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Screening Data of the Chromosomes in Congenital Disorders and Maldevelopment, from a Survey in a Japanese Population (1964 to 1967)¹⁾

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Following the pioneer work of Flemming in the end of the last century, the chromosomes of human beings have been investigated with a variety of tissues as well as of methods by many workers. However, the human chromosomes have been subjects of utter discrepancy for over 70 years, due mainly to technical difficulty and inadequate tissue specimens for study.

In recent years, rapid advances in cytogenetic techniques involving the use of tissue or blood cultures, colchicine and hypotonic solution pretreatments, have facilitated more precise and reliable analyses of chromosomes in man, than those done with older direct squash or testis section methods. With the discovery of a new chromosome number in man in 1956, and the establishment of significant associations of chromosomal aberrations to certain types of congenital disorders, maldevelopment and sexual anomalies, a new era began in human cytogenetics. Then, a number of investigators in the world have expanded their effort to define the normal karyotype in various human races, as well as to screen congenital syndromes, clinical defects and sexual abnormalities in man for chromosome abnormalities. This has led to a fruitful association with the medical clinic with an extensive development of clinical cytogenetics. To date, considerable information has been available for critical diagnosis, or for understanding of the etiological cause of various diseases diagnosed as congenital. Chromosomal analyses of somatic cells in man are now indispensable tools for the diagnosis of congenital diseases and sex malformations, and contributing greatly to clinical medicine and medical genetics.

The chromosome abnormalities which occur in association with congenital disorders and maldevelopment may involve both genic differences, and changes in number and structure of the chromosomes. Recent increase in technical competence has made possible to some extent the analysis of some of these numerical and structural changes of chromosomes. Generally, chromosome abnormalities in congenital diseases involve either changes in autosomes or in sex-chromosomes, but seldom in both. Usually, numerical abnormalities of the

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chromosomes common to human subjects involve polysomy (trisomy in many cases), monosomy, mosaicism and polyploidy (triploidy in most cases). Structural abnormalities generally occurring in human chromosomes are translocation, deletion (partial or total), inversion and some others such as enlarged satellites and isochromosomes. The plausible mechanism leading to polysomy and monosomy is nondisjunction in either autosomes or sex-chromosomes.

Various types of sexual abnormalities have been reported to be associated with abnormalities of the sex-chromosomes. The major structural abnormalities of the X chromosome are deletion of both the short and long arm (X_{DS} and X_{DL}), isochromosomes of both long and short arms (X_{IL} and X_{IS}), and ring chromosomes (X_R). The structural abnormalities of the Y chromosome are: unusually long or short Y, deleted Y, pericentric inversion, and isochromosome for the long arm (Y_{IL}). Polyploidy, on the other hand, may be ascribed in most cases to the union of non-reduced gametes.

Many cases have been reported in which certain definite chromosome aberrations have been associated with certain disorders. There are diseases principally associated with abnormalities of autosomes. Thus, no. 21-trisomy has been generally accepted as the usual cause of Down's syndrome, and the short arm deletion of a no. 5 chromosome is usually associated with 'cri du chat' syndrome. Congenital heart defects have been known to occur frequently in association with a partial deletion of the long arm of a no. 16 chromosome.

On the other hand, sexual anomalies are generally associated with the aberrations of sex-chromosomes. Well-known cases are Klinefelter's and Turner's syndromes in which abnormal combinations of sex-chromosomes, XXY for the former and XO for the latter, are usually accepted as possible causes. Cell-mosaicism, which consists of cell-lines with different chromosome constitutions, is also associated with the etiology of certain diseases. A variety of mosaic conditions involving sex-chromosomes has been known in correlation to sexual abnormalities. Further, in many congenital disorders or maldevelopment, no definite correlation has been detected between the chromosome abnormalities and the clinical anomalies. Examples have been furnished in multiple malformations, mental deficiencies, certain sexual anomalies and some others. But, it can be assumed that certain chromosome abnormalities are apparently instrumental in the etiology of those disorders.

In contrast, many cases of congenital and clinical defects have been reported which show no identifiable change or variation from a normal chromosome complement. A minute loss or rearrangement of chromosomal material is far more difficult to demonstrate than gross chromosome changes that can be detected with current techniques. A normal chromosome complement in a given patient with certain defects is not always an indication that chromosome aberrations have not occurred. Apparently a superficially normal chromosome constitution does not always imply a normal genetic pattern. We must grant the possibility that a variety of chromosome abnormalities, though not be detectable by current

technical methods or at a visual microscopic level, may be masked by a seemingly normal karyotype.

Whether detectable chromosome aberrations or changes alone are the sole etiological cause of congenital diseases is uncertain. Congenital syndromes may be associated with certain environmental or physiological factors other than by chromosomal changes. Abnormalities of sexual development and certain disorders are not necessarily associated with chromosomal disturbances, and there are cases which may be caused by endocrine imbalance or other allied factors. Further, most chromosome analyses were made with limited tissues, so a possibility exists that other types of tissue specimens would produce different results.

Recently, evidence is presented that certain chromosomal anomalies might be associated with intrauterine death and abortion, on the basis of the discovery of a high incidence of chromosome abnormalities in spontaneous abortuses, approximately 20 per cent in frequency. Evidently a significant proportion of spontaneous abortions, particularly those in the early stages of embryonic development, are associated with chromosome abnormalities. Chromosome anomalies as a cause of spontaneous abortion call now special attention of cytogeneticists as well as of clinicians with a variety of research projects. Recent report of the Geneva Conference (1966) pointed to that monosomy, trisomy, triploidy, tetraploidy, mosaicism, translocation and some others occurred in spontaneous abortions with varying frequencies, triploidy, trisomy and monosomy being specially frequent among them. As a link of the social problems, the fact is of utmost importance that most embryos with abnormal chromosome combinations are incompatible with livebirth and abort in early pregnancy. Carr (1965) studying the chromosomes of 200 cases of spontaneous abortuses, found 44 chromosomally abnormal individuals with an incidence of 22 per cent. According to Carr (1965), the incidence is 1 in 600 for Down's syndrome, 1 in 540 for sex-chromosome anomalies, 1 in 2,000 for E-trisomy syndromes and 1 in 4,000 for D-trisomy syndrome. Our studies of 558 induced abortuses revealed that 19 out of them, or 3.4 per cent, were chromosomally abnormal. They are 6 mosaic cases, 1 case of X-trisomy, 2 cases of X-monosomy, 1 case of D-trisomy, 1 case of D/D translocation, 1 case with an unusually elongated long arm of a A1 chromosome, 1 case with enlarged satellites of a D chromosome, and 6 males with an unusually long Y chromosome. Therefore, it is evident that the chromosome abnormalities occur much more frequently in spontaneous than in induced abortions.

One of the major contributions of modern human cytogenetics to biology is the role of the X and Y chromosomes in sex determination and differentiation, particularly of the Y as a carrier of effective masculinizing factor(s). The existence of a Y chromosome is always associated with male sex, irrespective of the number of the X chromosome. A single Y overrules the presence of two or more extra X chromosomes. In striking contrast, female sex always occurs in association with the absence of the Y chromosome, since XO, XX, XXX and XXXX individuals are phenotypically females. Further, the existence of two or more X chromosomes in

males affects their sexual phenotypes, such as in the rise of Klinefelter's syndrome. In contrast, two Y chromosomes do not seem to enhance the male characters: the XYY and XXYY individuals show a similar degree of masculinity to the XY and XXY males. Furthermore it has been shown that at least one normal X chromosome may be essential for survival. The nullo-X individuals such as those with OO, OY and YY sex-combinations are almost certainly nonviable.

Abnormalities of the Y chromosome are also of some interest. General conclusion can be reached: 1) a considerable variability occurs in size of the Y chromosome from case to case, 2) the abnormality in size of the Y is not always correlated to an abnormal phenotypic manifestation, 3) the unusual length of the Y is an inheritable character, and 4) the Y chromosome carries a strong male-determining factor. The occurrence of an extraordinarily long or short Y chromosome has been known in both phenotypically normal males, as well as in male patients with a variety of congenital and sexual disorders. Of particular interest is the behavior disorder of patients associated with the extra Y chromosomes. Recent communication points out that disordered personality has occurred in association with patients with an XYY complex. A similar trend of behaviour disorders has been reported also in XXYY males. In contrast, there is a general tendency in the Klinefelter patients that a certain physical and mental disability increases with the increase in number of the X chromosome.

Rapidly expanding knowledge in human cytogenetics has rendered it difficult to make any generalization underlying etiological problems in relation to congenital disorders, and it is also difficult to present here all cytogenetic features of congenital disorders from the ever-growing voluminous literature.

Beginning in 1959, and continuing to date, a survey of chromosomes has been going on in my laboratory of normal, congenital and pathological human subjects in collaboration with clinicians working in various fields, with special reference to etiological problems and differential diagnoses of diseases, as well as to the etiology of chromosome abnormalities in the general population in connection with spontaneous abortions and congenital defects. During a period from September 1959 to November 1967, some 600 cases with those diseases were screened for chromosomal abnormalities. I summarized data accumulated during 1959 to 1963 on 300 cases with congenital disorders, maldevelopment and sexual anomalies (Makino 1964: *Cytologia* 29, Nos. 1-3). Here I present screening data of the chromosomes collected from 275 cases with diseases or syndromes usually diagnosed as congenital during 1964 to 1967 in my laboratory.

It is a pleasure to acknowledge the cooperation of my colleagues and clinicians of various medical fields in much of this survey work.

Cytogenetic features of congenital disorders and clinical defects (1964 to 1967)

<i>Down's syndrome</i> (17 cases)	
47, XX, 21+	5 cases
47, XY, 21+	11 cases
47, XX, 21+, with a short arm deletion of a G chromosome	1 case
<i>Suspected Down's syndrome</i> (1 case)	
46, XY	1 case
<i>"Cri du chat" syndrome</i> (2 cases)	
46, XX, with a partial deletion of a short arm of a no. 5 chromosome	1 case
45, XX (absence of a G group chromosome)	1 case
<i>Suspected "Cri du chat" syndrome</i> (2 cases)	
46, XY.....	2 cases
<i>Congenital heart defects</i> (3 cases)	
46, XX	2 cases
46, XY	1 case
<i>Multiple malformations</i> (7 cases)	
46, XX	4 cases
46, XY	2 cases
47, XX, G+	1 case
<i>Laurence-Moon-Biedl's syndrome</i> (3 cases)	
46, XY	1 case
46, XY (long)	2 cases
<i>Cleft lip and cleft palate</i> (8 cases)	
46, XX	3 cases
46, XY	5 cases
<i>Mental deficiency</i> (5 cases)	
46, XY	2 cases
46, XY (long)	1 case
46, XY (minute)	1 case
46, XX with an enlarged short arm of a B chromosome	1 case
<i>Schizophrenia</i> (2 cases)	
46, XY (slightly long)	1 case
46, XY (small)	1 case
<i>De Lange's syndrome (Amsterdam type of mental defect)</i> (1 case)	
46, XX	1 case
<i>Microcephaly</i> (2 cases)	
46, XY	2 cases
<i>Recklinghausen's disease</i> (3 cases)	
46, XX	2 cases
46, XY	1 case

<i>Suspected Recklinghausen's disease</i> (1 case)	
46, XY	1 case
<i>Tuberous sclerosis</i> (2 cases)	
46, XX	2 cases
<i>Choreoathetosis</i> (2 cases)	
46, XY (long)	2 cases
<i>Ophthalmologic diseases</i> (40 cases)	
46, XX	12 cases
46, XY	18 cases
46, XY (long)	9 cases
46, XY (a C chromosome with a large secondary constriction) ..	1 case
<i>Craniostenosis</i> (2 cases)	
46, XX	2 cases
<i>Hereditary ataxis</i> (1 case)	
46, XY	1 case
<i>Dysplasia epiphysialis multiplex congenita</i> (1 case)	
46, XY	1 case
<i>Multiple exostosis</i> (1 case)	
46, XX	1 case
<i>Myoclonus epilepsy</i> (1 case)	
46, XY	1 case
<i>Marfan's syndrome</i> (2 cases)	
46, XX	1 case
46, XY	1 case
<i>Poikiloderma congenitale</i> (1 case)	
46, XY	1 case
<i>Von Willebrand's disease</i> (6 cases)	
46, XX	3 cases
46, XY	3 cases
<i>Congenital pulmonary stenosis</i> (1 case)	
46, XY	1 case
<i>Total albinism</i> (2 cases)	
46, XX	1 case
46, XY	1 case
<i>Wilson's disease</i> (1 case)	
46, XY	1 case
<i>Cystinuria</i> (1 case)	
46, XY (long)	1 case
<i>Dwarfism</i> (1 case)	
46, XX	1 case
<i>Failure to thrive</i> (1 case)	
46, XY	1 case

<i>Obesity</i> (3 cases)	
46, XX	3 cases
<i>Klinefelter's syndrome</i> (30 cases)	
49, XXXXY	1 case
48, XXXY	1 case
48, XXYY	3 cases
47, XXY	23 cases
47, XXY (long)	1 case
46,XX/47,XXY	1 case
<i>Suspected Klinefelter's syndrome</i> (1 case)	
46,XY/47,XXY	1 case
<i>Hypospadias</i> (13 cases)	
46, XY	10 cases
46, XY (long)	3 cases
<i>Hypogonadism</i> (4 cases)	
46, XY	4 cases
<i>Cryptorchism</i> (26 cases)	
46, XY	24 cases
46, XY (long)	1 case
46, XY, with an enlarged short arm of a D chromosome	1 case
<i>Monorchism</i> (1 case)	
46, XY	1 case
<i>Gynecomastia</i> (4 cases)	
46, XY	3 cases
45,XO/46,XY	1 case
<i>Azoospermia</i> (13 cases)	
46, XY	12 cases
46, XY (long)	1 case
<i>Small penis</i> (3 cases)	
46, XY	2 cases
46,XY/47,XXY	1 case
<i>Eunuchoidism</i> (5 cases)	
46, XY	4 cases
46, XY (long)	1 case
<i>Ectopic testis</i> (1 case)	
46, XY	1 case
<i>Atrophic testes</i> (1 case)	
46, XY	1 case
<i>Turner's syndrome</i> (1 case)	
45, XO	1 case

<i>Hermaphroditism</i> (8 cases)	
<i>True hermaphroditism</i> (1 case)	
46, XX	1 case
<i>Pseudohermaphroditism</i> (7 cases)	
46, XX	3 cases
46, XY	3 cases
45,XO/46,XY	1 case
<i>Testicular feminization</i> (4 cases)	
46, XY	4 cases
<i>Adrenogenital syndrome</i> (5 cases)	
46, XX	5 cases
<i>Atresia vagina</i> (9 cases)	
46, XX	8 cases
46, XX, with an enlarged short arm of a D chromosome	1 case
<i>Enlarged clitoris</i> (4 cases)	
46, XX	4 cases
<i>Epispadias</i> (1 case)	
46, XX	1 case
<i>Hypoplasia uteri</i> (1 case)	
46, XX	1 case
<i>Sexual hypoplasia</i> (3 cases)	
47, XXX	1 case
46, XY	1 case
45,XO/46,XY	1 case
<i>Oligomenorrhoea</i> (3 cases)	
46, XX	3 cases
<i>Primary amenorrhoea</i> (7 cases)	
46, XX	4 cases
45, XO	1 case
45,XO/46,XX	1 case
46, XX, Al with a large secondary constriction	1 case
<i>Sterility</i> (1 case)	
46, XX	1 case

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