karyotypes with banding techniques and incidence of chromosome abnormalities

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ABSTRACT

A cytogenetic study was conducted on 114 cases with heavy mental retardation who were admitted to National Sanatorium Kamo Hospital and Hiroshima Prefectural Handicapped Children's Hospital. Of the 114 cases, 69 cases were males and 45 cases were females. These patients were classified into two groups according to clinical features: Group I of 58 cases with cerebral palsy and Group II of 56 cases with 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 cases, 14 cases had abnormal karyotypes, showing an incidence of 12,3%. Of the 14 abnormal cases autosomal abnormalities were observed in 12 cases and sex-chromosome abnormalities in 2 cases. And normal variations of no.1, 9, and Y chromosome were found in 11 cases.

Out of the 58 cases with cerebral palsy belonging to Group I, 5 cases (8,6%) and out of 56 cases with behavior disorders belonging to Group II, 9 cases (16,1%) had abnormal karyotypes.

As a result of the chromosome analyses performed on available relatives of abnormal and normal cases with variations, one abnormal case and two of normal variations were found to be transmitted through the parental line.

A review of the etiology of mental retardation has shown that genetic causes contribute extensively to this handicap. To date, the relationship between mental retardation with multiple malformations and chromosome abnormalities has been well established, and an increasing number of chromosomal syndromes have been recognized. Minor chromosomal losses or gains may not, however, be associated with gross malformations. The significance of translocations as a cause of mental retardation remains to be elucidated.

As far as the author is aware of, ten previous surveys[6,7,10,11,14,15,18,44,47,52] have been published on karyotyping of mentally retarded patients. Of these reports, only those by Jacobs et al (1978)[14], Grase et al (1979)[10], Nielsen et al (1983)[47], and Kadotani et al (1980[15], 1984[18]) have employed banding techniques consistently in all patients.

It was found difficult by non-banding techniques to detect minor chromosome abnormali-

ties. In fact, the great majority of chromosome abnormalities were detected in patients with Down's syndrome by non-banding techniques. In addition, according to previous reports, the intelligence of patients ranged from border line ($60<IQ<75$) to profound ($IQ<20$).

In the present study, all the patients had heavy mental retardation ranging from severe ($20<IQ<35$) to profound ($IQ<20$). In order to detect even minor chromosome abnormalities, banding techniques were employed routinely in all the patients.

PATIENTS

The 114 cases examined in the present study consisted of 72 cases from National Sanatorium Kamo Hospital and 42 cases from Hiroshima Prefectural Handicapped Children's Hospital with 69 being males and 45 being females.

All the cases had heavy mental retardation with the degree of mental retardation ranging from severe in 4 cases being 20—35 in IQ score and profound in 110 cases being under 20 in IQ score.

According clinical features, the patients were divided into two groups; Group I of 58 cases (28 males and 30 females) with cerebral palsy and Group II of 56 cases (41 males and 15 females) with behavior disorders. In Group I, all the patients had dyskinesia, palsy or hemiplegia of the extremities, muscular atrophy, difficulty or inability in walking, and speech disorders. In Group II, the common clinical findings were various behavior disorders and speech disorders.

Furthermore, in terms of genetic consultation, chromosomal studies were also performed on available relatives of karyotypically abnormal patients.

METHODS

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

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

In abnormal or ambiguous cases, C-, or Q-banding staining was also employed as necessary, and the number of chromosome counts and of karyotyped cells was increased.

RESULTS

The details of the clinical and cytogenetic findings of all the patients have been presented in previous reports (Hiroshima J. Med. Sci. 35 (2), 149-161, 1968[38]; ibid. 35(3), 253—270, 1986)[4].

In Groups I and II, abnormal karyotypes were found in 5 cases (8,6%) and 9 cases (16,1%), respectively. In total, chromosome abnormalities were detected in 14 cases (12,3%) out of 114 cases (Table 1). Autosomal abnormalities were seen in 12 cases. Of these, 21 trisomy was observed in only two cases. Sex-chromosome abnormalities were detected in two cases.

Of all the cases, 11 cases (9,7%) had normal variations, of which 6 cases had autosomal variations, three cases had sex-chromosome variations, one case had autosomal and sex-chromosome variations coincidentally, and an autosomal variation was found in one abnormal case (Tables 1 and 2).

Table 1. Summary of Results

	Group I	Group II	Total
Number of patients	58	56	114
Normal karyotype	49	41	90
Normal with variations	4	6	10
Abnormal karyotype	5	9	14
% abnormal	8,6	16,1	12,3

Table 2. Summary of Abnormal and Variant Karyotypes

	Group I	Group II	Total
Trisomy 21	0	2	2
Other ahtosomal abnormalities	3	7	10
Sex-chromosome abnormalities	2	0	2
Autosomal variations	3	5*	8*
Sex-chromosome variations	1	3*	4*

* complicated in two cases (one was 1qh+,Yq+ and another was 1qh+, rcp t(3;4))

Abnormal karyotypes were seen in one case of reciprocal translocation between chromosome nos.3 and 4 and an elongated 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

Table 3. Details of Karyotypes of 114 cases

	Karyotype	Group I	Group II	Total	Reference
Normal	46,XY	26	29	55	
	46,XX	23	12	35	
Normal with variations	46,XY,1qh+		1	1	(34)
	46,XX,1qh+	2		2	
	46,XY,9qh+	1	1	2	(35)
	46,XX,9qh+		1	1	
	46,XYq+	1	2	3	
	46,XYq+,1qh+		1	1	
Abnormal	46,XY,1qh+,rcp t(3;4)		1	1	(23)
	46,XY,5p+		1	1	
	46,XY,5q-		1	1	(21)(32)
	46,XX,dir dup(7)	1		1	(24)
	46,XY,9q-		1	1	(20)(26)
	46,XY,inv(9)		1	1	(27)(40)
	46,XX,inv(9)	2		2	(29)(36)(40)
	46,XY,der(Y)ins(Y;15)		1	1	(17)(37)
	46,XY,+del(15)		1	1	(19)
	47,XX,+21		2	2	(30)
	47,XXX	1		1	
	45,X/46,XX/46,Xr(X)	1		1	(22)(33)
	Total	58	56	114	

long arm of no.5 (5q-), one case of a direct duplication of no.7 (dir dup(7)), one case of a deleted long arm of no.9 (9q-), three cases of a pericentric inversion of no.9 (inv(9)), two cases of partial trisomy of no.15 (one was der(Y) ins(Y;15) and another was +15q-), two cases of trisomy 21 (+21), one case of triplo-X (XXX), and one case of mosaic X chromosome (X/XX/Xr(X))(Table 3).

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

In the chromosomal study of the available relatives of karyotypically abnormal patients and normal patients with variations, 15 cases were karyotyped. The results showed that one case of chromosome abnormality and two cases of normal variations were found to be transmitted through the parental line.

The details of karyotypically abnormal cases and normal cases with variations were reported previously[17-24,26-36,38,40,41].

DISCUSSION

The relationship between mental retardation with multiple malformations and chromosome abnormalities has been established, but mental retardation does not always have multiple malformations. Among the patients in the present study, in fact, apart from those with Down's syndrome, only two cases (case of 47,XXX and case of 46,XX, dir dup(7)) had been previously examined cytogenetically with non-banding techniques. The recent studies have demonstrated that minor chromosomal losses or gains and translocations were not associated with gross malformations.

The advances made in differential staining methods have contributed much to the increase of knowledge in human cytogenetics. Among the previous reports in which mentally retarded patients were karyotyped, according the author's knowledge, only five studies routinely employed banding techniques. A G-band study of newborn babies by Buckton et al (1980)[9] showed that the frequency of structural rearrangements detected with the banding techniques was not significantly higher than in the non-banding techniques. The application of banding techniques, however, has made it possible not only to detect the chromosome abnormalities but also

to delineate the exact points of rearrangements. In order to detect even minor chromosome abnormalities, in the present study, the banding techniques were routinely employed in all the patients.

The incidence of chromosome abnormalities in normal population is 0,3%—0.5% (reviewed by Makino, 1975)[43]. The finding of 12,3% (14 cases out of 114 cases) of chromosome abnormalities in this population indicates their importance in the etiology of mental retardation. Furthermore, it is very interesting that an obvious difference was showed in the incidence of abnormal karyotypes between Group I (8,6%, 5 cases out of 58 cases) and Group II (16,1%, 9 cases out of 56 cases)(Table 1).

Group I[38] consisted of patients having cerebral palsy. As reason for the low incidence in this group, most of the patients had perinatal and postnatal causes such as asphixia, pracenta previa, inertia uteri, prolonged lavor, forceps operation, severe jaundice, meningitis and encephalitis. With the advances in medicine, it may be considered that the perinatal and postnatal causes will decrease and that the proportion of chromosome abnormalities as a prenatal cause will be found to increase in patients with cerebral palsy in future.

Group II[41] consisted of patients without cerebral palsy but having behavior disorders as the most common clinical findings. Most patients of this group had few malformations suggestive of chromosome abnormalities except two cases with Down's syndrome. Apart from two cases with Down's syndrome, none had been previously karyotyped. The high incidence (16,1%) observed in this group is remarkable. Prior to this study, in 4 abnormal cases out of 9 cases any cause of mental retardation was not found.

Of 14 abnormal cases out of all the patients, autosomal abnormalities were seen in 12 cases and sex-chromosome abnormalities in 2 cases. Of the autosomal abnormalities, trisomy 21 was seen in only two cases. Trisomy 21 was the commonest abnormality in previous reports. Approximately 10% of mentally retarded patients have Down's syndrome (Speed et al, 1976[51]; Jacobs et al, 1978)[12]. The remarkably low incidence (1,75%, 2 cases out of 114 cases) in the present study probably refrects the heavily retarded patients (4 severe cases and 110 profound cases) studies. The rate of sex-chromosome abnormalities among the newborns is around two per thousand (Nielsen and Sillesen, 1975)[46]. In the present study, this abnormality was found in 2 cases (1,75%), demonstrating a high incidence rate.

Chromosomal losses were found in 3 cases; one case of 5q-, one case of 9q-, and one case of X/XX/Xr(X), and chromosomal gains were observed in 6 cases; one case of 5p+, one case of dir dup(7), one case of +15q-, two cases of +21, and one case of XXX. The relationship between karyotype and phenotype in minor chromosomal losses or gains remains unclear except for several established syndromes.

Translocation-type abnormal karyotypes were found in 5 cases; one case of 1qh+,rcp t(3;4), one case of der(Y)ins(Y;15), three cases of inv(9). No precise explanation has been made, to date, on translocations as a cause of mental retardation. As suggested by Jacobs (1974)[13] this may be due to an association between *de novo* translocations and mental retardation presumably caused by a loss of chromosomal material in the translocation area or due to a position effect or a point mutation.

Normal variations were found in 11 cases, being 9,7% in incidence; 3 cases of an elongated long arm of no.1 (1qh+), 3 cases of an elongated long arm of no.9 (9qh+), 3 cases of long Y(Yq+), one case of an elongated long arm of no.1 associated with long Y (1qh+,Yq+), and one abnormal case of an elongated long arm of no.1 associated with reciprocal translocation between nos.3 and 4 (1qh+, rcp t(3;4)). The elongation occured at the area of the constitutive heterochromatin in all the variation cases.

Although the elongated long arm of no.1, 9 and Y chromosome has been found in both normal persons and subject with congenital anomalies[2,4,5,8,12,16,25,42,48,49,50,54,55] more morphological variations of those chromosomes were found in abnormal population than in normal (Gardner et al, 1978[8]; Ghosh, 1979)[9]. Tüür et al (1974)[53] made the chromosomal study on 208 normal adults and reported that the incidence of 1qh+ was 1,9%. Nielsen et al (1974)[45] reported that the incidence of 9qh+, based on the chromosomal examinations on 8712 persons, was 0,1%. In the present study, the incidence of 1qh+ was 4,4% (5 cases out of 114 cases) and

that of 9qh+ was 2,6% (3 cases out of 114 cases), showing higher incidence than that of previous reports, respectively. Unusually long Y chromosome is the commonest variation, but the significance of this feature in relation to mental retardation is uncertain. It has been suggested, however, that Yq+ may be indicative of increased risk of behavioral disturbance or mental defects (Alley and Grase, 1979)[1]. Similarly the relationship between autosomal variations and mental retardation also remains a matter for further investigation.

As a result of the chromosome analyses performed on available relatives of abnormal cases and normal cases with variations, one abnormal case (der (Y),ins(Y;15)) and two of normal variations (1qh+) were found to be transmitted through the parental line. Genetic consultation was provided to one case. In terms of etiological effects and genetic consultation, adequate family studies may be necessary for chromosomal studies.

The present study had confirmed that chromosomal abnormalities contribute significantly to the etiology of mental retardation and that the chromosome analyses are important to any retardate, especially when no obvious causes for the retardation was found.

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REFERENCES

1. **Ally, F.E. and Grace, H.J.** 1979. Chromosome abnormalities in South African mental retardates. Sa. Med. J. **28**: 710—712.
2. **Büchner, T., Wilkins, A. und Pfeiffer, R.** 1967. Asynchrone Reduplication bei Langenunterschied zwischen den homologen Chromosomen nr.1 beim Menschen. Exp. Cell Res. **46**: 58—64.
3. **Buckton, K.E., O'Riordon, M.L., Ratcliffe, S. Slight, J., Mitchell, M. and McBeath, S.** 1980. A G-band study of chromosomes on liveborn infants. Ann. Hum.Genet. **43**: 227—239.
4. **Cooper, H.L. and Hernis, R.** 1963. A familial chromosome variant in a subject with anomalous sex differentiation. Am. J. Hum. Genet. **15**: 465—475.
5. **Donachue, R.P., Bias, W.B., Renwick, J.H. and McKusick, V.A.** 1968. Probable assignment of the Duffy blood group locus to chromosome 1 in man. Proc. Nat. Acad. Sci. **61**: 949—955.
6. **Fead, M.J.W., Robertson, J., Field, M.A.S. and Mellon, J.P.** 1979. A chromosome survey of a hospital for the mentally subnormal. Clin. Genet. **16**: 191—204.
7. **Fisch, T.T.** 1977. Chromosome findings in the mentally retarded. J. Am. Med. Technol. **39**: 243—244.
8. **Gardner, R.J.M., McCreagor, H.R., Palskow, M.I. and Veale, A.M.O.** 1974. Are 1q+ chromosomes harmless ? Clin. Genet. **6**: 383—393.
9. **Ghosh, P.K.** 1979. Chromosome heteromorphism in children with congenital malformations. Ind. J. Exp. Biol. **17**: 1186—1189.
10. **Grace, H.J., Ally, F.E., Nelemans, A.P. and Kint, B.** 1979. A cytogenetic study of a mentally retarded population in South Africa. Sa. Med.J. **55**: 707—709.
11. **Gripenberg, U., Hongell, K., Knuutila, S., Kähkönen, M. and Leisti, J.** 1980. A chromosome survey of 1062 mentally retarded patients. Evaluation of a long-term study at a RinneKoti Institution, Finland. Hereditas **92**: 223—228.
12. **Jacobs, P.A., Brunton, M., Frackiewicz, A., Newton, M., Cook, P.J.L. and Robson, E.B.** 1970. Studies on a family with three cytogenetic markers. Ann. Hum. Genet. **33**: 325—335.
13. **Jacobs, P.A.** 1974. Correlation between euploid structural chromosome rearrangements and mental subnormality in humans. Nature **249**: 164—165.
14. **Jacobs, P.A., Matsuura, J.S., Mayer, M. and Newlands, I.M.** 1978. A cytogenetic survey of an institution for the mentally retarded: I. Chromosome abnormalities. Clin. Genet. **13**: 37—60.
15. **Kadotani, T., Watanabe, Y., Kiyuna, T., Kawamoto, T. and Takemura, I.** 1980. Cytogenetic data of 92 cases obtained in the Kojika-Gakuen, an institution for severe physically and mentally retarded patients. Proc. Japan Acad. **56B**: 431—436.
16. **Kadotani, T., Watanabe, Y. and Kiyuna, T.** 1980. Chromosome 1qh+ found in the husband of a couple with repeared abortions. CIS. **28**: 18—20.
17. **Kadotani, T., Kanata, S., Kubo, S., Kodama, H. and Watanabe, Y.** 1983. A case of partial trisomy for the long arm of No.15 chromosome. Proc. Japan Acad. **59B**: 355—358.
18. **Kadotani, T., Kanata, S., Kubo, S., Kodama,**

H. and Watanabe, Y. 1984. A chromosome study of the patients with heavy mental retardation. ibid. **60B**: 129—130.

19. **Kadotani, T., Kanata, S., Kubo, S., Kodama, H. and Watanabe, Y.** 1984. An additional case of partial trisomy for the No.15 chromosome. ibid: **60B**: 134—136.
20. **Kadotani, T., Kanata, S., Kubo, S., Kodama, H. and Watanabe, Y.** 1984. A case of partial monosomy for the long arm of No.9 chromosome. ibid: **60B**: 257—259.
21. **Kadotani, T., Kanata, S., Kubo, S., Kodama, H. and Watanabe, Y.** 1984. A case with the interstitial deletion of the long arm of No. 5 chromosome. ibid. **60B**: 406—408.
22. **Kadotani, T., Kanata, S., Kubo, S., Kodama, H. and Watanabe, Y.** 1985. A case of X/XX/Xr(X) derived from the father with the chromosome aberrations. ibid. **61B**: 35—36.
23. **Kadotani, T., Kanata, S., Kubo, S., Kodama, H. and Watanabe, Y.** 1985. A case of 1qh+, t(3;4)(q23;p14). ibid. **61B**: 83—85.
24. **Kadotani, T., Kanata, S., Naemura, M., Namba, Y., Matsuo, N. and Watanabe, Y.** 1985. A case with a long arm duplication of the No. 7 chromosome. ibid. **61B**: 131—133.
25. **Kamaryt, J., Adamek, R. and Vrba, M.** 1971. Possible linkage between uncoiler chromosome Un.1 and amylase polymorphism Amy 2 loci. Hum. Genet. **11**: 213—220.
26. **Kanata, S.** 1984. A case of mental retardation with a interstitial deletion for the long arm of No.9 chromosome. (in Japanese with English abstract). Iryo **38**: 1170—1173.
27. **Kanata, S., Kadotani, T., Watanabe, Y., Matsuo, N., Kodama, H. and Kubo, S.** 1985. A case of mental retardation having pericentric inversion on No.9 chromosome (inv(9)(p11q13)). Proc. Japan Acad. **61B**: 242—244.
28. **Kanata, S., Kadotani, T., Watanabe, Y., Namba, Y. and Naemura, M.** 1985. A chromosomal study on the 42 cases of the handicapped children. ibid. **61B**: 325—328.
29. **Kanata, S., Kadotani, T., Watanabe, Y., Matsuo, N., Kodama, H. and Kubo, S.** 1985. A heavy mentally retarded girl having pericentric inversion on No.9 chromosome (inv(9)(p13q21)). ibid. **61B**: 329—332.
30. **Kanata, S., Kadotani, T., Watanabe, Y., Kodama, H., Kubo, S. and Nishi, Y.** 1985. A case of Down's syndrome with primary hypothyroidism. ibid. **61B**: 387—389.
31. **Kanata, S., Kadotani, T., Watanabe, Y., Namba, Y., Naemura, M., Kubo, S. and Kodama, H.** 1985. A chromosomal study on the 56 cases of cerebral palsy. ibid. **61B**: 475—478.
32. **Kanata, S., Kadotani, T. and Watanabe, Y.** 1985. A case of heavy mental retardation with the interstitial deletion of the long arm of No.5 chromosome (in Japanese with English abstract). Med. Genet. Res. **7**: 6—13.
33. **Kanata, S., Kadotani, T., Kodama, H., Kubo, S. and Watanabe, Y.** 1985. A case of Turner syndrome with rare karyotype (45,X/46,XX/46, Xr(X))(in Japanese). Hiroshima Igaku **38**: 1076—1079.
34. **Kanata, S., Kadotani, T., Watanabe, Y., Kodama, H. and Kubo, S.** 1986. Elongated long arm of no.1 chromosome in heavy mental retardates. Proc. Japan Acad. **62B**: 61—64.
35. **Kanata, S., Kadotani, T., Watanabe, Y., Kodama, H. and Kubo, S.** 1986. Elongated long arm of no.9 chromosome in heavy mental retardates. ibid. **62B**: 95—97.
36. **Kanata, S., Kadotani, T., Watanabe, Y., Namba, Y. and Naemura, M.** 1986. A case of heavy mental retardation with cerebral palsy having pericentric inversion on no. 9 chromosome (inv(9)(p11q13)). ibid. **62B**: 129—132.
37. **Kanata, S.** 1986. A mentally retarded boy with partial trisomy 15 derived from the paternal insertional translocation (in Japanese with English abstract). Iryo **40**: 329—333.
38. **Kanata, S.** 1986. A cytogenetic study of heavy mental retardates. I. A study on heavy mental retardates with cerebrl palsy. Hiroshima J. M. Sci. **35**: 149—161.
39. **Kanata, S., Kadotani, T., Watanabe, Y., Kodama, H. and Kubo. S.** 1986. A chromosomal study on 56 cases with heavy mental retardation and behavior disorders. Proc. Japan Acad. **62B**: 165—168.
40. **Kanata, S., Kadotani, T., Watanabe, Y., Kodama, H., Kubo, S., Namba, Y. and Naemura, M.** 1986. Pericentric inversion on no.9 chromosome. (in Japanese) Hiroshima Igaku **39**: in press.
41. **Kanata, S.** 1986. A cytogenetic study of heavy mental retardates. II. A study on heavy mental retardates with behavior disorders. Hiroshima M.J. Sci. **35**: 253—270.
42. **Lobitz, J.A., McCaw, B.K. and Hecht, F.** 1972. Giemsa banding pattern of a heritable 1qh+ variant chromosome : A possible partial duplication. J. Med. Genet. **9**: 276—279.
43. **Makino, S.** 1975 Human chromosomes. Igakushoin LTD. Tokyo. North-Holland Publishing Company. Amsterdam-Oxford. 7—21.
44. **Nelson, M.M. and Smart, R.D.** 1982. The results of chromosome examinations in an institution for mental retardates in the Cape Provance. Sa. Med. J. **62**: 25—29.
45. **Nielsen, J., Friedrich, U., Hreidarsson, A.B. and Zeuthen, E.** 1974. Frequency of 9qh+ risk of chromosome aberrations in the progeny of individuals with 9qh+. Humangenetic **21**: 211—216.
46. **Nielsen, J. and Sillesen, I.** 1975. Incidence of chromosome aberrations among 11,148 newborn children. ibid. **30**: 1—12.
47. **Nielsen, K.B., Dyggve, H.V., Knudsen, H. and Olsen, J.** 1983. A chromosomal survey of an institution for the mentally retarded. Dan. Med.

Bull. **30**: 5—10.

48. **Philip, J., Frydenberg, O. and Sele, V.** 1965. Enlarged chromosome no.1 in a patient with primary amenorrhoea. Cytogenetics. **6**: 357—370
49. **Prigozina, E.L., Stravrovskaya, A.A., Ichalovskaya, T.A. and Umnova, M.A.** 1971. On the linkage of Duffy blood group locus to the human chromosome 1. Genetika **7**: 138—142.
50. **Sofuni, T. and Sandberg, A.A.** 1967. Chronology and pattern of human chromosome replication, VI. Further studies including autoradiographic behavior of normal and abnormal no.1 autosomes. Cytogenetics **6**: 357—370.
51. **Speed, R.M., Johnston, A.W. and Evans, H.J.** 1976. Chromosome survey of total population of mentally subnormal in North-East of Scotland. J. Med. Genet. **13**: 295—306.
52. **Sutherland, G.R., Murch, A.R., Gardiner, A.J., Carter, R.F. and Wiseman, C.** 1976. A cytogenetic Survey of a hospital for the mentally retarded. Hum. Genet. **34**: 231—245.
53. **Tüür, S., Käosaar, M. and Mikelsaar, A.V.** 1974. 1qh+ variants in a normal adult population (one with a pericentric inversion). Humangenetik **24**: 217—220.
54. **Ving, K.L. and Ives, E.J.** 1968. Asymmetry of chromosome 1 pair in three generations of phenotypically normal family. Canad. J. Genet. Cytol. **10**: 575—589.
55. **Yunis, J.J. and Gorlin, R.J.** 1963. Chromosomal study in patients with cysts of the jew, multiple nevoid basal cell carcinoma and bifid rib syndrome. Chromosoma **14**: 146—153.