

X-Linked Mental Retardation With Macro-Orchidism and the Fragile Site at Xq27 or 28

G. R. Sutherland* and P. L. C. Ashforth

Cytogenetics Unit, Department of Histopathology, Adelaide Children's Hospital,
North Adelaide, S.A. 5006, Australia

Summary. Data are presented suggesting that the form of X-linked mental retardation with macro-orchidism and the form associated with a fragile site at Xq27 or 28 are the same entity.

Introduction

Mental retardation with macro-orchidism in males, with probably X-linked inheritance, has been described by Turner et al. (1975) and Cantú et al. (1976, 1978). It has now been established that one form of X-linked mental retardation is associated with the fragile site on the distal end of the X chromosome (Harvey et al., 1977; Sutherland, 1977, 1979b). Data are presented suggesting that these two forms of mental retardation are the same entity.

Materials and Methods

Thirteen males with mental retardation and the fragile site at Xq27 or 28, identified from family histories and chromosomal surveys of retarded males (Sutherland, 1979b), were available for study. Measurements of testicular length (l) and width (w) were carried out with a ruler. The volume was calculated from the formula $\pi/6.l.w.^2$ (Cantú et al., 1976). Control values were obtained from the literature and by measurement of ten retarded males with normal karyotypes. Penile length (stretched) was measured with a ruler, and midshaft circumference with a measuring tape. Control values were obtained as for testicular volume.

Results

The ages and genital measurements of the males with the fragile site at Xq27 or 28 are shown in Table 1. All measurements are in centimetres, and the estimated accuracy of each measurement is ± 0.2 cm. The control group of retarded males

* To whom offprint requests should be sent

Table 1. Genital measurements (cm) of males with fra(X)(q27 or 28)

Subject	Age (years)	Penis		Testes					
		Length	Circum- ference	Right			Left		
				Length	Width	Volume (ml)	Length	Width	Volume (ml)
Family E^a									
III ₇	26	13.0	9.0	6.5	4.5	69	6.0	4.0	50
IV ₅	3 ⁷ / ₁₂	5.0	4.5	2.5	1.7	3.8	2.5	1.5	2.9
IV ₆	3 ⁷ / ₁₂	6.0	5.0	2.5	1.5	2.9	2.5	1.5	2.9
Family Ma^a									
IV ₅	10 ⁵ / ₁₂	6.0	5.0	2.5	2.0	5.2	2.7	2.0	5.6
IV ₆	6 ¹⁰ / ₁₂	6.5	4.5	2.5	1.0	1.3	2.5	1.2	1.8
IV ₇	5 ⁶ / ₁₂	5.0	4.0	2.5	1.5	2.9	3.0	1.5	3.5
P	13 ⁷ / ₁₂	12.0	7.5	5.5	3.5	35	5.0	3.0	24
Fe	18	9.0	10.0	5.5	3.5	35	5.5	3.0	31
Fi	23	9.0	9.0	5.0	3.5	32	5.0	3.5	32
Family B									
N	27	12.5	9.5	5.5	3.5	35	5.0	3.5	32
A	28	10.0	11.0	6.0	3.5	39	5.0	3.0	24
Mi	65	13.0	11.0	3.0	2.5	10	4.5	2.5	15
E	16	14.0	8.0	7.0	3.5	45	7.0	4.0	59
B ^a	30	10	7.0	6.5	4.0	54	7.0	4.0	59

^a From Sutherland (1979b); other subjects have not been published. Individuals from family B are brothers

ranged in age from 23 to 35 years (mean 29.0); penile length was 8–15 cm (mean 12.5 cm), penile circumference 8–12 cm (mean 9.2 cm), right testicular volume 9–24 ml (mean 17.8 ml), and left testicular volume 9–24 ml (mean 16.2 ml). Figure 1 compares the mean of the right and left testicular volumes of all those measured with normal values taken from the literature.

Discussion

The data in the literature regarding genital size are conflicting, due to various methods of measurement and possible population differences (Farkas, 1972). Prader (1974) gives 10–17 cm as the normal length of the stretched penis after puberty; the penile length of both groups of postpubertal males described in the present report approximates to this range, but this measurement is significantly affected by the degree of stretching during measurement. Prader (1974) gives the length of the stretched penis as 4–8 cm and the circumference as 3–6 cm before puberty. The prepubertal males in this report appear to have penises of normal

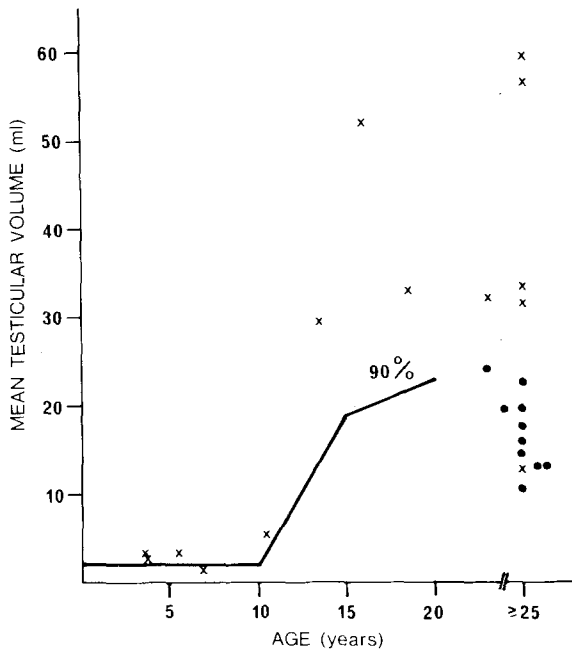


Fig. 1. Average (left and right) testicular volume of males with the fragile site (X) and control group (●). The 90% line is the percentile given by Prader (1974) from ages 10—20 and his upper limit of normal up to the age of 10 years. All males aged 25 years or more are shown as ≥ 25

size. Farkas (1972) gives the mean penile circumference, measured similarly to in the present study, as 9.6 cm, with a standard deviation of 0.83 cm and a range of 7.7—12.0 cm. The penile circumference of the present groups of postpubertal males is within this range.

Testicular volume can only be estimated, either by measurement of length and width or by the use of an orchidometer and comparative palpation. Using the orchidometer, Prader (1974) gives a prepubertal testicular volume range of 0.75 ml to a maximum of 2 ml. Zachmann et al. (1974) give a mean volume of about 19 ml in postpubertal males, with a volume of about 23 ml as the 90th percentile. Rundle and Sylvester (1962) reported larger volumes calculated from length and width measurements, but used a formula that would have given volumes about 35% greater than those calculated from the formula of Cantú et al. (1976).

The control group of retarded males in the present study had testicular volumes well within the range of Zachmann et al. (1974). The testicular volume of the postpubertal males with the fragile site ranged from 32 to 69 ml for the right, and from 24 to 59 ml for the left, if subject Mi is excluded. Subject Mi is 65 years old and may have undergone some testicular atrophy. These volumes are not as great as those recorded by Cantú et al. (1976, 1978), which ranged from 68 to 128 ml in adults, but are all above the 90th percentile. In three subjects in particular (Family E, III₇; D; and B) the testicular volume is far greater than that

of normal males. The volumes in the present study are more in accord with those found by Turner et al. (1975), which ranged from 25 ml in a 13-year-old up to approximately 45 ml in adults.

All the prepubertal males, except for one, have testicular volumes above the upper limit of normal (Prader, 1964). Cantú et al. (1976) indicated that testicular size was probably increased from birth, and the mother of one of the present subjects said that his genitals had always been larger than those of other males in the family. It would appear that increased testicular size is present in this form of retardation from birth and not only after puberty.

The results presented suggest that the X-linked mental retardation with macro-orchidism described by Turner et al. (1975) and by Cantú et al. (1976, 1978) is the same entity as X-linked mental retardation associated with the fragile site at Xq27 or 28. Reports of normal chromosomes in males with macro-orchidism by Turner et al. (1975) and by Cantú et al. (1976, 1978) cannot be regarded as definitive, since the need to use culture medium deficient in folic acid and thymidine for the demonstration of fragile sites (Sutherland, 1979a) was then unknown. Chromosome studies on the patients described by these authors should be repeated if possible, to determine whether they have the fragile site on Xq.

References

- Cantú, J.-M., Scaglia, H. E., Medina, M., González-Diddi, M., Morato, T., Moreno, M. E., Pérez-Palacios, G.: Inherited congenital normofunctional testicular hyperplasia and mental deficiency. *Hum. Genet.* **33**, 23—33 (1976)
- Cantú, J.-M., Scaglia, H. E., González-Diddi, M., Hernández-Jáuregui, P., Morato, T., Moreno, M. E., Giner, J., Alcántar, A., Herrera, D., Pérez-Palacios, G.: Inherited congenital normofunctional testicular hyperplasia and mental deficiency. *Hum. Genet.* **41**, 331—339 (1978)
- Farkas, L. G.: Basic morphological data of external genitals in 177 healthy central European men. *Am. J. Phys. Anthropol.* **34**, 325—328 (1972)
- Harvey, J., Judge, C., Wiener, S.: Familial X-linked mental retardation with an X chromosome abnormality. *J. Med. Genet.* **14**, 46—50 (1977)
- Prader, A.: *Clinical endocrinology. Theory and practice*, A. Labhart (ed.), pp. 1036. Berlin-Heidelberg-New York: Springer 1974
- Rundle, A. T., Sylvester, P. E.: Measurement of testicular volume. *Arch. Dis. Child.* **37**, 514—517 (1962)
- Sutherland, G. R.: Fragile sites on human chromosomes: demonstration of their dependence on the type of tissue culture medium. *Science* **197**, 265—266 (1977)
- Sutherland, G. R.: Heritable fragile sites on human chromosomes. I. Effect of composition of culture medium on expression. *Am. J. Hum. Genet.* (in press, 1979a)
- Sutherland, G. R.: Heritable fragile sites on human chromosomes. II. Distribution, phenotypic effects and cytogenetics. *Am. J. Hum. Genet.* (in press, 1979b)
- Turner, G., Eastman, C., Casey, J., McLeay, A., Procopis, P., Turner, B.: X-linked mental retardation associated with macro-orchidism. *J. Med. Genet.* **12**, 367—371 (1975)
- Zachmann, M., Prader, A., Kind, H. P., Häfliger, H., Budliger, H.: Testicular volume during adolescence. *Helv. Paediatr. Acta* **29**, 61—72 (1974)