Letter to the Editor

Large deletions of the \textit{MECP2} gene in Chinese patients with classical Rett syndrome

To the Editor:

Rett syndrome (RTT; MIM 312750), an X-linked disorder that almost exclusively affects girls (1), is caused by mutations in the \textit{MECP2} (methyl CpG binding protein 2) gene (2). DNA sequencing identifies mutations in the \textit{MECP2} gene in \textasciitilde 80\% of classic RTT patients. Recently, quantitative analysis has identified large deletions within the \textit{MECP2} gene in 20–38\% of those RTT patients with no mutation found on sequencing (3–9). We have studied 30 Chinese classical RTT patients without a defined \textit{MECP2} mutation using multiplex ligase-dependent probe amplification (MLPA) to detect large deletions of the \textit{MECP2} gene.

These 30 patients were referred from 11 provinces of China. All patients fulfilled the international diagnostic criteria (10) and did not have a defined \textit{MECP2} mutation. Genomic DNA was prepared and purified from peripheral blood (Qiagen, Valencia, CA). Informed consent was obtained. \textit{MECP2}-MLPA (covering each of the four exons of the \textit{MECP2} gene) was performed using kit P015C (MRC-Holland, Amsterdam) (11). X chromosome inactivation (XCI) was tested in all 11 patients with a large deletion in the \textit{MECP2} gene by analysing the androgen receptor gene (AR) in peripheral blood DNA (12). X inactivation was considered significantly skewed if the ratio equated or exceeded 80:20.

We detected 11 cases with large deletions of the \textit{MECP2} gene in the 30 Chinese classical RTT patients (36.6\%). Ten of the 11 deletions involved either exon 3 or both exons 3 and 4 (Table 1). In one case (R-111), the flanking \textit{IRAK1} gene was deleted along with the exons 3 and 4. The clinical features, the MLPA and XCI results of these 11 patients are summarized in Table 1.

This is the first report on the study of large deletions of the \textit{MECP2} gene in Chinese patients with classical RTT. A review of the literature showed nine studies on large deletions of the \textit{MECP2} gene on Caucasian classic RTT patients with a detection rate of 20–38\% in those with no mutation found on sequencing (3–9, 13). Little is known about Chinese patients with RTT. We reported previously the identification of 17 cases with a \textit{MECP2} mutation among 30 Chinese RTT patients by DNA sequencing (14). The present study identified 11 cases with large deletion in 30 Chinese classical RTT patients without \textit{MECP2} gene mutation on sequencing, a detection rate (36.6\% or 11/30) comparable to the reported data. In other studies, large deletions frequently involve either exon 4 or both exons 3 and 4 of the \textit{MECP2} gene (4, 5, 7–9). Our experience is consistent with previous observations. Archer et al. (8) reported five RTT patients with additional congenital anomalies, accounting for 22.7\% of those with large deletions involving the downstream DNA sequences. Deletions involving the adjacent \textit{IRAK1} gene and other genes were proposed as the cause of congenital anomalies. Ravn et al. (7) reported larger deletions involving the downstream \textit{IRAK1} gene in three patients, who did not display additional congenital anomalies or other clinical features. Our patient (R-111) with a deletion involving exons 3 and 4 of \textit{MECP2} gene as well as the \textit{IRAK1} gene does not have congenital anomalies or other clinical features. Based on these data, the cause of the congenital anomalies may not be an \textit{IRAK1} gene deletion.

Of our 11 patients aged between 3 and 23 years, the severity scores according to Kerr and Archer (8, 15), vary from 4 to 8. Because some of the symptoms are age-dependent and the number of subjects in this study is small, we were unable to establish any correlation between phenotype and different exon deletions of the \textit{MECP2} gene. In addition, skewed XCI pattern was found in two RTT patients (Table 1). Because of the small number of patients with large deletions in our study, we did not attempt to correlate the degree of XIC with the type/size of the \textit{MECP2} deletion.

Our experience is that MLPA, as a complement to DNA sequencing, is a useful tool for Rett syndrome molecular diagnosis especially in countries with a big population like China, where the number of patients requiring analysis can be large.
Acknowledgements

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References


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Table 1. Clinical and molecular results of the 11 Chinese RTT patients with MECP2 gene deletion

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (year/m)</th>
<th>Severity score</th>
<th>Walk</th>
<th>Hand use</th>
<th>Speech</th>
<th>Scoliosis</th>
<th>Seizure</th>
<th>Deleted exons</th>
<th>IRAK1 deletion</th>
<th>X-inactivation ratio</th>
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<tr>
<td>R-10</td>
<td>23/10</td>
<td>5</td>
<td>Yes</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>3–4.2</td>
<td>No</td>
<td>82:18</td>
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<td>R-20</td>
<td>11/1</td>
<td>6</td>
<td>Yes</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>1–2</td>
<td>No</td>
<td>80:20</td>
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<td>R-21</td>
<td>10/7</td>
<td>8</td>
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<td>None</td>
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<td>Yes</td>
<td>3–4.2</td>
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<td>NI</td>
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<td>R-28</td>
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<td>Yes</td>
<td>3–4.1</td>
<td>No</td>
<td>72:28</td>
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<td>R-50</td>
<td>5/6</td>
<td>4</td>
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<td>Single words</td>
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<td>No</td>
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<td>No</td>
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<td>R-91</td>
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<td>3</td>
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<td>No</td>
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<td>3–4.4</td>
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<td>R-109</td>
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<td>R-111</td>
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<td>7</td>
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</table>

NI, not informative. The 11 patients were clinically evaluated according to guidelines of Refs. (8) and (15). Severity score: composite for muscle tone, locomotor ability, scoliosis, feeding and seizure. 0, not present; 1, mild; 2, severely affected; 10, the most score.

Exon 4 of the MECP2 gene is subdivided into four sections (4.1–4.4) according to the sites of the MLPA probes (8).