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Molecular cytogenetics of Prader-Willi and Angelman syndromes

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Sir,—We read with interest Professor Hultén and colleagues' letter (Sept 7, p 638) on genomic imprinting in an Angelman syndrome (AS) and Prader-Willi syndrome (PWS) translocation family. The two syndromes differ phenotypically but have similar chromosome 15q deletions, inherited from the father in PWS¹ and mother in AS.² Hultén et al report an unbalanced 15;22 translocation in index children which was overlooked at first, the children being classified as having the 15q11–13 deletion typical of most patients with PWS and AS. The translocation was detected only after application of specialised cytogenetic techniques, including fluorescent in-situ hybridisation (FISH). Genomic imprinting for PWS and AS has important implications for counselling, and FISH with chromosome 15 probes should be undertaken on apparently sporadic PWS and AS patients to rule out subtle translocations of this chromosome involving the pericentromeric region.

We have seen a second instance of genomic imprinting for PWS and AS, and report our experience with FISH with a pericentromeric chromosome 15 probe in this family and in several sporadic PWS and AS cases. During an evaluation for behaviour and schooling difficulties, a 10-year-old girl was diagnosed as having PWS, on the basis of physical features and history. High-resolution chromosome analysis was normal. Review of the family history revealed that an 11-year-old male paternal cousin had been diagnosed at 4 years of age with AS. His chromosome analysis revealed the typical 15q deletion seen in AS, and G-banded chromosome 15 polymorphisms showed the deletion to be of maternal origin. Paternal high-resolution cytogenetic studies were normal. These cousins are related in a fashion consistent with the imprinting hypothesis—ie, the father of the PWS child and the mother of the AS child are brother and sister.

Our molecular cytogenetic study was extended to 4 males and 7 females with PWS (9 with del [15q] and 2 with normal chromosomes), 1 female and 2 males with AS (all del [15q]), and the parents of the cousin with AS. We used D15Z1, a satellite non-isotopic probe localised to the pericentromeric area of chromosome 15 (Oncor). By FISH at least 20 cells were analysed; several metaphases were photographed from each case and the presence and size of the fluorescent area on each chromosome 15 was recorded. When possible, the size of the fluorescent body from the deleted chromosome 15 and the normal chromosome was compared (table). Our results indicate a difference in the size of the fluorescent area detected

by FISH in 9 of 14 PWS or AS patients, but the smaller fluorescent area did not consistently correlate with the deleted chromosome previously identified by short-arm and stalk-length polymorphisms. A size difference was observed in 1 parent; thus, the technique may be useful for identification of chromosome 15 pericentromeric polymorphisms for parental origin studies. We did not identify any previously undetected translocations involving this region in either the PWS or AS patients or the parents of one of the AS patients.

Our study indicates that previously undetectable translocations involving the pericentromeric region of chromosome 15 are rare as a cause of the 15q deletion in PWS or AS patients—but FISH may be a useful technique identifying chromosome 15 polymorphisms so that parental origin can be determined.

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SUMMARY DATA FROM FISH STUDIES WITH D15Z1

Sex	del (15q)	Size difference on FISH	Smaller fluorescent body on del (15q)
<i>PWS</i>			..
M	+	ND	..
F	+	ND	..
M	+	ND	..
F	-	ND	..
F*	-	ND	..
M	+	Yes	No
F	+	Yes	Yes
F	+	Yes	Yes
F	+	Yes	Yes
F	+	Yes	?
M	+	Yes	?
<i>AS</i>			
F	+	Yes	No
M	+	Yes	No
M [†]	+	Yes	Yes
<i>Parents of[†]</i>			
F	-	ND	..
M	-	Yes	? polymorphism

*,[†] First cousins.

ND = no detectable difference.