Mandibuloacral dysplasia caused by homozygosity for the R527H mutation in lamin A/C

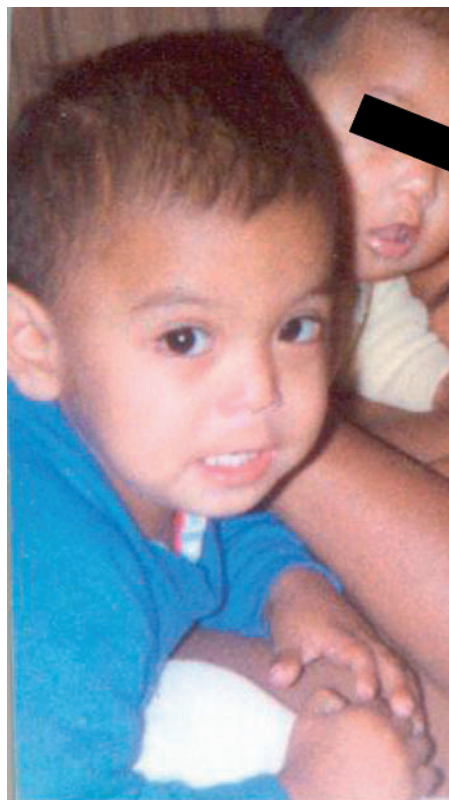## J J Shen, C A Brown, J R Lupski, L Potocki

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Lamins are intermediate filament proteins comprising a major structural component of the nuclear lamina, which underlies the inner membrane of the nuclear envelope in most somatic cells. In humans, seven alternatively spliced forms derive from three genes—*LMNA*, *LMNB1*, and *LMNB2*. Although their nuclear functions are currently being elucidated, it has been hypothesised that they are involved in membrane support, pore arrangement, envelope assembly, and chromatin organisation. Through these associations, the lamins may have more expanded roles at the cellular level and control diverse functions such as DNA synthesis, gene expression, and apoptosis.[1–6]

Disorders caused by defects in the nuclear lamina associated proteins are referred to as the laminopathies. Thus far among the lamins, these have been described only for *LMNA*, which maps to chromosome 1q21.2 and encodes lamin A and lamin C through alternative splicing. A disparate group of seemingly unrelated diseases with different affected organ systems has been attributed to lamin A/C mutations. These include Charcot-Marie-Tooth disease type 2B,[7] forms of dilated cardiomyopathy,[8] both autosomal dominant and autosomal recessive forms of Emery-Dreifuss muscular dystrophy,[9 10] limb girdle muscular dystrophy type 1B,[11] Dunnigan-type familial partial lipodystrophy,[12–14] and Hutchinson-Gilford progeria.[15 16] Recently, Novelli *et al* categorised mandibuloacral dysplasia as a laminopathy resulting from lamin A/C mutation.[17]

Mandibuloacral dysplasia (MAD; MIM 248370) is a rare autosomal recessive disorder. Affected individuals have a normal appearance at birth, then progressively develop

Key points

- Mandibuloacral dysplasia (MAD) is a rare disorder combining a characteristic facial appearance with acro-osteolysis and lipodystrophy.

- Lamins are integral structural components of the nuclear lamina hypothesised to be involved in numerous cellular processes. Mutations in these genes result in diverse diseases collectively referred to as the laminopathies. Recently, MAD has been shown to be caused by a specific mutation (R527H) in *LMNA*, which encodes lamins A and C.

- A boy with this disorder is described who has a homozygous R527H substitution in *LMNA*. Thus far, all families with MAD in whom a mutation was discovered harbour the identical base alteration. These families show distinct haplotypes, which indicates that each mutation originated independently.

- There is a highly specific genotype–phenotype correlation between the *LMNA* R527H mutation and MAD.

Figure 1 Photograph of the patient at approximately two years of age. Note normal overall appearance except for subtle distal phalangeal swelling.

lipodystrophy and dysmorphic craniofacial and skeletal features. Characteristic findings in MAD include mandibular hypoplasia, acro-osteolysis, prominent appearance of the eyes, dental overcrowding, beaked nose, delayed closure of the cranial sutures, clavicular dysplasia/osteolysis, joint contractures, and poikiloderma. Novelli *et al* analysed lamin A/C for mutations in five consanguineous Italian families with MAD.[17] Homozygosity for a single mutation (R527H) was found in all nine affected individuals, who also shared a common disease haplotype.

In this report, we describe the physical and radiographic features of a Mexican American boy with MAD. Mutational analysis of the lamin A/C gene revealed homozygosity for the identical R527H mutation as reported previously, but with a distinct haplotype.

METHODS
Clinical information
The patient was the full term product of a consanguineous union. The pregnancy history was unremarkable and he

appeared normal at birth. Subtle physical changes were first noted at approximately 18 months of age, when he developed persistently swollen fingertips (fig 1). Alterations in his skin and pattern of body fat distribution began when he was six years old; his mother described puffiness around his cheeks and neck region, as well as areas of dry and variably pigmented skin near his eyes, umbilicus, and axillae. Approximately two years later, he began to show dental crowding, micrognathia, and marked thickening of the nails on his fingers and toes. He continued to develop lipodystrophic changes and progressive joint contractures until our first encounter with him at 12 years of age. His past medical history was otherwise unremarkable, without major or chronic illnesses. He met his developmental milestones appropriately and he was enrolled at school in an age appropriate grade level. No other similarly affected individuals were reported in this family.

At age 12, many features of MAD were evident (fig 2). His weight, height, and fronto-occipital circumference were all within the 5th–10th centiles. He had a lipodystrophic body habitus with thin extremities and a central distribution of fat in his face, neck, and trunk. His face showed prominence of the eyes, a beaked nose, fullness of the cheeks, micrognathia, inability to open his mouth completely, and dental overcrowding. Acanthosis nigricans of the neck was present. He had markedly downward sloping shoulders. Examination of the lungs, heart, abdomen, and genitals was normal. Patchy areas of poikiloderma were present on his neck and lower abdomen and in the axillary and inguinal regions. Neurologically, his strength was intact without asymmetry, reflexes were bilaterally normal, and no sensory deficits were identified.

The most dramatic aspects on examination involved his musculoskeletal system and extremities. There was extreme paucity of subcutaneous fat in the extremities, and the overlying skin was taut and dry. He had mild contractures at his elbows and a restricted range of motion in his shoulder girdle and hips. His fingers and toes showed camptodactyly, short, broad and bulbous distal phalanges, and hypoplastic nail beds with varying degrees of nail hyperkeratosis.

Imaging and laboratory evaluation

A skeletal survey revealed generalised osteopenia, wormian bones with persistence of suture lines in his cranium, coxa valga, and distal phalangeal osteolysis. Clavicular abnormalities were not evident. On biochemical analysis there was hypercholesterolaemia and dyslipidaemia, but normal glycosylated haemoglobin and non-fasting serum glucose levels. Chromosome analysis revealed a normal 46,XY complement.

Sequencing of *LMNA* identified a homozygous G→A transition at nucleotide position 1580 (1580G>A) which, by conceptual translation, resulted in a missense arginine to histidine substitution at amino acid position 527 (R527H) (fig 3). The nucleotides at the *LMNA* exonic single nucleotide

Figure 2 Current photographs showing characteristic craniofacial appearance (A), lipodystrophy (B), and distal extremity and phalangeal findings (C) (D).
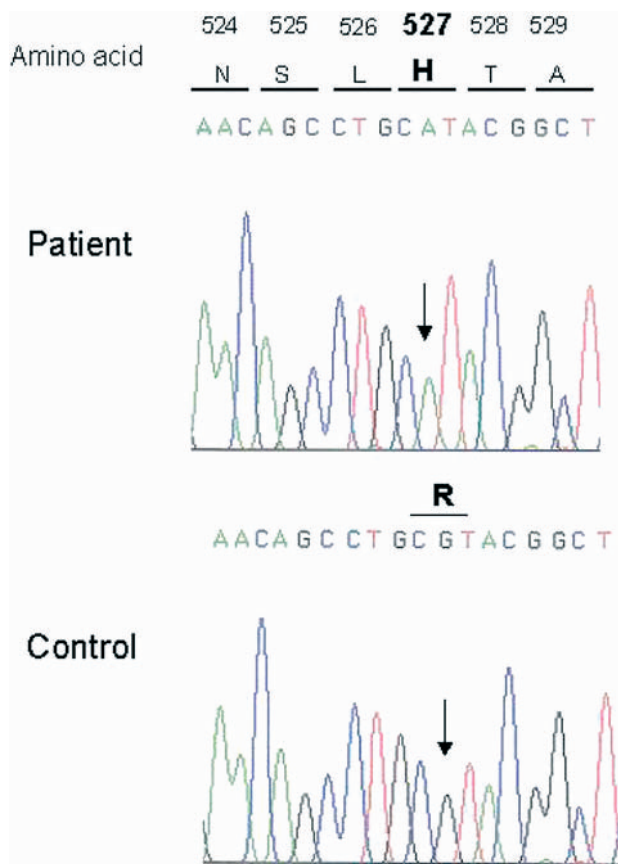
Figure 3 Sequence of LMNA showing the G→A transition and resulting arginine to histidine missense substitution at amino acid position 527.

polymorphisms (SNPs) previously reported[17] [18] were as follows: position 861, T; position 1338, T; position 1698, T.

DISCUSSION

We describe here another individual with mandibuloacral dysplasia. Apart from an earlier age of onset (1.5 v 4.3 years), the findings in this patient typify the physical and radiographic features previously associated with this disorder.[19] Another consistently reported aspect of MAD is insulin resistance and impaired glucose tolerance, and on examination this patient has acanthosis nigricans. Novelli et al have identified a homozygous LMNA missense mutation (R527H) in nine patients with MAD from five consanguineous Italian families.[17] Consistent with a founder effect, all affected individuals shared a common disease haplotype: LMNA exonic SNPs at nucleotide positions 861, 1338, and 1698 were C, C, and C. More recently, Simha et al reported two separate families with MAD in which the R527H substitution was present as well[20]; however, the exonic SNPs were different (T, T, and C at the corresponding SNP nucleotide positions), and intronic SNPs indicated separate origins for this mutation in each family. The patient we describe here harbours the same homozygous R527H lamin A/C mutation as the previously reported patients; this also originated independently as evidenced by a different haplotype (T, T, and T).

An intriguing aspect of the laminopathies is the diversity of phenotypes, despite the fact that many are caused by mutations in the same lamin A/C gene. Examples of allelic affinity include the androgen receptor locus in spinal and bulbar muscular atrophy (MIM 313200) and testicular feminisation (MIM 300068); fibroblast growth factor receptor mutations causing distinct craniosynostosis syndromes; and the ABCR locus and a range of retinal dystrophies and susceptibility to macular degeneration.[21] Diseases caused by LMNA mutations (MAD, Dunnigan-type familial partial lipodystrophy, forms of cardiomyopathy, limb girdle muscular dystrophy type 1B, autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD), Charcot-Marie-Tooth disease type 2B, and Hutchinson-Gilford progeria) provide a further and more dramatic example of this phenomenon as all manifest separate and distinctive phenotypic features including skeletal changes, skin findings, lipodystrophy, cardiomyopathy, muscular dystrophy, and neuropathy.[7–11] [15] [16] [22–26]

Although the wide ranging phenotypes of the laminopathies result from LMNA mutations that occur throughout the gene, a different scenario is emerging with MAD. The arginine at position 527 is located within the C-terminal immunoglobulin-like domain in the centre of a β sheet on the domain surface; mutations at this site are postulated to disturb intramolecular interactions and disrupt protein structure.[27] [28] Substituting a proline in this location (R527P) results in AD-EDMD with some but not all patients with lipodystrophy.[9] [10] [29] [30] However, substituting a histidine in this position (R527H) has now been shown in four separate instances to result in MAD. A founder effect was not suspected because of differing ethnic backgrounds, and haplotype analysis indeed supports the likelihood that each of the R527H mutations arose independently. This raises an intriguing possibility that there is a very specific genotype–phenotype correlation between this exact amino acid substitution and the characteristic constellation of lipodystrophy with skeletal and skin manifestations in this rare disease. Recently, Eriksson et al reported a similar result, as 19 of 20 de novo classical cases of Hutchinson-Gilford progeria harboured LMNA mutations, each predicted to result in the same internal 50 amino acid deletion.[16]

Among the approximately 40 patients with MAD reported so far, there is a certain degree of phenotypic variability. For example, the patient described in this report lacked clavicular hypoplasia. Other affected individuals have differed in the extent of acro-osteolysis or in whether hypogonadism is present.[31–33] Individuals with Hoepffner-Dreyer-Rudiger syndrome[34] lack acro-osteolysis but otherwise phenotypically resemble MAD. Simha and Garg[19] proposed two variant forms of MAD which are distinguished by the pattern of body fat distribution: type A, with preferential accumulation of subcutaneous fat centrally, and type B, with generalised loss of subcutaneous fat. They have recently confirmed that only type A MAD is caused by the R527H mutation in LMNA; no mutations were detected in four families with type B MAD.[20] Continued molecular analysis of patients with MAD will help determine the specificity of the LMNA R527H mutation to type A MAD, the variability of phenotypic expressivity for this mutation, and the molecular basis for additional forms of MAD.

Note added in proofs: Agarwal et al have described a patient with type B MAD and mutations in the ZMPSTE24 gene.[35]

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