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A New Lamin A Mutation Associated with Acrogeria Syndrome

TO THE EDITOR

Acrogeria (OMIM#201200), first described in 1940 (Gottron, 1940), is a form of skin atrophy combined with mottled hyperpigmentation and subcutaneous tissue atrophy giving an aged appearance. The pathogenesis of acrogeria seems heterogeneous, as abnormal biosynthesis of type III collagen is suspected in some cases, making Gottron-type acrogeria and vascular-type Ehlers–Danlos syndrome (vEDS, OMIM#130050) allelic diseases (Pope et al., 1996; Jansen et al., 2000; Hashimoto et al., 2004). Several clinical features of acrogeria recall the dermatologic defects observed in Hutchinson–Gilford progeria syndrome (HGPS OMIM#176670), mandibuloacral dysplasia type A (MADA, OMIM#248370), or mandibuloacral dysplasia type B (MADB, OMIM #608612) phenotypes, known to be caused by Lamins A/C defects, due to mutations either in the LMNA gene that encodes them or in the ZMPSTE24 gene, which encodes a protease involved in Lamin A processing (Novelli et al., 2002; De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003; Ahmad et al., 2010). Lamins are nuclear intermediate filaments that are involved in nuclear architecture and functions including chromatin organization or DNA replication, transcription, and repair, reviewed in Prokocimer et al., 2009.

The patient affected with acrogeria was born in 1969 from a healthy mother and a probably affected father, who was reported by the patient to have the same skin aspect and had a mitral and aortic valve replacement. The patient has a brother and a son who are not affected. At the age of 36 years, he was referred to our department for “prematurely aged” appearance. He presented with a thin nose and translucent skin on the face (Figure 1a, A). The distal portion of the lower limbs seemed lipodystrophic and the patient presented short clavicles (Figure 1a, B). Translucent skin of the arms and abdomen had pigmentation abnormalities (Figure 1a, B, C). The hands and the feet showed atrophic demis and loss of subcutaneous fat (Figure 1a, B, D). The hands had a very

Abbreviations: HGPS, Hutchinson–Gilford progeria syndrome; MAD, mandibuloacral dysplasia; RT-PCR, reverse transcription–PCR; vEDS, vascular-type Ehlers–Danlos syndrome
aged appearance with prominent veins and osteolyses of the distal phalanges (Figure 1a, D). All these clinical signs are strikingly evocative of HGPS or MAD phenotypes. Cardiovascular, pulmonary, ophtalmological, and central nervous system examinations revealed no abnormalities (data not shown). Liver and renal functions were normal, and the patient was not diabetic. The patient consented to his image being used.

A skin biopsy of the right arm showed slight epidermal hyperplasia (Figure 1a, E), irregular and fragmented elastic fibers (orcein staining, Figure 1a, F), and disorganization of collagen bundles with degenerative aspect of collagen network (Figure 1a, G). EDTA blood was obtained from the patient and family members following written consent, in adherence to the Declaration of Helsinki principles. We screened LMNA gene at the genomic level and observed the c.1771T>A heterozygous transition in exon 11 (Figure 1b). The mutation was observed only in the proband and was absent in the rest of the unaffected family. Unfortunately, the DNA of the affected father was not available because he died several years earlier (Figure 1c). At the protein level, the identified mutation was predicted to replace a Cysteine with a Serine at amino acid position 591 (p.Cys591Ser), in the C-terminal part specific to lamin A (from 567–664), being absent from lamin C (stop at 566). This mutation was absent in more than 100 healthy internal controls, as well as in 1500 other patients tested in our molecular diagnostic laboratory in other clinical contexts evocative of a laminopathy; it is not reported in the UMD-LMNA database (http://www.umd.be/LMNA/) nor in the 1000 genome resources (http://browser.1000genomes.org/index.html) or the UCSC genome browser (http://genome.ucsc.edu/) as a SNP.

On the basis of deleted Lamin A isoforms associated with LMNA exon 11 mutations, we performed cDNA explorations with overlapping and “full-length” primers but did not observe any shorter transcripts (data not shown). In concordance with the reverse transcription-PCR (RT-PCR) analyses, Western blots on primary dermal fibroblasts did not reveal any truncated form at the protein level and showed normal Lamin A/C amounts (Figure 2a, lane 1) in comparison with healthy control (lane 2). No band was evidenced with a progerin-specific antibody, opposite to a HGPS patient, used as a progerin positive “control” (lane 3; Figure 2a).

In parallel, as the vEDS and acrogeria are often misdiagnosed, and because a mutation in the COL3A1 gene has already been reported in a patient with Gottron-type Acrogeria (Jansen et al., 2000), we excluded COL3A1 mutations or transcript alterations by RT-PCR and direct sequencing from the COL3A1 cDNA issued from the patient’s fibroblast cell line (data not shown).

Several laminopathies are characterized by nuclear abnormalities, reflecting a nuclear fragility caused by nuclear lamina instability (Schreiber and Kennedy, 2013). To support the pathogenicity of the identified mutation, we performed indirect immunofluorescence experiments using anti-lamins A/C on patient and control fibroblasts and evidenced that 35.2% of patient’s nuclei presented a misshaped nuclear structure characterized by blebs (Figure 2b, asterisk), but also abundant micronuclei representing 8% of total nuclei (Figure 2b, arrowhead), compared with 11 and 1.3%, respectively, in control fibroblasts (Supplementary Figure S1 online). Antibodies directed against Emerin and Lamin B2, both Lamin A partners, confirmed these anomalies. Staining with NuMA antibody showed a heterogeneous nuclear staining in
“clumps” in our patient (Figure 2b, D) compared with the homogeneous punctuate staining observed in the control (Figure 2b, D’). Despite the fact that only one patient is described in this study, which is a frequent situation in extremely rare disorders as are some laminopathies, the segregation of the disease in the family, the absence of the mutation in large control populations and databases, the presence of nuclear abnormalities, and the fact that the same Cysteine residue is mutated, with a different substitution (p.Cys591Phe) in a patient affected with partial lipodystrophy, insulin resistance, aortic stenosis, and hypertrophic cardiomyopathy (Araújo-Vilar et al., 2008), all are very strong arguments in favor of its pathogenicity. It is well established indeed that in the context of Lamin A/C mutations, different changes of the same amino acid can give rise to different clinical phenotypes (Bonne et al., 1999).

The case we report points to the involvement of the LMNA gene in “acrogeria”, including this disease in the clinical spectrum of progeroid laminopathies. On the basis of the cardiac disease and dermatological manifestations observed in the father, another possible interpretation is that both cases, the father and the son, are affected with a form of atypical progeria syndrome with major dermatologic features found in this patient (Doubaj et al., 2012; Kane et al., 2013). In both cases, the patient we report, sharing p.Cys591Ser in Lamin A protein and characterized by nuclear abnormalities in fibroblast culture, extends the clinical spectrum of progeroid laminopathies and suggests that the LMNA gene should be screened in patients presenting with segmental progeroid traits, as well as in acrogeria patients presenting wild-type COL3A1 sequences. However, further functional studies will be needed to determine the

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**Figure 2. Functional analyses.** (a) Western blot. Merged pictures of western blots using anti-lamins A/C (red), anti-progerin (green), and anti-glyceraldehyde-3-phosphate dehydrogenase (GAPDH; green), as a loading control. Patient’s proteins are loaded in lane 1, the healthy control’s proteins in lane 2, and the Hutchinson–Gilford progeria syndrome patient’s proteins in lane 3. Progerin band is present only for the Hutchinson–Gilford progeria syndrome patient (middle band, lane 3). (b) Indirect immunofluorescence. Analyses on skin fibroblast cultures of patient (A–H) compared with control (A’–H’). Lamin A/C (A, A’), emerin (B, B’), and lamin B2 (C, C’) antibodies are in green. All these antibodies evidenced blebs indicated by asterisks and micronuclei by arrowheads. NuMA antibody (D, D’) is in red and shows a heterogeneous and mottled distribution pattern in patient (D) compared with control (D’). All images were counterstained with DAPI, in order to evidence DNA (E–H, E’–H’). Scale bars = 20 μm.
mutant function more precisely, and additional patient recruitment would be very helpful.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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