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

By

Sajiro Makino

Zoological Institute, Hokkaido University

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

---

1) Contribution No. 811 from the Zoological Institute, Faculty of Science, Hokkaido University, Sapporo, Japan.

Dedicated to Emeritus Professor Tanemoto Furuhata, with respect and admiration, on the occasion of his 77th birthday.

Jour. Fac. Sci Hokkaido Univ. Ser. VI, Zool. 16, 1968.

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 shrot 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 rearrangment 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 phenotipically 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 underlaying 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)

Down's syndrome (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

Suspected Down's syndrome (1 case)
- 46, XY ..... 1 case

"Cri du chat" syndrome (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

Suspected "Cri du chat" syndrome (2 cases)
- 46, XY..... 2 cases

Congenital heart defects (3 cases)
- 46, XX ..... 2 cases
- 46, XY ..... 1 case

Multiple malformations (7 cases)
- 46, XX ..... 4 cases
- 46, XY ..... 2 cases
- 47, XX, G+ ..... 1 case

Laurence-Moon-Biedl's syndrome (3 cases)
- 46, XY ..... 1 case
- 46, XY (long) ..... 2 cases

Cleft lip and cleft palate (8 cases)
- 46, XX ..... 3 cases
- 46, XY ..... 5 cases

Mental deficiency (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

Schizophrenia (2 cases)
- 46, XY (slightly long)..... 1 case
- 46, XY (small) ..... 1 case

De Lange's syndrome (Amsterdam type of mental defect) (1 case)
- 46, XX ..... 1 case

Microcephaly (2 cases)
- 46, XY ..... 2 cases

Recklinghausen's disease (3 cases)
- 46, XX ..... 2 cases
- 46, XY ..... 1 case

Suspected Recklinghausen's disease (1 case)
46, XY ..... 1 case
Tuberous sclerosis (2 cases)
46, XX ..... 2 cases
Choreoathetosis (2 cases)
46, XY (long) ..... 2 cases
Ophthalmologic diseases (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
Craniostenosis (2 cases)
46, XX ..... 2 cases
Hereditary ataxis (1 case)
46, XY ..... 1 case
Dysplasia epiphysialis multiplex congenita (1 case)
46, XY ..... 1 case
Multiple exostosis (1 case)
46, XX ..... 1 case
Myoclonus epilepsy (1 case)
46, XY ..... 1 case
Marfan's syndrome (2 cases)
46, XX ..... 1 case
46, XY ..... 1 case
Poikiloderma congenitale (1 case)
46, XY ..... 1 case
Von Willebrand's disease (6 cases)
46, XX ..... 3 cases
46, XY ..... 3 cases
Congenital pulmonary stenosis (1 case)
46, XY ..... 1 case
Total albinism (2 cases)
46, XX ..... 1 case
46, XY ..... 1 case
Wilson's disease (1 case)
46, XY ..... 1 case
Cystinuria (1 case)
46, XY (long) ..... 1 case
Dwarfism (1 case)
46, XX ..... 1 case
Failure to thrive (1 case)
46, XY ..... 1 case

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

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

Literature consulted

Carr, D.H. 1965. Chromosome studies in spontaneous abortions. Obstet. and Gynec. **26**: 308–326.

Dave, M.J. 1966. Cytogenetic studies in 14 sexually abnormal patients. Cytologia **31**: 11–18.

Geneva Conference 1966. Standardization of procedures for chromosome studies in abortion. Cytogenetics **5**: 361–393.

Ikeuchi, T., M. Mitani, and T. Tamura 1965. Chromosome studies in 2 patients with

suspected "Cri du chat" syndrome. Jour. Fac. Sci. Hokkaido Univ. Ser. VI, Zool. **15**: 706–711.

Ikeuchi, T., and S. Makino 1966. A chromosomal survey in thirty cases of congenital diseases. Proc. Japan Acad. **42**: 408–412.

Ikeuchi, T., S. Makino, M. Sasaki, T. Momma, and K. Oikawa 1967. A chromosome anomaly new to the "Cri du chat" syndrome. A preliminary note. Proc. Japan Acad. **43**: 986–990.

Ikeuchi, T., and S. Fujimoto 1966. A survey of chromosomes in ten sexually abnormal patients. Jour. Fac. Sci. Hokkaido Univ. Ser. VI, Zool. **16**: 54–59.

Ikeuchi, T., and M. Ochi 1967. A study of chromosomes in 28 cases with congenital ophthalmologic diseases. Jour. Fac. Sci. Hokkaido Univ. Ser. VI, Zool. **16**: 142–147.

Ito, N., and S. Makino 1966. A preliminary note on a case of trisomic Down's syndrome with a short arm deletion of a G group (21–22) chromosome. Proc. Japan Acad. **42**: 1207–1210.

Kato, T., N. Takagi, and S. Makino 1965. A chromosome study in seven neuropsychiatric patients, with special regard to the abnormality of the Y chromosome. Japan. J. Genetics **40**: 105–112.

Kato, H., T. Omura, S. Tabata, and S. Makino 1965. A preliminary note on an aberrant autosome (group 13–15) in a male child and in his father. Proc. Japan Acad. **41**: 477–481.

Makino, S. 1964. Chromosomal studies in normal human subjects and in 300 cases of congenital disorders. Pt. I-III. Cytologia **29**: 12–31, 125–150, 233–262.

Makino, S., N. Takagi, and M. Hikita 1964. Two phenotypic males with XXXXY and XXXY sex choromosomes. Proc. Japan Acad. **40**: 427–431.

Makino, S., N. Takagi, T. Makita, and M. Hikita 1964. A chromosome study of ten sexually abnormal patients. Proc. Japan Acad. **40**: 566–571.

Makino, S., and J. Muramoto 1964. Some observations on the variability of the human Y chromosome. Proc. Japan Acad. **40**: 757–761.

Makino, S. 1966. Chromosome studies in 150 sexually abnormal patients (a summarized report) Pt. I, II. Cytologia **30**: 309–323, 349–374.

Maruyama, W., H. Shimba, and S. Kohno 1968. A chromosome study in 20 sexually abnormal patients. (Japan. J. Genet.) (*in press*).

Muramoto, J., and N. Takagi 1964. Chromosome studies in 14 cases of Down's syndrome and in one suspected case. Jour. Fac. Sci. Hokkaido Univ. Ser. VI, Zool. **15**: 360–365.

Muramoto, J., T. Aya, and M. Sasaki 1966. A chromosome study of patients with cleft lip and cleft palate based on lesion biopsies in culture. Jap. J. Human Genet. **11**: 31–35.

Nakagome, Y., M. Sasaki, I. Matsui, M. Kawagome, and Y. Fukuyama 1965. A mentally retarded boy with a minute Y chromosome. J. Pediat. **67**: 1163–1167.

Shimba, H., S. Makino, M. Sasaki, M.C. Yoshida, and T. Ikeuchi 1967. A chromosome study in 32 sexually abnormal patients. Japan. J. Genet. **42**: 307–315.

Takagi, N., T. Kato, and S. Morita 1964. Chromosome studies in 10 congenital neuropsychiatric patients. Proc. Japan Acad. **40**: 674–678.

Takagi, N., S. Makino, S. Takai, and M. Hikita 1965. A phenotypical XXYY human male with notes on two regular Klinefelter cases. Proc. Japan Acad. **41**: 175–180.

Takagi, N., T. Makita, H. Kato, S. Takai and M. Hikita 1966. A chromosome survey in 40 sexually abnormal patients. Japan. J. Genet. **41**: 1–7.