Electronic letter

Idiopathic multicentric osteolysis presents early and is not linked to chromosome 18q21.1

EDITOR—Idiopathic multicentric osteolysis (IMO) is a rare skeletal disorder first described by Jackson in 1938. Also known as the “disappearing bone disease”, there have been almost 100 cases reported. The condition is inherited as an autosomal dominant trait (MIM 166300) but many isolated or de novo cases have been described. Autosomal recessive inheritance has also been suggested. The symptoms may present as early as the first year of life and most often affect the carpal and tarsal bones in an inflammatory-like fashion. Frequent recurrences eventually lead to crippling deformities of the limbs and to contractures. A typical facies develops in these patients, including maxillary hypoplasia and associated exophthal-
has been associated with IMO in some families. Familial
mia, a slender nose, and micrognathia. Nephropathy
Figure 3 Photograph of the typical hand deformity (II.1).
has recently been reported to cause familial expansile osteolysis.

We present a three generation family in which nine
members are affected with idiopathic multicentric osteolysis (fig 1).
They all showed the typical facies with a slender	nose, maxillary hypoplasia, and micrognathia already
detectable in childhood (fig 2). The adults had rheumatoid
arthritis-like hand deformities (fig 3), limitation at the
elbows, camptodactyly, and hammer claw toes. Radiological
examination showed osteolysis of the distal ends of the
long bones (fig 4). There was no hearing loss or dental
anomalies. A routine Giemsa banded karyotype was
carried out on II.3 and III.4.

DNA was extracted by standard methods from peripheral
white blood cells from both affected and unaffected
members of the family. Analysis of microsatellite markers
mapping to the candidate locus on chromosome 18 was
performed by means of the polymerase chain reaction (PCR).
The following markers were tested: D18S35, D18S64, D18S60, D18S55, D18S61, and D18S43. Oligo-
nucleotide primer sequences were obtained from GDB.
One primer pair of each pair was fluorescently labelled
(FITC, fluorescein-isothiocyanate). Genomic DNA (300
ng) was used for 30 cycles in an amplification in 50 µl of
PCR mix containing 200 µmol/l dNTPs, 0.5 µmol/l each primer, and 1 U Taq polymerase (Perkin-Elmer). Cycling
conditions were one minute at 94°C, one minute at 55°C,
and one minute at 72°C. All PCR products were electrophoresed on an ALF DNA sequencer (Amersham
Pharmacia Biotech) and analysed using Fragment Manager
software (Amersham Pharmacia Biotech).

Two point and multipoint lod scores were calculated using the FASTLINK 4.1 PC version of the MLINK
and LINKMAP computer programs, with penetrance set at
1.0 for heterozygotes and a gene frequency of 0.0001. A
loop in the pedigree was broken at subject II.2. Allele
frequencies for the different markers in white populations
were obtained from GDB.

The karyotypes were normal. The results of the marker
analysis are shown in fig 1. The affected members do not
have a common ancestral haplotype. Two point lod scores
are shown in table 1. Multipoint analysis showed lod scores
lower than –2 in every interval between the different markers.
In the centromeric region the lod score was lower than
–2 from marker D18S35 to 3 cM of this marker. In the
telomeric region the multipoint lod score was lower than –2
from marker D18S43 to 20 cM telomeric of this marker.

Although almost 100 cases of idiopathic multicentric
osteolysis have been reported, few have been part of large
families. Linkage for the gene responsible for this condition
has not previously been carried out. However, familial
osteolysis has been linked to chromosome 18q21.1-q22.
This condition is also inherited as an autosomal dominant
trait, and the affected subjects also have associated
defauness, dental anomalies, pain, disabling deformities,
and a tendency to fracture. The focal lesions in familial
expansile osteolysis mainly affect the long bones leading to
progressive medullary and cortical expansion of the bone.
Generalised skeletal changes occur as well. On the basis of
this and because osteolysis occurs, it was thought that the
locus on chromosome 18q21.1-q22 would be a suitable
candidate for IMO, but we show here that the defect in this
two generation family with idiopathic multicentric
osteolysis detectable at an early age is not linked to
chromosome 18q21.1-q22.

It has been previously reported that a clinical diagnosis
may be made within the first year of life. As the condition
is well known to the family, the subjects in the third
generation were diagnosed by the family as having the condi-
tion within the first few months of life. This was clinically
confirmed and borne out by the radiological changes seen
within the first few years of life.

Figure 3


www.jmedgenet.com


Figure 4  (A) Radiograph of the hand showing the osteolysis in the metacarpals and phalangeal bones in III.4 at 7 years of age. (B) Radiograph of the elbow of III.4 at 7 years of age. Note the osteopenic bone and irregularities of the joint surfaces. (C) Radiograph of the heel and toes showing the osteolysis of the calcaneum and the hammer toes in II.1 aged 43 years.

Table 1  Two point lod score table: osteolysis v chromosome 18q21.1 markers

<table>
<thead>
<tr>
<th></th>
<th>0.000</th>
<th>0.010</th>
<th>0.050</th>
<th>0.100</th>
<th>0.200</th>
<th>0.300</th>
<th>0.400</th>
</tr>
</thead>
<tbody>
<tr>
<td>D18S35</td>
<td>−99.000</td>
<td>−2.851</td>
<td>−0.910</td>
<td>−0.210</td>
<td>0.252</td>
<td>0.286</td>
<td>0.128</td>
</tr>
<tr>
<td>D18S64</td>
<td>−99.000</td>
<td>−6.741</td>
<td>−3.391</td>
<td>−2.066</td>
<td>−0.920</td>
<td>−0.395</td>
<td>−0.123</td>
</tr>
<tr>
<td>D18S60</td>
<td>−99.000</td>
<td>−4.504</td>
<td>−2.442</td>
<td>−1.586</td>
<td>−0.786</td>
<td>−0.373</td>
<td>−0.132</td>
</tr>
<tr>
<td>D18S55</td>
<td>−99.000</td>
<td>−10.694</td>
<td>−5.832</td>
<td>−3.784</td>
<td>−1.851</td>
<td>−0.859</td>
<td>−0.291</td>
</tr>
<tr>
<td>D18S61</td>
<td>−99.000</td>
<td>−12.113</td>
<td>−6.627</td>
<td>−4.356</td>
<td>−2.233</td>
<td>−1.126</td>
<td>−0.442</td>
</tr>
<tr>
<td>D18S43</td>
<td>−99.000</td>
<td>−2.574</td>
<td>−1.265</td>
<td>−0.780</td>
<td>−0.417</td>
<td>−0.276</td>
<td>−0.151</td>
</tr>
</tbody>
</table>
Idiopathic multicentric osteolysis presents early and is not linked to chromosome 18q21.1

T J L DE RAVEL, G MATTHIJS, M HOLVOET, C WOUTERS, E LEGIUS and J P FRYNS

J Med Genet 2000 37: e34
doi: 10.1136/jmg.37.11.e34