167. *Chromosome Studies in Seventeen Cases of Congenital Diseases*^{*)}

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Many current workers in the field of human cytogenetics have made notable contributions towards the elucidation of cellular events in connection with the rise or cause and diagnosis of congenital syndromes, sex abnormalities and developmental deficiencies. In the laboratory of the senior author (S. M.), with the co-operation of clinicians, various types of congenital diseases have been screened for chromosomal aberrations, in order to gain criteria for understanding chromosomal changes in association with those disease states.

The present paper deals with chromosome studies in 17 patients with congenital diseases and in some parents. Clinical diagnoses of those patients and parents, together with sampling of the culture material for chromosome study, were made in the Department of Pediatrics. All the cytological work was done in the Makino laboratory, Department of Zoology. Diagnostic features along with clinical findings of those patients are provided in summary form in Table I.

Chromosome counts and karyotype analyses were carried out on metaphasic cells derived from a short-term culture of leucocytes separated from the heparinized peripheral blood. Leucocytes in 3-days-culture were exposed to colchicine and squashed according to the water-pretreatment acetic dahlia method.

Seventeen cases of congenital diseases under study were as follows: six cases of Down's syndrome generally referred to as mongolism (nos. 1-6), idiocy carrying certain features of Down's syndrome (no. 7), hypogonadism (no. 8), diabetes insipidus renalis (no. 9), Hurler's syndrome (no. 10), sepsis with leukemoid reaction (no. 11), cerebromuscular dystrophy (no. 12), idiocy of unknown etiology (no. 13), progressive muscular dystrophy (no. 14), multiple malformation (no. 15), postpartum psychosis (no. 16), and mental retardation (no. 17). In every case careful chromosome counts and karyotype analyses were made on two to three cells showing well-delineated chromosomes. The results are summarized in Table II (Figs. 1-5).

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Table I. Clinical and diagnostic features in seventeen cases of congenital diseases under study

Case no.	Age & Sex	Diagnosis	Clinical feature
1	11yr. ♂	Down's syndrome	Malformed ears and epicanthus, broad and short neck, constantly open mouth, flat and small nose, short and broad hands with short fingers, small teeth and fissured lips, low pitched voice.
2	11yr. ♂	Down's syndrome	Wrinkled forehead, rough and scaly cheeks, slanting eyes and malformed ears, small mouth and furrowed tongue, broad and short neck, short and broad hands, palmar horizontal lines in right hand.
3	12yr. ♂	Down's syndrome	Wrinkled forehead, rough and scaly cheeks, slanting eyes, flat and small nose with flat nasal bridge, constantly open mouth and raucous voice, palmar horizontal lines and tapering fingers, acrocyanosis.
4	1yr. ♀	Down's syndrome	Open fontanel skull and brachycephaly, rough and scaly cheeks, slanting eyes and epicanthus, small or absent lobule of ear, constantly open mouth and fissured lips, hyperextensible joints and hypotonic muscles, short and broad hands with short fingers.
5	1yr. ♀	Down's syndrome	Short and broad neck, funnel chest and dorsolumbar kyphosis, hyperextensible joints and umbilical hernia, acrocyanosis and hypotonic muscles, short and broad hands with tapering fingers, flabby hands and palmar horizontal lines.
6	4yr. ♀	Down's syndrome	Rough and scaly cheeks, slanting eyes and epicanthus, constantly open mouth, large, furrowed and protruding tongue, funnel chest and umbilical hernia, short and broad hands with tapering fingers, palmar horizontal lines and short 5th finger.
	3yr. ♀	Idiocy with certain features of Down's syndrome type	Brachycephaly, abnormally big eyes, excessive hypertelorism, depressed nasal bridge, small and incurved 5th fingers, transverse palmar fold on right.
8	9yr. ♂	Hypogonadism	Undescended testicle of the right side, underdeveloped penis and scrotum, normal mentality.
9	3yr. ♂	Diabetes insipidus renalis	Vasopressin-resistant polydipsia and polyuria, obstipation, dwarfism, frequent episodes of fever in infancy, hyperchloremia and hypernatremia.
10	10yr. ♂	Hurler's syndrome	Frequent episodes of respiratory infection, noisy respiration, mental retardation, hepatosplenomegaly, umbilical hernia, claw-like hand, limited extensibility of joints.
11	3m. ♂	Sepsis with leukemoid reaction	Intestinal and subcutaneous bleeding since a week after birth, erroneously diagnosed as acute leukemia, but later confirmed as sepsis on autopsy.
12	4yr. ♀	Congenital cerebromuscular dystrophy	Early onset of diffuse and extensive muscular weakness, mental retardation, increased activity of serum G-O-T and G-P-T, on biopsy, diffusely atrophic and generative muscle fibers, showing increased number of plump nuclei among and within fibers.
13	10m. ♀	Idiocy of unknown etiology	Apparent mental retardation, bilateral transverse palmar creases.
14	12yr. ♀	Progressive muscular dystrophy	Facioscapulo-humeral type, typical electromyogram, slightly impaired mentality, an elder sister died of the same disease.
15	1m. ♂	Multiple malformation	Arthrogryposis multiplex congenita, bilateral congenital dislocation of the hip, absence of uvula.

Table I. (Continued)

Case no.	Age & Sex	Diagnosis	Clinical feature
16	28yr. ♀	Postpartum psychosis	Depression and desire for committing suicide.
17	15yr. ♂	Mental retardation	Without any malformation, of unknown etiology.

Table II. Chromosome constitution in seventeen cases of congenital diseases under study

Case no.	Distribution of chromosome counts												Chromosome constitution	No. of cells obs.
	41	42	43	44	45	46	47	48	91	92	94			
1						1	19					47/2A+XY+no. 21	20	
2					1	2	18		1			"	22	
3					1	2	11	1				"	15	
4			1		1	5	26				1	47/2A+XX+no. 21	34	
4-M			1		1	4						46/2A+XX	6	
5					1	2	15					47/2A+XX+no. 21	18	
5-M					2	17						46/2A+XX	19	
6					2	1	7					47/2A+XX+no. 21	10	
6-F				1	2	4						46/2A+XY	7	
7	2		1		4	20	1			1		46/2A+XX	29	
7-M					3	27	1					46/2A+XX	31	
8					1	15	1					46/2A+XY	17	
9					1	12	2					46/2A+XY	15	
10					1	4	1					46/2A+XY	6	
11				2	2	18	1					46/2A+XY	23	
12					4	13	1					46/2A+XX	18	
13	1	1	1	2	7	21				1		46/2A+XX	34	
14				1	2	20						46/2A+XX	23	
15				1	4	13	2					46/2A+XY	20	
16				1	1	16				1		46/2A+XX	19	
17				2	4	22	2					46/2A+XY	30	

M=Mother. F=Father.

The six cases of Down's syndrome (mongolism) were three boys and three girls. Chromosome counts showed that cells derived from all patients possessed consistently 47 chromosomes. Karyotype analyses indicated that the 47 chromosomes comprised a normal complement of 46 chromosomes and one extra small acrocentric chromosome in addition which apparently corresponded to chromosome no. 21. The sex-chromosome constitution was XX in the female patients and XY in the male. No other abnormality was detected in the chromosomes of those cases. Apparently the six Down's syndrome cases studied here are characterized by a trisomic condition for no. 21, as

is commonly known in the majority of cases of this syndrome. The two mothers of cases 4 and 5, and the father of case 6 were subjected to chromosomal studies. The results indicated that their chromosomes were of normal pattern in both morphology and number, so far as the scope of the present study is concerned.

Figs. 1-5. Somatic chromosome complements based on leucocyte culture. 1, a male patient with Down's syndrome (no. 1). 2, a female patient with Down's syndrome (no. 4). 3, a patient with hypogonadism (no. 8). 4, a patient with idiocy of unknown etiology (no. 13). 5, a patient with progressive muscular dystrophy (no. 14).

Chromosome counts and karyotype analyses carried out in a patient (no. 7) with idiocy showing certain characters of Down's syndrome type revealed that she possessed an apparently normal complement consisting of 44 autosomes and two X elements. The chromosomes of the mother of this patient were examined but did not show any detectable abnormality.

Chromosome studies in the following eleven cases of congenital deficiencies: hypogonadism (no. 8), diabetes insipidus renalis (no. 9),

Hurler's syndrome (no. 10), sepsis with leukemoid reaction (no. 11), cerebromuscular dystrophy (no. 12), idiocy of unknown etiology (no. 13), progressive muscular dystrophy (no. 14), multiple malformation (no. 15), postpartum psychosis (no. 16) and mental retardation (no. 17), revealed that all the cases considered showed no visible chromosome abnormality under microscopical observations with leucocyte cultures: each patient possessed a normal chromosome complement consisting of 44 apparently normal autosomes and a pair of sex chromosomes, XX in the female patients and XY in the male.

Remarks: A large number of cases of congenital diseases, sexual anomalies and developmental defects have been subjected to chromosome screening, many important correlations having been made between chromosome aberrations and disease states. Current knowledge regarding the chromosome abnormality of Down's syndrome was excellently reviewed by Carr (1962). The results of the present study with six cases of this syndrome are essentially identical with those generally shown in a great many cases by previous workers.

There have been reported many examples of congenital diseases and developmental deficiencies without any detectable change or visible variation from a normal complement in either number or morphology (for example, refer to Hamerton 1961, Makino *et al.* 1962 a, b, c, d, e). Eleven cases of congenital disorders dealt with in this study provided no evidence of chromosome aberration; they showed 44 seemingly normal autosomes and a pair of sex-chromosomes. It should be commented here that identifiable chromosome changes do not always have connection with the etiological cause of congenital diseases or clinical disorders, since structural alterations of chromosomes, if any, are not necessarily reflected in morphologically visible changes of chromosomes in many cases.

In conclusion, seventeen cases of congenital diseases were subjected to chromosome studies. Six cases of Down's syndrome showed 47 chromosomes with trisomy for chromosome no. 21. Eleven cases of congenital disorders and developmental deficiencies showed no identifiable changes of chromosomes from a normal complement.

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