Electronic letter

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Recurrence risks in undiagnosed mental retardation

EDITOR—In 1998, Crow and Tolmie¹ drew attention to the problem of giving recurrence risks to families with undiagnosed mental retardation. Published empirical risks vary widely and are based on data which have been collected in many different ways and are decades old. Clinical practice in the UK, as derived from their postal survey,¹ showed similarly wide variations. Thus, in a standardised situation where the index patient is a boy with either mild or severe mental retardation, published recurrence risks vary from 3.5 to 17.8% and the UK clinicians used a similar wide range of figures. We would like to make some suggestions for approaching this common problem based on new empirical data and to offer some theoretical guidelines for estimating risks for the sibs of both male and female index cases.

We have just completed a clinical genetics review of 429 subjects with mental retardation in the Australian Child and Adolescent Developmental (ACAD) project, which is a longitudinal study of behaviour in the mentally retarded. A comprehensive, representative, community based sample of children was recruited into the study in 1990/91 for a first behavioural assessment.^{2,3} The genetics review was at the time of their second assessment some five years later when the subjects ranged in age from 10 to 24 years. In about two thirds the IQ had been measured as less than 50, 8% had not been tested, and the rest were over 50. All were seen by one or more of three clinical geneticists except for 74 patients in whom the diagnosis was clear cut (for example, documented trisomy 21). We found that when all those patients in whom the cause of their mental retardation was known and all those with recognised clinical entities without a known cause (for example, cerebral palsy, epilepsy, autism) were removed, 119 (28%) remained undiagnosed. Nearly all of these had been tested for the fragile X syndrome. We found an overall excess of males (M/F=1.38) in the group as a whole which was still present (M/F=1.76) in the undiagnosed subgroup.⁴

The empirical recurrence risks for sibs in the 101 families from this subgroup for which family histories were obtained are shown in table 1. The ages of the index cases were such that most families had been completed so that the data are retrospective and include children born both before and after the index case. Half sibs were included only if they were maternal, as the informant was usually the mother and information on the paternal half sibs was much less reliable.

The male excess of index cases and the higher recurrence risk in brothers than in sisters if the index cases were male are obvious. This accords with the observations of others in the past.¹ These findings strongly suggest that genes on the X chromosome are important contributing factors to the recurrence risk in undiagnosed mental retardation.

Table 1 Observed recurrence risks for mental retardation in the sibs of index cases

Index case	Number	Brothers	Sisters	All
Male	69	11/83 (1 in 7.5)	3/60 (1 in 20)	14/143 (1 in 10)
Female	32	3/36 (1 in 12)	2/30 (1 in 15)	5/66 (1 in 13)

Another contributing factor to recurrence has been brought out by the work of Knight *et al*,⁵ who showed, by a battery of FISH telomeric probes, that chromosomal rearrangements not normally visible by routine light microscopy may account for up to 7% of undiagnosed mental retardation. In their study of 284 subjects with moderate to severe handicap, 21 (7.4%) were identified as being partially monosomic or trisomic. Ten cases were familial and 11 had de novo rearrangements. The sex ratio of the index cases in the familial translocations was equal but in the de novo cases there was an unexplained excess of males (10 out of 11). In their series about one third were randomly ascertained and the rest were recruited from genetic units and learning disability teams, which may have introduced bias from the family history or dysmorphic features. Our much more limited experience has been that cryptic chromosomal rearrangements are found not only in the dysmorphic but also in the non-dysmorphic. By previous standards, in the absence of a positive family history (especially of disparate phenotypes), chromosome studies would not have been indicated in such people except for a search for the fragile X. In the ACAD survey one such family with a cryptic translocation had been identified,⁴ but we know of four other similar families. Also we have recently reviewed a pair of brothers previously diagnosed as non-specific or non-syndromic X linked mental retardation (XLMR) in whom a cryptic translocation has been found by FISH. Comprehensive testing as described by Knight *et al*⁵ is expensive and not readily available but we were able to test 20 patients in the undiagnosed group with an incomplete battery of telomeric probes but found no further cases.

Theoretically other factors contributing to recurrence could be dominant conditions with incomplete penetrance, undiagnosed autosomal recessive entities, genes on the Y chromosome with a second allele on the X, and X linked male lethals with skewed inactivation in the mother. Yet other unknown mechanisms may be at play which could be genetic or environmental.

In practice the clinician has to answer the family's questions about recurrence even though supporting evidence may be weak. Based on both our research findings and clinical experience, we would like to offer some suggestions for an approach to this difficult problem.

It goes without saying that every effort should be made to see and examine the index case and other affected members of the family personally. This is not always possible and photographs, case records, or other written descriptions may have to suffice. But the geneticist brings his or her own particular slant to the physical examination and often has a rich experience of rare conditions so that we would recommend persistence, which may entail visits to the home or to institutions, sheltered workshops, or special classes in schools.

The next point is the family history. This should be taken from more than one member of the family and at different times. It is remarkable how often mentally retarded older members of the family may be forgotten or overlooked by the consultants at the first interview. It is important to note quantitative differences in intellectual performance particularly in females within the family. Research on the fragile X syndrome has shown that 50% of females with a full mutation are recognised by the schools as having significant learning problems. We believe the same applies

Figure 1 Schematic pedigrees showing different counselling situations. Solid symbols indicate mental retardation; arrows indicate consultands.

in most families with non-syndromic or non-specific XLMR. Extracting such information from the family requires tact, patience, and the development of good rapport. Given these, it is usually found that most families know who are and who are not intellectually slow or bright. Often this is more easily recognised and acknowledged in the older generations. Family members are usually well able to rank order themselves on these parameters with good agreement between individual assessments. We believe that if the mother or the maternal aunt of an affected male is deemed to be slow and out of step with her sibs, this is strong suggestive evidence of XLMR.

Clues to a cryptic chromosome translocation in the family may be significant differences in the physical phenotype of affected subjects or large differences in the degree of mental handicap even if the physical appearance is normal or near normal.⁵

We present a number of common clinical situations (fig 1). It is assumed that the usual investigations have been carried out including a routine chromosome study and search for the fragile X, that the mother is of normal intelligence, and there are no other affected members of the extended family. In both situations IA and IB, the recurrence risks quoted in table 1 seem to be appropriate. However, if the index case is female and has mild rather than severe mental retardation, this makes XLMR more likely since only a very small proportion of moderate to severe handicap in females is the result of XLMR.

In situation IIA and IIB, where the brother and sister are the consultands, autosomal recessive conditions are not relevant unless there is intended consanguinity. The main concern is for the sister should the proband have XLMR and for both sibs if a parent has a balanced translocation. An estimate of the probability of XLMR can be made as follows. From table 1, the empirical recurrence risk for the parents is 1 in 7.5, in round figures 1 in 8. If the mother is a carrier, the risk for each son will be 1 in 2. As the empirical observed risk is 1 in 8 one can estimate that only 1 in 4 ($1/2 \times 1/8$) of such families will have an X linked disorder. It follows that the sister's risk of being a carrier is, at worst, 1 in 8 with a final risk of having a retarded son of 1 in 32. From the observations on known carriers of XLMR this risk can probably be reduced if she is or has been a bright

student. The risk for a chromosomal rearrangement in a child from either the brother or the sister can be estimated in much the same way. From the data of Knight *et al.*,⁵ one can expect that subtle chromosomal rearrangements will be the underlying mechanism in 7% of undiagnosed, mentally retarded patients; half will occur de novo and half will be from a balanced translocation in one or other parent. Such a parent will pass the balanced translocation on to 50% of the offspring. So, in situation IIA, the risk to both sibs of being carriers will be 3.5%. The risk that a carrier of a cryptic translocation will pass an unbalanced translocation on to his or her offspring is unknown but likely to be less than half. An approximate overall risk would be less than 1.7% ($3.5 \times 1/2$) or about 1-2%. For the sister this should be added to her risk of being an X linked carrier (1/32-1/64 or about 1.5-3%) giving her a final risk of having a retarded child of about 2-5%.

In situation IIB mild mental retardation in the sister points to XLMR whereas moderate to severe mental retardation suggests that a chromosomal rearrangement is more likely, with risks to both sibs as estimated for situation IIB. In situation IIIA the probability that the two retarded boys have XLMR can be estimated in a slightly different way. In previous work by one of us⁶ and by others,⁷ the argument was presented that the excess of pairs of brothers over pairs of sisters with mental retardation found in epidemiological samples represents the contribution made by X linked genes. In the present study, this excess was 11-2=9. Thus, nine of the 11 pairs of brothers or about 80% are likely to be the result of X linked genes. There is, therefore, an 80% chance that the retardation in the two brothers is caused by X linked mutations. It follows that the risk that the sister is a carrier is 40% and of her having a retarded son is 1 in 10 ($4/10 \times 1/4$). As argued previously, this risk may be reduced if she is or has been a bright student.

We realise that these recurrence risk figures are higher than those presented by Bundy.⁸ However, her calculations were based on some assumptions which are now questionable. She estimated a higher population frequency of the fragile X syndrome than currently accepted and assumed that the fragile X syndrome accounts for half of all XLMR whereas it now seems to account for considerably less. Furthermore, the assumption that the excess of affected sisters over affected brothers represents the proportion of mental retardation caused by autosomal recessive genes we know now is unlikely since many such pairs are the result of X linked entities.

The situation IIIB is rare and our suggestions correspondingly weaker. XLMR, cryptic translocations, and autosomal recessive inheritance would have to be considered but we suspect that the best we could say to the brother and sister is that we just don't know.

In reality more complicated situations are encountered, such as when one or other parent is also mentally handicapped. Each case has to be assessed individually but in our experience genes on the X chromosome should always receive serious consideration.

These views are provisional and will be revised as diagnosis is improved and more reliable, up to date epidemiological data emerge. Telomeric probes should soon become generally available and more genes for syndromic and non-syndromic XLMR will be identified. But for some years yet the clinical geneticist will be faced with the kind of problems described here. We hope this letter will provoke comments and discussion from others who are tackling this common and difficult problem.

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GILLIAN TURNER
MICHAEL PARTINGTON

*Hunter Genetics, The Hunter Area Health Service and the Faculty of
Medicine and Health Sciences, The University of Newcastle, PO Box 84,
Waratah, New South Wales 2298, Australia*

Correspondence to: Dr Turner, huntergenetics@doh.health.nsw.gov.au

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