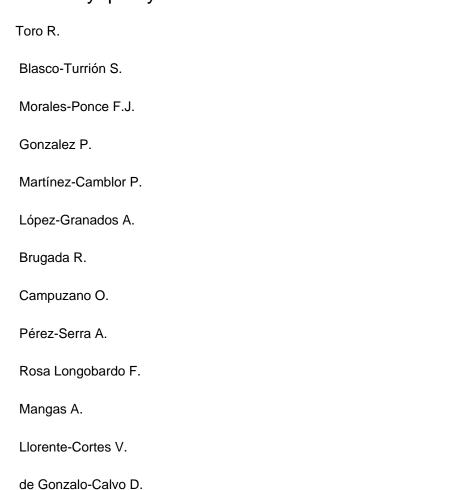
Plasma microRNAs as biomarkers for Lamin A/C-related dilated cardiomyopathy



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 &It; 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. © 2018, Springer-Verlag GmbH Germany, part of Springer Nature.

Biomarkers

Circulating microRNAs

Dilated cardiomyopathy

Lamin A/C (LMNA)

circulating microRNA

genomic DNA

lamin A

Iamin 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