Plasma microRNAs as biomarkers for Lamin A/C-related dilated cardiomyopathy.

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Abstract

Lamin A/C gene (LMNA)-related familial dilated cardiomyopathy (fDCM) is an aggressive heart disease that often leads to transplantation and sudden death. The aim of our study was to evaluate the circulating microRNA (miRNA) profiles of patients with LMNA pathogenic mutations. The study population (N = 75) included (i) patients with pathogenic LMNA mutations responsible for fDCM (LMNA\textsuperscript{MUT}), (ii) age- and sex-matched LMNA wild-type controls (LMNA\textsuperscript{WT} control), and (iii) LMNA wild-type idiopathic DCM (iDCM) patients (LMNA\textsuperscript{WT} iDCM). Detailed clinical information was obtained from each participant. A panel of 179 plasma miRNAs was evaluated using RT-qPCR. An initial screening study was performed in LMNA\textsuperscript{MUT} carriers and age-matched LMNA\textsuperscript{WT} controls (N = 16). Forty-four miRNAs were specifically deregulated in LMNA\textsuperscript{MUT} carriers. Ten miRNA candidates were selected for subsequent validation after coexpression analyses and filtered for expression levels and statistical significance. Among the candidates, let-7a-5p, miR-142-3p, miR-145-5p and miR-454-3p levels were significantly increased in LMNA\textsuperscript{MUT} carriers compared to LMNA\textsuperscript{WT} controls and iDCM patients (P < 0.050). These circulating miRNAs, and their combination, were also associated with the presence of pathogenic mutations in regression and ROC analyses. This signature also discriminates between LMNA\textsuperscript{WT} healthy subjects and LMNA\textsuperscript{MUT} carriers who are phenotypically negative for DCM and between LMNA\textsuperscript{WT} iDCM and LMNA-related DCM patients. Correlation and functional enrichment analyses supported their association with the pathophysiology of the disease. We demonstrated for the first time that a specific miRNA signature could serve as a novel non-invasive tool to assist in the diagnosis of patients with fDCM caused by LMNA pathogenic mutations.

KEY MESSAGES: Let-7a-5p, miR-142-3p, miR-145-5p and miR-454-3p are differentially expressed in LMNA\textsuperscript{MUT} carriers. A composite score based on these miRNAs is a biomarker of mutations in the LMNA gene. This miRNA signature can be associated with the pathophysiology of familial DCM. The circulating miRNA profile can assist in the diagnosis of familial DCM.

KEYWORDS: Biomarkers; Circulating microRNAs; Dilated cardiomyopathy; Lamin A/C (LMNA)