Metabolic and cardiac phenotype characterization in 37 atypical Dunnigan patients with nonfarnesylated mutated prelamin A.

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Abstract

BACKGROUND: Laminopathies are associated with a broad spectrum of clinical manifestations, from lipodystrophy to cardiac diseases. The purpose of this study was to assess genotype-phenotype correlations in a lipodystrophic laminopathy caused by the Lamin A (LMNA) mutation T655fsX49. This mutation leads to synthesis of nonfarnesylated-mutated prelamin A that does not undergo the physiologic lamin A maturation process.

METHODS AND RESULTS: We studied 35 patients originating from Reunion Island who carried the LMNA T655fsX49 mutation. Comparisons of cardiac and endocrinologic features were made between homozygous and heterozygous patients. Homozygous patients presented more overlapping syndromes with severe cardiac phenotypes, defined by cardiolaminopathy, early atheroma with coronary heart disease (CHD) and high-degree conduction disorder compared with heterozygous (40% vs 4%; P = .016). Moreover, homozygous patients had earlier onset (49.6 vs 66 years old; P = .0002). Left ventricle lowered ejection fraction associated with heart failure was more frequent in homozygous than in heterozygous patients (40% vs 0%, respectively). Lipodystrophic traits were more marked in the homozygous group but only reached statistical significance for L4 subcutaneous fat measurement (2.8 ± 2.16 vs 18.7 ± 8.9 mm; P = .008) and leptin levels (2.45 ± 1.6 vs 11.26 ± 7.2 ng/mL; P = .0001).

CONCLUSIONS: Our results suggest that there is a relationship between mutated prelamin-A accumulation and the severity of the phenotypes in homozygous familial partial lipodystrophy type 2 patients who harbor the LMNA T655fsX49 mutation. A dose-dependent effect seems likely.

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