58. A Cytogenetic Study of 103 Cases of Down's Syndrome from Hiroshima District

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After the establishment of the normal chromosome number of man in 1956, there was about two years' delay until Down's syndrome was described as the first instance of congenital diseases in which a chromosome abnormality was definitely demonstrated (Lejeune, Gautier and Turpin 1959). The cytogenetics of Down's syndrome has been extensive in the past some ten years and the underlying chromosome error known as G-trisomy has been well recognized in the vast majority of cases studied. The extra G chromosome has now been traditionally accounted for as chromosome No. 21. G-trisomy as a standard chromosome abnormality of this clinical syndrome is common to patients of different ethnic origins. Major variants of this standard abnormality are D/G and G/G translocations. In addition, mosaicism has been found to occur in some patients as a chromosome abnormality of this syndrome.

Following the initial study by Makino, Tonomura, and Matsunaga in 1960, a considerable survey work on the cytogenetics of Down's syndrome has been carried out in several laboratories in Japan with major concern to the chromosome features and maternal age effect in affected subjects (Makino 1964, 1968, 1969; Tonomura, *et al.* 1966, 1971; Tanaka 1966; Slavin, *et al.* 1967; Kikuchi *et al.* 1969; Yanagisawa 1968; Higurashi, *et al.* 1969; Konishi 1970; *etc.*). It is principal aim of the present communication to present cytogenetic and parental age data derived from 103 patients with Down's syndrome which would supplement other recent reports from Japan and foreign countries.

A total of 103 patients with Down's syndrome from Hiroshima district was subjected to the present chromosome study. The patients varied in age from 0 to 33 years. Most were accompanied by their mothers, so that the chromosomes of the mothers were also examined. In some cases, karyotypes of fathers, siblings, and other relatives

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were examined. Chromosome slides were exclusively prepared according to the routine short-term leucocyte culture method.

Results and comment. Out of the 103 patients (61 females and 42 males) diagnosed as Down's syndrome, standard G-trisomy (47, XX, or XY, G+) accounted for 81 cases (43 females and 38 males) or 78.64 per cent, one of which showed a G-trisomy together with heterozygosity for No. 16 chromosome (47, XX, 16q+G+). Consistent with other reports, G-trisomy accounted for the majority of cases in our study. There were seven cases of translocation at a frequency of 6.80 per cent. Among them, four cases (3 females and 1 male) had a D/G translocation having a karyotype of 46, XX, or XY, D-, t (DqGq)+, and three (females) showed a G/G translocation with 46, XX, G-, t (GqGq)+. There were three cases of mosaicism (2.91%) involving normal and G-trisomic cell lines (46, XX/47, XX, G+). Except one case having a D/D translocation (45, XX, D-, D-, t (DqDq)+), the remaining 11 cases were found to have an apparently normal karyotype including one case with 46, XX, 16q+, though a suspicion remains of masked chromosome aberrations among them (see Table I).

The chromosomes of parents were investigated in 81 affected cases which were available. The parents of the G-trisomic cases were found to possess a normal karyotype with the exception of one case born to the triplo-X mother who showed 47 chromosomes having an extra chromosome in the C group. Based on the results of the nuclear sexing tests, the karyotype of this mother was determined as 47, XXX (Kadotani, Ohama and Makino 1970). The father of this patient was karyotypically normal. Both the mother and father were phenotypically as well as mentally normal. This couple had no history of abortion and stillbirth. In the familial Down's Syndrome survey,

Table I. Karyotype distribution in 103 cases diagnosed as Down's syndrome

Karyotype	Female	Male	Total (%)
G-trisomy	43*	38	81(78.64)
t(DqGq)+ t(GqGq)+	3 3	1 0	7(6.80)
Normal/G-trisomy	3	0	3(2.91)
45, XX, D-, D-, t(DqDq)+ Normal	1 8**	0 3	12(11.65)
Total	61	42	103

*) One case had 47, XX, 16q+, G+.

**) One case had 46, XX, 16q+, regarded as a normal variant.

Breg, *et al.* (1962) found two triplo-X females, each of whom had sibling or cousin associated with G-trisomic Down's syndrome. Bergman (1962) reported a familial occurrence of the XXX/XXXX mother and a G-trisomic Down's syndrome daughter.

In the four cases with D/G translocation, the parents of three cases had a normal karyotype, while the mother of one case was a carrier who had a balanced translocation showing 45, XX, D-, G-, t(DqGq)+. The parents of three G/G translocation cases had an apparently normal karyotype in each.

From the above findings, it is apparent that six out of the seven translocation cases here concerned are sporadic in occurrence leaving one case of the t(DqGq) type in which the translocation is transmitted from the mother.

Table II. Mean parental ages at birth of 91 Down's patients with G-trisomy, translocation and mosaicism

		Case	Mean maternal age	Mean paternal age
Control		100	27.01±4.17	30.35±4.67
Down's syndrome	G-trisomy	81*	30.48±6.22	34.35±6.75
	t(DqGq)+ t(GqGq)+	7	27.43±3.68	30.00±3.68
	Normal/G-trisomy	3	27.00±4.55	33.00±1.41
	Total	91	29.86±6.00	33.79±6.52

*) Containing one case with 47, XX, 16q+, G+.

Mean ages of parents at the birth of patients of Down's syndrome were assessed in 91 available cases. The results are presented in Table II. It was shown that mean maternal and paternal ages for G-trisomic series were 30.48±6.22 and 34.35±6.75, respectively; those for translocation series were 27.43±3.68 and 30.00±3.68, respectively; and those for mosaic cases were 27.00±4.55 and 33.00±1.41, respectively. It is apparent from the above pictures that the mean parental ages are considerably higher in the G-trisomic series than in the translocation series. Further, the mean maternal age of the G-trisomics is greater than the controls (see Table II). This suggests a maternal age effect on the occurrence of G-trisomic Down's syndrome. In general, the situation is consistent with reports from other laboratories in Japan (Slavin, *et al.* 1967; Higurashi, *et al.* 1969; Matsunaga 1970; Tonomura, *et al.* 1971), as well as in foreign countries (Penrose 1933; Hayashi 1963; Gustavson 1964; Chitham and MacIver 1965; *etc.*). Based on cytogenetic studies of 1000 cases with Down's syndrome,

Tomomura, *et al.* (1971) reported that the mean maternal age at the patients, birth was 29.83 for the G-trisomic cases and 29.27 for the mosaic cases, apparently higher than in the control (27.05 ± 4.32). In contrast the mean maternal age for the translocation type was 28.36. Kikuchi, *et al.* (1969) mentioned that the means for maternal as well as paternal ages in the group of patients of $t(DqGq)$ type were rather close to the means in the general population, and there was no significant difference between the cases and the controls. On the other hand, the mean ages of both parents in the group of $t(GqGq)$ type were generally higher than the control means.

Recently Largey and Largey (1971) announced a significantly higher mean maternal age for 35 male Down's patients (36.25 years) than for 39 female ones (33.28 years). We have analyzed maternal age data on 81 available trisomic cases in relation to sex difference. The mean maternal age for 43 female trisomic patients was 29.78 ± 5.93 and for 38 male patients was 31.31 ± 6.42 . The mean maternal ages of the male patients seem to be slightly higher than that of the females. The data are however insufficient for estimation, and even the feature presented seems to be in favor of the view of Perry (1971) and Fedrick (1971) that sex differences are probably not important factors to be considered in etiological studies of the relationship between maternal age and Down's syndrome.

Birth orders were assessed in 92 cases which were available. In accordance with the arguments of Tomomura, *et al.* (1966, 1971), our data do not admit to make any conclusive statements on the possible effect of birth rank on the occurrence of this syndrome, the accumulation of further data being requested.

We examined birth-weight in 56 cases of Down's syndrome which were available. It was shown that mean birth-weights were 2838.99 ± 485.20 for 48 trisomic cases, 2655.00 ± 106.13 for 5 translocation cases and 2633.33 ± 385.86 for 3 mosaic cases. The above data seem to show that birth-weights of the affected series are lower than those of controls which were obtained as 3115.90 ± 193.57 for 100 normal births.

Sato (1964) reported the chromosomes of four Down's syndrome children born to mothers who were exposed to radiation in Hiroshima on August 6, 1945, and one of them was a pregnant woman in her 2nd trimester. It was shown that all of the four mongoloid children had a standard G-trisomic karyotype (47, XX or XY, G+). The karyotypes of their mother were apparently normal. Uchida and Curtis (1961) suggested a possible association of the maternal diagnostic abdominal radiation with the appearance of Down's syndrome. Sigler, *et al.* (1965) showed that there was a significant increase of Down's syndrome infants in radiation-exposed mothers. Carter, *et al.*

(1961) found no significant or even suggestive difference between the maternal preconceptive abdominal radiation exposure of 51 Down's patients and the controls. Schull and Neel (1962) also showed no significant association of this syndrome with the maternal exposure in three patients from 5582 mothers exposed to the atomic bomb in Hiroshima and Nagasaki in comparison with 12 from 9452 non-exposed mothers. On the basis of a cytogenetic study of 92 patients with Down's syndrome from Hiroshima and Nagasaki, Slavin *et al.* (1967) have stated that there is clearly not sufficient data upon which to base any conclusion about the relative frequency of Down's syndrome in the exposed and non-exposed parents.

Summary. Results of chromosome studies of 103 patients with Down's syndrome from Hiroshima district are presented (Table I).

Mean maternal and paternal ages are assessed in available cases (Table II), and some comment is given in comparison with data from other laboratories.

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