Duplication of medial 15q confirmed by FISH

EDITOR—The proband was a male infant born to a 28 year old mother and 24 year old father. The parents were healthy and non-consanguineous. There was no significant family history. The pregnancy was complicated by intrauterine growth retardation. At term, birth weight was 2300 g and bilateral talipes were noted, as were a number of dysmorphic features. These included an enlarged anterior fontanelle with widely spaced sutures, downward slanting palpebral fissures, a flat occiput, a smooth philtrum, prominent nasal bridge, fleshy nasal tip, prominent forehead, and micrognathia (fig 1A). Deep creases were noted on both hands and feet, and the second, third, and fourth fingers of both hands were unusually long (fig 1B, C). The infant suffered from respiratory complications and failure to thrive. Further investigations showed hypothyroidism and a vascular ring (which was subsequently repaired). At 8 months old he had occasional feeding difficulties and moderate growth retardation.

Short term peripheral blood lymphocyte cultures were initiated and harvested by standard protocols. G banded analysis was carried out using trypsin digestion followed by Leishman staining. All metaphases examined showed a male karyotype with an interstitial duplication of the long arm of chromosome 15 between bands q21 and q24 (fig 2). Parental karyotypes were normal. Fluorescence in situ hybridisation (FISH) was undertaken using a TRITC labelled whole chromosome 15 specific paint (wcp15) by the method provided by the supplier (Oncor Ltd, Banbury, UK). This confirmed the duplicated material to be of chromosome 15 origin (fig 3, above). Subsequently, FISH was undertaken using four band specific YAC probes, 900D08, 958H02, 812E02, and 928D07 (supplied by the YAC Screening Centre, Milan; http://www.spr.it/iger/home.html), which map to the regions 15q21-q22, 15q23, 15q24, and 15q24-q25, respectively. Fig 3 (below) shows the FISH results using the probes 900D08 and 812E02 only. The results confirmed the cytogenetic findings; therefore, the proband’s karyotype was 46,XY,dir dup(15)(q21q24) de novo.ish dup(15)(wcp15+, 900D08++,958H02++,812E02++,928D07++).

A review of published reports (table 1) showed 18 families (29 subjects) with partial trisomy for the region of 15q duplicated in our case.1–16 The majority of cases (15/18) had breakpoints within 15q21→q22, while one had a breakpoint at 15q14, one at 15q15, and one at 15q23. Almost all cases (16/18) were the result of a parental rearrangement and, therefore, also involved partial monosomy for another chromosome. However, most of these had distal breakpoints and the monosomic material most likely contributed minimally to the phenotype. Only two cases involved a tandem duplication41 5 and one of these was in mosaic form. The other case was interstitial involving the region 15q14→q21.1, therefore overlapping only minimally with our case.15

Features common to the majority of cases with distal 15q trisomy included growth and mental retardation, hypothyroidism, and distinctive facial features including facial asymmetry, puffy cheeks, a short neck, downward slanting, narrow, palpebral fissures, ptosis, prominent nose with a broad nasal bridge, an abnormal philtrum, downturned mouth, high arched palate, midline crease in the lower lip, micrognathia, and microcephaly. The presence of congenital heart disease, skeletal abnormalities, respiratory distress/
To our knowledge, the first de novo interstitial tandem infection, and seizures varied among patients. Our case is, 
(928DO7 produced the same result.) 
(FISH using YACs 958HO2 and (Below) FISH using the YAC probes 900DO8 (red) and 812EO2 
Figure 3 (Above) FISH with wcp15 indicating dup(15) paints entirely.

infection, and seizures varied among patients. Our case is, 
to our knowledge, the first de novo interstitial tandem 
duplication of only the medial region of 15q. The abnormalities seen in this patient are consistent with previously reported cases of partial trisomy 15q and suggest a clinically recognisable phenotype.

Table 1  Clinical features in reported cases of medial/distal 15q trisomy

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Present case</th>
<th>Previous case</th>
<th>Previous interstitial duplication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental deficiency</td>
<td>?</td>
<td>27/27</td>
<td>+</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>-</td>
<td>14/24</td>
<td>0</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>-</td>
<td>7/25</td>
<td>0</td>
</tr>
<tr>
<td>Seizures</td>
<td>-</td>
<td>9/27</td>
<td>+</td>
</tr>
<tr>
<td>Growth delay</td>
<td>+</td>
<td>14/25</td>
<td>+</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>+</td>
<td>15/29</td>
<td>+</td>
</tr>
<tr>
<td>Sloping forehead</td>
<td>+</td>
<td>12/27</td>
<td>-</td>
</tr>
<tr>
<td>Facial asymmetry</td>
<td>-</td>
<td>17/24</td>
<td>0</td>
</tr>
<tr>
<td>Downward slanting palpebral fissures</td>
<td>+</td>
<td>19/26</td>
<td>-</td>
</tr>
<tr>
<td>Ptosis</td>
<td>-</td>
<td>9/16</td>
<td>-</td>
</tr>
<tr>
<td>Prominent nose, broad nasal bridge</td>
<td>+</td>
<td>26/27</td>
<td>+</td>
</tr>
<tr>
<td>Long, smooth, or well defined philtrum</td>
<td>+</td>
<td>22/28</td>
<td>+</td>
</tr>
<tr>
<td>Downturned mouth</td>
<td>-</td>
<td>18/21</td>
<td>0</td>
</tr>
<tr>
<td>High arched palate</td>
<td>-</td>
<td>17/17</td>
<td>+</td>
</tr>
<tr>
<td>Midline crease lower lip</td>
<td>+</td>
<td>12/14</td>
<td>0</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>+</td>
<td>25/28</td>
<td>+</td>
</tr>
<tr>
<td>Puffy cheeks</td>
<td>+</td>
<td>14/20</td>
<td>0</td>
</tr>
<tr>
<td>Pectus excavatum</td>
<td>-</td>
<td>15/21</td>
<td>0</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>-</td>
<td>12/18</td>
<td>+</td>
</tr>
<tr>
<td>Short neck</td>
<td>+</td>
<td>17/25</td>
<td>+</td>
</tr>
<tr>
<td>Arachnodactyly</td>
<td>+</td>
<td>9/12</td>
<td>+</td>
</tr>
<tr>
<td>Camptodactyly</td>
<td>-</td>
<td>7/7</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular defects</td>
<td>-</td>
<td>19/29</td>
<td>-</td>
</tr>
</tbody>
</table>

- not present, + present, 0 not mentioned, ? unknown


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