Coding Sequence Rare Variants Identified in **MYBPC3**, **MYH6**, **TPM1**, **TNNC1**, and **TNNI3** From 312 Patients With Familial or Idiopathic Dilated Cardiomyopathy

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**Background**—Rare variants in >30 genes have been shown to cause idiopathic or familial dilated cardiomyopathy (DCM), but the frequency of genetic causation remains poorly understood. We have previously resequenced 9 genes in a cohort of idiopathic or familial DCM probands for rare variants, and now we report resequencing results for 5 more genes with established relationships to DCM.

**Methods and Results**—Blood samples were collected, and DNA specimens were prepared from 312 patients, 181 with familial DCM and 131 with idiopathic DCM. Genomic DNA underwent bidirectional sequencing, and DNA of additional family members underwent analysis when a rare variant was identified. We identified rare variants in 34 probands (10.9% overall), including 29 unique protein-altering rare variants and 2 splicing variants that were absent in 246 control subjects (492 chromosomes). These variants were 12 **MYBPC3** (myosin-binding protein C) in 13 (4.2%) probands, 8 **MYH6** (α-myosin heavy chain) in 10 (3.2%), 6 **TPM1** (tropomyosin) in 6 (1.9%), 4 **TNNC1** (cardiac troponin C) in 4 (1.3%), and 1 **TNNI3** (cardiac troponin I) in 2 (0.6%). Variants were classified as likely or possibly disease causing in 13 and 20 probands, respectively (n=33; 10.6% overall). One **MYH6** variant was classified as unlikely to be disease causing.

**Conclusion**—Rare variants in these 5 genes likely or possibly caused 10.6% of DCM in this cohort. When combined with our prior resequencing reports, ≈27% of DCM probands had possible or likely disease-causing variants identified.


**Key Words:** cardiomyopathy ■ dilated cardiomyopathy ■ genetics

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**Clinical Perspective on p 161**

Despite these experimental issues, gaining knowledge of the identities, character, and frequencies of mutations in known DCM genes is essential to understanding the phenomenon that underlies a great deal of heart failure morbidity and mortality. Such knowledge is crucial to the emerging practice of cardiovascular genetic medicine and to the design of DCM genetic epidemiology studies.

To begin to address this problem, we recently resequenced exonic and intron/exon junctions of 6 DCM genes (β-myosin heavy chain [MYH7]; cardiac troponin T [TNNT2]; sodium channel, voltage-gated, type V, alpha subunit [SCN5A]; cysteine- and glycine-rich protein 3 [CSRP3], LIM domain binding 3 [LDB3], and telethonin [TCAP]) in 313 DCM probands with support from the National Heart, Lung, and Blood Institute Resequencing and Genotyping Service (Table 1).

We found 32 variants (10.2%) not identified in 253 control DNAs. Although the reference (wild-type) sequence has been established for these DCM genes, determining whether a newly identified variant is disease causing is challenging. In discovery studies, confirming that a candidate gene indeed harbors a causative mutation usually is resolved by a combination of a significant log of the odds (lod) score, segregation of a variant with the disease phenotype in 1 or more large families, and
definitive functional studies. However, such approaches, especially functional studies, exceeded the scope of our prior gene survey study and were not included in the initial publication (although some functional studies, eg, for TNNT2 and lamin A/C [LMNA], have been published, and others are under way). Hence, we developed conservative standards to classify these variants as possibly or likely disease-causing.

To extend these findings, we have now performed bidirectional sequencing of 5 additional genes in the same cohort, again with Resequencing and Genotyping Service support. These 5 genes included myosin-binding protein C (MYBPC3), α-myosin heavy chain (MYH6), tropomyosin 1 (TPM1), tropomyosin C (TNNC1), and cardiac troponin I (TNNI3). By using the same approach, we present here the variants identified in this study thought to be possibly or likely disease causing.

Methods

Patient Population
Written informed consent was obtained from all subjects, and the Institutional Review Board at the Oregon Health & Science University (Portland, Ore) approved the project. The study included 312 probands (311 subjects from the prior cohort and 1 additional DCM case), 290 whites (of whom 7 were of Hispanic descent), 16 African Americans, 3 Asians, and 3 Native Americans/Alaskan Natives, and used methods of clinical categorization of FDC versus idiopathic DCM (IDC) as previously described. These 312 probands included 298 of the 304 previously described in detail. Families with confirmed and probable histories of familial disease were classified as having FDC; those with histories consistent with possible FDC or a negative family history were classified as having IDC. In cases classified as confirmed FDC, the subject and at least 1 closely related relative had IDC, defined as left ventricular enlargement accompanied by systolic dysfunction on exclusion of other detectable causes of DCM as previously described.

Gene Selection

The 5 genes reported herein were chosen by following the same selection and analysis strategy described in our 6-gene resequencing report. In brief, by using the published FDC literature available in early 2005, we estimated the number of exons needed to be sequenced to find a single mutation in each gene, on the basis of the number of exons in that gene and an estimate of the frequency of mutations in that gene in DCM, in an effort to conserve resequencing resources at the National Heart, Lung, and Blood Institute. We selected genes in that study with a threshold of sequencing up to 1000 exons to identify 1 putative disease-causing variant (as shown in Table 1 of that report). The prior estimates for TNNC1 (1500 exons), TNNI3 (1600 exons), and TPM1 (1667 exons) were used for this study’s gene selection, as previously reported, as well as estimates from the single studies for MYH6 (estimated at 907 exons) and MYBPC3 (estimated at 1591 exons).

Genetic Analysis

Genomic DNA was extracted from whole blood as previously reported. Bidirectional sequencing was conducted for the following 5 genes: MYBPC3 (NM_002563, chr11:47309535 to 47330829), MYH6 (NM_002471, chr12:42921039 to 22947322), TPM1 (NM_001018004.1, NM_001018005.1, NM_001018006.1, NM_001018007.1, NM_001018008.1, NM_001018020.1, spanning chr15:61121891 to 61151166), TNNC1 (NM_003280, chr3:52460158 to 52463098), and TNNI3 (NM_000363.3, chr19:60354948 to 60360912). All exons and intron/exon boundaries were polymerase chain reaction amplified by standard methods at SeattleSNPs under contract with the National Heart, Lung, and Blood Institute sequencing service. Samples from probands identified by the resequencing service as carriers of protein-altering variants and any available samples from their relatives were sequenced in our laboratory for confirmation and segregation analysis. Nucleotide changes were evaluated only if they were absent from all 246 (186 white, 23 Yoruban, 19 Asian, and 18 Hispanic) control samples analyzed at the sequencing center. Any possible disease-causing nucleotide alterations identified in African American samples were further evaluated in an additional 167
control African American DNA samples in our laboratory, for a total of 190 controls of African descent (380 chromosomes). As per our prior report, nucleotide changes were considered possibly disease causing if they predicted a change in a conserved amino acid, a frameshift, a premature truncation, or a missplicing event and were absent in ethnically matched normal controls. Nucleotide changes were considered likely disease causing if they met the criteria previously described and segregated with disease in multiple affected individuals within a family or were identified in multiple unrelated probands or had previously been reported as causative of DCM. Nucleotide changes that did not segregate with disease were considered unlikely to be associated with IDC or FDC.

Haplotype analysis was performed with the program Cocaphase for variants identified in multiple subjects to rule out founder effects. All individuals with the mutations in question were of white origin; thus, haplotype estimation was carried out on white samples only. Markers at each gene locus with minor allele frequencies >0.1 in the whole sample were selected for analysis.

Results

The bidirectional sequencing of 5 genes known to cause DCM was completed for DNA samples from 312 unrelated probands with IDC or FDC. Protein-altering variants, none of which were present in 246 control specimens, were identified in 34 (10.9%) of 312 probands (Table 2). Most unique variants (29 of 31; 94%) were missense mutations and altered highly conserved amino acids; 2 were predicted to affect splicing. Some had previously been reported with DCM or hypertrophic cardiomyopathy (HCM) (Table 2).

Of the 5 genes examined, the most rare variants were identified in the gene encoding MYBPC3, with variants identified in 13 of the 312 probands (4.2%). All MYBPC3 variants were considered possibly or likely disease causing (Table 2). One mutation (Ala833Thr; A.8), which was observed to segregate with disease, also was found in 2 additional families in our cohort (A.7 and A.9), neither of whom were known to be related and who were geographically remote to each other; haplotype sharing was identified near to the mutation, suggesting that this may be a founder mutation. This same variant had been previously reported in an individual with familial HCM. In that report, the variant was identified in the proband with HCM as well as in his brother and father who both had mild cardiac hypertrophy. Two probands (A.11 and A.12) had novel, possibly disease-causing splicing variants. Tissue samples were not available from either proband to assess the impact of these variants on mRNA splicing. One of the subjects with a splicing variant (A.12) also carried an MYBPC3 Gly1260Asp variant in trans (A.13). DNA from relatives was not available in either case with splicing variants; therefore, segregation could not be assessed. The Gly5Arg variant (A.1) was previously reported in a patient with early onset HCM harboring this and another MYBPC3 variant; however, segregation was not assessed in that report. DNA from other affected relatives was not available to assess segregation, so we classified the Gly5Arg variant as possibly disease causing. The Arg272Cys variant (A.3) was considered possibly disease causing if they predicted a change in a conserved amino acid and segregated with DCM. The Ala1004Ser variant (B.3, B.4, and B.5) occurred at a highly conserved site, was previously reported in a sporadic DCM case, and was, therefore, considered likely disease causing. The likely disease-causing Ala1440Pro (B.7) occurred at a highly conserved amino acid and segregated with DCM. The Asp1826Asn variant (B.9 and B.10), caused by 2 G>A substitutions in cis at positions 25743 and 25744, was identified in 2 probands. The affected sister of 1 of these probands was found to carry the same alteration; thus, the variant (B.9) was classified as likely disease causing. The second proband, who also carries the Asp1826Asn variant (B.10), has sporadic DCM and was reported to have an in-frame G474_D475insQ LMNA variant (family R in a study by Parks et al) and a TCAP Pro141Ala variant (denoted as D.3 and categorized as unlikely to be disease causing in a study by Hershberger et al). Two MYH6 variants (B.1 and B.8) were identified in the same individual: a female proband who had been diagnosed with DCM at age 8 who was previously reported as carrying the disease-causing TNNT2 Lys210del mutation (B.7 in a study by Hershberger et al). The remaining MYH6 nucleotide variants were considered possibly disease causing (B.2, B.6) or unlikely to be disease causing because of lack of segregation (B.11).

We screened the exons from 7 different transcripts at the TPM1 locus, encoding the TPM1 gene. Six different novel protein-altering variants were identified among 6 probands (Table 1), and all of the nucleotide changes were considered possibly or likely disease causing. With the exception of Ser16Ile, all the TPM1 variants were located in exons found to be present in the TPM1κ isoform, which unlike other TPM1 isoforms has been reported to be expressed uniquely in cardiac tissue. Two novel variants, Lys15Asn and Ile92Thr (C.1 and C.4), segregated with DCM in the respective families of each proband and were considered likely disease causing. The Ala277Val variant (C.6) was identified in a severely affected patient with IDC requiring transplant at age 13. This proband was previously reported as carrying a likely disease-causing Glu244Asp TNNT2 variant shown to cause decreased calcium sensitivity. Segregation could not be assessed in this family; thus, the Ala277Val TPM1 variant was considered possibly disease causing.

Four private protein-altering variants were identified in TNNC1 in 4 probands. One of the variants (D.2) occurred at a conserved site, segregated with disease, and was considered likely disease causing. The Tyr5His variant (D.1) occurred in a proband with early onset DCM known to carry a possibly disease-causing Arg1045Cys variant in MYH7. Segregation could not be assessed; therefore, the Tyr5His variant was categorized as possibly disease causing. The individual with variant D.3 (also found to carry MYBPC3 Pro910Thr denoted as A.10), carries a TNNC1 Asp145Glu variant previously reported in a male proband with a family history of HCM. This variant was shown to increase Ca2+ sensitivity of force recovery. The Asp145Glu variant is novel for DCM, and segregation data are lacking for this individual; therefore, we categorized this case as possibly disease causing.

The Asp180Gly nucleotide alteration was identified in TNNI3 in 2 unrelated probands (variants denoted E.1 and E.2). The variant was predicted to change a highly conserved amino acid; however, no family DNA specimens were
available in either case, and the variant was therefore considered possibly disease causing. Twenty-one of 181 (11.6%) probands categorized as having FDC and 12 of 131 (9.2%) probands categorized as having IDC carried possibly or likely disease causing variants.

Haplotype analysis was consistent with a possible founder effect in the shared mutations for the MYBPC3 Ala833Thr and MYH6 Asp1826Asn variants, where haplotype sharing was present. However, the high degree of linkage disequilibrium between the observed variations at the MYBPC3 locus

<table>
<thead>
<tr>
<th>Gene/Proband</th>
<th>Exon*</th>
<th>UCSC Coordinates</th>
<th>Nucleotide Change†</th>
<th>Amino Acid Change‡</th>
<th>Conservation§</th>
<th>Disease Associated?</th>
<th>Diagnosis FDC</th>
<th>or IDC¶</th>
<th>Segregation#</th>
<th>Previously Reported Reference</th>
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UCSC indicates University of California Santa Cruz, Hg18.

*Exon number is per National Center for Biotechnology Information Information Reference Sequence.
†Nucleotide numbering is per the SeattleSNPs resequencing service.
‡Amino acid numbering is per previous publications.
§Human sequence was assessed in chimp (C), mouse (M), rat (R), dog (D), tetraodon (T), fugu, and zebrafish.
‖Probable FDC was considered IDC (see Methods section).
#Segregation means multiple affected carrying mutation; the number affected are given within parentheses; entry left blank because of insufficient clinical data or DNA specimens to assess segregation.
**A.10 and D.3 are found in the same proband.
††A.12 and A.13 are found in the same proband.
‡‡B.1 and B.8 are found in same proband. This proband also carries a TNNT2 Lys210del mutation.
§§White of Hispanic descent.
¶¶This proband also carries an LMNA G474_D475insQ mutation and a TCAP Pro141Ala mutation.
##Proband carries TNNT2 Glu244Asp mutation.
***Proband carries possibly disease-causing MYH7 Arg1045Cys mutation.
makes it difficult with this limited data set to decipher whether this is a potential founder effect or a chance finding.

**Discussion**

To our knowledge, the present study, when combined with our prior reports,4–6 provides the most extensive resequencing data to date in one of the largest and most well-characterized cohorts of probands with DCM.4 We used Sanger-based sequencing, which is still the gold standard for sequencing sensitivity and specificity, and have now established ≈27% of putative genetic cause within this cohort of patients with DCM: 10.6% from this study of 5 genes (MYBPC3, MYH6, TPM1, TNNC1, and TNNI3), 10.2% from the prior resequencing study of 6 other genes4 (MYH7, TNNT2, SCN5A, CSRP3, LDB3, and TCAP) (Table 1), 5.9% from a study of the LMNA gene,4 and 1.0% from a resequencing study of PSEN1 and PSEN2 encoding presenilins 1 and 2. Approximately 3% of these probands have been found to carry multiple variants in the same or different DCM genes.

The genetics of DCM vary significantly from that of other genetic cardiomyopathies, most strikingly with >30 genes reported to be involved but with each accounting for only a small fraction of our cohort (0.3% to 5.9%), as shown in this and our prior resequencing studies (Table 1). In contrast, mutations in 2 genes, MYH7 and MYBPC3, collectively account for ≈40% to 45% of HCM (or 80% to 90% of detectable genetic cause when a genetic cause can be identified, which has estimated to occur in 42%23 to 65%24 of HCM cases). Similarly, 3 genes, PKP2 (phakomatin 2), DSP (desmoplakin), and DSG2 (desmoglein 2) account for 40% to 50% of arrhythmogenic right ventricular dysplasia/cardio-myopathy.25 Further, although HCM and arrhythmogenic right ventricular dysplasia/cardio-myopathy are largely genetic disorders of genes encoding sarcomeric or desmosomal proteins, respectively, genes encoding proteins of exceedingly diverse function have been implicated to cause genetic DCM. For example, LMNA, to date the most frequent genetic contributor of DCM, encodes a structural protein of the inner nuclear membrane with as yet undefined disease pathways. Other genes implicated to cause DCM range from sarcomeric proteins; transcription factors; Z-disc proteins; channel proteins, including Na+, Ca2+, and K+; and, most recently, a protein of the RNA spliceosome.26

These findings have several implications. One key insight is that despite the large number and variety of genes involved, a unitary, homogenous DCM phenotype results. Careful phenotyping by our group and others has distinguished “DCM with prominent conduction system disease” as the only subphenotype of nonsyndromic DCM, observed principally with mutations in LMNA and SCN5A in a small fraction of cases.1,2 Very few other Mendelian conditions show this degree of locus heterogeneity while manifesting 1 homogeneous phenotype. Examples include retinitis pigmentosa or hereditary deafness, encompassing >40 genes each.27

Furthermore, how this homogeneous DCM phenotype occurs from such a broad array of genetic cause remains largely unexplained. Although our colleagues have suggested a final common pathway for DCM,28 we suggest that the DCM phenotype results from several different genetic injury pathways. This multilocus pathway hypothesis resulting in a final DCM phenotype will need to have the gene network injury pathways and their respective injury mechanisms elucidated to lay this important question to rest.

Our nomenclature of likely or possibly disease causing implies that the variant alone causes or could cause disease, reflecting common usage in rare-variant classical Mendelian disease. An alternative descriptor would be disease associated, a term more commonly used to describe risk alleles in genome-association studies aimed to determine genetic cause in multifactorial, polygenic disease. For a genetically heterogeneous Mendelian disease such as DCM, we favor the disease causing nomenclature, although we recognize that our emerging data suggest that 2 (or more) nonsynonymous rare variants appear to be causative of DCM, suggesting a more complex genetic model in some cases. Additionally, although we sequenced 246 control DNAs (492 chromosomes), it is possible that some of the variants reported herein as possibly disease causing may still be rare benign or neutral mutations that do not directly account for disease. For that reason, we have taken a conservative approach to categorizing these variants as possibly disease causing. Conversely, we also recognize that variants excluded from this analysis because they were identified at low frequency in control DNAs could still be relevant for DCM pathogenesis. Furthermore, some variants had been previously identified as disease-causing HCM mutations that were identified in this study in probands with DCM. Considerable locus and allelic heterogeneity of sarcomeric genes for DCM and HCM has been reported previously.29 For example, 1 mutation in TNNT2 identified in our prior study in a proband with DCM and previously reported in HCM4 had a mixed picture at functional studies.7 Another report showed DCM, HCM, and restrictive phenotypes with the same sarcomeric variant in 1 large family, although the mechanisms, whether genetic or environmental, of this phenotypic variability remain to be discovered.30

Assessing the significance of a novel, nonsynonymous rare variant in a patient with DCM but no affected family members presents special challenges because the most powerful clinical genetics finding to establish that a specific rare variant is disease causing is the segregation of that variant with the disease phenotype in multiple affected family members (and, ideally, in multiple families) accompanied by the absence of the variant in multiple unaffected family members. This standard is stringent but critical for resequencing data to be translated into clinical care. Determining which of the variants reported herein might be useful for genetic counseling of probands and family members regarding DCM risk is particularly challenging. Although specific criteria for diagnostic molecular genetics laboratories vary, most diagnostic standards would follow the general outline of our approach to categorize variants; rare, nonsynonymous variants identified in genes established to have mutations that cause DCM would be considered at least as possibly disease causing, and in the absence of segregation, prior reports, or other supporting data, predictive testing of family members usually would not be recommended. However, if 1 of these possibly disease-causing variants reported herein would be observed in additional DCM probands undergoing diagnostic testing, in most cases the variants would be assigned as likely disease causing. Functional studies of the variant in gene-targeting experiments

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2. Approximately 3% of these probands have been found to carry multiple variants in the same or different DCM genes.

4. Our nomenclature of likely or possibly disease causing implies that the variant alone causes or could cause disease, reflecting common usage in rare-variant classical Mendelian disease. An alternative descriptor would be disease associated, a term more commonly used to describe risk alleles in genome-association studies aimed to determine genetic cause in multifactorial, polygenic disease. For a genetically heterogeneous Mendelian disease such as DCM, we favor the disease causing nomenclature, although we recognize that our emerging data suggest that 2 (or more) nonsynonymous rare variants appear to be causative of DCM, suggesting a more complex genetic model in some cases. Additionally, although we sequenced 246 control DNAs (492 chromosomes), it is possible that some of the variants reported herein as possibly disease causing may still be rare benign or neutral mutations that do not directly account for disease. For that reason, we have taken a conservative approach to categorizing these variants as possibly disease causing. Conversely, we also recognize that variants excluded from this analysis because they were identified at low frequency in control DNAs could still be relevant for DCM pathogenesis. Furthermore, some variants had been previously identified as disease-causing HCM mutations that were identified in this study in probands with DCM. Considerable locus and allelic heterogeneity of sarcomeric genes for DCM and HCM has been reported previously.29 For example, 1 mutation in TNNT2 identified in our prior study in a proband with DCM and previously reported in HCM4 had a mixed picture at functional studies.7 Another report showed DCM, HCM, and restrictive phenotypes with the same sarcomeric variant in 1 large family, although the mechanisms, whether genetic or environmental, of this phenotypic variability remain to be discovered.30

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in animals or in heterologous cell systems also could increase the evidence that a rare variant is disease causing, but such approaches have not been conducted by diagnostic molecular genetics laboratories for DCM-associated genes. Hence, all of these issues will need to be resolved with research-based resequencing studies of much larger cohorts of patients with DCM and their family members, regardless of whether they appear to have familial or sporadic DCM. These studies also should include longitudinal follow-up accompanied by large numbers of reference DNAs and combined with functional studies.

As in our prior study, the fraction of likely and possibly disease-causing mutations was similar for probands categorized as FDC or IDC. This finding, although preliminary in nature, again suggests that a significant proportion of what has been categorized as IDC may rather have a rare-variant genetic basis. If replicated in much larger cohorts of patients with IDC, that is, apparently sporadic DCM, this finding would affect our approach of determining DCM causes in a fundamental way, bringing diagnostic molecular genetics to the clinic for thousands of patients with DCM of unknown cause.

Limitations

Family data were not available in 19 of the 34 cases, so we were unable to assess segregation of the variant with disease. We have not sequenced 2 very large DCM genes (titin and dystrophin) to apply our resequencing resources to greater numbers of smaller numbers of reference DNAs and combined with functional studies. We also note that we examined only coding sequences represented in genetic DCM. Less-expensive screening methods (eg, denaturing high-performance liquid chromatography or single-strand conformation polymorphism) that might have screened greater numbers of genes with equivalent resources are less sensitive and may have missed gene variation relevant to DCM that could be identified with Sanger-based sequencing methods. We also note that we examined only coding sequences and intron/exon boundaries for variation, and hence, additional genetic variation, including copy number variants or variation in regulatory areas (promoters, 5′- and 3′-untranslated regions) or introns of these 5 genes would not have been detected. The difficulties of assessing variants in sporadic DCM have been noted in the paragraphs above.

Conclusions

The nonsynonymous rare variants identified in 5 genes implicated in FDC and IDC account for only a small fraction of the underlying genetic cause of DCM. Taken with prior data from this cohort and others, the genetic landscape of DCM is distinctive from that of other known genetic cardiomyopathies. Future studies in larger cohorts, ideally with family members screened for disease, with many genes sequenced and accompanied by functional studies, will be needed to confirm and extend these findings.

Acknowledgments

We thank the many families and referring physicians for their participation in the Familial Dilated Cardiomyopathy Research Project, without whom these studies would not have been possible.

Sources of Funding

This work was supported by the National Institutes of Health awards R01-HLS8626 (Dr Hershberger) and 5 M01 RR000334. Resequencing services were provided by the University of Washington, Department of Genome Sciences, under US federal government contract number N01-HV-48194 from the National Heart, Lung, and Blood Institute.

Disclosures

None.

References

Several studies have focused on discovering the genetic causes of dilated cardiomyopathy (DCM) that occurs in families (familial DCM). Mutations in >30 genes have now been shown to be associated with DCM. To extend our understanding of DCM genetics, we conducted resequencing studies (where the DNA samples from patients with DCM were sequenced for nucleotide variation in selected genes) in a large cohort of patients with familial DCM and in patients with apparently nonfamilial DCM of unknown cause (idiopathic DCM). In this study, 5 sarcomeric genes were resequenced in 312 DCM probands, 181 with familial DCM, and 131 with idiopathic DCM. Variants that were considered rare (ie, not present in 492 chromosomes from control subjects) and that changed highly conserved amino acids or affected intron/exon splicing were identified in 34 probands (10.9% overall). These variants were classified as likely disease causing in 13 or possibly disease causing in 20 probands and included 12 MYBPC3 (myosin-binding protein C) in 13 (4.2%) probands, 8 MYH6 (α-myosin heavy chain) in 10 (3.2%), 6 TPM1 (tropomyosin) in 6 (1.9%), 4 TNNC1 (cardiac troponin C) in 4 (1.3%), and 1 TNNI3 (cardiac troponin I) in 2 (0.6%). A similar fraction of rare variants were identified in familial DCM and idiopathic DCM, suggesting that idiopathic DCM also may have a genetic basis. This investigation, when combined with previous resequencing studies of 9 genes, suggests that 27% of DCM probands have had a possibly or likely genetic cause identified.
Coding Sequence Rare Variants Identified in MYBPC3, MYH6, TPM1, TNNC1, and TNNI3 From 312 Patients With Familial or Idiopathic Dilated Cardiomyopathy
Ray E. Hershberger, Nadine Norton, Ana Morales, Duanxiang Li, Jill D. Siegfried and Jorge Gonzalez-Quintana

Circ Cardiovasc Genet. 2010;3:155-161; originally published online March 9, 2010; doi: 10.1161/CIRCGENETICS.109.912345
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1942-325X. Online ISSN: 1942-3268

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