Reviewer’s report

**Title:** Molecular breakpoint cloning and gene expression studies of a novel translocation t(4;15)(q27;q11.2) associated with Prader-Willi syndrome

**Version:** 2  **Date:** 19 April 2005

**Reviewer:** Arthur L Beaudet

**Reviewer’s report:**

General: This report extends the molecular analysis of patients with partial or complete PWS phenotypes caused by balanced translocations disrupting the SNRPN transcript. On the one hand, the conclusion is the same as in the previous report by Gallagher et al from this group. On the other hand, PWS potentially represents the first or one of the first human diseases caused by mutation of a noncoding regulatory RNA if the interpretation of the authors is correct, as I believe it most probably is. There certainly are remaining questions as to the phenotypic variability in these patients, particularly as regards intellectual function and degree of hyperphagia and obesity; the obesity may be altered by dietary restriction and/or growth hormone therapy. In addition, there are conflicting reports as to whether necdin deficiency in mice causes an obvious phenotype or not, but there are no known single gene deficiency mutations in the Ndn locus to my knowledge. Overall, this report adds weight to the argument that deficiency of the HBII-85 snoRNA cluster is the central component of the molecular basis of PWS.

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**Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)**

None

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**Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)**

1. There are some questions regarding figures and legends. In Fig. 1c, the difference in a line vs a box is not clear. There is orange in the fig but the legend refers to B&W. In fig 5, I would expect a doublet of 10 kb and 11.5 kb for the patient but this is not obvious. Either state that the original appearance is compatible with a doublet or explain why no 10 kb band. The significance of the 12.6 kb band in Fig 5 is not clear, extra band? marker?

2. It would be desirable to have a better understanding of whether the patient lives relatively independently particularly as to imposed dietary control. If he is on his own for food control, the obesity is particularly mild. His ability to live independently is also of interest as to how to interpret the "normal IQ"? vs development delay in the table. Is the IQ normal? Why not give a number? The fact that the patient and his acquaintances might read the publication could make this difficult. Was the patient ever and is he now on growth hormone treatment?

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**Discretionary Revisions (which the author can choose to ignore)**

1. For completeness in the introduction, could mention that there are nondeletion cases of imprinting defect PWS.

2. The sentence The modification targets of the imprinted C/D box snoRNAs in the PWS/AS region are still unknown. (might be changed to) The modification targets, if any, of the imprinted C/D box snoRNAs in the PWS/AS region are still unknown.

3. There are some minor style issue. Hybridization or hybridisation. favourite vs favorite, 122kb interval vs 122-kb interval.

4. A period should replace a comma here. While the sequence across the breakpoint is contiguous
on the der(15), an extra A is inserted on the der(4) chromosome (Fig. 6b). Furthermore, the breakpoint on chromosome 4 falls in a large intron between exons 10 and 11 of a spliced transcript (BC045668).

**What next?:** Accept after minor essential revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests