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Early Onset Mandibuloacral Dysplasia due to Compound Heterozygous Mutations in *ZMPSTE24*

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Abstract

Mandibuloacral dysplasia (MAD) is an autosomal recessive disorder characterized by hypoplasia of the mandible and clavicles, acro-osteolysis and lipodystrophy due to mutations in *LMNA* or *ZMPSTE24*. Only six MAD patients are reported so far with *ZMPSTE24* mutations and limited phenotypic data are available for them. Here, we report on two brothers (4 years and 9 months old) with early onset MAD due to *ZMPSTE24* mutations in whom thin skin was noted as early as 5 months of age. Both had micrognathia, mottled hyperpigmentation, and enlarged fontanelles but little evidence of lipodystrophy. There was no delay of mental development. The older brother showed small pinched nose, short clavicles, acro-osteolysis, stunted growth, joint stiffness, and repeated fractures. There was no evidence of renal disease. Both patients were compound heterozygotes harboring a previously reported missense *ZMPSTE24* mutation, p.Pro248Leu and a novel null mutation, p.Trp450stop. These patients and the review of literature reveals that compared to MAD patients with *LMNA* mutations, those with *ZMPSTE24* mutations develop manifestations earlier in life. Other distinguishing features in MAD due to *ZMPSTE24* mutations may include premature birth, renal disease, calcified skin nodules, and lack of acanthosis nigricans. We conclude that in patients with MAD due to *ZMPSTE24* mutations, the onset of disease manifestations such as thin skin and micrognathia occurs as early as 5 months of age. In these patients, skeletal phenotype presents earlier whereas lipodystrophy and renal disease may occur later in life.

Keywords

Lipodystrophy; *ZMPSTE24*; Lamin A/C; mandibuloacral dysplasia

INTRODUCTION

Mandibuloacral dysplasia (MAD; OMIM 248370 and 608612) is a rare, genetically and phenotypically heterogeneous, autosomal recessive disorder characterized by skeletal abnormalities including hypoplasia of the mandible and clavicles, acro-osteolysis, cutaneous atrophy, progeroid features and lipodystrophy [Garg 2004]. Using positional cloning and candidate gene approach, two loci have been identified for MAD. The first locus discovered was lamin A/C (*LMNA*) [Novelli et al., 2002] which encodes integral nuclear lamina proteins, lamins A and C, belonging to the intermediate filament family. The second locus,

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ZMPSTE24 [Agarwal et al., 2003], encodes a zinc metalloproteinase which is involved in post-translational processing of prelamin A to mature lamin A.

Based on in-depth evaluation of body fat distribution pattern, we had suggested two patterns of lipodystrophy in patients with MAD: type A (partial) type B (generalized) [Simha et al., 2003]. So far, approximately 28 MAD patients have been reported to harbor homozygous or compound heterozygous missense mutations in the C-terminal of lamin A/C [Novelli et al., 2002; Cao and Hegele 2003; Simha et al., 2003; Plasilova et al., 2004; Garg et al., 2005; Van Esch et al., 2006; Kosho et al., 2007; Lombardi et al., 2007; Agarwal et al., 2008; Zirn et al., 2008; Garavelli et al., 2009; Madej-Pilarczyk et al., 2009]. Nearly all of them have type A pattern of partial lipodystrophy. However, only 6 MAD patients have been reported with either compound heterozygous or homozygous mutations in *ZMPSTE24* [Agarwal et al., 2003; Shackleton et al., 2005; Agarwal et al., 2006; Denecke et al., 2006; Miyoshi et al., 2008]. Of these, three patients had already died before their genetic basis was determined [Agarwal et al., 2003; Shackleton et al., 2005; Agarwal et al., 2006] and therefore, only limited information was available about the phenotype of these patients. We report in-depth phenotype analysis of two male siblings with early onset MAD due to compound heterozygous *ZMPSTE24* mutations.

CLINICAL REPORTS

MAD 4700.3 (Patient 1): This 4-year-old boy was born to nonconsanguineous healthy parents of European descent. His mother went into preterm labor at 32 weeks gestation after spontaneous rupture of membranes. His birth weight was 1.94 kg and Apgar scores were 6 at 1 minute and 8 at 5 minutes. He required continuous positive airway pressure for the first 24 h of life and remained in the neonatal intensive care unit for 2–3 weeks because of jaundice and feeding difficulties.

At five months of age, his parents noted thin skin and stunted growth. Computed tomography of the head with 3D reformations at 7 months showed multiple Wormian bones on both the lambdoid sutures and plagiocephaly on the right (Fig. 1). Joint stiffness was noted at the age of 8 months.

At 13 months of age, he presented to the Genetics Center at Children's Hospital Philadelphia for evaluation of failure to thrive, mixed tone and delayed motor milestones. Radiographs of the hands showed deformity and irregularity of the tufts of all the digits consistent with acro-osteolysis (Fig. 1), and radiographs of the feet showed irregularity of the distal phalanges.

He started walking at 14 months, but continues to have difficulty going up and down the stairs. Dentition has been delayed: the first teeth erupted at 15 months, and the teeth were crowded. A skeletal survey at 19 months was remarkable for widening of the cranial sutures, extensive Wormian bones along the lambdoid sutures bilaterally, and short clavicles. Hair loss started at 1.5–2 years of age at the vertex. Hair shaft analysis revealed twisted hair suggestive of pili torti and the patient was started on biotin supplementation. There has been no delay of cognitive, social, emotional or language milestones. Evaluation of growth retardation included a gastric emptying study at 3 years of age showing decreased rate of gastric emptying. At 4 years of age, a zinc level was 56 µg/dL [normal range 60–120] and he was started on zinc supplementation.

His clinical course has also been remarkable for multiple fractures including buckle fractures of the right distal radius and ulna at 2 years of age and a skull fracture at 30 months. Dual energy X-ray absorptiometry (Hologic Densitometer, Waltham, MA) at the age of 3 years showed a lumbar-spine bone mineral density of 0.38 g/cm² with a Z-score of −1.8 ("low bone density for chronological age" is defined as lumbar spine Z score less than

or equal to -2.0 in children [Writing Group for the International Society for Clinical Densitometry Position Development Conference 2004; Baim et al., 2008]). He received cyproheptadine for appetite stimulation from 6 months of age to 8 months. Initially his appetite increased but later cyproheptadine did not have any effect. It was restarted at the age of 3 years and parents noted that he had increased weight by 0.45 kg. He was also taking erythromycin for delayed gastric emptying; polyethylene glycol 3350 and lactulose for constipation; and loratadine as needed.

He weighed 11.1 kg (3rd centile) and was 90 cm tall (3rd centile). He had low-set ears, prominent cheeks, micrognathia, and slight double chin. He had a small, thin, overhanging nose with telangiectasias. He had 7 maxillary teeth and 4 mandibular teeth. Posterior occipital fontanelle and left parietal fontanelle were both open while anterior fontanelle and right parietal fontanelle were closed. A hematoma was noted at the vertex. He had bright red hair with areas of hair thinning and alopecia particularly on the back of scalp and on the left side. The hair seemed dry and straight. No loss of eyebrows or eyelashes was noted. He had normal male external genitalia. The Tanner stage was A0P1G1. Musculoskeletal examination revealed narrow sloping shoulders and reduced mobility in the ankles with dorsiflexion to 20 degrees. Hips could be abducted to only 25 degrees with limited internal and external rotation. Acro-osteolysis of the fingers was observed. The feet were narrow. He walked with heel-to-toe gait. He had prominent veins on the scalp, chin, and nose. There was no overt loss of fat from the extremities, but he seemed to have relatively decreased fat in the lower neck, lower legs and feet, and mid-back.

Laboratory data revealed total cholesterol of 119 mg/dL (normal range 125-170), high density lipoprotein cholesterol of 55 mg/dL (reference range not established), triglycerides of 76 mg/dL (normal range 30-104), and low density lipoprotein cholesterol of 49 mg/dL (normal range < 110 mg/dL). Lactate dehydrogenase was high at 565 U/L (normal range 155-345). Fasting glucose was 83 mg/dL (normal range 65-99). Creatinine was 0.26 mg/dL (normal range 0.29-0.68) and blood urea nitrogen was 14 mg/dL (normal range 7-20). He had a slightly high aspartate aminotransferase 47 U/L (normal range 20-39) with normal alanine aminotransferase 20 U/L (normal range 8-30) and alkaline phosphatase 220 U/L (normal range 93-309). Creatine phosphokinase was normal at 111 U/L (normal range < 160). Complete blood counts were unremarkable. Hemoglobin A1C was 5.2%. Urinalysis was unremarkable without any proteinuria. An electrocardiogram was normal.

MAD 4700.4 (Patient 2): This 9-month-old boy was born at 32 weeks gestation after premature rupture of membranes. He remained in the neonatal intensive care unit for 3 weeks due to difficulties with oxygenation, feeding, jaundice, and low birth weight. At about 5 months of age, his parents noted thin tight skin, similar to his older brother, prompting them to seek further evaluation. He was taking cyproheptadine since age 6 months for appetite stimulation, nizatidine for reflux, and lactulose for constipation.

He was an alert and interactive child. Height was 64 cm (3rd centile) and weight was 4.2 kg (3rd centile). He had normal hair on the scalp, eyebrows, and eyelashes. Anterior fontanelle was open. Eyes and cheeks were prominent. He also had micrognathia (Fig. 2), and no teeth were present. Examination of his fingers did not reveal any overt signs of clubbing or acro-osteolysis although they appeared slightly bulbous. He had thin tight skin with prominent superficial veins on the legs and the scalp anteriorly. There was no obvious decrease in subcutaneous fat. A urinalysis was normal.

MATERIALS AND METHODS

Both the patients and their family members were evaluated at the Clinical and Translational Research Center at the UT Southwestern. A written informed consent was obtained from both the parents, and the study was approved by the Institutional Review Board of UT Southwestern.

Height and body weight were measured by standard procedures. Skinfold thickness was measured with a Lange caliper (Cambridge Scientific Industries, Cambridge, Maryland) at five truncal sites (chest, mid-axillary, abdomen, subscapular, and suprailiac), six peripheral sites (biceps, triceps, forearm, hip, thigh and calf) on the right side of the body, and at the chin.

Whole body and regional fat in the head, trunk, upper and lower extremities were determined using a dual-energy x-ray absorptiometry (DEXA) scan with a multiple detector fan-beam Hologic QDR-2000 densitometer (Hologic, Inc., Waltham, MA).

Lipids, lipoproteins, chemistries, and blood hemoglobin A1C were analyzed as part of a systematic multichannel analysis (Synchron CX9 ALX Clinical System, Beckman, Fullerton, CA).

Mutational analysis was performed by PreventionGenetics, Marshfield, WI, for *ZMPSTE24* on both the patients and their parents. In addition, MAD 4700.3 was screened for *LMNA* mutations. Using genomic DNA extracted from the patients' cells, all coding regions as well as ~50 bases of flanking non-coding sequences were amplified and sequenced. The patients' sequences were then aligned and compared to the reference sequences. For sequence analysis, Applied Biosystems software as well as Mutation Surveyor software was used. The sequence electropherograms were also manually reviewed.

RESULTS

Sequencing of *LMNA* in MAD 4700.3 revealed no disease causing variants. Compound heterozygous mutations, however, were found in both the patients at exon 6 (c.743C>T; p.Pro248Leu) and exon 10 (c.1349G>A; p.Trp450stop) of *ZMPSTE24* gene. The patients' father carried the heterozygous variant, p.Pro248Leu, while the mother carried the heterozygous variant, p.Trp450stop.

Measurement of skinfold thickness at truncal sites of MAD 4700.3 revealed chest 7 mm, mid-axillary 4.5 mm, abdomen 11 mm, subscapular 4.5 mm (normal values, 10th to 90th centile: 4.2–8.1 mm [McDowell et al., 2005]), and suprailiac 10 mm. At the peripheral sites, biceps skinfold was 5 mm, triceps 12 mm (normal values, 10th to 90th centile: 6.3 – 12.4 mm [McDowell et al., 2005]), forearm 11 mm, hip 44.5 mm, thigh 14 mm, and calf 10 mm. His skinfold at the chin measured 5 mm. A whole body DEXA scan revealed total body fat of 27.5% (mean $\pm$ SD for 12 white 3–5 year old boys with BMI 15.7 ± 0.9 kg/m² was 17.6 ± 2.0 %, [Ellis, 1997]). Fat in the upper extremities was 31.7%, in the lower extremities was 45.2%, and in the trunk was 21.8%.

Measurement of skinfold thickness at truncal sites of MAD 4700.4 revealed chest 8 mm, mid-axillary 6 mm, abdomen 9 mm, subscapular 6 mm (normal values, 15th to 85th centile: 5.9–9.1 mm [McDowell et al., 2005]), and suprailiac 11 mm. At the peripheral sites, biceps skinfold was 8 mm, triceps 12 mm (normal values, 15th to 85th centile: 8.4–13.1 mm [McDowell et al., 2005]), forearm 9 mm, hip 36.75 mm, thigh 12 mm, and calf 1 mm. Skinfold thickness at the chin was 6 mm.

DISCUSSION

We report on two brothers (4 years and 9 months old) with MAD harboring a previously reported missense *ZMPSTE24* mutation, p.Pro248Leu, and a novel null mutation, p.Trp450stop. Similar to previously reported MAD/Progeria-like cases due to mutations of the same gene [Agarwal et al., 2003; Shackleton et al., 2005; Agarwal et al., 2006; Denecke et al., 2006; Miyoshi et al., 2008], our patients demonstrated early onset of symptoms, postnatal growth retardation, feeding difficulty, delayed dentition, micrognathia, delayed closure of cranial sutures, joint stiffness, mottled hyperpigmentation, and thin skin with prominent superficial vasculature. The older brother also demonstrated a thin nose, short clavicles, acro-osteolysis, hair loss, Wormian bones, and dental overcrowding while the younger one did not demonstrate hair loss or a thin nose.

Serum chemistry values in the older brother did not show any evidence of metabolic disturbances, and the DEXA study did not show decreased total body fat. Total body fat values using DEXA have been reported in only one previous *ZMPSTE24* MAD patient, MAD3300.3 [Miyoshi et al., 2008]. At the age of 7 years, she had total body fat of 18.3% and was noted to have lipodystrophy that excluded the cheeks, arms and thigh. Skinfold thickness was measured in both of our patients; subscapular and triceps skin folds were normal. Normal values for very young children under the age of 4 years are not available for the other sites measured; however, the younger brother had calf skinfold thickness of only 1 mm, suggesting a lack of subcutaneous fat.

In contrast to previously reported MAD cases due to *ZMPSTE24* mutations, our patients did not show generalized lipodystrophy, suggesting that this two finding may manifest later in childhood (Fig. 3). In fact, a previously reported Japanese patient was not noted to have any loss of subcutaneous fat until the age of 7 years [Miyoshi et al., 2008]. Also, two previous patients have been reported to develop focal sclerosing glomerulosclerosis at age 19 [Agarwal et al., 2006] and 25 [Agarwal et al., 2003] years, and urinalysis in both the patients from Japan showed microhematuria at ages 7 and 3.5 years [Miyoshi et al., 2008] (Fig. 3). Our patients so far did not show any early signs of renal dysfunction.

When compared to MAD patients with *LMNA* mutations, patients with *ZMPSTE24* mutations develop clinical manifestations earlier in life, are premature at birth and can develop focal segmental glomerulosclerosis and calcified skin nodules later during adulthood. The differential diagnosis between MAD due to *LMNA* and *ZMPSTE24* mutations may be difficult especially in infancy, because the main clinical features are common (Table I), the type of lipodystrophy can be similar and the classical patterns named type A (partial) and type B (generalized) may not be evident in childhood. Telltale features of MAD in infancy may be micrognathia, overhanging nasal tip, thin nose and bulbous distal phalanges. Radiographic examination of the hands may confirm the presence of acro-osteolysis, and mutational analysis of *LMNA* and *ZMPSTE24* may confirm the diagnosis. Acanthosis nigricans and other metabolic disturbances have not been reported so far in MAD due to *ZMPSTE24* mutations. The early diagnoses of the two conditions, MAD due to *ZMPSTE24* or *LMNA* mutations, are of clinical significance since the late complications are different: severe progressive glomerulopathy in the former and metabolic complications due to insulin resistance and diabetes in the latter.

Interestingly, the features of MAD due to *ZMPSTE24* mutations show significant clinical overlaps with both Hutchinson-Gilford progeria syndrome (HGPS; OMIM 176670), characterized by precocious development of aging-like phenotypes, and atypical progeroid syndrome (APS) (Table I). Both HGPS and APS are usually caused by *de novo* heterozygous *LMNA* mutations. In comparison to MAD due to *ZMPSTE24* mutations,

lipodystrophy, prominent subcutaneous vasculature, and pinched nose are more prominent in HGPS [Hennekam 2006], while acro-osteolysis, clavicular hypoplasia, and mandibular hypoplasia are less prominent in APS [Garg et al., 2009]. Hennekam [2006] had reported slowly progressive lipodystrophy in patients with “autosomal recessive, non-classical progeria” with reported survival into adulthood and severe osteolysis resulting in increased risk of fractures. Since the molecular basis of “autosomal recessive, non-classical progeria” has not been elucidated, it is likely that some of them may have had MAD with severe progeroid manifestations due to *LMNA* or *ZMPSTE24* mutations as reported by us and others [Plasilova et al., 2004; Shackleton et al., 2005; Denecke et al., 2006; Agarwal et al., 2008; Miyoshi et al., 2008].

ZMPSTE24 mutations can also cause restrictive dermopathy (RD; OMIM 275210, [Navarro et al., 2004; Moulson et al., 2005; Navarro et al., 2005] and when compared to MAD due to *ZMPSTE24* mutations, both disorders manifest with prematurity, micrognathia, small pinched nose, sparse or absent hair, enlarged fontanelles, dysplastic clavicles, and acro-osteolysis. However, RD is lethal within the newborn period and has more profound manifestations including intrauterine growth retardation (IUGR), birth weight < 1500 g, fixed facial expression, mouth in the “o” position, skin erosions and denudations, and contractures [Morais et al., 2009]. Nearly all reported cases of RD harbored homozygous or compound heterozygous null *ZMPSTE24* mutations [Smigiel et al., 2010]. In contrast, patients with compound heterozygous *ZMPSTE24* mutations with a null mutation on one allele and a missense mutation on the other allele have always presented with MAD phenotype [Agarwal et al., 2003; Shackleton et al., 2005; Agarwal et al., 2006; Miyoshi et al., 2008]. Thus, those with RD have almost no detectable *ZMPSTE24* enzymatic activity whereas those with MAD may have some residual *ZMPSTE24* enzymatic activity. In fact, in a yeast halo assay, the mutant p.Pro248Leu, as seen in our patients, was nearly as active as the wild-type *ZMPSTE24* construct [Miyoshi et al., 2008]. As such, since the pathophysiological mechanisms in MAD and RD involve defective processing of prelamin A by *ZMPSTE24*, the variable manifestations of the two disorders can be explained by varying amounts of prelamin A accumulation.

The early diagnosis and slowly progressive nature of MAD due to *ZMPSTE24* in our patients offers an opportunity to prevent the disease’s complications, such as renal disease. Thus far, no such therapeutic option is available, but in the *Zmpste24*^{-/-} mice, farnesyl-transferase inhibitors (FTIs) and the combination of statins with bisphosphonates have been tried to inhibit accumulation of farnesylated prelamin A [Fong et al., 2006; Varela et al., 2008]. Fong et al [2006] administered an FTI inhibitor, ABT-100, to *Zmpste24*^{-/-} mice and reported significant improvement in grip strength, reduced rib fractures, increased body weight and improved survival (although all mice were killed at 20 weeks). However, benefits of FTIs may be limited because prelamin A may be alternatively prenylated by geranylgeranyltransferase I. Varela et al [2008] explored the treatment of *Zmpste24*^{-/-} mice with an aminobisphosphonate, zoledronate, and a statin, pravastatin, with the rationale of inhibiting both farnesylation and geranylgeranylation. Although no survival benefit was seen with either pravastatin or zoledronate alone, the combination therapy improved body weight, increased subcutaneous fat, reduced kyphosis and alopecia, improved bone density, and increased median survival of mice from 101 days to 179 days. Thus, which therapeutic approach will be more beneficial for patients with MAD due to *ZMPSTE24* deficiency remains to be determined.

In conclusion, we describe two young children with MAD who were found to harbor compound heterozygous mutations in *ZMPSTE24*. The report of these patients confirms early onset of disease manifestations such as thin skin, micrognathia, small pinched noses, mottled hyperpigmentation, and enlarged fontanelles as early as 5 months of age. It appears

that in patients affected with MAD due to *ZMPSTE24* mutations, the skeletal phenotype presents earlier whereas evident lipodystrophy and renal disease may occur later in life.

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Figure 1.

Clinical Features of Patient MAD4700.3. *A*, The patient has a small nose with telangiectasias, prominent cheeks, prominent superficial veins, low-set ears, micrognathia, and slight double chin. *B*, Bulbous appearance of distal fingers consistent with acro-osteolysis. *C*, Radiograph of the hand at 13 months showing irregularity of the tufts of all terminal phalanges, consistent with acro-osteolysis. *D*, Lateral view of the patient showing near normal body fat distribution and lack of overt lipodystrophy. *E*, Dry, straight, bright red hair with areas of hair thinning and alopecia particularly on the back of scalp and on the left parietal and frontal region. *F*, Computerized tomography of the head at 7 months with 3-D reconstructions showing multiple Wormian bones in both lambdoid sutures. *G*, Mottled pigmentation in the abdomen and inguinal areas.

Figure 2. Clinical Features of Patient MAD4700.4. *A, B*, The patient has low-set ears, prominent cheeks, and micrognathia. Skin on the face was thin and superficial veins were seen on the forehead. No hair loss from the scalp, eyebrows or eyelids. *C*, Mottled pigmentation in the abdomen and inguinal areas. *D*, Base of the fingers appeared slightly bulbous but there were no overt signs of acro-osteolysis. *E*, Normal appearance of the toes.

Figure 3. Onset of disease manifestations in *ZMPSTE24* MAD/Progeria-like cases. Each patient is represented by a different symbol.

TABLE I

Clinical features of two types of MAD/Progeria-like syndromes due to *ZMPSTE24* or *LMNA* mutations, APS, and HGPS

Clinical Feature	<i>ZMPSTE24</i> MAD cases (n=8)* [Agarwal et al., 2003; Shackleton et al., 2005; Agarwal et al., 2006; Denecke et al., 2006; Miyoshi et al., 2008]	<i>LMNA</i> MAD/Progeria-like syndrome cases (n=28) [Novelli et al., 2002; Cao and Hegele 2003; Sinha et al., 2003; Plasilova et al., 2004; Garg et al., 2005; Van Esch et al., 2006; Koshio et al., 2007; Lombardi et al., 2007; Agarwal et al., 2008; Zirn et al., 2009; Madej-Pilarczyk et al., 2009]	APS (n=26) [Garg et al., 2009] [Caux et al., 2003; Chen et al., 2003; Csoka et al., 2004; Jacob et al., 2005; Kirschner et al., 2005; Morry et al., 2008; Doh et al., 2009; McPherson et al., 2009; Renard et al., 2009]	HGPS** (n=41) A= [Gordon et al., 2007] B= [Merideth et al., 2008]	HGPS*** (n=142) [Hennekam 2006]*
Birth ≤ 33 wk gestation	3/7 (43%)	0	0	NA	12/86 (14%)
Post-natal growth retardation	4/5 (80%)	20/24 (83%)	4/6 (67%)	15/15 (100%) [B]	75–100%
Median Age of onset of symptoms	4 months (range: birth – 18 months)	7 years (range: birth - 30 years)	6.4 years (range: 5 months – 17 years)	NA	NA
Dental overcrowding	5/5 (100%)	21/23 (91%)	7/8 (88%)	7/7 (100%) [A]	NA
Delayed closure of cranial sutures	6/6 (100%)	16/20 (80%)	0	NA	50–75%
Sparse/absent hair or alopecia	4/5 (80%)	13/21 (62%)	8/9 (89%)	15/15 (100%) [A]	75–100%
Mottled hyperpigmentation	7/7 (100%)	22/23 (96%)	7/7 (100%)	15/15 (100%) [B]	NA
Acanthosis nigricans	0/4 (0%)	15/17 (88%)	2/8 (25%)	NA	NA
Calcified skin nodules	2/4 (50%)	0	0	0	0
Acro-osteolysis	6/7 (86%)	25/26 (96%)	5/12 (42%)	14/14 (100%) [A]	NA
Dysplastic/hyoplastic clavicles	6/7 (86%)	24/27 (89%)	4/11 (36%)	15/17 (88%) [A]	NA
Joint stiffness or contractures	6/7 (86%)	25/27 (93%)	10/10 (100%)	19/19 (100%) [A]	75–100%
Fractures	3/4 (75%)	3/7 (43%)	0	1/19 (5%) [A]	10 families
Focal sclerosing glomerulosclerosis	2/4 (50%)	0	0	0	NA
Lipodystrophy	5/7 (71%)	27/27 (100%)	19/22 (86%)	15/15 (100%) [B]	75–100%

NA, not available;

MAD, mandibuloacral dysplasia

APS, atypical progeroid syndrome

HGPS, Hutchinson-Gilford Progeria Syndrome

* Includes the two patients described in this paper.

These studies had overlapping patients with HGPS-causing G608G *LMNA* mutations.

**

Not all patients were confirmed to have a HGPS causing *LMNA* mutation.