The frequency of the fragile X chromosome among schoolchildren in Coventry

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SUMMARY A population study has been carried out among schoolchildren in the City of Coventry in order to ascertain the frequency of mental retardation associated with the fragile X chromosome. The prevalence of the fragile X mental retardation syndrome in the 11 to 16 year age group (the age of greatest ascertainment) was about 1·0 per 1000 and therefore indicates that the syndrome is a major cause of mental retardation.

Estimates of the prevalence of mental retardation in males associated with the fragile X chromosome have ranged from 0·19 to 0·92 per 1000.^{1–3} A study based on schools for the educationally subnormal (ESN) in Coventry has enabled us to estimate the prevalence of the fragile X chromosome in schoolchildren of that city, in both males and females.

Methods

The study took place between 1 April 1982 and 31 December 1985. Children were included if they were born before 31 August 1978 and if they were at school during the study period. We studied children with home addresses in Coventry who either lived at home and attended day schools for the educationally subnormal (ESN) or who were in residential care, either in or outside the city. We visited four ESN(S) and four ESN(M) schools in Coventry together with one mental deficiency hospital and two schools for the physically handicapped. We also examined at home two children who were resident during term time at schools outside Coventry.

We chose to study certain groups of children among whom we anticipated that some would have the fragile X chromosome associated with their mental retardation. It was necessary to omit certain groups in whom the fragile X chromosome was less likely to be found because the techniques required to identify the fragile X chromosome are laborious^{4,5}

and could not be performed on an entire population. The groups initially chosen for study were boys attending ESN(S) schools with severe mental retardation of unknown cause and boys and girls attending ESN(M) schools with mild mental retardation of unknown cause. Children not studied were those with a cause for their mental retardation that was obvious from the school medical records and those attending normal schools.

At the beginning of the study it was decided not to study girls at ESN(S) schools. This decision was based on reported experience that the fragile X syndrome was unlikely to give rise to severe (IQ < 50) mental retardation in females.⁶ However, during family studies we ascertained five fragile X positive females who were severely retarded, indicating that this omission was incorrect. Consequently, at the end of the study girls in the four ESN(S) schools in Coventry were also studied; there were no girls in residential care. The girls with a date of birth before 31 August 1980 were included in an effort to compensate for those older girls who left the school during the period 1982 to 1984 when the boys were being tested.

After scrutiny of school medical records and exclusion of those children who had an obvious cause for their mental retardation, parents were asked for permission to examine and take blood from their children. Where such permission was given, blood was taken from the child for cytogenetic examination, using regular culture and staining methods, together with the additional techniques

necessary to demonstrate the fragile X chromosome.^{4,5} These involve setting up the cultures in media which do not have available folic acid or thymidine. This is achieved both by direct deficiency and by the use of the folate antagonists methotrexate (MTX) and FUdR. At least five such cultures were set up for each subject and a minimum of 50 mitoses were examined for each. Although the original screening for chromosome fragility was performed on solid stained slides, the presence of fra(X)(q27) was always confirmed by analysis of at least a further 50 G banded mitoses. Children were classified as 'positive' for the fragile X if the abnormal chromosome was present in 3% or more of their cells.

The results for the boys from the four ESN(S) schools, combined with those from nine other ESN(S) schools elsewhere in the West Midlands, have been reported previously.⁵

Results

The number of children selected for the study, and those for whom parental permission was obtained, are presented in table 1. Twenty-nine Coventry schoolchildren (16 males and 13 females) were identified as having the fragile X chromosome.

The numbers of children in Coventry attending primary, secondary, and special schools fell between 1982 and 1984 from 57 882 to 53 708.⁷ The number at school in January 1983, the mid-point of the period, was 55 556 and we have used this as the appropriate total of our study. There were 28 611 schoolboys and 26 945 schoolgirls. The total annual births in Coventry number about 4500.⁷

Discussion

THE PREVALENCE OF FRAGILE X MENTAL RETARDATION IN SCHOOLCHILDREN

In assessing the prevalence of affected schoolchildren we have assumed, firstly, that all children have been

correctly identified as fragile X positive or fragile X negative, for in our experience failure to detect the fragile X in female heterozygotes only occurs in those who are mentally normal.⁸ Secondly, we have assumed that the prevalence of the fragile X chromosome in the 31% of ESN(M) schoolchildren not studied because their parents refused permission was the same as the prevalence in the ESN(M) children studied, namely 1 in 16 for males and 1 in 10 for girls. Therefore, we believe that we have 'missed' five affected males and three affected females, all from ESN(M) schools. Compliance was higher among the parents of ESN(S) children.

This means that the prevalence of the fragile X syndrome in boys with idiopathic severe mental retardation is 6/60 (1 in 10); in girls with idiopathic severe mental retardation is 3/24 (1 in 8); in boys with idiopathic mild retardation is 10/159 (1 in 16); in girls with idiopathic mild retardation is 10/104 (1 in 10); in all mentally retarded boys, regardless of severity or cause, is 21/452 (1 in 22); and in all mentally retarded girls, regardless of severity or cause, is 16 to 17/277 (1 in 16 to 1 in 17). The prevalence of fragile X mental retardation in all schoolboys is 21/28 611 (1 in 1362) and in all schoolgirls is 16 to 17/26 945 (about 1 in 1630).

It is possible that the prevalence of the fragile X chromosome in the children not studied is different from that in children studied and we have therefore calculated the prevalence of the fragile X chromosome based on the premise that the prevalence in the children not studied was half, or double, that in the children studied. The figures are given in table 2 and we consider them to represent the upper and lower limits of our prevalence estimates.

Our figures suggest that, if there were no increased mortality of fragile X children, nor any disproportionate emigration or immigration during childhood, then the number of new cases of fragile X mental retardation likely to be born each year is, for Coventry, about 3 per 4500 births or about 6 per

TABLE 1 Numbers of Coventry schoolchildren in study.

	Total numbers of retarded children at these schools		Numbers of children with idiopathic mental retardation selected for study		Numbers of mentally retarded children studied (numbers with fragile X in parentheses)	
	M	F	M	F	M	F
Four ESN(S) schools	124	94 (87)*	54	25*	52 (6)	24* (3)
One mental deficiency hospital	12	0	10	0	8 (0)	0
Three ESN(M) day schools	244	150	208	124	138 (10)	94 (9)
One ESN(M) residential school	30	15	30	15	19 (0)	10 (1)
Two schools for physically handicapped	42	26	3	0	2 (0)	0
Totals	452	285 (278)	305	164	219 (16)	128 (13)

*In 1985 the numbers of retarded females had dropped from 94 to 87, of whom 25 had idiopathic retardation, all but one of whom were investigated.

TABLE 2 *Prevalence of fragile X chromosome in groups of schoolchildren.*

Group of schoolchildren	If the prevalence in the children not studied when compared to the observed prevalence in the children who were studied is					
	The same		Half as common		Twice as common	
Boys with idiopathic severe mental retardation	6/60*	(1 in 10)	6/60*	(1 in 10)	6/60*	(1 in 10)
Boys with idiopathic mild mental retardation	10/159*	(1 in 16)	12/241	(1 in 20)	20/241	(1 in 12)
Boys with all types of mental retardation	21/452	(1 in 22)	18/452	(1 in 25)	26/452	(1 in 17)
All schoolboys	21/28 611	(1 in 1362)	18/28 611	(1 in 1589)	26/28 611	(1 in 1100)
Girls with idiopathic severe mental retardation	3/24*	(1 in 8)	3/24	(1 in 8)	3/24	(1 in 8)
Girls with idiopathic mild mental retardation	10/104*	(1 in 10)	11/139	(1 in 13)	17/139	(1 in 8)
Girls with all types of mental retardation	16-17/277	(1 in 17)	15/277	(1 in 18)	20/277	(1 in 14)
All schoolgirls	48-51/26 945	(1 in 544)	45/26 945	(1 in 599)	60/26 945	(1 in 449)

*Observed prevalences from which others are derived.

10 000 births. However, Coventry Education Department figures show that there are twice as many children in special schools in Coventry between the ages of 11 and 16 (707 in 1982) than between 5 and 10 (343 in 1982). This is because many mentally retarded children start in normal schools before being transferred to special schools. Therefore, the prevalence of the fragile X in the 11 to 16 year olds is the most accurate. Among the children born in 1968 to 1973 there were 23 with the fragile X; if seven more are added to account for those from the 31% of children who refused to participate in the study, it gives a total of 30 for this age group. There are 28 570 children at Coventry schools in the corresponding age range. This gives a prevalence of the fragile X mental retardation syndrome of 1 in 952 for all schoolchildren, or about 1.05 per 1000.

THE PREVALENCE OF THE FRAGILE X CHROMOSOME IN SCHOOLCHILDREN WHO ARE ATTENDING NORMAL SCHOOLS

We can only make suppositions about these prevalences. Although it is unlikely that males with the fragile X syndrome will be present in normal schools, we have detected one mentally normal fragile X positive male and two mentally normal male transmitters in 12 pedigrees studied so far. However, the size of the error must be small, since no fragile X was found in a study of 1810 newborn males.⁹

With regard to females, there is evidence^{6 10} that two-thirds of female carriers are mentally normal although they cannot always be identified by present cytogenetic techniques. We have therefore assumed that twice as many girls as those we have found in special schools will be found in normal schools in Coventry, that is 32 to 34. This would give a prevalence of all schoolgirls possessing the fragile X

chromosome of 48 to 51/26 945 (1 in 561 to 1 in 528). These mentally normal carrier girls must not be forgotten because of their 1 in 2 risk that each son will be mentally retarded and their 1 in 6 risk that each daughter will be mentally retarded.

Two previous estimates of the prevalence of the fragile X chromosome in the population^{1 2} have given figures ranging from 0.19 to 0.92 per 1000 males and 0.45 to 1.22 per 1000 females. These estimates were calculated from the prevalence of non-specific X linked mental retardation in a group of retarded children and extrapolation from these figures to the prevalence in the general population, and the contribution made to X linked mental retardation by the fragile X chromosome. A study from Sweden³ attempted to identify all children retarded on account of the fragile X chromosome in one county and obtained a figure of 0.66 per 1000 males, but no estimates were made for females. The Swedish figure for males is similar to the present study where our estimate of the prevalence of mental retardation associated with the fragile X chromosome is 0.75 per 1000 males (range 0.63 to 0.91). Our estimated prevalence of the presence of the fragile X chromosome in females (with or without mental retardation) is 1.8 per 1000 females (range 1.67 to 2.2).

The fragile X chromosome is clearly often associated with mental retardation and should be searched for in any child with unexplained mental retardation. It is important to recognise the fragile X chromosome and to study the families so ascertained since carrier females have a risk of 1 in 2 (or perhaps slightly less⁸) of having a mentally retarded son. Prevention of the births of further affected cases in a family is now possible since prenatal diagnosis of the fragile X chromosome in a fetus can now be

performed.¹¹ Although screening of females who are mentally retarded is reliable, the cytogenetic techniques identify only two-thirds of mentally normal female carriers⁸ and so population screening of female carriers is not yet feasible.

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References

- ¹ Fishburn J, Turner G, Daniel A, Brookwell R. The diagnosis and frequency of X-linked conditions in a cohort of moderately retarded males with affected brothers. *Am J Med Genet* 1983;14:713-24.
- ² Herbst DS, Miller JR. Nonspecific X-linked mental retardation. II. The frequency in British Columbia. *Am J Med Genet* 1980;7:461-9.
- ³ Blomquist HK, Gustavson KH, Holmgren G, Nordenson I, Palsson-Strae U. Fragile X syndrome in mildly mentally retarded children in a Northern Swedish county. A prevalence study. *Clin Genet* 1983;24:393-8.
- ⁴ Sutherland GR. Heritable fragile sites on human chromosomes. I. Factors affecting expression in lymphocyte culture. *Am J Hum Genet* 1979;31:125-35.
- ⁵ Bunday S, Webb TP, Thake A, Todd J. A community study of severe mental retardation in the West Midlands and the importance of the fragile X chromosome in its aetiology. *J Med Genet* 1985;22:258-66.
- ⁶ Turner G, Brookwell R, Daniel A, Selikowitz M, Zilibowitz M. Heterozygous expression of X-linked mental retardation and X-chromosome marker fra(Xq27). *N Engl J Med* 1980;303:662-4.
- ⁷ Annual Abstracts of Statistics, 1981-1984. The Central Statistical and Research Unit, West Midlands County Council.
- ⁸ Webb T, Thake A, Todd J. Twelve families with fragile Xq27. *J Med Genet* 1986;23:400-6.
- ⁹ Sutherland GR. Heritable fragile sites on human chromosomes. XII. Population cytogenetics. *Ann Hum Genet* 1985;49:153-61.
- ¹⁰ Sherman SL, Morton NE, Jacobs PA, Turner G. The marker (X) syndrome: a cytogenetic and genetic analysis. *Ann Hum Genet* 1984;48:21-7.
- ¹¹ Webb T, Gosden CM, Rodeck CH, Hamill MA, Eason PE. Prenatal diagnosis of X-linked mental retardation with fragile (X) using fetoscopy and fetal blood sampling. *Prenat Diag* 1983;3:131-7.

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