Growth characteristics of a girl with multicentric carpo-tarsal osteolysis caused by novel mutation in the MAFB gene

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Introduction
Multicentric carpo-tarsal osteolysis (MCTO) is a rare skeletal disorder characterised by extensive bone resorption predominantly of the carpal and tarsal bones and frequently accompanied by progressive renal impairment. Recently, causative mutations in the highly conserved region of MAFB gene (v-maf musculoaponeurotic fibrosarcoma oncogene ortholog B) have been identified by exome sequencing. The MafB, a basic leucine zipper transcription factor is involved in the regulation of osteoclastogenesis and renal development via RANK (receptor activator of nuclear factor κB) signaling pathway. Clinical presentation in MAFB mutation carriers is rather heterogeneous.

Objectives
To describe genetic background and growth characteristics in a child with clinical suspicion of MCTO.

Methods
A single exon of the MAFB gene (NM_005461.4) was analysed by direct sequencing.

Results
Genetic testing
The diagnosis of MCTO has been proven by detection of a heterozygous p.Thr581le (c.173C>T) substitution in the MAFB gene. The observed mutation was novel, but located within the mutation hotspot region and predicted to be damaging.

Case presentation
A 6-years-old girl presented with progressive restricted mobility, pain and edema of the wrists. Radiographs revealed osteolysis of proximal phalanges of thumbs, cuneiform and scaphoid bones on both ankles. The carpal bones had atypical configuration. Markers of inflammation and juvenile idiopathic arthritis associated antibodies were negative. She has mild proteinuria (297 mg/l) and normal blood pressure.

The pQCT analysis of the forearm showed sarcopenia (Muscle Area Z-score -3.8), but normal bone strength index (Polar SSI Z-score -1.8) and trabecular bone mineral density (Z-score -0.8).

Growth characteristics
In spite of chronic disease and prepubertal status, the patient has accelerated bone age (TW3-RUS 8 years at CA 6 years) and dentition. Growth has been accelerated since the age of 2 years, the last 2 year’s growth velocity has been 8 cm/year (2.5 SD). She has dysmorphic signs (strabisms, retrognatism, short mandibula and gothic palate).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>124.4 cm (1 SD)</td>
</tr>
<tr>
<td>BMI</td>
<td>15.4 cm (0.1 SD)</td>
</tr>
<tr>
<td>Sitting height</td>
<td>63.3 cm (0.7 SD)</td>
</tr>
<tr>
<td>Arm span (%) height</td>
<td>124.5 cm (100%)</td>
</tr>
<tr>
<td>Head circumference</td>
<td>54 cm (2 SD)</td>
</tr>
<tr>
<td>Foot length</td>
<td>20 cm (1.4 SD)</td>
</tr>
<tr>
<td>Wrist circumference</td>
<td>13.6 cm (1.6 SD)</td>
</tr>
</tbody>
</table>

Conclusion
We report a girl with sporadic MCTO confirmed by detection of novel mutation in the transactivation domain of MAFB gene. Beside the typical clinical signs, she displays accelerated growth and bone age. To our knowledge, this is the first description of atypical growth and bone maturation in a patient with MCTO.

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