Angelman’s syndrome, abnormality of 15q11-13, and imprinting

Pembrey et al. and Fryns et al. have reported transmission of pericentric inversions of chromosome 15 (inv(15) (p11q13)) from phenotypically normal mothers to children who have Angelman’s syndrome. They cite this as evidence that in some cases Angelman’s syndrome must be autosomal recessive (that is, that the inversion had caused a gene mutation and was uncovering the recessive gene transmitted by father). However, their cases are exactly what would be expected with maternal imprinting, that is, the abnormality expresses when transmitted from the mother, but will not express when transmitted from the father.2 4 Thus if the chromosome 15 involved in the rearrangement came from the mother’s father in these cases, the abnormality would not be expected to express in the mother. Neither report indicates whether the parental origin of the mother’s rearranged chromosome 15 has been determined. It seems quite possible that the rearrangement could have been present in the grandfathers and not expressed in them either if the chromosome 15 involved was inherited from their fathers.

That some translocations, inversions, insertions, and other chromosomal rearrangements will result in phenotypic abnormalities only when transmitted from mother or from father is one of the expectations of imprinting. Thus, families with chromosomal rearrangements that come to attention because of a phenotypically abnormal child need to be re-evaluated in relation to the sex of the parent transmitting the rearrangement. In the past, when a phenotypically normal parent had the same rearrangement as the abnormal child, the chromosomal abnormality has been dismissed as not causative.

Similarly when two children (particularly of opposite sex) have a disorder and the parents are phenotypically normal we have assumed autosomal recessive inheritance. However, recent studies using DNA markers in Prader-Willi,5 6 Miller-Dieker,7 8 and Wolf-Hirschhorn syndrome9 have shown that submicroscopic deletions defined by DNA studies may lead to classical phenotypes. Assuming maternal imprinting is active in Angelman’s syndrome,4 if the mother’s paternally derived 15 had a submicroscopic deletion, she could be phenotypically normal but would have a 50% recurrence risk rather than 25% to have more affected children, since she would be expected to transmit the submicroscopically deleted chromosome 15 half the time. Willems et al.10 have estimated empirically that the recurrence risk for Angelman’s syndrome is 1 to 2% which would mean that, if maternal imprinting is active in Angelman’s syndrome, parental germ-line mosaicism must be quite low. On the other hand there appear to be seven or eight families with phenotypically normal parents and two affected children among the 50 to 70 reported cases of Angelman’s syndrome,1 2 10 11 suggesting that the recurrence risk may be more in the order of 5 to 10%, which fits with the rate of germ-line mosaicism seen in many other conditions12 and is still quite compatible with maternal imprinting.

Finally, it is not yet clear whether the imprinting phenomenon involves parts of chromosomes, a segment, several genes, or single genes. It seems possible that imprinting in the 15q11-13 region may involve single genes or a group of genes in different parts of the region being imprinted differently. Thus, the translocation breakpoints in these two families are particularly interesting whatever the pathogenic mechanisms in Angelman’s syndrome and should be cloned.

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Unilateral disomy as a possible explanation for Russell-Silver syndrome

The excellent paper on severe Russell-Silver syndrome by Donnai et al.1 helps to define the spectrum of patients who fit in to what has been called the Russell-Silver syndrome. It is a relatively common condition but has defied explanation. The recent observation in mice that uniparental disomy is associated with intrauterine growth retardation3 raises the possibility that both intrauterine retardation and postnatal growth retardation may be explained on the basis of uniparental disomy. The two recent cases of cystic fibrosis in which maternal isodisomy has been proven5 had the association...