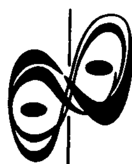

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Dosage and Imprinting Effects in Abnormalities of Human Chromosome 15

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Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are distinct mental retardation disorders caused by paternal deficiency (PWS) or maternal deficiency (AS) of gene(s) in 15q11.2-q13. We have constructed a 3.5 Mb yeast artificial chromosome (YAC) contig of the PWS/AS region and cosmid contigs of selected YACs at D15S13, SNRPN, S10, and S113. Cosmid clones have been used for fluorescence in situ hybridization (FISH) detection of deletions in PWS and AS patients. In addition, a total of 28 short tandem repeat polymorphisms (STRs) have been mapped to specific YACs in the contig, providing a highly informative set of markers for detection of deletion or uniparental disomy (UPD) in PWS and AS patients. Use of the 3 most informative markers in this region (S542, S128, and ASSCA-1) plus 3 markers distal on 15q (S123, S125, and S131) provide an efficient diagnostic strategy for UPD15.

A combination of FISH and STR analysis has identified small deletions in one sporadic and one familial case of PWS (family O). Both deletions involve all or part of the SNRPN gene but do not extend telomeric to PAR-5 or PAR-1, two novel transcripts expressed exclusively from the paternal chromosome. However, expression of SNRPN, PAR-5, and PAR-1 is lost in both cases, implying the presence of an imprinting control region near SNRPN. The smallest deletion in family O is estimated at approximately 30-40 kb in size and involves a newly identified CpG island at the 5' end of SNRPN which is methylated on the maternal chromosome. This small deletion in two PWS affected siblings was present in the father and the paternal grandmother, both of whom were phenotypically normal.

These data are consistent with the developing model of a large imprinted domain in 15q11-q13 extending from ZNF127 approximately 1.5 Mb proximal to SNRPN distal to the as yet unidentified Angelman gene, a total size of approximately 2 Mb. The presence of at least one cis-acting regulatory element and widely separated coding regions for genes involved in PWS and AS significantly alter the concept of a "critical region" for each disease and has important implications for diagnostic strategies employed.

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