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EDITORIAL

X-linked mental retardation[1]

More males than females are intellectually handicapped. This male excess is approximately 25%. In 1971 Lehrke, an educational psychologist, was the first to put forward the hypothesis that the male excess might result from genes on the X chromosome. Prior to that there had been a few isolated case reports of families where intellectual handicap showed an X-linked pattern of inheritance. In diseases inherited on the X chromosome the female is a carrier; she having two X chromosomes will be partially or completely protected, because one of her X chromosomes is inactive in every cell. Half of her sons will receive the X chromosome carrying the abnormal gene and will therefore be affected; half of her daughters will be carriers. If X-linked conditions are important as a cause of intellectual handicap, then it would be anticipated that many more families would have two intellectually handicapped sons than two intellectually handicapped daughters. In a survey of moderately retarded school-age children in New South Wales, Australia (Turner & Turner, 1974), it was found that there were three times as many families with two affected sons than families with two affected daughters. A similar excess of male sibships was reported by Davison (1973) in a survey in Oxfordshire and, more recently, by Herbst (1980) in British Columbia. Calculations from the survey in New South Wales suggested that a prevalance figure of X-linked genes associated with mental handicap among the moderately retarded was 5·8/10000; in British Columbia a prevalance figure of 18/10000 was found from a survey involving both the moderately and mildly intellectually handicapped. This means that approximately 20% of intellectual handicap in the male is caused by genes on the X chromosome.

There are a number of clinical conditions associated with intellectual handicap which are coded on the X chromosome. These include the Coffin Lowry Syndrome, Hunter's Syndrome, Lesch Nyhan Syndrome and the intellectual handicap associated with a proportion of boys with Duchenne Muscular Dystrophy. These are all relatively rare conditions. In the majority, the affected males have no detectable metabolic abnormality and no obvious clinical stigmata; in fact, this lack of physical stigmata may be diagnostic of X-linked mental retardation (Turner *et al.* 1971). In a moderately retarded population the majority of affected individuals have microcephaly, neurological signs or a dysgenic appearance.

THE DISCOVERY OF THE MARKER X CHROMOSOME

In 1969 Lubs described an X-linked family in which the affected males had a marker which was visible on the end of the long arm of the X chromosome in approximately 30% of the metaphases. A proportion of the carrier females also showed the marker, but in a more variable proportion of metaphases. In 1977 Harvey *et al.* described four families showing the marker. Sutherland (1977) showed that the demonstration of the marker in lymphocyte culture was dependent on characteristics of the media in which the cells were growing. It was consistently visible in culture mediums deficient in folic acid. In 1975 Turner *et al.* described two families with X-linked mental retardation in which the affected males had unexplained testicular enlargement post-pubertally. On a re-examination of twenty-three X-linked families looking for the presence of the marker (Turner *et al.* 1978), this was found in the affected males of seven families and all these males were also found to have testicular enlargement. The marker X chromosome is nearly always found associated with testicular enlargement, although some families have now been described with testicular enlargement not showing the marker and the reverse is also recorded in one family (Jennings *et al.* 1980).

[1] Address for correspondence: Dr Gillian Turner, The Prince of Wales Children's Hospital, High Street, Randwick, NSW 2031, Australia.

Table 1. *Fragile X-linked mental retardation: clinical features*

Intelligence	IQ range 30–65, rarely borderline normal
	Occasional picture of hyperactivity or autism in childhood
	Generally friendly, shy, non-aggressive as teenagers
	Repetitive speech
Growth	Birth weight normal; usually bigger than normal sibs
	Height above 50th percentile in infancy and childhood
	Head circumference above 50th percentile, occasionally above 97th percentile
Facies	Prominent forehead, jaw and big ears
Testes	May be 3–4 ml in childhood (normal 2 ml)
	Post pubertal boys 30–60 ml (normal below 25 ml)
Occasional features	Epilepsy; increased reflexes in lower limbs
	Gynaecomastia striae, fine skin
	Thickening of scrotal sac

CLINICAL FEATURES

The clinical features of the male with the marker X is shown in Table 1.

CARRIER FEMALES OF X-LINKED MENTAL RETARDATION

The intelligence of the carrier female is usually normal, but one-third have learning difficulties. This is probably related to the random inactivation of one of the X chromosomes in each cell which may affect the CNS function in a proportion of cells. In the past some of these families have been erroneously classified as cultural–familial retardation due to the normal appearance of the affected males and the mild retardation of the carrier mother. The mild intellectual handicap of some of the carriers of X-linked mental retardation stimulated us into surveying for the marker one hundred and twenty-eight mildly retarded schoolgirls. The marker was found in five, and in four there were moderately retarded males in the family history. Assuming that heterozygous expression also occurs in X-linked mental retardation without the marker, X-linked genes may account for 10% of mild retardation in the female (Turner *et al.* 1980).

GENETIC COUNSELLING

Any family with an intellectually handicapped son with no physical stigmata should be assumed to have X-linked mental retardation. If the family history is positive for other affected males on the maternal side the diagnosis is confirmed, and further offspring will then be at 50–50 risk of the sons being intellectually handicapped or the daughters being carriers. If there is no family history of other affected males, then it is reasonable to consider a recurrence risk rate of at least 1 in 10 for subsequent children being affected. The families in which the affected males show the marker enable the diagnosis to be confirmed in the singleton, but the problem then is that only a proportion of the carrier females show the marker in adult life. In childhood and adolescence the carrier female can usually be identified in that the sisters of affected males are found to have the marker in 50%, which is the expected proportion. As yet, there have been no longitudinal studies confirming that the marker may actually disappear with age. At present, all that can be offered in terms of antenatal diagnosis is foetal sexing and termination of the male foetus. There has been difficulty in reliably demonstrating the marker in fibroblast culture, but this problem is likely to be solved in the near future.[1] Once this is available then, in families with the marker X, any female at risk of being a carrier can have her pregnancy monitored by amniocentesis.

The recognition of X-linked mental retardation with and without the marker is a big step forward.

[1] Successful demonstration of the marker, both by amniocentesis and by foetal blood sampling, has recently been reported in correspondence in the *Lancet*.

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It means that another large chip has been taken off the block of undiagnosed intellectual handicap. It opens up new possibilities for reducing the prevalence of intellectual handicap by genetic counselling and by antenatal diagnosis. The families themselves are relieved at long last to have a diagnosis, even though this has implications that the mother may be a carrier. We are still only at the descriptive phase of this disease or diseases, and other subgroups may well be defined. The next awaited breakthrough is the delineation of the biochemical defect underlying this intellectual handicap. This will provide us with considerable insight into the nature of the learning process and the biochemical background behind conceptual thought. Future developments in this field should be exciting.

GILLIAN TURNER

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