Lamin A/C-Related Cardiac Disease: Late Onset With a Variable and Mild Phenotype in a Large Cohort of Patients With the Lamin A/C p.(Arg331Gln) Founder Mutation.

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Abstract

BACKGROUND: Interpretation of missense variants can be especially difficult when the variant is also found in control populations. This is what we encountered for the LMNA c.992G>A (p.(Arg331Gln)) variant. Therefore, to evaluate the effect of this variant, we combined an evaluation of clinical data with functional experiments and morphological studies.

METHODS AND RESULTS: Clinical data of 23 probands and 35 family members carrying this variant were retrospectively collected. A time-to-event analysis was performed to compare the course of the disease with carriers of other LMNA mutations. Myocardial biopsies were studied with electron microscopy and by measuring force development of the sarcomeres. Morphology of the nuclear envelope was assessed with immunofluorescence on cultured fibroblasts. The phenotype in probands and family members was characterized by atrioventricular conduction disturbances (61% and 44%, respectively), supraventricular arrhythmias (69% and 52%, respectively), and dilated cardiomyopathy (74% and 14%, respectively). LMNA p.(Arg331Gln) carriers had a significantly better outcome regarding the composite end point (malignant ventricular arrhythmias, end-stage heart failure, or death) compared with carriers of other pathogenic LMNA mutations. A shared haplotype of 1 Mb around LMNA suggested a common founder. The combined logarithm of the odds score was 3.46. Force development in membrane-permeabilized cardiomyocytes was reduced because of decreased myofibril density. Structural nuclear LMNA-associated envelope abnormalities, that is, blebs, were confirmed by electron microscopy and immunofluorescence microscopy.

CONCLUSIONS: Clinical, morphological, functional, haplotype, and segregation data all indicate...
that LMNA p.(Arg331Gln) is a pathogenic founder mutation with a phenotype reminiscent of other LMNA mutations but with a more benign course.

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KEYWORDS: atrial fibrillation; atrioventricular block; cardiomyopathy, dilated; lipodystrophy; survival

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