Cardiometabolic assessment of lamin A/C gene mutation carriers: A phenotype-genotype correlation.


Abstract

AIMS: Mutations of the LMNA gene encoding lamin A/C induce heterogeneous phenotypes ranging from cardiopathies and myopathies to lipodystrophies. The aim of this study was to compare cardiometabolic complications in patients with heterozygous LMNA mutations at the 482nd codon, the 'hotspot' for partial lipodystrophy, with carriers of other, non-R482 LMNA mutations.

METHODS AND RESULTS: This study included 29 patients with R482 LMNA mutations, 29 carriers of non-R482 LMNA mutation and 19 control subjects. Cardiac and metabolic phenotypes were compared between groups. A family history of either cardiac implantable electronic devices (CIEDs; \( P < 0.001 \)) or sudden death (\( P < 0.01 \)) was more frequent in non-R482 than R482 carriers. The non-R482 carriers also had more abnormalities on electrocardiography and received CIEDs more often than R482 carriers (\( P < 0.001 \)). On cardiac ultrasound, non-R482 patients had greater frequencies of left atrial enlargement (\( P < 0.05 \)) and lower left ventricular ejection fractions (\( P < 0.01 \)) than R482 carriers. In contrast, R482 carriers had lower BMI (\( P < 0.05 \)), leptin (\( P < 0.01 \)) and fat mass (\( P < 0.001 \)), but higher intra-/total abdominal fat-mass ratios (\( P < 0.001 \)) and prevalences of diabetes (\( P < 0.01 \)) and hypertriglyceridaemia (\( P < 0.05 \)) than non-R482 carriers, with a trend towards more coronary artery disease. However, non-R482 carriers had higher intra-/total abdominal fat-mass ratios (\( P < 0.02 \)) and prevalences of diabetes (\( P < 0.001 \)) and hypertriglyceridaemia (\( P < 0.05 \)) than the controls.

CONCLUSION: Non-R482 carriers present more frequently with arrhythmias than R482 carriers, who twice as often have diabetes, suggesting that follow-up for laminopathies could be adjusted for genotype. Non-R482 mutations require ultra-specialized cardiac follow-up, and coronary artery disease should not be overlooked. Although overlapping phenotypes are found, LMNA mutations essentially lead to tissue-specific diseases, favouring genotype-specific pathophysiological
mechanisms.

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**KEYWORDS:** Coronary artery disease; LMNA gene; Laminopathy; Lipodystrophy; Rhythm disorders

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