

# PREVALENCE OF CHROMOSOMAL ANOMALIES OF THE MENTALLY RETARDED — REPORT OF A STUDY OF 124 INSTITUTIONALISED CHILDREN IN KUALA LUMPUR

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## SYNOPSIS

A cytogenetic survey of 124 children in four special schools for the mentally handicapped was carried out to determine the contribution of chromosomal abnormalities to the aetiology of mental retardation in these children. All the children were karyotyped employing the G-banding technique of 43 (34.7%) with an abnormal chromosome complement, 40 had Down's Syndrome, and 3 had other chromosomal abnormalities, namely a translocation 1;17, a mosaic male/trisomy 18 and a Klinefelter's Syndrome.

Polymorphic variants involving chromosomes 1, 9, and 14 were also observed. Two other children showed variants of the Y chromosome (one a small Y and the other a metacentric Y). The possible contribution by these abnormal variants to mental retardation is discussed. Details of the abnormal cytogenetic findings are reported.

## INTRODUCTION

A mentally retarded person is someone whose mental development has been impeded or handicapped. It is a condition in which intelligence is prevented from attaining its full development, limiting the child's ability to learn and to put learning to use, and retarding social adjustment (2).

Causes leading to mental retardation include German measles contracted by the mother during the first three months of pregnancy, excessive x-rays during early pregnancy, injuries to the brain during birth, abnormal brain growths, certain infections and other diseases stemming from faulty body biochemistry. This last category includes numerous congenital metabolic disorders which are all very rare.

The relationship between mental retardation or multiple congenital malformations and unbalanced chromosome aberration is well established and an increasing number of chromosomal syndromes is recognised. The extent of this association, however, as regard both the types of mental disorder involved, is as yet unknown. Establishing the degree to which chromosomal abnormalities contribute to the total pool of mental illness is an additional task ahead for the human population cytogenetics (2).

Several cytogenetic investigations of institutionalized mentally subnormal persons have been performed. Speed et al presented one survey of a complete population of mentally subnormal persons (3). Jacobs et al reported a cytogenetic survey of 475 individuals in an institution for the mentally retarded (4). Newton and her colleagues reported the results of a survey of all patients over 15 years of age in an English hospital for the mentally subnormal (5,6). Sutherland et al reported their findings in a cytogenetic survey of all patients in a hospital for the mentally retarded in South Australia (7). In the same year, Doyle published her cytogenetic work on 90 patients with idiopathic mental retardation and compared it to 90 normal subjects (8).

A cytogenetic survey of 449 persons in a Japanese institution for the mentally retarded was also carried out by Kondo and colleagues (9), the second report in Japan after Fujita and Fujita (10). The first report from India of cytogenetic abnormalities in 74 patients with idiopathic mental retardation was published by Moghe and his co-workers (11). Rasmussen et al surveyed cytogenetically an unselected group of 2,157 mentally retarded persons in a geographically delimited area of Denmark (12).

Subsequently, Nielsen et al also reported on all 476 inmates in a Danish institution for the mentally retarded (13). A report based on all 223 retarded children of school age in the island of Hawaii was presented by Proops et al (14).

The present study was undertaken at various special schools for the mentally handicapped. We intend to determine the frequency and types of chromosomal abnormalities in our mental retardation population in order to assess the relative significance of chromosomal aberrations as causes of such handicaps. Further more, the frequency of various chromosomal abnormalities in patients with mental

retardation from Malaysia has not been determined. However, the number of individuals investigated was not large enough to permit statistical analysis and hospitalized patients have not been included in the study. Similarly, mentally retarded individuals who are not institutionalized have been excluded.

## MATERIAL AND METHODS

As of October 1982, about 200 mentally retarded children were registered to attend special Day-Care Centres in Brickfields, Sentul, Ceras and Jalan Ipoh, all in the Federal Territory. These centres are run by the Selangor and Federal Territory Association for Retarded Children. The children attend normal class hours from 8.00 a.m. to 2.30 p.m. The aim of our investigation was explained to all the teachers and families in a letter and consent was obtained to take a blood sample for chromosome analysis. Only 124 subjects, their age ranging from 6 years to 32 years, responded to this study. No I.Q. assessment and dermatographic examination were done.

Phytohemagglutinin stimulated whole blood was cultured in RPMI medium for 71 hours. Chromosome analysis was undertaken on G-banded metaphases (1). A minimum of 30 metaphases were examined in each subject. Cytogenetic studies were also performed in available parents of karyotypically abnormal children.

## RESULTS

Of the 124 individuals studied, a total of 43 (34.7%) were found to have an abnormal chromosome constitution (Table 1). There are 40 individuals (10 males: 21 females) with trisomy 21 (32.3%). One case with translocation Karyotype  $2n = 46, XY, t(14q 21q)$  and one with mosaicism Karyotype  $2n = 46, XY/47, XY, +21$  were found among the children with Down's Syndrome. The age distribution of the children with Down's Syndrome is shown in Table II.

In addition, we found two children with autosomal abnormalities other than trisomy 21: one child exhibits mosaicism of a normal male cell-line and a trisomy 18 in 1: 1 ratio — Karyotype  $2n = 46, XY/47, XY, +18$ , (Fig. 1); and one with a probable unbalanced translocation of chromosome 1 and 17 — Karyotype  $2n = 46, XY, 1p-, ?17q+$ , (Fig. 2). The parents of the earlier case did not turn up for family study, but in the latter,

TABLE 1: SUMMARY OF CHROMOSOME ABERRATIONS SEEN IN THE 124 INSTITUTIONALIZED MENTALLY RETARDED CHILDREN

Karyotype	No. of cases	Percentage of the total studied
<b>A: Autosomal</b>		
1. 47, XX, +21 or 47, XY, +21	38 )	32.3
46, XY, -14, t(14q 21q)	1 )	
46, XY/47, XY, +21	1 )	
2. 46, XY/47, XY, +18	1	0.8
3. 46, XY, 1p-, ?17q+	1	0.8
<b>B. Sex Chromosome</b>		
1. 47, XXY	1	0.8
Total	43	34.7

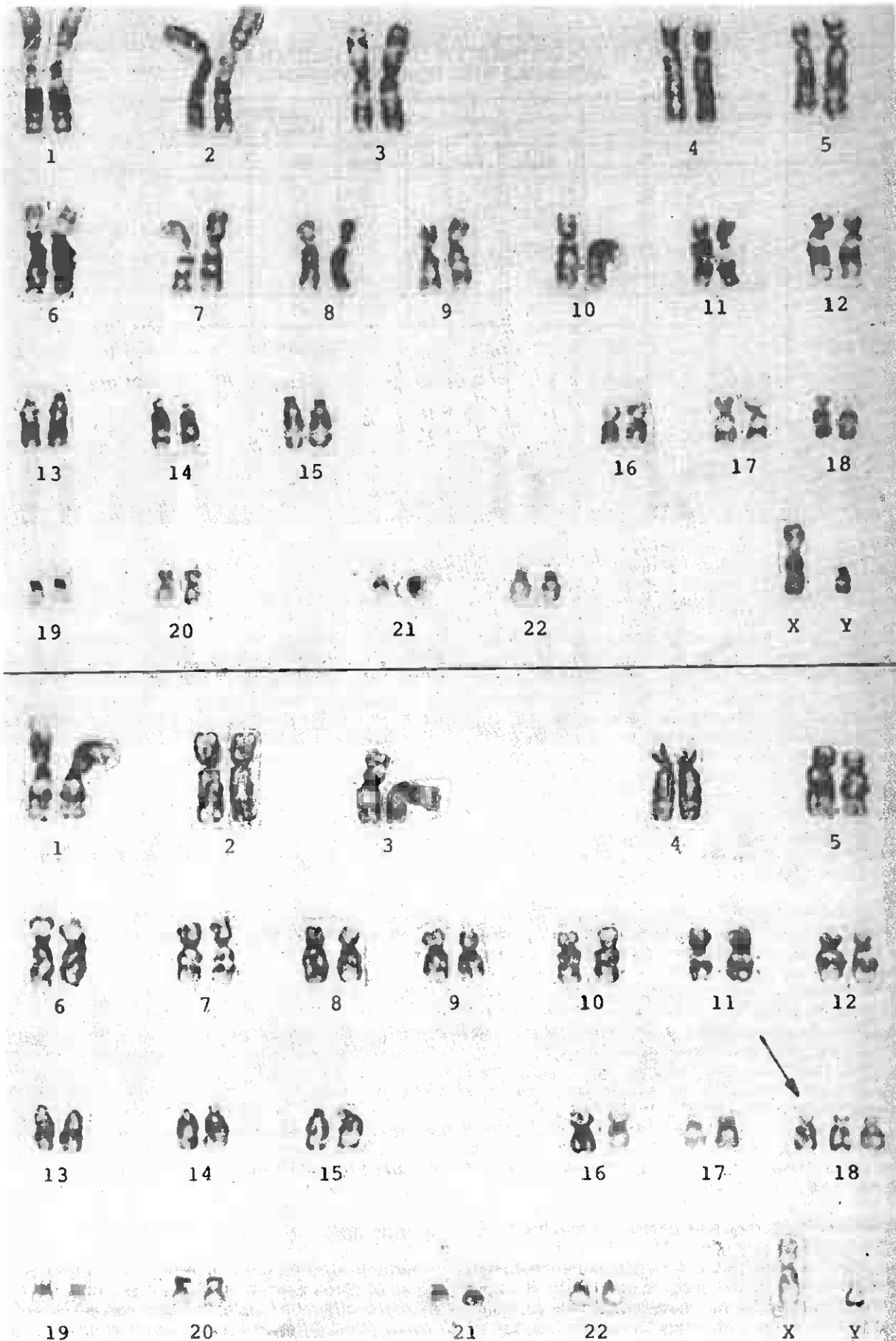


Fig. 1 G-banded karyotype of an individual showing mosaicism, 46, XY/47, XY, +18. Arrow indicates the extra chromosome.

TABLE II: AGE DISTRIBUTION OF THE CHILDREN STUDIED AND THOSE WITH DOWN'S SYNDROME

Age	Total Studied			Patient with Down's Syndrome	
	Male	Female	Total	No.	%
5 — 10	21	9	30	17	56.7
11 — 15	31	26	57	12	21.1
16 — 20	20	11	31	9	29.0
21 & above	4	2	6	2	33.3
Total	76	47	124	40	32.3

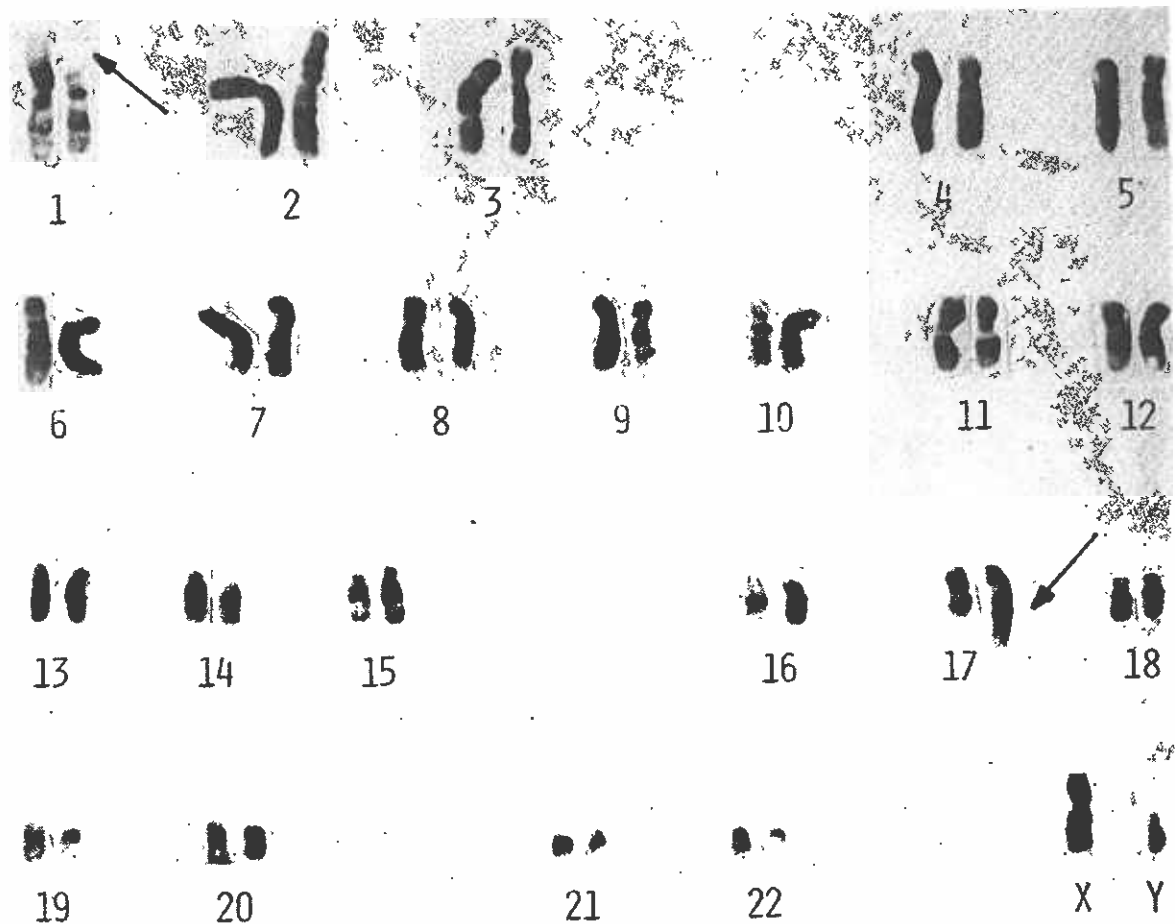


Fig. 2 G-banded karyotype of an individual showing translocation; 46, XY, 1p-, ?17q+. Arrow indicate chromosome abnormalities.

upon cytogenetic studies both parents were found to be normal.

Five children were found to have chromosomal anomalies that could not account for their conditions. All were considered to have heterochromatic variants. One case had a 1qh+ chromosome, one had a 9qh+ chromosome and another had a 14p+ chromosome.

In 2 cases a polymorphic variant of the Y chromosome was seen. One had a small Y and another had a metacentric Y. In none of these cases of heterochromatic variants except one were parents available for study. Cytogenetic investigation on the father of this one case showed that the metacentric Y chromosome had been inherited. He is phenotypically normal.

**DISCUSSION**

Several surveys have reported the frequency and types of chromosomal abnormalities in patients with mental retardation (Table III). Jacobs et al presented a review of the different surveys on unselected mentally retarded persons (3,4,15). More recent surveys have been conducted by Kondo and his co-workers, a Japanese group (9), Moghe et al on an India group (11). Rasmussen et al (12) and Nielsen et al (13) on a Danish population.

The most common chromosome abnormality in patients in institutions is Down's Syndrome, accounting for 7.3 — 14.7% of all patients studied previously

TABLE III: CYTOGENETIC SURVEYS IN MENTAL RETARDATION: SUMMARY OF RESULTS

Authors	Age range	Down's Syndrome		Other autosomal abnormalities		Sex chromosome abnormalities		Total No. Studied
		No.	%	No.	%	No.	%	
Sutherland + Wiener 1971	3 mths — 12 yrs							
Sutherland et al 1976	4 — 75 yrs	90	14.0	16	2.1	4	0.5	747
Newton et al 1972 a, b	16 — 70 yrs	103	8.2	15	1.2	10	0.8	1255
Cassiman et al 1975	< 18 yrs	111	13	18	2.1	3	0.35	857
Jacobs et al 1978	≤ 27 yrs	40	8.4	14	1.6	3	0.6	475
Kondo et al 1980	5 — 66 yrs	33	7.3	3	0.6	1	0.2	449
Moghe et al 1981	> 4 mths	0	0	7	10.0	7	9.4	74
Rasmussen et al 1982	6 — 60 yrs	281	14.7	45	2.4	33	1.7	1905
Nielsen et al 1983	12 — 77 yrs	58	12.2	13	2.7	5	1.05	476
Present study 1984	6 — 32 yrs	40	32.3	2	1.6	1	0.8	124
Total:		756	11.9	133	2.1	67	1.1	6362

In the present study the frequency of abnormal karyotypes was 34.7% and the incidence of Down's Syndrome was 32.3%. The high incidence of children with Down's Syndrome in this study could be due to the fact that patients with Down's Syndrome are more concentrated in institutions for the mentally retarded. The relative frequency of this chromosomal abnormality in the unselected population of the mentally retarded in Malaysia is not known. Moghe et al (11) reported no cases under the Down's Syndrome group, because their subjects were taken from patients without known causes of mental retardation, thus excluding easily recognisable conditions as Down's Syndrome. This explains the high frequency reported by them for the other autosomal abnormalities and sex chromosome abnormalities — 10% and 9.4% respectively.

The fact that of the inmates less than 10 years of age, more than half (56.7%, see Table II) are Down's Syndrome is significant; this condition is found less frequently in older children and adults. This difference probably reflects the limited longevity this condition gives to its sufferers.

One male individual in our series had 46 chromosomes and a Robertsonian translocation involving chromosomes 14 and 21. Examination of the parents was not helpful to determine if either one of them was a translocation carrier or the translocation was a new mutation. Another male individual was a 46, XY/47, XY, +21 mosaic. Only 1 trisomic cell was found in the lymphocyte but the subject showed clinical features of Down's Syndrome.

Mental retardation is typical of individuals with extra X chromosomes. Three or more X's lead to mental retardation; the more X's, the more the disability. There have been reports of abnormal numbers of X chromosomes (4,5,9,12) in studies of mental retardation. Besides XXY males (7), there are Klinefelter's mosaic (11,12), as well as Turner's mosaic (5,11,12). Extra Y chromosomes also tend to be associated with mental defects, but the effect of the extra Y chromosome is rather small compared to that of the extra X. Previous reports on XYY males have identified males with the 47, XYY karyotype (7,8,12,16) in high

numbers in patients who have behaved antisocially and been admitted to institutions via the courts of law. In one study (4), one individual was also found to have an additional Y chromosome, but was mildly retarded. In this case, the contribution of the additional chromosome to the mental retardation is unclear.

Only one sex chromosome abnormality was found in the present survey, accounting for 0.8% of all individuals studied. This is consistent with the established finding that persons with a sex chromosome anomaly, if mentally retarded, would most often belong to the high grade group of mentally retarded persons who can manage on their own in society.

There have been reports on autosomal numerical as well as structural aberrations in mental retardation. In the past, the following findings have been established; trisomies (1,2,4), partial trisomies (8), deletions (4,8,9,11,12), inversions (7), duplications (11,12), supernumerary chromosomes (4), and marker chromosomes (4,7,8,9,12). Being rare, it is difficult to evaluate the significance of ring chromosomes in mental retardation (7,12). The majority of recognisable unbalanced chromosome re-arrangements are associated with severe mental retardation and physical abnormalities which often result in death during infancy or childhood (11,12). While the majority of balanced rearrangements are without obvious phenotypic effects, it may be that a small proportion are associated with mental or physical abnormality (4,7,9,11,12).

The frequency of other autosomal abnormalities in our series is 1.6% which is comparable to the finding in other reports. One child had a mosaic cell line — 50% of his cells being normal, the other cells being trisomic for chromosome no 18. This child had no features of Edward's Syndrome.

Jacobs has suggested that the presence of de novo structural rearrangements may be of aetiological significance in mental retardation (16). In the present study, there was an apparent structural rearrangement involving chromosomes 1 and 17. This translocation with an unbalanced rearrangement was shown to have arisen de novo — a new mutation. Both parents have normal karyotypes. The finding of one such mutant

lends some support to Jacob's hypothesis as apparently euploid de novo structural rearrangements are rare (16).

de la Chapelle et al (7), reported a case of trisomy 21 with a balanced translocation between chromosomes 1 and 17, with the distal portion of the short arm of chromosome 1 attached to the proximal part of the short arm of chromosome 17. In contrast, in our case the portion of the short arm of chromosome 1 was attached to the distal part of the long arm of chromosome 1.

It is generally assumed that heterochromatic variants are unrelated to abnormal phenotypes (18,19). Variants involving heterochromatin are known to be found in the general population with a high frequency (18,19). The variants found in this study involved chromosomes 1, 9, 14 and Y. For each case with a chromosome abnormality, attempts were made to study the chromosomes of both parents or in the case of Y abnormality, the chromosomes of the father, to determine whether the abnormality has been inherited. Such family studies were done in a case that apparently involved the metacentric Y. The abnormal chromosome had been inherited from his phenotypically normal father. This indicates that once an aberration that involves little or no quantitative changes in euchromatin arises, it continues in the population. Since minor chromosome abnormalities apparently are more frequently inherited, the frequency in the population must depend, to a great extent, on the mutation rate.

The families of most of the children were not always available for examination; no conclusion could be drawn in the present study as to the prevalence of de novo rearrangements among the mentally retarded children. If the parents had been available in all the cases of structural abnormalities, it might have been possible to clarify whether de novo balanced aberrations are responsible for the increased prevalence seen in a population of mentally retarded persons (4,16).

The contribution of chromosome abnormality to the aetiology of mental retardation as seen in the present and similar surveys is highly significant. It serves to stress the importance of a chromosome analysis in any mentally retarded child, especially when no obvious cause for the retardation has been found. In every case where an abnormality is observed, it is wise to determine if this is inherited from either parent, as the implications for genetic counselling are tremendous.

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