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# Gene expression profiling of fibroblasts in a family with LMNA-related cardiomyopathy reveals molecular pathways implicated in disease pathogenesis

Halida P Widyastuti [1], Trina M Norden-Krichmar [2], Anna Grosberg [3], Michael V Zaragoza [4]

Affiliations

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## Abstract

**Background:** Intermediate filament proteins that construct the nuclear lamina of a cell include the Lamin A/C proteins encoded by the LMNA gene, and are implicated in fundamental processes such as nuclear structure, gene expression, and signal transduction. LMNA mutations predominantly affect mesoderm-derived cell lineages in diseases collectively termed as laminopathies that include dilated cardiomyopathy with conduction defects, different forms of muscular dystrophies, and premature aging syndromes as Hutchinson-Gilford Progeria Syndrome. At present, our understanding of the molecular mechanisms regulating tissue-specific manifestations of laminopathies are still limited.

**Methods:** To gain deeper insight into the molecular mechanism of a novel LMNA splice-site mutation (c.357-2A > G) in an affected family with cardiac disease, we conducted deep RNA sequencing and pathway analysis for nine fibroblast samples obtained from three patients with cardiomyopathy, three unaffected family members, and three unrelated, unaffected individuals. We validated our findings by quantitative PCR and protein studies.

**Results:** We identified eight significantly differentially expressed genes between the mutant and non-mutant fibroblasts, that included downregulated insulin growth factor binding factor protein 5 (IGFBP5) in patient samples. Pathway analysis showed involvement of the ERK/MAPK signaling pathway consistent with previous studies. We found no significant differences in gene expression for Lamin A/C and B-type lamins between the groups. In mutant fibroblasts, RNA-seq confirmed that only the LMNA wild type allele predominately was expressed, and Western Blot showed normal Lamin A/C protein levels.

**Conclusions:** IGFBP5 may contribute in maintaining signaling pathway homeostasis, which may lead to the absence of notable molecular and structural abnormalities in unaffected tissues such as fibroblasts. Compensatory mechanisms from other nuclear membrane proteins were not found. Our results also demonstrate that only one copy of the wild type allele is sufficient for normal levels of Lamin A/C protein to maintain physiological function in an unaffected cell type. This suggests that

affected cell types such as cardiac tissues may be more sensitive to haploinsufficiency of Lamin A/C. These results provide insight into the molecular mechanism of disease with a possible explanation for the tissue specificity of LMNA-related dilated cardiomyopathy.

**Keywords:** Cardiomyopathy; Fibroblasts; Gene expression; IGFBP5 gene; LMNA gene; Lamin; Laminopathies; RNA sequencing; Signaling pathway.

## Figures

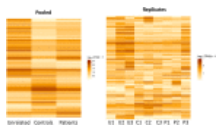

**Fig. 1** 5 Gene expression profiling of fibroblast...

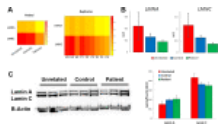

**Fig. 2** 5 Nuclear lamina-associated gene expression profiling...

**Fig. 3** 5 *LMNA* allelic expression. Top panel...

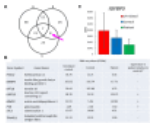

**Fig. 4** 5 Eight differentially expressed genes are...

**Fig. 5** 5 Ingenuity Pathway Analysis (IPA) of...

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