

Electronic letter

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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 1938.¹ 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.²⁻⁵ Autosomal recessive inheritance has also been suggested.⁶ The symptoms may present as early as the first year of life² 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-

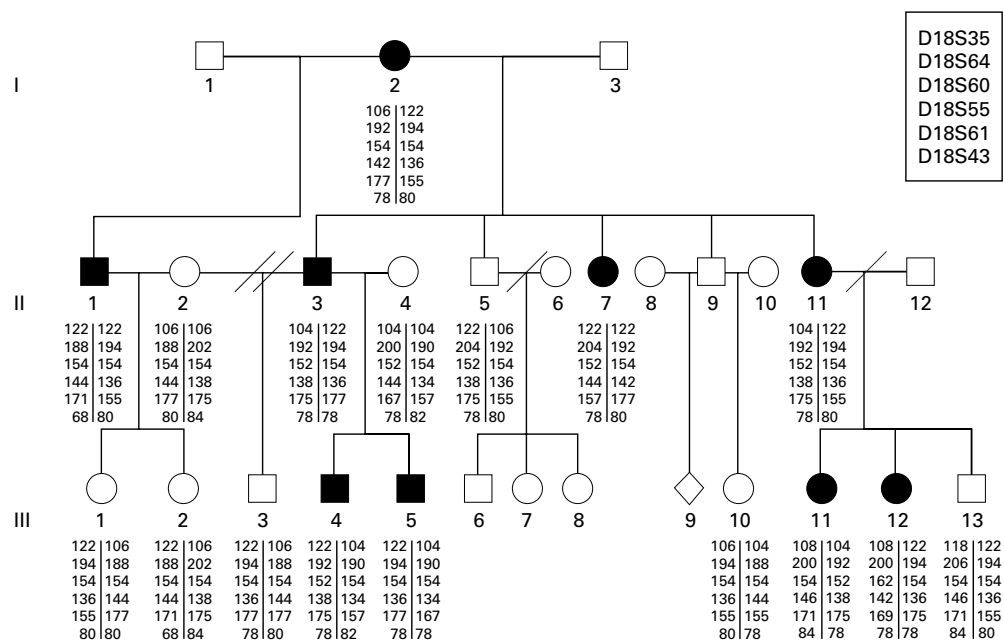


Figure 1 The family pedigree showing affected and unaffected members and the linkage results.

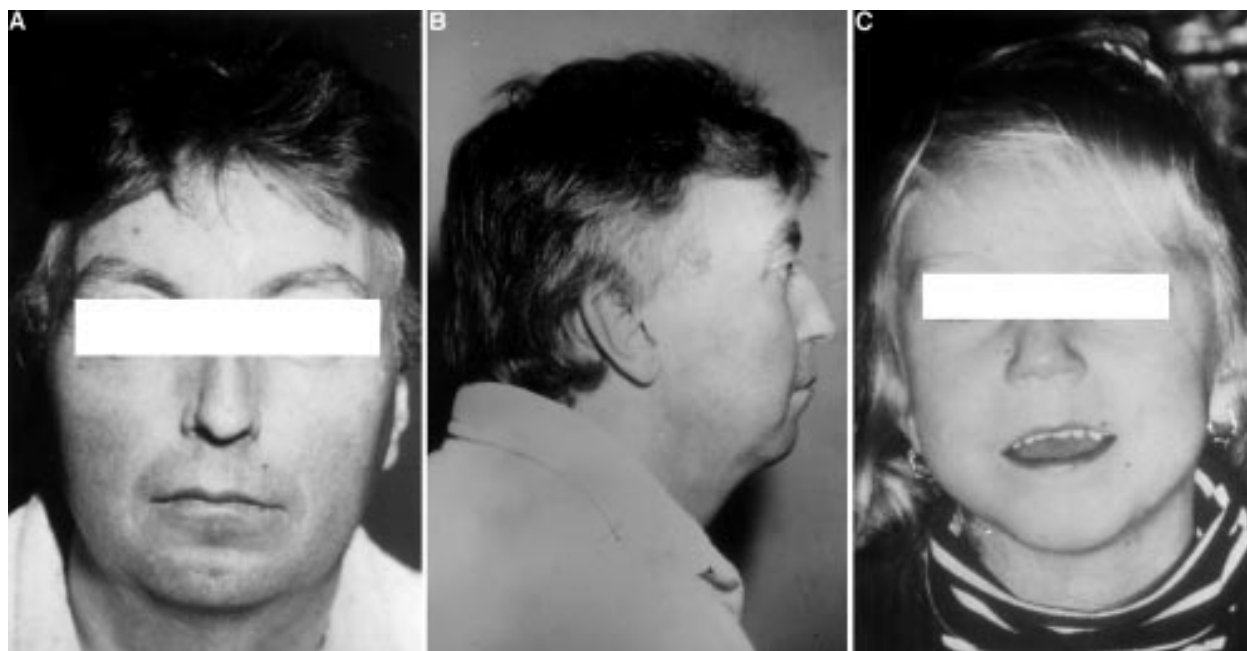


Figure 2 Photograph of the typical facies: note the maxillary hypoplasia, slender nose, and micrognathia. (A) Front view of II.1 aged 43 years. (B) Lateral view of II.1. (C) Front view of III.12 aged 6 years.



Figure 3 Photograph of the typical hand deformity (II.1).

mia, a slender nose, and micrognathia.^{2 3 7} Nephropathy has been associated with IMO in some families.⁸ Familial expansile osteolysis had been linked to chromosome 18q21.1-q22,⁹ and mutations in the *TNFRSF11A* gene have recently been reported to cause familial expansile osteolysis.¹⁰

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 18⁹ was performed by means of the polymerase chain reaction (PCR). The following markers were tested: D18S35, D18S64, D18S60, D18S55, D18S61, and D18S43. Oligonucleotide 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,¹¹ 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-q22.⁹ This condition is also inherited as an autosomal dominant trait, and the affected subjects also have associated deafness, 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 three 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.² As the condition is well known to the family, the subjects in the third generation were diagnosed by the family as having the condition 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.

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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 osteoporotic 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

	θ						
	0.000	0.010	0.050	0.100	0.200	0.300	0.400
D18S35	-99.000	-2.851	-0.910	-0.210	0.252	0.286	0.128
D18S64	-99.000	-6.741	-3.391	-2.066	-0.920	-0.395	-0.123
D18S60	-99.000	-4.504	-2.442	-1.586	-0.786	-0.373	-0.132
D18S55	-99.000	-10.694	-5.832	-3.784	-1.851	-0.859	-0.291
D18S61	-99.000	-12.113	-6.627	-4.356	-2.233	-1.126	-0.442
D18S43	-99.000	-2.574	-1.265	-0.780	-0.417	-0.276	-0.151

in *TNFRSF11A*, affecting the signal peptide of RANK, cause familial expansile osteolysis. *Nat Genet* 2000;24:45-8.
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