Breakage in the *SNRPN* locus in a balanced translocation patient with Prader-Willi syndrome

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Submitted to the faculty of the University Graduate School
in partial fulfillment of the requirements
for the degree
Doctor of Philosophy
in the Department of Medical and Molecular Génetics
Indiana University

February 1996

Accepted by the Graduate Faculty, Indiana University, in partial fulfillment of the requirements for the degree of **Doctor of Philosophy**.

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ABSTRACT

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The Prader-Willis syndrome (PWS) is associated with a genetic abnormality of chromosomal region 15q11-13. However, the critical genes responsible for the phenotype have not been defined. A PWS patient with a translocation between chromosomes 15 and 19, 46,XY,t(15;19)(q12;q13.41), was studied to further understand the genetics of PWS. Identification of the translocation breakpoint provided insights into the genetic cause of the PWS phenotype in the patient. Study of the patient's chromosomes showed that the *de novo* translocation had disrupted a gene called *SNRPN* (small nuclear ribonucleoprotein N), suggesting that this gene may be critical for PWS. By using a variety of cytogenetic, molecular cytogenetic and molecular genetic techniques including DNA sequencing of the breakpoint, the translocation breakpoint in chromosome 15 was found to be in an intron between the second and third exons of the *SNRPN* gene. Sequence analysis revealed that the breakpoint is localized within an *Alu* sequence approximately 550 base pairs upstream of the third exon, suggesting the translocation may be mediated by *Alu* sequence. The translocation chromosome was found to be inherited from the father. Other genetic abnormalities including deletion of chromosomal region 15q11-13, inheritance of both chromosomes 15 from mother, and abnormal DNA methylation in 15q11-13 were ruled out in the

patient. Gene expression analysis of five imprinted, paternal allele-only expressed genes (*ZNF127, SNRPN, IPW, PAR-5*, and *PAR-1*) in 15q11-13 revealed that all genes except the full-length *SNRPN* in this region were expressed. Each portion of the *SNRPN* gene, now on different chromosomes, also exhibited RNA expression, even though the full-length RNA was not expressed. Therefore, the PWS phenotype of the patient is likely the result of the lack of expression of the full-length *SNRPN* gene, suggesting that *SNRPN* is a critical gene for the development of the Prader-Willi syndrome.

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