Lamin A/C Gene Mutation Associated With Dilated Cardiomyopathy With Variable Skeletal Muscle Involvement

To the Editor:

We read with great interest the article by Brodsky et al on a new mutation in exon 6 within the LMNA gene encoding lamin A/C. This defect causes familial dilated cardiomyopathy. Most interestingly, they describe how this mutation is also associated, to a variable degree, with skeletal myopathy. This, in turn, underlines the findings by Bonne et al and Fatkin et al on mutations within the LMNA gene resulting in cardiac and skeletal myopathy. Therefore, patients with a lamin A/C mutation should be screened for both cardiac and skeletal myopathy, independent of their primary symptoms. Functional analysis of lamin A/C expression and the colocalization of proteins such as emerin, lamin B2, actin, and dystrophin within both cardiac and skeletal muscular tissue may give more insights into the pathogenesis of myopathy.

Lamins form the major constituents of the nuclear lamina. Lamins A and C arise from alternative splicing within exon 10 of the lamin A/C gene. Currently, mutations within the a-helical rod domain of lamin A/C (exons 1, 3, 6, 7, and 9) or within the carboxyterminal domain of lamin C (exon 10) affect cardiac and/or skeletal muscle.1-3 In addition, we identified a deletion of the base adenine at codon 466 (1397delA) of exon 8, resulting in a frameshift mutation with a stop codon at residue 479 in a patient with familial dilated cardiomyopathy without any clinical signs of skeletal myopathy.

The mutation analysis within the LMNA gene revealed even more fascinating aspects of the functionality of the nucleophilic lamin A/C, including the fact that substitution mutations at codons 482 and 486 within exon 8 of LMNA cause familial partial lipodystrophy.4,5 This disease is characterized by skeletal muscular hypertrophy and partial atrophy of subcutaneous fatty tissue but not muscular dystrophy. Cardiac involvement has not been substantially proven in familial partial lipodystrophy. Affected patients may complain of myalgia, especially after exercise, and of tachycardia, especially during exercise. Both symptoms may reflect a malfunction of the muscle compensated for by muscular hypertrophy. These patients also characteristically develop hyperlipidemia and insulin-resistant diabetes mellitus in young adulthood. The interaction of lamin A/C in the genesis of these cardiovascular risk factors is not known thus far. However, it would be of great interest to learn more about the impact of lamin A/C in lipoprotein and glucose metabolism. Therefore, the prospective analysis of patients with skeletal and/or cardiac myopathy should also include the characterization of glucose, insulin, and lipids.

Hartmut H.-J. Schmidt, MD
Herbert Lochs, MD
IV Med Klinik
Charité Campus Mitt
Berlin, Germany
hartmut.schmidt@charite.de


Response

Diseases known to be linked to LMNA gene mutations include the autosomal-dominant form of Emery-Dreifuss muscular dystrophy (EDMD2), dilated cardiomyopathy with conduction defects (CMD1A), dilated cardiomyopathy with muscle disease (MDDC), and familial partial lipodystrophy (FPLD). The phenotypic heterogeneity observed within our study family suggests that LMNA gene mutations may also account for the autosomal-dominant form of limb-girdle muscular dystrophy (LGMD1B). In particular, the phenotypes observed in the MDDC1 kindred include dilated cardiomyopathy with early arrhythmia and late conduction defects, which may or may not be accompanied by EDMD- or LGMD-like muscular dystrophy. In addition to demonstrating a link between these diseases, our findings also indicate the potential existence of different pathogenic mechanisms and suggest that other modifier genes and/or epigenetic factors may alter the expressivity of the disease gene.

The recent finding of LMNA mutations in FPLD supports the hypothesis that although the lamin A/C proteins are expressed in most terminally differentiated cell types, there are protein domains that have tissue-specific functions. This could lead to diseases characterized by the degeneration of specific cell types in particular anatomical distributions.1

FPLD is characterized by a loss of subcutaneous fat in the trunk and limbs due to a site-specific degeneration of adipocytes. In this disease, myocardial or muscular abnormalities have never been reported. Interestingly, however, an inappropriate muscular hypertrophy of unclear origin has been described.2 In these cases, the occurrence of pseudohypertrophy due to muscle dystrophy should be considered among the possible pathogenic mechanisms.

In our patients, the presence of lipodystrophy was considered. However, we found no clinical or MRI evidence (data not shown) of the abnormal subcutaneous fat distribution characteristic of FPLD, nor of any abnormality of glucose or lipid metabolism. These findings may indicate that mutations in the lamin protein domain encoded by exon 81,3 are required to cause regional defects in adipose tissue.

Gary L. Brodsky, PhD
Luisa Mestroni, MD
Molecular Genetics
University of Colorado Cardiovascular Institute
Denver, Co
Luisa.Mestroni@UCHSC.edu

Francesco Muntoni, MD
Caroline Sewry, PhD
Department of Paediatrics
Hammersmith Hospital
Imperial College School of Medicine
London, UK

Snjezana Miocic, MD
Gianfranco Sinagra, MD
Division of Cardiology
Ospedale Muggiore
Trieste, Italy

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