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 MUT), (ii) age- and sex-matched LMNA wild-type controls (LMNA WT control), and (iii) LMNA wild-type idiopathic DCM (iDCM) patients (LMNA 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 MUT carriers and age-matched LMNA WT controls (N = 16). Forty-four miRNAs were specifically deregulated in LMNA 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 MUT carriers compared to LMNA 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 WT healthy subjects and LMNA MUT carriers who are phenotypically negative for DCM and between LMNA 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 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.

Biomarkers

Circulating microRNAs

Dilated cardiomyopathy

Lamin A/C (LMNA)

circulating microRNA

genomic DNA

lamin A

lamin C

let 7a

microRNA

microRNA 125a

microRNA 142

microRNA 145

microRNA 154

microRNA 185

microRNA 191

microRNA 197

microRNA 27a

microRNA 28

microRNA 423

microRNA 454

unclassified drug

biological marker

circulating microRNA

lamin A

microRNA

transcriptome

adult

Article

congestive cardiomyopathy

controlled study

disease association

female

human

limit of detection

major clinical study

male

mutation

pathophysiology

real time polymerase chain reaction

reverse transcription polymerase chain reaction

wild type

allele

amino acid substitution

biology

blood

congestive cardiomyopathy

echocardiography

gene expression profiling

genetic predisposition

genetics

genotype

heart function test

middle aged

receiver operating characteristic

Adult

Alleles

Amino Acid Substitution

Biomarkers

Cardiomyopathy, Dilated

Circulating MicroRNA

Computational Biology

Echocardiography

Female

Gene Expression Profiling

Genetic Predisposition to Disease

Genotype

Heart Function Tests

Humans

Lamin Type A

Male

MicroRNAs

Middle Aged

Mutation

ROC Curve

Transcriptome