Exclusion of chromosome 9 helps to identify mild variants of acromesomelic dysplasia Maroteaux type

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Abstract

Acromesomelic dysplasia Maroteaux type (AMDM) is an autosomal recessive disorder belonging to the group of acromesomelic dysplasias. AMDM is characterised by severe dwarfism with shortening of the middle and distal segments of the limbs. An AMDM gene has recently been mapped to human chromosome 9p13-q12 by homozygosity mapping in four consanguineous families. Here, we show linkage of the disease gene to chromosome 9p13-q12 in four of five consanguineous AMDM families and its exclusion in a fifth family with two children affected with a mild form of the disease. This study suggests that genetic heterogeneity accounts for the variable clinical and radiological severity of AMDM.

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First described by Maroteaux in 1971,[1] AMDM is an autosomal recessive disorder characterised by severe dwarfism (height below 120 cm) with shortening of the middle and distal segments of the limbs. This condition is usually diagnosed at birth and becomes more obvious in the first two years of life. *X* rays show short, broad fingers, square, flat feet, and shortening of the long bones (particularly the forearms). The radius is bowed, the ulna is shorter than the radius, and its distal end is occasionally hypoplastic. The skull is dolichocephalic and a shortness of the trunk, with decreased vertebral height and narrowing of the lumbar interpedicular distances, is consistently observed. The facial appearance and intelligence are normal.[2] AMDM is clinically and radiologically distinct from, and less severe than, the two other autosomal recessive acromesomelic dysplasias (AMD), namely Hunter-Thompson type and Grebe type AMD[3 4] (table 1). The two disorders have been ascribed to mutations in the cartilage derived morphogenetic protein 1 (*CDMP1*) gene on human chromosome 20q.[5 6]

Recently, Kant *et al*[7] reported the mapping of a gene for AMDM to human chromosome 9p13-q12 by homozygosity mapping in four inbred families. All four families were consistent with mapping of the disease gene to the 6.9 cM interval defined by loci D9S1853 and D9S1874. This observation supports the view that typical AMDM is genetically distinct from the other two autosomal recessive AMDs.

We have recently observed two sibs born to first cousin Lebanese parents (birth length 44 and 47 cm) with clinical and radiological features typical of AMDM, including short, broad extremities, short middle long bones, and the ulna shorter than the radius (fig 1B). However, the disease was slightly less severe than typical AMDM. Indeed, growth failure was moderate (−3 and −2.5 SD respectively), shortening of the extremities was milder, and

Table 1 Clinical profile of autosomal recessive acromesomelic dysplasias (AMD) and comparison with the mild AMD Maroteaux type variant

		Grebe type	*Hunter-Thompson type*	*Maroteaux type, classical*	*Maroteaux type, mild*
Clinical features	Adult size	100 cm	100–130 cm	120 cm	? (−2.5 to −3 SD at age 4)
	Long bones	Severely shortened and deformed	Shortening progression proximal to distal, large joint dislocations	Shortening of middle and distal segments	Shortening of middle and distal segments
	Hands and feet	Ball shaped fingers, occasional polydactyly, possibly absent joints	Severely affected Normal distal phalanges	Short and broad fingers without fusions	Short and broad fingers
Radiological features	Long bones	Short femoral neck, absent tibial and fibular diaphyses, hypoplasia of the ulna, malformed radial head	Bowing of the radius, hypoplastic femoral condyles	Ulna shorter than radius, bowing of the radius	Ulna shorter than radius
	Hands and feet	Fusion of carpal and tarsal bones, absence of several metacarpal and metatarsal bones, absence of proximal and middle phalanges	Single phalangeal bone on digit 5, abnormally shaped carpal bones	Short and broad phalanges, metacarpal and metatarsal bones	Short and broad phalanges, metacarpal and metatarsal bones
	Vertebral abnormalities	Absent	Absent	Present	Minor
Molecular findings	Mapping	20q11.2	20q11.2	9p13-q12	Unknown
	Mutations	Homozygous missense mutation in *CDMP-1* (G1199A) Brachydactyly in heterozygotes	Homozygous 22 bp tandem duplication, frameshift mutation in the mature region of *CDMP-1*	—	—

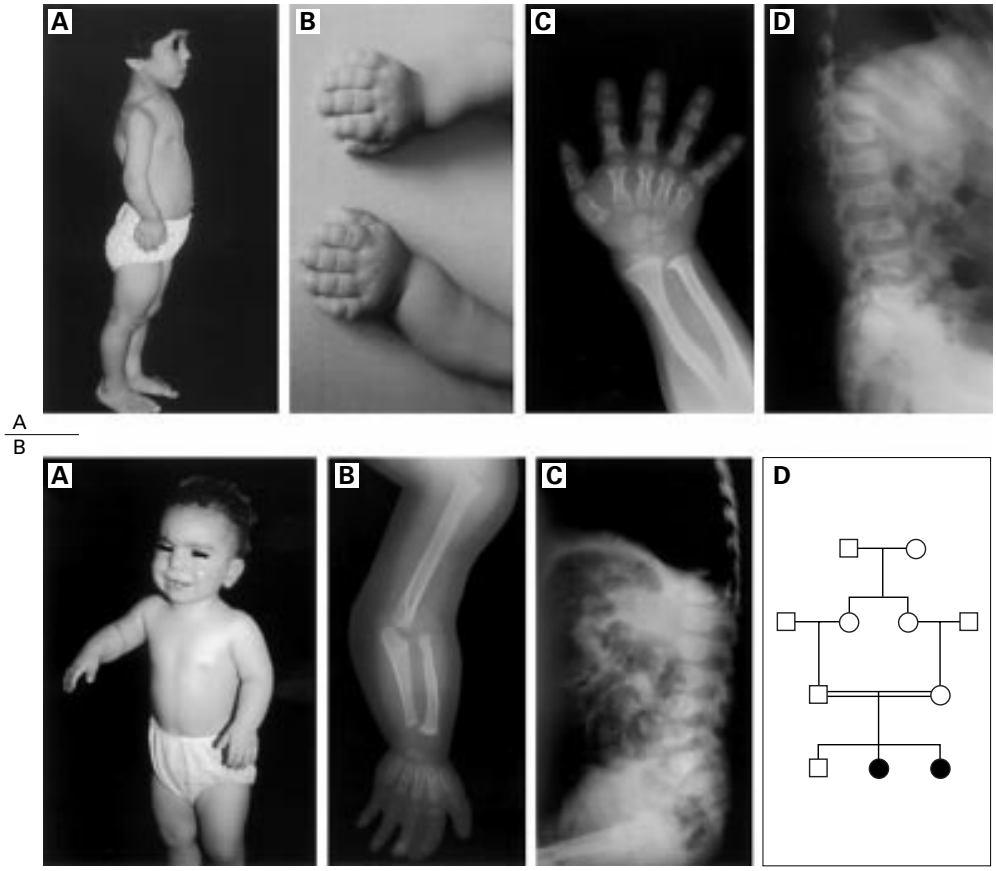

Figure 1 (Top row) Clinical and radiological features of a patient with classical AMDM aged 6 (photographs reproduced with permission). (Bottom row) Clinical and radiological features of a patient with mild AMDM. (A) Patient at the age of 3. Note that the shortening of the forearms and extremities is less obvious than in fig 1A (top row). (B, C) X rays at the age of 2. Note the short, broad hands, short middle long bones, and the ulna shorter than the radius. The vertebrae are almost normal. (D) Pedigree of the mild AMDM family.

the vertebrae were almost normal. This mild AMDM variant was distinct from Grebe and Hunter-Thompson type AMDs, as none of the clinical criteria specific for these two AMDs was observed in our patients, namely joint dislocations, ball shaped fingers, and fused or absent bones (table 1).

DNA extraction and microsatellite analyses were performed as previously described[8] and primers of the chromosome 9p13-q12 region were chosen from the Genethon map.[9] Homozygosity mapping was performed according to Lander and Bostein[10] and two point linkage analyses using the MLINK option of the LINKAGE package were performed according to Lathrop *et al*.[11] The frequency of the disease allele was estimated to be 0.005 and penetrance was set at 100%, assuming an autosomal recessive mode of inheritance. Inbreeding loops but not allele frequencies were taken into account as no controls were available for the population studied. The mutation rate was set at 0. For homogeneity tests, the Morton likelihood ratio (LR) test was used.[12]

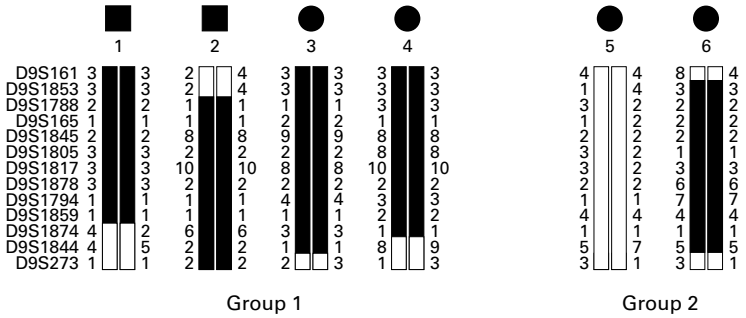

Figure 2 Haplotypes of the affected subjects in typical (group 1) and variant AMDM (group 2) at the 9p13-q12 locus. Subjects 1 to 4 are the probands of four classical AMDM families (group 1). Patients 5 and 6 have a mild AMDM variant (group 2). The region of homozygosity is shown in black. The common region of homozygosity for group 1 is between microsatellites D9S1853 and D9S1874 (6.9 cM). Haplotypes of family 5 (group 2) exclude linkage to chromosome 9p13-q12 as the two affected subjects received different parental chromosomes in this region.

Linkage of the disease gene to chromosome 9p13-q12 was excluded in this family, as the two affected subjects received different parental chromosomes in this region (fig 2). Linkage of the family to the *CDMP1* region was tested by using microsatellites at flanking loci D20S191 and D20S195 and an intragenic $[CA]_n$ dinucleotide repeat,[13] but was inconclusive owing to a lack of informativity.

However, linkage analyses in four consanguineous AMDM families of Turkish and Lebanese ancestry supported the mapping of a gene for typical AMDM to chromosome 9p13-q12 (Zmax=3.27 and Zmax=3.23 at θ=0 at loci D9S1878 and D9S1817 respectively). All probands presented with clinical features typical of AMDM including severe growth failure (−5.5 SD and −7 SD) (fig 1A). The Morton likelihood ratio test supported genetic heterogeneity between typical AMDM and

mild variants ($p<0.01$, $p<0.02$, and $p<0.03$ for loci D9S1878, D9S165, and D9S1817, respectively).

The present study supports the mapping of a gene for typical AMDM to chromosome 9p13-q12 and shows that mild AMDM variants are unlinked to this region. It is worth remembering that the existence of mild AMDM was suggested by Borrelli *et al*,[14] who described a boy moderately affected with AMDM with a birth length of 50 cm and a growth pattern of −2.6 SD at the age of 2½ years. Studies of additional families with mild AMDM will help to confirm whether genetic heterogeneity indeed accounts for the variable clinical and radiological severity of the disease.

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