Lamin mutation location predicts cardiac phenotype severity: combined analysis of the published literature.

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Abstract

OBJECTIVE: Two LMNA genotype-phenotype cardiac correlations are reported: first, that cardiac involvement in multisystem laminopathies prevails with mutations upstream of the nuclear localisation signal (NLS); second, that worse outcomes occur with non-missense (compared with missense) mutations. We tested whether LMNA mutation DNA location and mutation subtype can predict phenotype severity in patients with lamin heart disease.

METHODS: We used a semantic workflow platform and manual electronic literature search to identify published LMNA mutations with cardiac-predominant phenotype. Hierarchical cluster analysis (HCA) assembled lamin heart disease into classes based on phenotype severity. 176 reported causative mutations were classified and any relationships to mutation location/subtype assessed by contingency analysis.

RESULTS: More adverse phenotype was associated with mutation location upstream of the NLS (p=0.014, OR 2.38, 95% CI 1.19 to 4.80) but not with non-missense mutations (p=0.337, OR 1.36, 95% CI 0.72 to 2.57), although an association with non-missense mutations was identified in a subcluster with malignant ventricular arrhythmia (p=0.005, OR 2.64, 95% CI 0.76 to 9.21). HCA limited to the 65 mutations described on ClinVar as pathogenic/likely pathogenic showed similar findings (upstream of NLS, p=0.030, OR 4.78, 95% CI 1.28 to 17.83; non-missense, p=0.121, OR 2.64, 95% CI 0.76 to 9.21) as did analysis limited to pathogenic/likely pathogenic variants according to the American College of Medical Genetics and Genomics standards.

CONCLUSION: Cardiac patients with an LMNA mutation located upstream versus downstream of the NLS have a more adverse cardiac phenotype, and some missense mutations can be as harmful as non-missense ones.

KEYWORDS: gene association; heart failure; systolic dysfunction
Conflict of interest statement

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