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Molecular Genetic and Functional Characterization Implicate Muscle-Restricted Coiled-Coil Gene (*MURC*) as a Causal Gene for Familial Dilated Cardiomyopathy

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Molecular Genetic and Functional Characterization Implicate Muscle-Restricted Coiled-Coil Gene (*MURC*) as a Causal Gene for Familial Dilated Cardiomyopathy

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Background—Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are classic forms of systolic and diastolic heart failure, respectively. Mutations in genes encoding sarcomere and cytoskeletal proteins are major causes of HCM and DCM. *MURC*, encoding muscle-restricted coiled-coil, a Z-line protein, regulates cardiac function in mice. We investigated potential causal role of *MURC* in human cardiomyopathies.

Methods and Results—We sequenced *MURC* in 1199 individuals, including 383 probands with DCM, 307 with HCM, and 509 healthy control subjects. We found 6 heterozygous DCM-specific missense variants (p.N128K, p.R140W, p.L153P, p.S307T, p.P324L, and p.S364L) in 8 unrelated probands. Variants p.N128K and p.S307T segregated with inheritance of DCM in small families (χ^2=8.5, P=0.003). Variants p.N128K, p.R140W, p.L153P, and p.S364L were considered probably or possibly damaging. Variant p.P324L recurred in 3 independent probands, including 1 proband with a *TPM1* mutation (p.M245T). A deletion variant (p.L232-R238del) was present in 3 unrelated HCM probands, but it did not segregate with HCM in a family who also had a *MYH7* mutation (p.L907V). The phenotype in mutation carriers was notable for progressive heart failure leading to heart transplantation in 4 patients, conduction defects, and atrial arrhythmias. Expression of mutant MURC proteins in neonatal rat cardiac myocytes transduced with recombinant adenoviruses was associated with reduced RhoA activity, lower mRNA levels of hypertrophic markers and smaller myocyte size as compared with wild-type MURC.

Conclusions—*MURC* mutations impart loss-of-function effects on MURC functions and probably are causal variants in human DCM. The causal role of a deletion mutation in HCM is uncertain. **(*Circ Cardiovasc Genet.* 2011;4:349-358.)**

Key Words: heart failure ■ genetics ■ cardiomyopathy ■ mutation ■ RhoA

Heart failure is a major cause of mortality and morbidity.[1] It is associated with >270 000 deaths in the United States alone.[1] Primary dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are prototypic genetic forms of systolic and diastolic heart failure, respectively. Molecular genetic studies have led to partial elucidation of causal genes and identification of several hundred mutations in families and cases with cardiomyopathies.[2–5] Accordingly, mutations in genes coding for sarcomere and cytoskeletal proteins have emerged as important causes of primary cardiomyopathies.[2–5] Genetic studies also have highlighted the genetic heterogeneity of cardiomyopathies, particularly for DCM.[3,4] Accordingly, the most common known gene for DCM account for ≈5% of all primary HCM cases.[4] Collectively, the known causal genes are responsible for approximately two-thirds of HCM families and a much smaller fraction of DCM families.[4,5] Thus, the causal genes for a significant number of HCM and DCM cases and families remain to be identified.

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The conventional approach for identification of the causal genes for single-gene disorders is genetic linkage analysis. However, the approach does not provide sufficient resolution

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to identify the causal mutations in small families or sporadic cases. Direct DNA sequencing of the candidate genes, particularly in view of the recent advances in DNA sequencing technologies, is an alternative approach that is being used increasingly to identify the causative mutations/genes. Among the candidate genes for cardiomyopathies are genes encoding the Z-disc proteins.[6,7] We recently identified and characterized Muscle-Restricted Coiled-Coil (*MURC*), which encodes a Z-line component protein.[8,9] We showed that MURC activates the RhoA/ROCK pathway and expression of atrial natriuretic peptide (ANP) and regulates myofiber organization.[8] MURC is also a member of the cavin complex, associated with sarcolemmal caveaolae of muscle cells.[10] Subcellular distribution of MURC is altered in myopathic fibers.[10] Collectively, the experimental data implicate MURC as a biologically plausible gene for human cardiomyopathies.[10] To delineate the causal role of *MURC* in cardiomyopathies, we sequenced the coding regions and the splice junctions of *MURC* in 690 cases with cardiomyopathies and 509 control subjects, and, whenever available, we extended the genetic analysis to family members. We complemented the genetic studies with in vitro functional studies in cardiac myocytes. The findings, collectively, implicate *MURC* as a novel gene for DCM.

Methods

Study Population

The study protocol was approved by the institutional review board and was in accord with the Human Subjects Committee guidelines. The participating individuals signed informed consent. The main study population comprised 383 cases with DCM, 307 cases with HCM, and 277 normal individuals.[7] We obtained phenotypic data, including 12-lead ECGs and echocardiograms in all participants. Cardiomyopathies were diagnosed according to the conventional criteria.[11] Given the relatively small number of the African Americans in the main control group, we included a second group of 232 African Americans who had normal ECGs and echocardiograms.[12] On identification of a putative mutation, defined as insertion/deletion or frame-shift, nonsynonymous, or splice sequence variants, we recruited and phenotyped additional family members whenever available.

DNA Sequencing

We sequenced all exons and exon-intron boundaries of *MURC* in 1199 participants by the Sanger method in sense and antisense directions (primer sequence is provided in online-only Data Supplement Table I), using the Big Dye Terminator Reactions in an Applied Biosystems 3730xl Genetic Analyzer (Applied Biosystems, Inc, Foster City, CA). We analyzed the output using Variant Reporter software (Applied Biosystems, Inc). In addition, 2 investigators analyzed every sequence printout to detect the variants. We compared the sequence with the published GenBank sequence for *MURC* (GRCh37 reference genome assembly, chromosome 9, region 103340336.103350180). To reduce the possibility of sequencing errors, we repeated the sequencing reactions in all samples that contained a sequence variant. Only variants that were detected in sense and antisense directions and confirmed in independent sequencing reactions were considered as real variants.

Mutation Calling

To ascertain a causal role, we analyzed segregation of the variants with the phenotype in the families whenever available and analyzed evolutionary conservation of the involved amino acid using PRRN (http://align.genome.jp/prrn/), charge change, and hydropathy index. We used PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/index.shtml) to predict functional effects of the variants.[13] Nonsynonymous variants that were present only in the cases with cardiomyopathies but absent in the normal control subjects were considered likely disease-causing mutations and selected for in vitro functional studies.

Sequencing of Known Common Causal Genes for Cardiomyopathies

We sequenced the coding regions and exon-intron boundaries of *LMNA*, encoding Lamin A/C, a known gene for DCM in 103 proband with a compound phenotype of DCM and conduction defect and/or atrial fibrillation.[4] Likewise, we had previously sequenced all exons and exon-intron boundaries of *MYH7*, *MYBPC3*, *ACTC1*, *TNNT2*, *TNNI3*, *TPM1*, and *MYOZ2* in 81 probands with familial HCM. Finally, to detect compound mutations in those who carried a mutation in *MURC*, we sequenced *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC1*, and *LMNA*, known as relatively common genes for HCM and DCM in all *MURC* mutation carriers.[5,14,15]

Genotyping for Short Tandem Repeat Markers

To determine whether the recurring mutations occurred de novo or shared a common ancestral allele, we genotyped the individuals for 3 short tandem repeat (STR) markers (D9S180, D9S910, and D9S176) that spanned an approximately 2.5-Mbp genomic region on 9q31.1 locus. Genotyping was performed by polymerase chain reaction (PCR), using fluorescent-labeled primers and capillary electrophoresis on an ABI 3730xl Genetic Analyzer and analyzed using the GeneMapper v4.1 (Applied Biosystems).

Plasmid Constructs

We cloned human FLAG-tagged MURC cDNA into a pcDNA3.1 vector (pcDNA3.1-hMURC). We introduced the p.N128K, p.R140W, p.L153P, p.S307T, p.P324L, and p.S364L mutations by site directed mutagenesis.[8] Sequences of mutant-specific oligonucleotide primers are shown in online-only Data Supplement Table I.

Isolation and Culture of Neonatal Rat Cardiac Myocytes

We isolated and prepared neonatal rat cardiac myocytes (NRCM) from 1-day-old Sprague-Dawley rats as described.[8] Briefly, we digested ventricular tissues enzymatically and separated cardiac myocytes over a Percoll gradient. We changed the culture medium to serum-free medium after 24 hours and maintained the cells under serum-free conditions before experiments.

Replication-Deficient Recombinant Adenoviruses and Gene Transfer

We generated recombinant adenoviruses expressing FLAG-tagged human wild-type (Ad-hMURC-WT), each of the mutant MURC protein or β-galactosidase (Ad-LacZ), as described previously.[8] The Ad-LacZ and Ad-hMURC-WT served as controls. We infected the NRCM with the recombinant adenoviruses at a multiplicity of infection of 10. After incubation at 37°C for 1 hour, the viral suspension was removed, and cells were cultured with serum-depleted culture media for 48 hours.

Immunoblotting

To detect expression of the WT or mutant MURC, we electrophoresed the cell lysates in 10% SDS-polyacrylamide gels and transferred the proteins to polyvinylidene difluoride membranes (Millipore, Billerica, MA). We incubated the membranes with primary antibodies against FLAG (SIGMA, St Louis, MO) and GAPDH to detect FLAG-tagged MURC and GAPDH proteins, respectively. The secondary antibody was horseradish peroxidase–conjugated anti-mouse IgG (GE Healthcare, Waukesha, WI).

RhoA Activation Assay

We determined RhoA activity in the protein extracts from NRCM transduced with the recombinant adenoviruses using an absorbance-