118. *Chromosome Studies in Sixteen Cases of Human Congenital Diseases*^{*)}

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Since the beginning in 1959, over 230 cases of congenital diseases in Japanese have been subjected to chromosome survey in the senior author's laboratory, the work having been carried out with the aid of clinicians in various fields of medicine.³⁾⁻¹⁴⁾ In the present paper are reported studies of chromosome conditions in sixteen cases with congenital diseases which included twelve cases of Down's syndrome, one case of a Down's-like syndrome, two cases of congenital mental retardations and one case of Laurence-Moon-Biedl's syndrome. Clinical diagnosis of each patient, together with sampling of the culture material for chromosome study, was made in the Department of Pediatrics, Aiku Research Institute, Tokyo. All the cytological work was done in the Makino Laboratory. The diagnostic and clinical data of the patients herein studied are summarized in Table I.

White blood cells, separated from peripheral blood of each patient, were cultivated by means of a short-term culture method (for detail, see 8, 10). Chromosome preparations were made according to the water pretreatment acetic dahlia squash technique.

The twelve patients with Down's syndrome were eight girls and four boys. Clinically they showed facial and other diagnostic features generally characteristic of this syndrome known under the general term of "mongolism" (Table I). Cytologically, they showed without exception a typical chromosome pattern widely known in Down's syndrome, showing a consistent count of 47 instead of 46, due to the presence of one additional small acrocentric chromosome (Figs. 1 and 2, Table II). The extra element was found to correspond almost certainly to chromosome no. 21 in size and shape. It was then concluded that all the Down's syndrome cases here considered had 47 chromosomes, being trisomic for chromosome no. 21. A quite identical feature has been reported to date in a large number of cases of this syndrome.

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Table I. Diagnostic features in sixteen cases of under study

Case no.	Age & sex	Diagnosis	Clinical findings
1	13 yr. 5 m. ♀	Down's syndrome	A typical facial configuration, upward eyes, small bridged underdeveloped nose, scrotal tongue, macroglossia, short hand, incurved 5th finger, dry skin obesity, strabismus, microcephalus, poor muscle tone.
2	15 yr. 3 m. ♀	"	Typical face, scrotal tongue, developmental anomalies of the extra ears, upward eyes, microcephalus, small bridged underdeveloped nose, poor muscle tone.
3	10 yr. ♀	"	Typical face, upward eyes, small bridged underdeveloped nose, dry skin.
4	12 yr. 6 m. ♀	"	Typical face, scrotal tongue, brachycephalic head, funnel thorax, small bridge underdeveloped nose.
5	12 yr. 2 m. ♀	"	Typical face, upward eyes, strabismus, scrotal tongue, brachycephalic head, small bridged underdeveloped nose, poor muscle nose.
6	11 yr. 4 m. ♀	"	Typical face, retarded body growth, upward eyes, small bridged underdeveloped nose, scrotal tongue, short hand and incurved 5th finger, dry skin, poor muscle tone.
7	6 yr. 3 m. ♀	"	Typical face, retarded body growth, upward eyes, small bridged underdeveloped nose.
8	5 yr. 6 m. ♀	"	Typical face, retarded body growth, upward eyes, small bridged underdeveloped nose, pigeon breast, poor muscle tone, marked joint laxity.
9	14 yr. 2 m. ♂	"	Typical face, upward eyes, small bridged underdeveloped nose, scrotal tongue, dry skin, brachycephalic head, congenital heart anomaly.
10	10 yr. 5 m. ♂	"	Typical face, scrotal tongue, upward eyes, brachycephalic head, small bridged underdeveloped nose, short hand incurved 5th finger, poor muscle tone, marked joint laxity, congenital heart disease, genital organ underdevelopment, pigeon breast.
11	7 yr. 10 m. ♂	"	Typical face, brachycephalic head, upward eyes, small bridged underdeveloped nose, developmental anomalies of the extra ears, 1st and 2nd toes widely spaced feet.
12	8 yr. ♂	"	Typical face, small and underdeveloped nose, scrotal tongue, short hand, dry skin, poor muscle tone, underdeveloped genital organ (hypo-genitalism).
13	7 yr. 9 m. ♂	Down's-like syndrome	Mental retardation, small bridged underdeveloped nose, small eyes, short hand, obesity.
14	16 yr. 8 m. ♂	Laurence-Moon-Biedl's syndrome	Mental retardation, obesity, hypogenitalism, optic atrophy, retinitis pigmentosa, microcephalus, developmental anomalies of the extra ears.
15	13 yr. 5 m. ♀	Congenital mental retardation	Mental retardation, retarded body growth, hypertelerism, strabismus, epilepsy, coxa valga, skin covered with lanugo.
16	7 yr. 5 m. ♀	"	Mental retardation, microcephalus, obesity, micrognathia, congenital hip dislocation, epilepsy.

Table II. Chromosome constitution in sixteen patients under study

Case no.	Chromosome counts					Chromosome constitution	No. of cells ana.	No. of cells obs.
	44	46	47	48	94			
1			13			47, trisomy 21	1	13
2			6			"	2	6
3			37			"	2	37
4			17			"	1	17
5			17		1	"	2	18
6			6			"	2	6
7			3			"	1	3
8			3			"	1	3
9			16			"	2	16
10			3			"	1	3
11			17	2		"	4	19
12			17			"	1	17
13		12				46, XY	3	12
14	1	9				46, XY	2	10
15		11				46, XX	2	11
16		12				46, XX	2	12

A patient diagnosed as Down's-like syndrome (case no. 13) was characterized by mental retardation, small bridged underdeveloped nose, small eyes and short hands. It was found cytologically that the patient had a diploid complement of 46 chromosomes, containing an XY mechanism (Fig. 3, Table II). After morphological analysis the karyotype was proved to be of apparently normal pattern, so far as the superficial configuration of each chromosome is concerned.

The one case of Laurence-Moon-Biedl's syndrome and two cases of congenital mental retardation were found to have consistently 46 chromosomes. Karyotype analysis revealed no detectable change or variation in the chromosomes either morphologically or numerically; each case comprised 44 autosomes in superficially normal configuration and a pair of sex chromosomes, two X's in the female patient, and X and Y in the male (Fig. 4).

Remarks. Promoted advantageously by sound advances of simple and reliable technical methods, clinical cytogenetics has recently undergone much development and many congenital human disorders have been chromosomally screened for various types of chromosome aberrations. Current findings in this field have been reviewed by several authors (see, 9, 11, 12, 14).

The twelve cases of Down's syndrome studied here all showed trisomy for no. 21, the chromosome number being 47, with a feature quite in agreement with many cases of this syndrome so far cytolo-

Figs. 1-4. Somatic chromosome complement based on leukocyte cultures. 1, from a case of Down's syndrome (no. 2). 2, from a case of Down's syndrome (no. 9). 3, from a case of Down's syndrome (no. 13). 4, from a case of congenital mental retardation (no. 15).

gically studied. Current literature shows, however, several instances of this syndrome in which the trisomic 21 appears translocated to another autosome. Recently Böök *et al.*¹³ reported that a Down's-like syndrome patient having certain symptoms and signs characteristic of Down's syndrome showed 46 chromosomes involving trisomy for no. 21 and monosomy for no. 16. In a mental retarded boy clinically diagnosed as Down's syndrome, Schmid *et al.*¹⁵ reported a normal diploid complement containing 46 chromosomes. The case of Down's-like syndrome considered here was found to possess 46 chromosomes and a consistently normal karyotype.

There have been reported many cases of congenital disorders in which no visible change or detectable variation from a normal chromosome complement has occurred.^{2), 8) - 12), 14)} The case of Laurence-Moon-Biedl's syndrome and two cases of congenital mental retardations herein considered showed superficially no chromosomal change from a normal complement. It should be noted, however, that a variety of chromosomal aberrations may be masked by a superficially normal karyotype, being non-detectable by current techniques.

In conclusion, sixteen cases of congenital syndromes subjected to cytological studies are discussed in this paper. Twelve cases of Down's syndrome (mongolism) showed a trisomy for no. 21 with a chromosome number of 47. The one case of Down's-like syndrome, one case of Laurence-Moon-Biedl's syndrome and two cases of con-

genital mental retardation were each found superficially to possess a normal chromosome complement.

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References

- 1) Böök, J. A., K.-H. Gustavson and B. Santesson (1961): *Acta Paediatrica*, **50**, 240-248.
- 2) Ferguson-Smith, M. A. and S. D. Handmaker (1961): *Lancet*, i, 638-640.
- 3) Makino, S. and M. Sasaki (1960): *Proc. Japan Acad.*, **36**, 156-161.
- 4) Makino, S. and M. Sasaki (1961): *Amer. J. Human Genet.*, **13**, 47-63.
- 5) Makino, S. *et al.* (1960): *Proc. Japan Acad.*, **36**, 664-669.
- 6) Makino, S. *et al.* (1960): *Ibid.*, **36**, 670-674.
- 7) Makino, S. *et al.* (1962): *Ibid.*, **38**, 31-36.
- 8) Makino, S. *et al.* (1962): *Ibid.*, **38**, 47-51.
- 9) Makino, S. *et al.* (1962): *Ibid.*, **38**, 52-56.
- 10) Makino, S. and Y. Kikuchi (1962): *Ibid.*, **38**, 124-128.
- 11) Makino, S. *et al.* (1962): *Ibid.*, **38**, 166-170.
- 12) Makino, S. *et al.* (1962): *Ibid.*, **38**, 356-360.
- 13) Makino, S., Y. Kikuchi, M. S. Sasaki, M. Sasaki and M. Yoshida (1962): *Chromosoma (Berl.)*, **13**, 148-162.
- 14) Makino, S., M. Sasaki, M. S. Sasaki, Y. Kikuchi, M. Mizutani, M. Nagahata, Y. Nakagome and K. Yoshikawa (1962): *Proc. Zool. Soc. Calcutta, India* (in press).
- 15) Schmid, W. *et al.* (1961): *Amer. J. ment. Defic.*, **66**, 449-455.