Recurrence risks in undiagnosed mental retardation

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

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

Another contributing factor to recurrence has been brought out by the work of Knight *et al.*, 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 patient with a cryptic translocation had been identified, 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.* 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 consultands 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.
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 siblings, 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 mental handicap even if the physical appearance is normal or near normal.5

![Figure 1: Schematic pedigrees showing different counselling situations. Solid symbols indicate mental retardation; arrows indicate consultands.](http://jmg.bmj.com/Downloadedfrom)

The risk of 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; 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 x ½) 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 us and by others, 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 x 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.5 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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