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

A Vogels, G Matthijs, E Legius, K Devriendt, J-P Fryns

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 defect). The 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 was not available.

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 then 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).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Current age</th>
<th>Age at onset</th>
<th>Genetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>17</td>
<td>14</td>
<td>IC defect</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>17</td>
<td>15</td>
<td>Heterodisomy</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>24</td>
<td>19</td>
<td>Heterodisomy*</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>30</td>
<td>15</td>
<td>Heterodisomy*</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
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</tr>
<tr>
<td>6</td>
<td>F</td>
<td>41</td>
<td>19</td>
<td>Heterodisomy*</td>
</tr>
</tbody>
</table>

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

Six out of these 59 patients have experienced a psychotic episode with “acute onset and shifting and polymorphous symptomatology” as defined by Perris in 1988 and described in PWS patients by Clarke in 1993. 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...
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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