Letter to the Editor

New CBP mutations in Brazilian patients with Rubinstein–Taybi syndrome

To the Editor:

Rubinstein–Taybi syndrome (RTS) is a rare autosomal dominant disease (OMIM 180849), characterized by craniofacial dysmorphisms, broad thumbs and toes, mental and growth deficiency (1). RTS has been associated with CREB binding protein (CBP) mutations and less frequently with EP300 mutations (2). CBP and p300 have high homology and are critical for many signaling pathways, especially as transcriptional coactivators and for histone acetylation (3, 4). CBP has 32 exons and no mutation hot spots (5).

This study included 20 patients (13 females and 7 males, aged 5 months to 32 years), all with typical RTS phenotype, assessed by a clinical geneticist with extensive experience (S. M. M. S.). All patients were from Brazilian families, that characteristically result from a mixture of Portuguese, African and native Indian descents, who have been merging since the 16th century. The study was approved by the institutional Ethics Committee. All patients had normal G-banding karyotype, except for one that presented an apparently balanced translocation t(2;16). A subsequent analysis using fluorescence in situ hybridization (FISH) revealed a karyotype 46,XX.ish t(2;16) (p11.2, p13.3) (+RT100, RT166-), showing a break in the exact region of the CBP. A comparative genomic hybridization (CGH) preliminary analysis was performed in 11 patients and two CBP deletions were detected. Sequencing of all CBP exons was then accomplished for the remaining 17 patients.

Genomic DNA was extracted from peripheral blood using blood genomic Spin Mini Prep kit (GE Healthcare, Piscataway, NJ) and amplified using 38 primer pairs flanking all exons and exon/intron boundaries. The primers used in this study for exons 1–31 were described by Coupry et al. (5) and the primers for exon 32 were those described by Udaka et al. (6). Amplicons were purified by column-purification kit GFX PCR DNA (Amersham Pharmacia Biotech, Piscataway, NJ) and sequenced in a MegaBace 1000 DNA Sequencer (Amersham Pharmacia Biotech). Statistical analysis of correlation between the phenotype characteristics described in in Schorry et al. (7) and CBP mutation found in the RTSs patient was performed using Fisher’s exact test (GraphPad Prism®; GraphPad Software Inc., San Diego, CA). The significance was p ≤ 0.05. Sequencing analysis was performed using the CHROMASPRO version 1.34 (Technelysium Pty Ltd, Helensvale, Australia) and compared with the sequence contained in the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov).

DNA sequencing resulted in the identification of eight mutations in the 17 RTSs patients evaluated: (i) two deletions (NM_004380.2:c.2444-2451delATGAACCA and c.3236delC), (ii) two nonsense mutations (c.4225C>T, c.4696C>T), (iii) three missense mutations (c.2015T>C, c.4076A>G and :c.5923G>A), (iv) single-nucleotide polymorphism was also identified (rs115594471/:c.5874C>T), as shown in Table 1. Six of these are new mutations (Table 1). CBP mutation detection rate by DNA sequencing in this RTSs series was of 47%. The overall rate of mutation detection in CBP was 55%, considering the combination of different techniques (FISH, array-CGH and DNA sequencing). No significant correlation genotype–phenotype of RTSs patients could be established in this study.

The rarity of the syndrome, the broad spectrum of variability in clinical expression and underestimation of intellectual disability in patients with RTSs often complicate the clinical diagnosis. Molecular studies were helpful to confirm the RTSs diagnosis in this series, thus allowing better clinical management and adequate genetic counseling.

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KT Suzuki,a LC Torese,b SMM Sugayamaa B da Costa Agüdar Alvesc CA Moreira-Filhoa M Carneiro-Sampaioa

aDepartment of Pediatrics, Laboratório de Investigação Médica – LIM 36, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil,
Letter to the Editor

Table 1. CBP mutations found in Rubinstein–Taybi syndrome patients (reference NCBI – NM_004380.2)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Location</th>
<th>Nucleotide mutation</th>
<th>Consequence</th>
<th>Domain</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>P14a</td>
<td>Exon 8</td>
<td>c.2015T&gt;C</td>
<td>p.Leu604Pro</td>
<td>KIX</td>
<td>Missense</td>
</tr>
<tr>
<td>P7a</td>
<td>Exon 12</td>
<td>c.2444del8bpfs</td>
<td>p.M747fs*830</td>
<td>PAT1</td>
<td>Deletion</td>
</tr>
<tr>
<td>P12a</td>
<td>Exon 15</td>
<td>c.3236delG</td>
<td>p.G1011fs*1021</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>P16a</td>
<td>Exon 22</td>
<td>c.4076A&gt;G</td>
<td>p.His1291Arg</td>
<td>PHD</td>
<td>Missense</td>
</tr>
<tr>
<td>P10a</td>
<td>Exon 24</td>
<td>c.4225C&gt;T</td>
<td>p.Arg1341X</td>
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</tr>
<tr>
<td>P20</td>
<td>Exon 27</td>
<td>c.4696C&gt;T</td>
<td>p.Arg1498X</td>
<td>KAT11</td>
<td>Nonsense</td>
</tr>
<tr>
<td>P21</td>
<td>Exon 27</td>
<td>c.4696C&gt;T</td>
<td>p.Arg1498X</td>
<td>KAT11</td>
<td>Nonsense</td>
</tr>
<tr>
<td>P20b</td>
<td>Exon 31</td>
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<td>p.Pro1890Pro</td>
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<td>Silent</td>
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<td>P11a</td>
<td>Exon 31</td>
<td>c.5923G&gt;A</td>
<td>p.Arg1907Trp</td>
<td>–</td>
<td>Missense</td>
</tr>
</tbody>
</table>

P, patient.
aNew mutations first described in this study.

Laboratory of Translational Medicine Professor CA Hart, Instituto de Medicina Integral Professor Fernando Figueira (IMIP), Recife, Brazil, and Clinical Laboratory, Faculdade de Medicina do ABC, São Paulo, Brazil

References


Correspondence:
Leuridan Cavalante Torres, PhD
Laboratório de Medicina Translacional Professor CA Hart
Instituto de Medicina Integral Professor Fernando Figueira (IMIP)
Rua dos Coelhos
300-Boa Vista
Recife (PE)
Brazil
Tel.: +55 81 2122 4702
Fax: +55 81 2122 4702
e-mail: leuridan.torres@gmail.com