

Homozygous missense mutation in the lamin A/C gene causes autosomal recessive Hutchinson-Gilford progeria syndrome

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Hutchinson-Gilford progeria syndrome (HGPS; MIM 176670) is an extremely rare genetic disorder displaying features reminiscent of premature senescence.^{1,2} Typically, affected children appear normal at birth, but begin to develop characteristic symptoms within the first years of life such as failure to thrive, alopecia, lipodystrophy, and scleroderma-like skin changes. Though the first HGPS cases were described more than 100 years ago,^{1,3} its extreme rarity (1:4–8 000 000) and mostly sporadic occurrence made it difficult to identify the underlying genetic cause. By means of homozygosity mapping as well as candidate gene analysis, two research groups recently reported that heterozygous, recurrent de novo point mutations in the lamin A/C gene (*LMNA*; MIM 150330), a component of the filamentous meshwork of the nuclear lamina, caused HGPS.^{4,5}

LMNA encodes two A-type lamins, lamin A and C, which are the result of alternative splicing and share the first 566 amino acids.^{6,7} Together with B-type lamins, they represent the main components of the nuclear lamina. In contrast to B-type lamins, which are ubiquitously expressed in all cell types at all developmental stages, A-type lamins are absent in the cells of the early embryo, embryonic stem cells, stem cells of the immune and haematopoietic systems as well as in cells of the neuroendocrine system (reviewed in Goldman *et al*⁸ and Mounkes *et al*⁹).

Besides HGPS, germline mutations in *LMNA* have been shown to cause seven phenotypically different disorders, inherited in an autosomal dominant and/or recessive manner.^{4,5,10} Considering the tissue(s) affected, they can be grouped into those involving mainly (i) striated and cardiac muscle, (ii) peripheral nerves, and (iii) white adipose tissue and bones.⁹ Together with HGPS, two of them belong to the so-called progeroid syndromes: an atypical form of Werner syndrome (WRN; MIM 277700) and mandibuloacral dysplasia (MAD; MIM 248370).^{11,12}

The observation of heterozygous de novo *LMNA* mutations in HGPS patients supports the prevailing hypothesis that HGPS essentially represents a sporadic autosomal dominant disorder.^{4,5} In this study, performing genome-wide linkage analysis and subsequent *LMNA* mutation screening in a consanguineous family, we provide molecular evidence for autosomal recessive inheritance of HGPS, which was already hinted at by a few clinical reports and a recent *Lmna* mouse knock-out model.^{2,13–15} Furthermore, the phenotypic features observed in this kindred raise the question whether autosomal recessive MAD and HGPS represent essentially the same, that is, allelic disorder albeit with varying degrees of disease severity.

METHODS

Subjects

The HGPS family originates from North India and the parents are first degree cousins (fig 1A). Of their seven children, the

Key points

- Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare genetic disorder with children displaying features reminiscent of premature senescence. Recently, heterozygous, recurrent de novo point mutations in the *LMNA* gene encoding lamin A/C, a component of the filamentous meshwork of the nuclear lamina, have been reported to cause HGPS, supporting the prevailing hypothesis that HGPS represents a sporadic autosomal dominant disorder.
- Following detailed medical examination, genome-wide linkage mapping (prior to recent identification of the gene) and subsequent *LMNA* mutation analysis were performed on a consanguineous Indian family with four living children affected with HGPS.
- Genome-wide mapping excluded all chromosomal regions except for 1p13.3–1q23.3 where the *LMNA* gene is located. Consequent mutation analysis found all children affected with HGPS shared the same homozygous missense mutation G1626C (K542N) in *LMNA*. Both parents and one healthy daughter were found to be asymptomatic, heterozygous K542N mutation carriers.
- We provide molecular evidence for autosomal recessive inheritance of HGPS. Furthermore, given the phenotypic overlap commonly observed among the laminopathies and the extent of skeletal lesions present in this HGPS kindred, our observations question whether autosomal recessive mandibuloacral dysplasia and HGPS represent essentially the same genetic disorder albeit with varying degrees of disease severity.

first child (IV:1) died of unknown causes shortly after birth. Child IV:2 had suffered from HGPS, based on photographic documentation, and had died of pneumonia at age 16. Four more affected sibs (IV:3, IV:4, IV:6, and IV:7) and one healthy (IV:5) sib were alive at the time of consultation (fig 2A–D). According to the family history, no further affected relatives are known.

After the death of the 10 year old girl (IV:6), skin biopsies from the lower right abdomen as well as biopsies from the liver, abdominal muscle (m. rectus abdominis), and the right Achilles tendon were taken and fixed in 4% formaldehyde

Abbreviations: HGPS, Hutchinson-Gilford progeria syndrome; *LMNA*, lamin A/C gene; MAD, mandibuloacral dysplasia

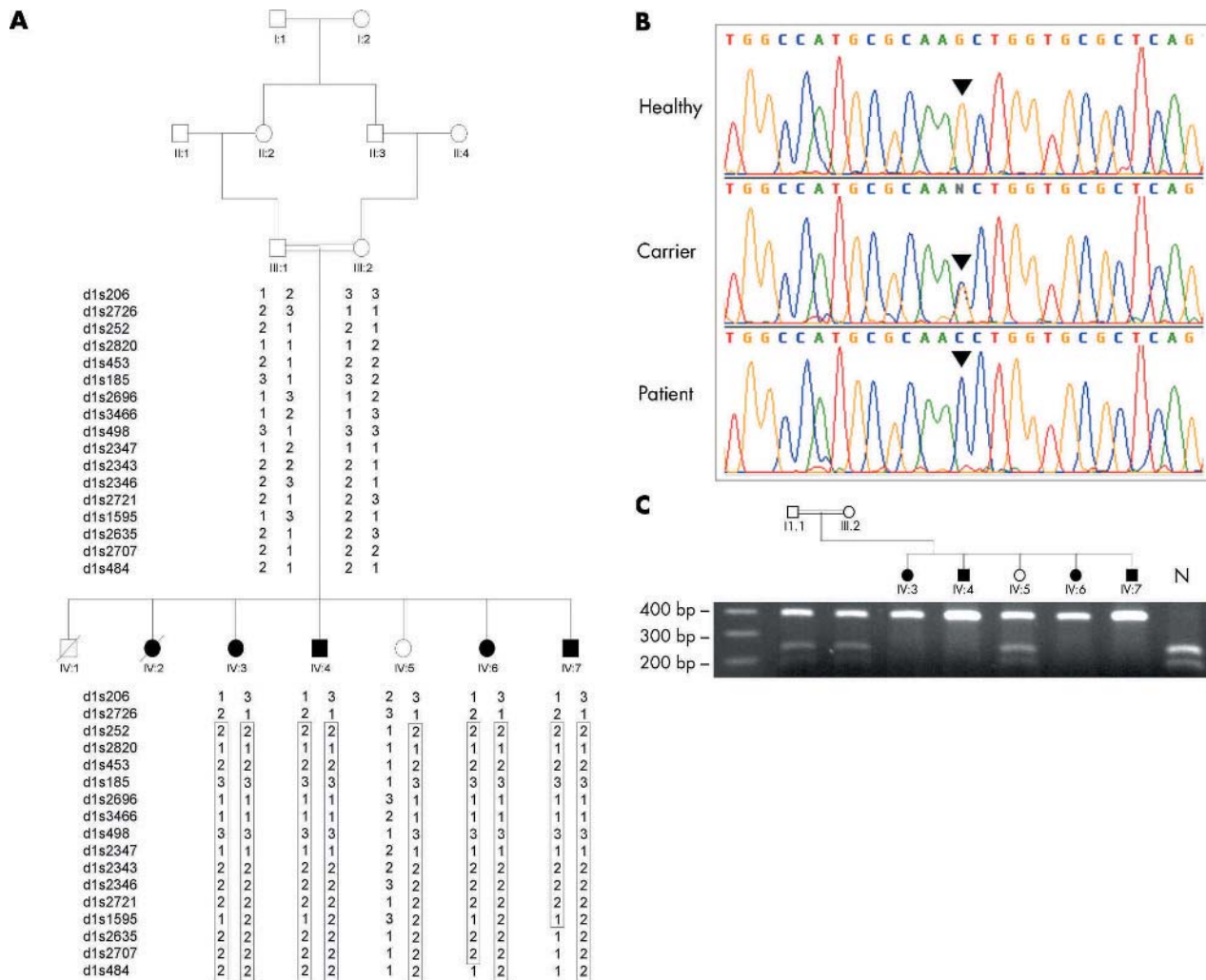


Figure 1 Molecular genetic findings in the HGPS kindred. (A) Pedigree with localisation of the HGPS gene to a 46 Mb interval on chromosome 1p13.3-1q23.3 (D1S2726-D1S2635); (B) identification of *LMNA* germline mutation 1626G>C (arrowheads): wild-type sequence, unaffected, healthy sibling as heterozygous carrier and HGPS patient with homozygous mutation; (C) confirmation of the 1626G>C mutation by *AluI* restriction enzyme digestion. "N" denotes a negative control.

(pH 7.0) for histopathological examination. Written informed consent was obtained for the clinical, histopathological, and molecular genetic investigation of the family.

Genome-wide linkage analysis

Genome-wide linkage analysis was performed on the seven members of the HGPS family, including the parents, four affected children and one healthy sib. DNA was extracted from peripheral blood leukocytes according to the manufacturer's protocol (QIAamp DNA Blood Maxi Kit, Qiagen). Genotyping of the polymorphic microsatellite markers was carried out using fluorescently-labelled primers from the ABI Prism Linkage Mapping Set-MD10 (Applied Biosystems), encompassing a total of 382 short tandem repeat markers with 10 cM resolution, and analysed on an ABI PRISM 3700 DNA Analyzer (Applied Biosystems). Statistical linkage analysis was performed using the MLINK program from the LINKAGE package.¹⁶ Based on the linkage results, ten additional microsatellite markers (fig 1A) from the candidate region 1p13.3-1q23.3 were analysed to verify and refine the locus of the HGPS gene (primer and marker information retrieved from UCSC genome browser: <http://genome.ucsc.edu>).

LMNA gene mutation analysis

Coding regions and exon-intron boundaries of the *LMNA* gene (GenBank accession number NM_170707) were directly sequenced in forward and reverse direction using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems) and analysed on an automated sequencer (ABI PRISM 310 Genetic Analyser, Applied Biosystems). The mutation identified was further verified by *AluI* restriction enzyme digests. The presence of the *LMNA* mutation K542N identified in the HGPS kindred was subsequently investigated in 50 healthy controls originating from North India.

RESULTS

Clinical features

The clinical examination of the four affected children revealed age-related features of HGPS (figs 1A and 2A-D), in particular early age of onset (18-24 months), failure to thrive (weight, height, and BMI below the third percentile of the Indian population), diffuse fronto-temporo-occipital alopecia with absent eyebrows and eyelashes, large open fontanelles, and impaired or absent sexual maturation (table 1). The patients' skin in general appeared to be dry, thin, and shiny. The fingers and toes showed scleroderma-like changes

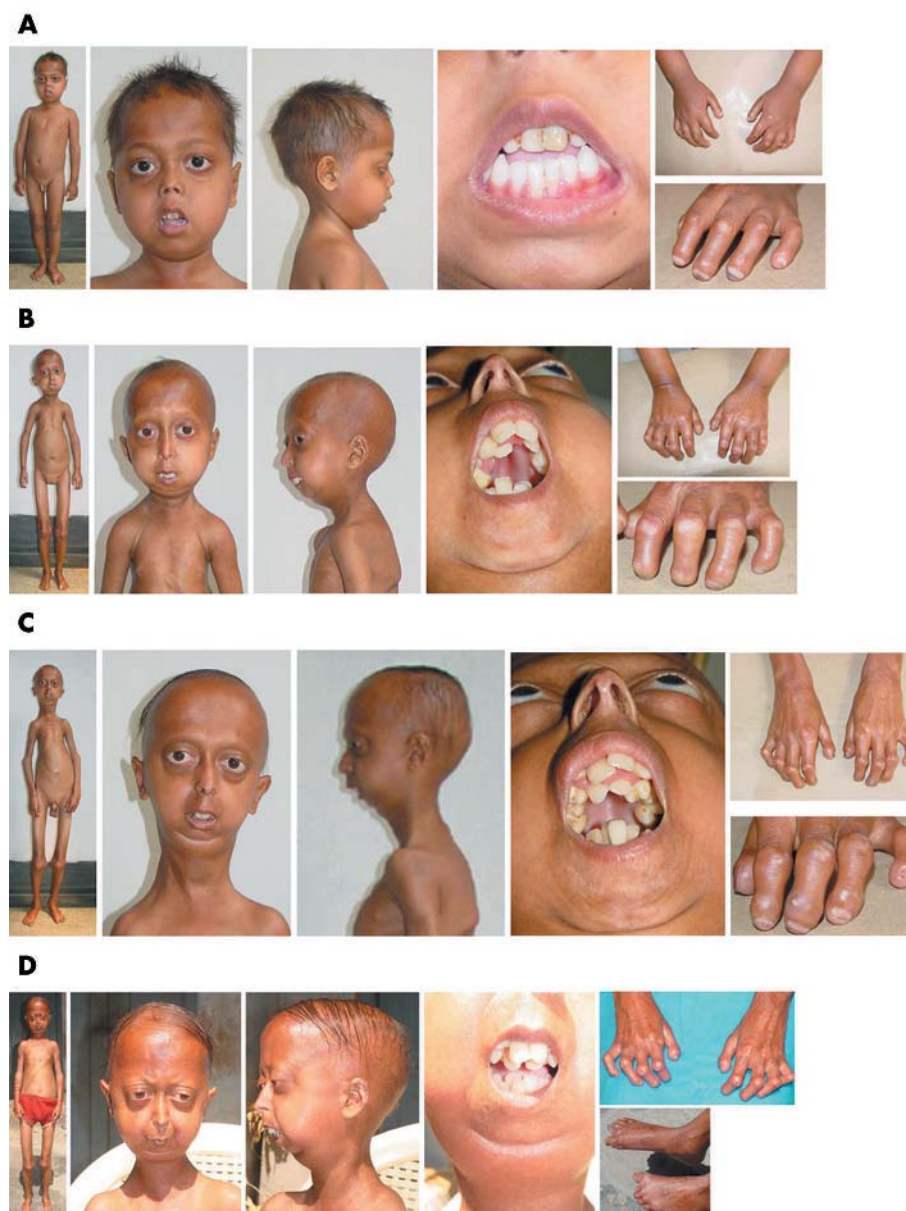


Figure 2 Clinical features observed in four affected HGPS family members. (A) 4 year old male patient IV:7; (B) 10 year old female patient IV:6; (C) 15 year old male patient IV:4; (D) 17 year old female patient IV:3.

with the nails being short and dystrophic (fig 2A–D). In addition, skeletal abnormalities such as micrognathia, hypoplastic and absent clavicles as well as acro-osteolysis of the distal phalanges of the hands and feet were observed. The older children were also suffering from stiffness of their joints, which severely impaired their movements. Medical examination including dermatological, neurological, and cardiological assessment did not reveal any obvious pathological findings in the parents or the healthy daughter.

Three patients (IV:4, IV:6, and IV:7) were available for laboratory and radiological investigations. Besides the skeletal lesions mentioned above, no old or current fractures were present. Electrocardiogram and echocardiography showed no pathological findings. Abdominal ultrasound revealed that the size, shape, and position of the internal organs corresponded with the children's age. Fasting blood glucose and cholesterol levels were within the normal range, as were neurodevelopment and intelligence. A few weeks after initial assessment of the family, patient IV:6 died of respiratory failure due to severe pneumonia.

Histopathological examination of the liver, abdominal muscle, and achilles tendon biopsies taken from the deceased 10 year old girl (IV:6) was unremarkable. The skin displayed several pathological features. The deep reticular dermis contained thickened and hyalinised, sclerotic collagen bundles with an obliteration of interbundle spaces (fig 3). In contrast to the sweat glands, which were very prominent because of the compact connective tissue, hair follicles and sebaceous glands were completely absent. The subcutaneous tissue was atrophic, without any sclerotic changes.

Linkage analysis

Preceding the recent identification of the gene responsible for HGPS, genome-wide linkage analysis encompassing 382 short tandem repeat markers with a 10 cM resolution was performed on the HGPS kindred displaying an autosomal recessive mode of inheritance (fig 1A). Because the parents were first degree cousins, affected children were expected to share the same (identical by descent) polymorphic marker alleles from the region of the HGPS gene and to harbour the

Table 1 Phenotypic features in affected HGPS family members

Patient ID	IV:7	IV:6	IV:4	IV:3
Sex	Male	Female	Male	Female
Age at presentation (years)	4½	10	15	17
Weight (kg)	10.5* (-6.6 SD)	8* (-11 SD)	13* (-11.8 SD)	13* (-18 SD)
Height (cm)	96* (-3 SD)	95* (-7.7 SD)	124* (-5.1 SD)	120* (-12 SD)
Body mass index (kg/cm ²)	11.4* (-2.4 SD)	8.8* (-6 SD)	8.5* (-10 SD)	9* (-7.3 SD)
Alopecia	+	++	++	++
Eyebrows and eyelashes	Present	Absent	Absent	Absent
Scleroderma-like skin atrophy	+	++	++	++
Mottled pigmentation of the skin	Present	Present	Present	Present
Generalised lipodystrophy	+	++	++	++
Sexual maturation	Prepubertal	Absent	Impaired	Absent
Prominent eyes/proptosis	++	+++	++	++
Pinched nose/beaked profile	+	++	++	++
Open fontanelles	Present	Present	Present	Present
Micrognathia	+	++	++	++
Crowded teeth	Milk teeth	Present	Present	Present
Clavicles	Hypoplastic	Absent	Absent	Absent
Acro-osteolysis	+	++	++	+++
Joint stiffness/arthrits	+	++	++	++

Number of "+" denotes degree of severity (also see fig 2).

*Denotes below the third percentile, with z-score in parentheses (Indian population).

same HGPS mutation. Segregation analysis revealed identical alleles by descent exclusively for markers in the chromosomal region 1p13.3–1q23.3, which was further supported by linkage analysis, using the MLINK program,¹⁶ with a two-point LOD score of 2.83 at a recombination fraction $\theta = 0$. Investigation of additional microsatellite markers from this region refined the borders of the HGPS locus between markers D1S2726 and D1S2635, an interval of 46 Mb (fig 1A).

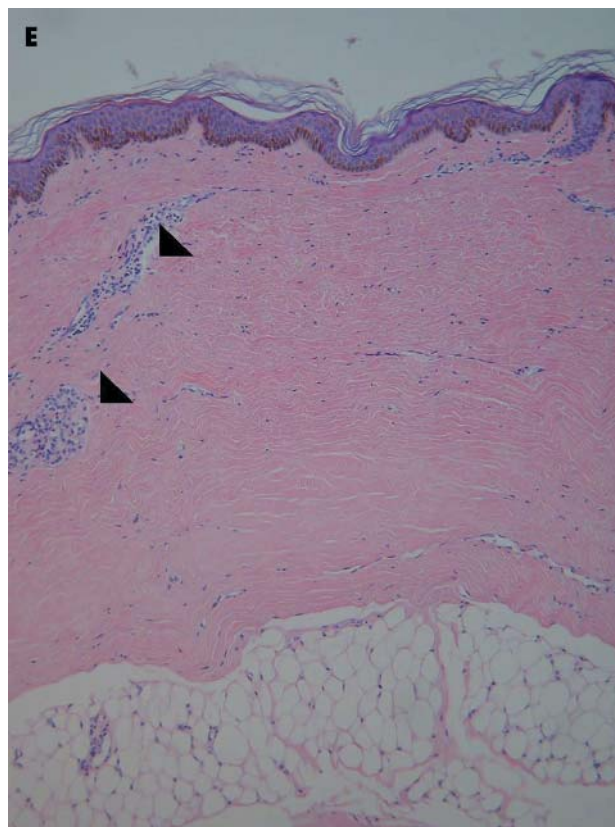


Figure 3 Haematoxylin-eosin stained section of skin biopsy taken from the 10 year old female patient IV:6. Note the tightly packed, sclerotic collagen fibre bundles in the dermis, and, in contrast to the sweat glands (arrowheads), the absence of hair follicles and sebaceous glands.

LMNA mutation analysis

At the same time, progeria mice carrying an autosomal recessive *Lmna* gene mutation as well as HGPS patients harbouring heterozygous de novo mutations in *LMNA*, located in the 1q22 region, were reported.^{4, 5, 15} In subsequent mutation analysis all four affected HGPS family members were found to be homozygous for a G to C transversion at nucleotide 1626 (1626G>C) in exon 10 (fig 1B). This mutation results in a non-conservative substitution of lysine (K) to asparagine (N) at codon 542 (K542N), an evolutionary highly conserved amino acid across species, including mouse (GenBank accession number P48678), rat (GenBank accession number P48679), chicken (GenBank accession number P13648), zebrafish (GenBank accession number NP_694503), and *X. laevis* (GenBank accession number P11048). The mutation was verified by *AluI* digests (fig 1C). K542N was not present in 100 chromosomes from healthy individuals originating from North India.

Using three different splice site recognition software tools (NetGene2, NNSplice, and SpliceView) there was no evidence that the 1626G>C mutation would generate a cryptic splicing site (data not shown). Functional significance of the K542N mutation could not be further assessed since no cultured cells or mRNA were available for investigation.

Table 2 Clinical differences between classical HGPS, the reported HGPS kindred, and *LMNA* mutation positive MAD patients

	Classical HGPS ²	Reported HGPS kindred	MAD ^{11, 25}
<i>LMNA</i> germline mutation	–	K542N/K542N	R527H/R527H
Age of onset	1	1–2	3–5
Age of death	12–15	10 and 16	>30
Alopecia	Present	Present	Mostly absent
Eyebrows and eyelashes	Absent	Absent	Present
Skin atrophy	Present	Present	Absent ²⁵
Generalised lipodystrophy	Present	Present	Mostly extremities
Open fontanelles	Present	Present	Absent ²⁵
Premature loss of teeth	Absent	Absent	Present
Sexual maturation	Absent/ impaired	Absent/ impaired	Present

DISCUSSION

To date, 29 sporadic HGPS cases with *LMNA* germline mutations have been described.^{4 5 17} Twenty five (86%) of them carry a heterozygous G608G splicing mutation which occurred de novo (that is, not detected in parents) and is presumed to act in a dominant negative fashion. In this study, we present molecular evidence that HGPS is also transmitted in an autosomal recessive mode of inheritance as previously hinted at by consanguineous families with more than one affected sib.^{2 13 14}

The homozygous K542N *LMNA* germline mutation identified in our consanguineous HGPS kindred is most likely pathogenic given that it changes an evolutionary highly conserved, charged residue to an uncharged residue and that it is absent in 100 chromosomes from a North Indian control population. Further, indirect evidence stems from genome-wide linkage analysis performed in this family, which significantly excluded all chromosomal loci except the 1p13.3–1q23.3 region.

The fact that the heterozygous mutation carriers (parents, child IV:5) were phenotypically normal strongly argues against a dominant negative effect of the K542N mutation in this family as well as against the hypothesis of recessive HGPS being the result of germinal mosaicism.⁵ In contrast to the most prevalent *LMNA* mutation G608G impinging only on the lamin A protein, the K542N mutation alters the coding sequence shared by both *LMNA* splice variants and thus affects lamin A and C. Based on the results from our in silico analysis, 1626G>C (K542N) is unlikely to affect *LMNA* splicing as observed in the de novo G608G mutation.^{4 5} Since K542 is localised in the globular C-terminal portion of the lamin A/C molecule, within the emerin and LAP2 α interaction, as well as the DNA binding domains, substitution of a charged lysine to an uncharged asparagine is likely to affect both the organisation of the internal nuclear envelope structure and the lamin–DNA interaction.^{18–23} The functional consequence(s) of this missense mutation, though, remain to be established in future molecular and immunocytochemical investigations on cell cultures from affected family members.

In this HGPS kindred, affected members display remarkably uniform phenotypic features, albeit with age-related expressivity (table 1, fig 2A–D). All patients exhibited marked failure to thrive (well below the third percentile), large fontanelles, scleroderma-like skin alterations, generalised lipodystrophy as well as diffuse to almost total alopecia with loss of eyebrows and eyelashes. Besides the hallmark features of HGPS, patients also showed uniform skeletal malformations such as acro-osteolysis of the digits, micrognathia, and clavicular aplasia/hypoplasia, as previously reported.^{2 24} These characteristics are shared with MAD, a rare, autosomal recessively inherited disorder.¹¹ Intriguingly, MAD also belongs to the so-called laminopathies, a set of eight allelic disorders caused by germline mutations in *LMNA*.^{4 5 9 12} Thus far, 11 MAD patients from seven families with a *LMNA* mutation have been reported and all were found to carry the same, homozygous R527H mutation.^{11 25}

In table 2 some of the clinical differences between classical HGPS, the HGPS kindred described in this report, and MAD patients with identified *LMNA* mutation are listed. The assessment is partly limited by the fact that no detailed clinical descriptions from the reported *LMNA* mutation-positive HGPS patients are currently available, thus impeding direct comparison with known *LMNA* mutation carriers.^{2 11 25}

In contrast to the considerable phenotypic variation observed in MAD patients carrying the R527H mutation, all affected individuals from our HGPS kindred display a remarkably uniform, age-related pattern of disease expression.^{11 25} The fact that this family presents with the typical features of HGPS, but in addition also exhibits substantial

skeletal changes, commonly observed in MAD, places it at the cross-roads of these two clinical entities. It confirms the assumption put forward by Mounkes *et al*¹⁵ that HGPS and MAD represent a clinical spectrum of related disorders rather than separate diseases. The clinical overlap between HGPS and MAD seen in our kindred has also been described for other laminopathies, such as between the Dunnigan type familial partial lipodystrophy (FPLD; MIM 151660) and MAD²⁶ or between FPLD and dilated cardiomyopathy with conduction system disease (CMD1A; MIM 115200).²⁷

Intriguingly, heterozygous *LMNA* mutations located in the vicinity of K542N, like R527P and L530P, have been shown to give rise to different, predominantly muscular phenotypes.²⁸ Given the significant phenotypic heterogeneity exerted by the type and site of a specific *LMNA* germline mutation in other laminopathies,^{9 19 27 29–31} genotype–phenotype correlation studies are mandatory for HGPS. They should allow (i) assessment of disease variability and severity in patients carrying an identical *LMNA* mutation, (ii) establishment of clinical differences between autosomal dominantly and recessively inherited HGPS, and (iii) determination of the degree of phenotypical overlap between HGPS and other laminopathies. On a cellular level, molecular and biochemical studies on cell lines from healthy heterozygous and affected homozygous K542N mutation carriers should allow determination of the functional consequences of this alteration. Further research on the precise role of lamin A/C within the nuclear envelope and on its interaction(s) with tissue-specific proteins is needed to understand the broad phenotypic spectrum observed within the laminopathies.

In conclusion, this is the first report of a consanguineous HGPS family providing molecular evidence for autosomal recessive inheritance of HGPS. Thus, in addition to Emery-Dreifuss muscular dystrophy (EDMD2, MIM181350; EDMD3, MIM604929), HGPS represents the second laminopathy where germline mutations in the *LMNA* gene can cause disease in both a dominant and recessive mode of inheritance. Furthermore, the extent of skeletal lesions observed in this kindred raises the question whether autosomal recessive MAD and HGPS represent essentially the same, that is, allelic disorder albeit with varying degrees of disease severity.

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ELECTRONIC-DATABASE INFORMATION



Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/>; UCSC Genome Browser, <http://genome.ucsc.edu/>; NCBI Nucleotides Database, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Nucleotide>; NCBI Proteins Database, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein>; NetGene2, <http://www.cbs.dtu.dk/services/NetGene2/>; NNSplice, http://www.fruitfly.org/seq_tools/splice.html; SpliceView, <http://l25.itba.mi.cnr.it/~webgene/www/spliceview.html>

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