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 expression when transmitted from the mother, but will not express when transmitted from the father. 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, Miller-Dieker, and Wolf-Hirschhorn syndrome have shown that submicroscopic deletions defined by DNA studies may lead to classical phenotypes. Assuming maternal imprinting is active in Angelman’s syndrome, 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. 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, suggesting that the recurrence risk may be in the order of 5 to 10%, which fits with the rate of germ-line mosaicism seen in many other conditions 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. 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 retardation 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 proven had the association...
of intrauterine and postnatal growth retardation. The Russell–Silver syndrome, and also cases of intrauterine growth retardation without asymmetry, may well be related to constitutional or mosaic uniparental disomy. In mice there are at least six segments of chromosomes which exhibit phenotypic differences depending on whether there is maternal duplication with paternal deficiency or paternal duplication with maternal deficiency. Extrapolating from the man/mouse homologous map one can predict that chromosomes 2p, 5q, 6p and q, 7p and q, 9q, 11p and q, 16p and q, 19q, 20q, 21q, and 22q in humans might show phenotypic differences when there was uniparental disomy for those segments. Again, judging from the mouse and from the human example of cystic fibrosis, one would anticipate growth and behaviour abnormalities but not true malformations in these situations (assuming that a gene that in the homozygous state could produce a syndrome with congenital anomalies was not carried on the particular chromosome). Since both chromosome and DNA markers are available it seems worthwhile to pursue the possibility that patients with Russell–Silver syndrome and other conditions with severe intrauterine growth retardation (where specific congenital anomalies are not present) be evaluated for the possibility of uniparental disomy as the explanation for the intrauterine growth retardation.

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A video presentation ‘Talking about Tay-Sachs’

“It’s not in my family”, or perhaps an admission that you have not heard of the condition before, may be the typical response from someone when asked what they know about Tay–Sachs disease. However, this is no protection against Tay–Sachs occurring in your family.

A 23 minute video presentation about Tay–Sachs and carrier testing is available on loan for a four week period. Families who have personally experienced Tay–Sachs talk frankly about the condition and how it has affected them. Though these parents have suffered the loss of a young child, there is through screening a message of great hope for the future for those watching the programme. Medical and community leaders discuss aspects of counselling and testing which can prevent this family tragedy. Emphasis is placed on the benefits of people knowing their result; before marriage for some, but certainly before starting a family. That carriers are completely healthy and are only at risk of having an affected child if both are carriers is highlighted.

The majority of babies born with Tay–Sachs are born into families with no previous history of the condition. Among the Jewish community carriers are found at the rate of one person in 25. It is for each subject to decide when they would like to be tested, either as a younger single person or when a marriage is planned. We would be pleased to arrange talks with discussion for groups in the UK, show the video, and to offer testing at a later date. Community testing sessions have been particularly well received by younger people. Details about forthcoming testing sessions are available. If you would like to have a copy of this video, or further information, please contact Zahavah Hecksher or Debbie Seedburgh, Programme Coordinators, Tay–Sachs Carrier Testing Centre.

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This volume was published as the companion to volume 62 in this series and comprises the second part of the proceedings of the 4th Congress of the International Retinitis Pigmentosa Association. It is devoted to issues of direct interest to patients with retinitis pigmentosa (RP) and this is apparent from chapter headings which include researchers help patients, technical aids, therapy, genetics, living with RP, the RP societies. The majority of contributions are from German authors (the host country for the Congress in Germany) and an attempt has been made to deal with complex issues in a simple language. The text is clearly presented and fairly comprehensive on the treatment of the topics which have been chosen for discussion. This book is directed primarily to a lay readership of patients with retinitis pigmentosa and may therefore have a limited appeal to a medically qualified audience.

MARCELLE JAGGARD


First published in 1983, this textbook was outstanding in several respects. The overall plan was a logical exploration.