

Chromosome 15 maternal uniparental disomy and psychosis in Prader-Willi syndrome

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In the 16 January 2002 issue of the *Lancet*, Boer *et al*¹ reported that psychotic illness in Prader-Willi syndrome (PWS) is associated with chromosome 15 maternal uniparental disomy. Here, we report the findings of a 10 year follow up study at the Centre for Human Genetics in Leuven, confirming the results of the previous study.

MATERIALS AND METHODS

Fifty-nine PWS patients with the diagnosis confirmed by DNA methylation testing had regular and long term follow up at the Centre for Human Genetics in Leuven. For more than 10 years, these patients have been seen at least once a year by a clinical geneticist and a psychiatrist skilled in the assessment of people with learning disabilities. Detailed information on clinical and psychiatric history was recorded in the medical files for all patients. For the past two years all patients were offered a DNA methylation test using probes PW71B and KB17 and FISH analysis for 15q11-12 deletion detection. If FISH analysis did not show a deletion, blood samples were taken from the parents to test for uniparental disomy. If no uniparental disomy was found, an imprinting centre deletion was examined (Essen, Germany).

RESULTS AND DISCUSSION

In 51 out of the 59 patients, the exact genetic type was established: 37 patients had a deletion, eight patients had uniparental heterodisomy, and one patient had uniparental isodisomy. Three patients with a typical PWS clinical phenotype showed only a typical PWS methylation abnormality with probes PW71B and KB17 but no further abnormality was detected (no uniparental disomy, no microdeletion, no IC deletion). These three patients presumably have a sporadic imprinting centre defect. A *de novo* translocation 46,XX,t(11;15)(q25;q11.2) was found in one patient. Blood samples from the parents for analysis of uniparental disomy were not available in one patient.

Table 1 Summary of sex, current age, age at onset, and genetic status of six people with PWS and psychotic illness with distressed perplexity, acute onset, and polymorphous and shifting symptomatology. All patients are above 13 years

Patient	Sex	Current age	Age at onset	Genetic abnormality
1	M	17	14	IC defect
2	M	17	15	Heterodisomy
3	F	24	19	Heterodisomy*
4	M	30	15	Heterodisomy*
5	F	33	13	Heterodisomy
6	F	41	19	Heterodisomy*

The results marked with * are compatible with maternal heterodisomy, but this could not be proven because paternal blood was not available.

Key points

- Prader-Willi syndrome (PWS) is known to be associated with a high rate of psychotic disorders and an association between psychotic illness in PWS and chromosome 15 maternal uniparental disomy has been reported.
- Fifty-nine patients with the PWS diagnosis confirmed by DNA methylation testing had a full psychiatric assessment. In all patients, the exact genetic subtype (15q11-12 deletion, uniparental disomy, imprinting centre defect) was established.
- Six patients (15.7%) had experienced a psychotic episode with an age of onset varying from 13 to 19 years. Five out of these six patients had uniparental disomy and the sixth patient had an imprinting centre defect.
- These data further support the hypothesis that an abnormal imprinting pattern of genes might lead to development of psychotic illness in PWS.

Six out of these 59 patients have experienced a psychotic episode with “acute onset and shifting and polymorphous symptomatology” as defined by Perris in 1988² and described in PWS patients by Clarke in 1993.³ The age of onset of the psychotic episodes in the six patients in the present study varied from 13 years to 19 years. In the patient group older than 13 years (mean age 27.7 years), six out of 38 (15.7%) had psychotic episodes. The somewhat higher rate in the English population (28% or 7/25) is probably the result of the older age of that PWS population (28 years and older), but the difference is not statistically significant. Because we have included all patients older than 13, there is a risk that some of them might still develop a psychotic episode.

Table 1 shows the sex, age at onset, genetic status, and symptoms in these six patients. Five out of six patients with psychotic illness had uniparental disomy. Two patients had confirmed maternal heterodisomy. The results in the other

Table 2 Summary of sex, current age, and genetic abnormality of two patients with uniparental disomy and one patient with an IC defect but without psychiatric symptomatology. All patients are above 13 years

Patient	Sex (male/female)	Current age	Genetic abnormality
1	F	17	Isodisomy
2	F	26	IC defect
3	F	32	Heterodisomy

three patients were compatible with heterodisomy, but these results could not be proven because the father of these patients had died. None of the psychotic patients had a deletion.

In the total group of patients older than 13 years, none of the 28 patients with a deletion had psychotic episodes in the past, compared with five of seven patients with uniparental maternal disomy and one of two with a sporadic imprinting centre defect. The patients with uniparental maternal disomy who are not psychotic are 17 and 32 years old. The patient with the sporadic imprinting centre defect is 26 years old. All three are still at risk for developing a psychotic episode (table 2). Our data further support the hypothesis that an abnormal imprinting pattern of genes on chromosome 15 might lead to development of psychotic illness in PWS.

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REFERENCES

- 1 **Boer H**, Holland A, Whittington J, Butler J, Webb T, Clarke D. Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. *Lancet* 2002;**359**:135-6.
- 2 **Perris C**. The concept of cycloid psychotic disorder. *Psychiatr Dev* 1988;**1**:37-56.
- 3 **Clarke DJ**. Psychosis and Prader Willi. *Br J Psychiatry* 1993;**163**:680-4.

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