Homozygosity mapping of a Dyggve-Melchior-Clausen syndrome gene to chromosome 18q21.1

C Thauvin-Robinet, V El Ghouzzi, W Chemaitilly, N Dagoneau, O Boute, G Viot, A Mégarbané, A Sefiani, A Munnich, M Le Merrer, V Cormier-Daire

Dyggve-Melchior-Clausen syndrome (DMC) is an autosomal recessive condition characterised by short trunk dwarfism, scoliosis, microcephaly, coarse facies, mental retardation, and characteristic radiological features. X rays show platyspondyly with double vertebral hump, epiphysal dysplasia, irregular metaphyses, and a characteristic lacy appearance of the iliac crests. Electron microscopy of chondrocytes have shown widened cisternae of rough endoplasmic reticulum and biochemical analyses have shown accumulation of glucosaminoglycan in cartilage, but the pathogenesis of DMC remains unexplained. Here, we report on the homozygosity mapping of a DMC gene to chromosome 18q21.1 in seven inbred families (Morocco, Tunisia, Portugal, and Lebanon), this condition was genetically homogeneous in our series. Continuing studies will hopefully lead to the identification of the disease causing gene.
ACAA2 which encodes a mitochondrial enzyme catalysing the last step of the mitochondrial fatty acid beta oxidation\textsuperscript{13} and MYO5B which belongs to the class V myosin family that function as motors for actin dependent organelle trafficking.\textsuperscript{14} Finally, we found that MBD1 and hCGBP are highly expressed in fetal brain, osteoblasts, and chondrocytes (data not shown). Whether any of these genes is involved in DMC is under investigation.

It is important to note that all DMC families but one were of Arab origin in our series. Whether the DMC gene frequency is
high in the Middle East and North Africa or the DMC mutation confers a genetic advantage remains open to discussion.

In conclusion, we show here that a DMC gene maps to chromosome 18q21.1. Our results are consistent with genetic homogeneity of this condition. Continuing studies will help to decide whether Smith-McCort syndrome, which causes the same skeletal manifestations but no mental retardation, also maps to this region. Identifying the DMC gene will hopefully help to elucidate the pathogenesis of this poorly understood bone dysplasia-mental retardation syndrome.

Figure 2  (A) Pictures of patients II.2 and II.3 (family 7) at 8 and 4 years. Note the rhizomelic dwarfism with short trunk, scoliosis, and coarse facies. (B) Pelvis and hip joints of patient II.2. Note the characteristic lacy appearance of iliac crest, the deformities of the femoral epiphyses, and the metaphyseal irregularities. (C) Spine of patient II.2. Note the double vertebral hump.

Table 1  Clinical and radiological features in nine DMC families

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<th>7</th>
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<td>P</td>
<td>M</td>
<td>T</td>
<td>M</td>
<td>L</td>
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<td>Facial dysmorphism</td>
<td>Thoracic anomalies</td>
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<td>Rhizomelic dwarfism</td>
<td>Mental retardation</td>
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<td>+</td>
</tr>
</tbody>
</table>
|                  | ++  | ++  | ++  | +++ | ++  | ++  | +    | N: normal; ?: not available; L: Lebanon; M: Morocco; P: Portugal; T: Tunisia.

Table 2  Pairwise lod scores for linkage of the DMC gene to chromosome 18q21.1

<table>
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<th>Recombination fraction</th>
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