Chromosome studies of males in an institution for the mentally handicapped

C J ENGLISH*, E V DAVISON*, M S BHATE†, AND L BARRETT‡

From *the Department of Human Genetics, University of Newcastle upon Tyne; †the Department of Psychiatry, Prudhoe Hospital, Northumberland; and ‡the Child and Family Psychiatric Unit, Queen Elizabeth Hospital, Gateshead, Newcastle upon Tyne.

SUMMARY Karyotypes were examined in 512 (91.9%) of 557 male patients in an institution for the mentally handicapped. A total of 110 (21.5%) had an abnormal karyotype: 65 (12.7%) with Down's syndrome, 30 (5.9%) with the fragile X syndrome, 13 (2.5%) with autosomal anomalies other than Down's syndrome (12 unbalanced, one balanced), and two (0.4%) with sex chromosome anomalies.

The prevalence of chromosome anomalies in mentally handicapped male populations has been reported as 11.9% in north-east Scotland,¹ with various levels up to 17.6% in Australia.² These studies were before the importance of the fragile X syndrome in male mental handicap was established, and subsequent investigations have concentrated on the prevalence of fragile X males in mentally handicapped populations.³ This paper documents the results of a cytogenetic survey (G banded and fragile X) of the male population of Prudhoe Hospital, Northumberland.

At the time of study there were 557 males resident at the institution. In 24 cases permission for cytogenetic investigation was refused by the next of kin and 15 males with a known non-chromosomal cause of their mental handicap were excluded. The diagnoses in these patients were phenylketonuria (4), encephalopathy (4), meningitis (2), surgical complications (2), birth trauma (1), hypoxaemia at birth (1), and haemolytic disease at birth (1). In a further six cases it was impossible to obtain a blood sample. In all, 512 (91.9%) of the patients were studied.

Methods

Venous blood was cultured for 72 hours in RPMI 1640 medium (Gibco BRL) using standard laboratory techniques, and in Iscove's modified medium (Flow Laboratories) for fragile X induction. Ethidium bromide (final concentration 1 g/l) was used to

produce longer chromosomes. G banding was by a standard trypsin/Leishman method.

One hundred metaphases were examined for the fragile X chromosome and 10 G banded metaphases fully analysed from each male for other chromosome anomalies.

Results

The abnormal karyotypes are listed in table 1. Of the 512 males, 110 (21.5%) were shown to have an abnormal karyotype. There were 66 aneuploid (64 autosomal and two sex chromosome) and 14 structurally abnormal karyotypes. The structural abnormalities comprised one balanced translocation and

TABLE 1 *Abnormal karyotypes.*

Abnormal karyotypes	No
46,XY,dup(8)(p21.73-p23.71)	1
46,XY,inv(9)(p11q12),10q+	1
46,XY,del(10)(p15)	1
46,XY,del(10)(q26)	1
46,XY,del(13)(q21q31)	1
46,XY,-13,+t(8;13)(q23;p13)	1
46,XY,del(15)(q11.1q12)	4
46,XY,del(18)(p11.1)	1
46,XY,t(19;22)(q13.2;qter)	1
46,XY,-14,+t(14;21)	1
47,XY,+21	62
47,XXY	1
47,XYY	1
46,XY=4/46,XY,del(9)(q11q21.2)=26	1
46,XY=5/47,XY,+21=25	1
47,XY,+21=27/47,XY,+21,t(14;14)(q32.3;q22)=3	1
Fragile X (7% to 48%)	30
Total	110

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TABLE 2 Cytogenetic surveys of four mentally handicapped populations.

Reference	Population description*	No of males in survey	Chromosome abnormality								Total		Total (excluding Down's)	
			Sex chromosome		Autosomal									
					Down's		Others							
			No	%	No	%	No	%	No	%				
4	<18 y IQ<50	661	2	0.3	88	13.3	15	2.3	105	15.9	17	2.6		
2	4-75 y 86% IQ<51	330	3	0.9	49	14.9	6	1.8	58	17.6	9	2.7		
1	All ages IQ<70	1565	25	1.6	153	9.8	8	0.5	186	11.9	33	2.1		
5	<29 y 91% IQ<50	284	3	1.1	26	9.2	9	3.2	38	13.4	12	4.2		
Total		2840	33	1.2	316	11.1	38	1.3	388	13.7	71	2.5		
This study	15-85 y IQ<70	512	2	0.4	65	12.7	13	2.5	80	15.6	15	2.9		

*Population of Speed *et al*¹ resident in institution and at home; all others resident in institution.

TABLE 3 Chromosome abnormalities in males of four mentally handicapped populations.

Reference	No in survey	Chromosome abnormality																		
		Sex chromosome	Autosomal (non-Down's)								Down's syndrome									
			Balanced				Unbalanced				Total		Trisomy 21		Trans 21		Mosaic trisomy 21		Total	
			No	%	No	%	No	%	No	%	No	% (of Down's)	No	% (of Down's)	No	% (of Down's)	No	%		
4	661	2	0.3	2	0.3	13	2.0	15	2.3	81	92.1	6	6.8	1	1.1	88	13.3			
2	330	3	0.9	1	0.3	5	1.5	6	1.8	47	95.9	1	2.0	1	2.0	49	14.9			
1	1565	25	1.6	0	0	8	0.5	8	0.5	144	94.1	2	1.3	7	4.6	153	9.8			
5	284	3	1.1	3	1.1	6	2.1	9	3.2	22	84.6	4	15.4	0	0	26	9.2			
Total	3036	34	1.1	6	0.2	32	1.1	38	1.3	294	93.0	13	4.1	9	2.9	316	11.1			
This study	512	2	0.4	1	0.2	12	2.3	13	2.5	63	96.9	1	1.5	1	1.5	65	12.7			

13 unbalanced karyotypes (five with extra chromosomal material and eight with deleted material). Of the four males with the del(15)(q11.1q12) karyotype, none showed the classic Prader-Willi symptoms. Thirty males expressed the fragile X chromosome at levels ranging from 7% to 48%. All were clinically fragile X, with only one patient not showing macro-orchidism. Clinical details on all patients will be discussed in further papers (Davison *et al*, in preparation; Bhate *et al*, in preparation).

There have been many cytogenetic investigations of mentally handicapped populations and the results for males in four of these are summarised in tables 2 and 3 together with the results obtained from this study.

Discussion

The most significant finding in this study was the prevalence of autosomal structural abnormalities, 2.5% with 2.3% being unbalanced, which is almost double the 1.3% found in the other surveys. The

most obvious explanation is the use of extended banding techniques. At least six of the unbalanced chromosome anomalies detected were small deletions or extra material which could have been missed using standard G banding. The population of this institution was examined cytogenetically 16 years ago^{6,7} using only unbanded chromosome preparations and a frequency of only 1% of autosomal anomalies other than Down's syndrome was reported. Accepting that over 16 years the population would have changed, and the prognosis for chromosomally abnormal subjects improved, the higher prevalence in our study is still most probably the result of the use of more sophisticated techniques.

The frequency of balanced structural rearrangements (0.2%) agrees with the other surveys. Although it is well established that de novo structural rearrangements can have a deleterious phenotypic effect,^{8,9} it was not possible to determine the origin of our apparently balanced translocation as parental karyotypes were not available.

The prevalence of fragile X males was 5.9% overall and 6.7% in the non-Down's syndrome population. Published surveys report the frequency varying from 0%¹⁰ to 8%.³ Our results confirm the findings of others^{3 11 12} that it is the second largest group of cytogenetically abnormal males in institutions for the mentally handicapped.

The largest cytogenetically abnormal group in our population was Down's syndrome (12.7%). This frequency is in agreement with the other surveys, which vary from 9.2% to 14.9%. However, our population had a lower proportion of patients with a translocation, 1.5% as opposed to 4.1% in the other surveys and 5% quoted by Giraud and Mattei.¹³ These discrepancies could be accounted for by differences in maternal age distributions.

Frequencies of mosaicism in Down's syndrome patients are reported from 2.7%¹³ to 2.9% (table 3). Only 1.5% of cases in our population had mosaic karyotypes. This may reflect the severity of mental handicap in our institution; the majority of patients have an IQ of less than 50.

The prevalence of sex chromosome anomalies was 0.4%, compared to 1.2% in the other surveys. In the general population the prevalence of 47,XXY and 47,XYY is 0.12% and 0.11%, respectively.¹⁴ Thus, sex chromosome anomalies are only slightly over-represented in this institution. Again our low prevalence may be a reflection of the severity of handicap of the patients; sex chromosome anomalies are more frequently found with mild mental handicap and behavioural disorders.¹⁵

With the use of good cytogenetic technology our study has shown that more than one in five subjects in our institution have a chromosomal cause of their mental handicap. As a large majority of these anomalies have implications for other family members, it is crucial that these subjects are identified. All of the disorders we have detected can be diagnosed prenatally and family members at risk of producing a handicapped child should be given the opportunity of prenatal screening. We would therefore recommend cytogenetic screening of institutions for the mentally handicapped using current cytogenetic technology.

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Correspondence to Dr C J English, Department of Human Genetics, University of Newcastle upon Tyne, 19 Claremont Place, Newcastle upon Tyne NE2 4AA.