Homozgyosity 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 Munnoch, M Le Merrer, V Cormier-Daire

Dyggve-Melchior-Clausen syndrome (DMC, MIM 223800) is a rare autosomal recessive condition first described in 1962 by Dyggve et al. and further studied by Naflah. The patients present with severe progressive short stature (<5 SD), microcephaly, and facial dysmorphism. Clinical features include coarse facies with bulky jaws, short trunk, scoliosis, proximal limb shortening, broad hands and feet, and mental retardation. Radiological features include platyspondyly with double vertebral hump, epiphyseal 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 (Zmax=9.65 at θ=0 at locus D18S1126) in the genetic interval (1.8 cM) defined by loci D18S455 and D18S363. Despite the various geographical origins of the families reported here (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.

METHODS AND RESULTS

Informed consent and blood samples were obtained from all family members. Genomic DNA was purified from peripheral blood leucocytes according to standard techniques. Microsatellite DNA markers from the entire genome were used at an average spacing of 10 cM. For regions of interest, all samples were analysed with extra markers of the Genethon map using a single set of primers in each amplification reaction. The homozygosity mapping strategy was based on the assumption that affected subjects of the same kindred are homozygous by descent for the disease causing mutation and two point linkage analyses were performed using the MLink option of the LINKAGE package version 5.1. The disease gene frequency was set to 0.01 assuming an autosomal recessive mode of inheritance with complete penetrance. We took into account the inbreeding loops but allele frequencies were not available in the populations studied.

Six affected subjects from four families were initially tested (families 1-4) and four of six were homozygous for a marker at locus D18S363. Eleven additional markers were then tested in all nine families and we found linkage of the disease gene to polymorphic markers of chromosome 18q21.1. Pairwise linkage between a polymorphic marker at locus D18S1126 and the disease locus gave a maximum lod score of Z=9.65 at θ=0 (table 2). Heterozygosity at locus D18S455 in affected subjects II.1-3 (family 1) and II.1 (family 4) indicated that a recombination event had occurred between loci D18S455 and D18S363, thus defining the proximal boundary of the genetic interval. Similarly, heterozygosity at locus D18S363 in affected subjects II.1, II.4, and II.5 (family 3) defined the distal boundary of the genetic interval encompassing the DMC gene (D18S455-D18S363, 1.8 cM, fig 3).

In this interval, we found heterozygosity for a CA repeat within KIAA0427 in affected subject II.1 (family 4), therefore reducing the shared region of homozygosity.

DISCUSSION

Eight genes were considered as possible candidate genes by their position, namely the mothers-against-decapentaplegic-homologue 7 (MADH7), signal recognition particle 72 KD-like (SRP72-like), 3-oxoacyl-CoA thiolase (ACAA2), myosin Vb (MYOVb), MAP-kinase 4 (MAPK4), methyl-CpG binding domain protein 1 (MBD1), and the human CpG binding protein gene (hCGBP). Several of them are currently regarded as possible candidate genes by their function, namely
ACAA2 which encodes a mitochondrial enzyme catalysing the last step of the mitochondrial fatty acid beta oxidation and MYO5B which belongs to the class V myosin family that function as motors for actin dependent organelle trafficking. 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.

---

**Table 1** Clinical and radiological features in nine DMC families

<table>
<thead>
<tr>
<th>Families</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic origin</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>P</td>
<td>M</td>
<td>T</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>1/16</td>
<td>1/16</td>
<td>1/16</td>
<td>1/64</td>
<td>1/16</td>
<td>1/16</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Affected children</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>&lt;−3 SD</td>
<td>−4 SD</td>
<td>&lt;−3 SD</td>
<td>−4 SD</td>
<td>&lt;−3 SD</td>
<td>&lt;−3 SD</td>
<td>&lt;−3 SD</td>
<td>&lt;−3 SD</td>
<td>&lt;−3 SD</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Facial dysmorphism</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thoracic anomalies</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rhizomelic dwarfism</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Radiological features</td>
<td>Platyspondyly</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Epiphyseal dysplasia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Metaphyseal dysplasia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lacy appearance of the iliac crests</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urinary keratan sulphate excretion</td>
<td>?</td>
<td>N</td>
<td>?</td>
<td>?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</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>
<thead>
<tr>
<th>Loci</th>
<th>Distance (cM)</th>
<th>Recombination fraction</th>
<th>Zmax</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>D18S1126</td>
<td>9.65</td>
<td>8.47</td>
<td>7.29</td>
<td>4.98</td>
</tr>
<tr>
<td>D18S470</td>
<td>8.32</td>
<td>7.37</td>
<td>6.41</td>
<td>4.49</td>
</tr>
<tr>
<td>D18S472</td>
<td>7.61</td>
<td>6.56</td>
<td>5.60</td>
<td>3.79</td>
</tr>
<tr>
<td>D18S363</td>
<td>8.18</td>
<td>8.11</td>
<td>7.25</td>
<td>5.24</td>
</tr>
<tr>
<td>D18S1110</td>
<td>1.06</td>
<td>4.08</td>
<td>3.94</td>
<td>3.02</td>
</tr>
</tbody>
</table>

---

**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.
ACKNOWLEDGEMENTS

The first three authors contributed equally to this work. We are grateful to Stanislas Lyonnet for helping discussion and comments.


Authors’ affiliations
C Thauvin-Robinet, V El Ghouzzi, W Chemaitilly, N Dagoneau, A Munnich, M Le Merrer, V Cormier-Daire, Département de Génétique et INSERM U393, Hôpital Necker Enfants Malades, Paris, France
O Boute, Service de Génétique, Hôpital Jeanne de Flandres, Lille, France
G Viot, Service de Génétique, Hôpital Cochin, Paris, France
A Mégarbané, Unité de Génétique Médicale, Université Saint-Joseph, Beirut, Lebanon
A Sefiani, Département de Génétique et de Biologie Moléculaire, Institut National d’Hygiène, Rabat, Morocco

REFERENCES
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 and V Cormier-Daire

doi: 10.1136/jmg.39.10.714

Updated information and services can be found at:
http://jmg.bmj.com/content/39/10/714

These include:

References
This article cites 14 articles, 4 of which you can access for free at:
http://jmg.bmj.com/content/39/10/714#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Calcium and bone (307)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/