Imprinting and Angelman's syndrome

The revision of the conclusions of two recent reports of Angelman's syndrome^{1,2} by Professor Hall³ is correct in pointing out the consistency of the observations with those expected owing to genetic imprinting. However, the importance of the results is understated even in this revision. The essential observation made was that the maternal transmission of pericentric inversions of chromosome 15 (inv(15)(p11q13)) resulted in offspring with Angelman's syndrome, while the mothers carrying the inversion were unaffected. Whereas the authors of the original reports postulated that the inversion 'unmasked' a recessive gene for the condition transmitted by the father, the role of imprinting in this parentally determined susceptibility was highlighted by Professor Hall, who predicted that the mothers would have to have inherited the rearrangement from their fathers to be unaffected. On first appraisal, this conclusion contradicts what is known about imprinting on chromosome 15, that the area deleted to yield Angelman's syndrome or Prader-Willi syndrome is identical, not only in cytogenetic (15q11-13)⁴ but also in molecular terms,⁵ dependent only on the parent of origin of the deleted chromosome (AS maternal, PWS paternal). If this were true, then the paternal inheritance of the rearrangement by the probands' mothers in these cases should have resulted in maternal Prader-Willi syndrome.

The pathological effect of imprinting apparently results from the production of nullisomy at a locus when a genetic event removes a functioning allele, the homologue of which has been rendered inactive owing to the imprinting process.⁶ In the 15q11-13 region, several (a minimum of two) such loci must exist, inactive alleles occurring on both paternal and maternal chromosomes, in order to produce the discrete phenotypes. The pericentric inversions should be interpreted in this light, while adhering to the assumption implicit in the previous assessments: that, as the mothers express the rearrangement in a non-mosaic manner in their somatic cells, they probably inherited the inversion. Firstly, if the inverted segment has led to incapacitation of the 15q11-13 region, and as it is being inferred that the individual loci giving rise to Prader-Willi and Angelman's syndromes are

distinct, it may be concluded that the locus (loci) for the former is located more distally, beyond the breakpoints in these cases. If there is indeed a submicroscopic deletion associated with the inversion, then the status of the rearranged segment is crucial. If the rearranged segment is not inactivated, which would be more consistent with viability, then the pathological consequences are mostly attributable to the deletion. In this case, the locus (loci) for Angelman's syndrome are within the deleted segment, and the Prader-Willi locus (loci) may be proximal or distal to this. Furthermore, the rearrangement could indeed be inherited from grandfathers. It is also possible that further genetic events have taken place in the Angelman patients. The final possibility is that the mothers do in fact have loci nullisomic owing to imprinting, but that the deletion is sufficiently small that compensatory mechanisms to prevent the development of Prader-Willi syndrome are effective.

Whatever the molecular event, the main conclusion which may be drawn is that, apart from the last possibility, these cases confirm the independence of the Prader-Willi and Angelman loci, suggest that if multiple loci govern Angelman's syndrome they are within a relatively restricted stretch of DNA uninterrupted by Prader-Willi loci, and confirm the importance of imprinting in the region. In short, the loci for Prader-Willi and Angelman's syndromes may be distinguishable using the DNA of these patients, and the chromosomal status of the maternal grandparents must be ascertained, a point stressed by Professor Hall.

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- 2 Fryns JP, Kleczkowska A, Decock P, Van den Berghe H. Angelman's syndrome and 15q11-13 deletions. *J Med Genet* 1989;26:538.
- 3 Hall JG. Angelman's syndrome, abnormality of 15q11-13, and imprinting. *J Med Genet* 1990;27:141.
- 4 Magenis RE, Brown MG, Lacy DA, et al. Is Angelman syndrome an alternate result of del(15)(q11q13)? *Am J Med Genet* 1987;28:829-38.

5 Donlon TA. Similar molecular deletions on chromosome 15q11.2 are encountered in both the Prader-Willi and Angelman syndromes. *Hum Genet* 1988;80:322-8.

6 Solter D. Differential imprinting and expression of maternal and paternal genomes. *Annu Rev Genet* 1988;22:127-46.

BOOK REVIEWS

The Ichthyoses. A Guide to Clinical Diagnosis, Genetic Counselling, and Therapy. H Traupe. (Pp 253; £62.50.) Berlin: Springer-Verlag. 1989.

A book intended to bring together the modern concepts of ichthyosis is long overdue, and Dr Traupe has, almost singlehandedly, made a brave attempt to meet the challenge. His classification includes 20 genetic disorders which are grouped into 'isolated' and 'associated' forms, each with 'congenital' and 'vulgar' (meaning later onset) categories. For example, X linked recessive ichthyosis is an isolated vulgar condition, whereas neutral lipid storage disease and Sjögren-Larsson syndrome are associated congenital ones. On the whole, this didactic approach works quite well, especially as it incorporates numerous lists for sorting out the different forms according to cutaneous signs and symptoms, non-cutaneous disease manifestations, and microscopical and biochemical findings.

There is an excellent historical chapter including an illustrated account of the 'porcupine' members of the Lambert family from Suffolk. Other chapters deal systematically with the four main categories. In addition, there is a comprehensive and up to date chapter by B Melnik on epidermal lipids and the biochemistry of keratinisation. This is the only chapter not written by Dr Traupe himself.

The book is liberally illustrated with superb black and white clinical photographs, picking out the detailed topography of scaly skin, and with photomicrographs and electron micrographs, which are helpful in delineating some of the rarer forms.

The generally excellent presentation and uniformity of style will ensure this book's success with most readers. It