Dilated Cardiomyopathy Panel, Sequencing

Dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement with impaired contractility and systolic dysfunction (typically defined as a left ventricular ejection fraction of <50%). DCM is a leading cause of symptoms requiring heart transplantation in children and adults. Although it is often an acquired condition, it may also be familial or a feature of a heritable syndrome. Familial DCM is most commonly inherited in an autosomal dominant manner. It typically manifests in adults during the fourth to sixth decade of life; however, it can present at any age and risk for developing DCM after 50 years of age is reduced.

Affected individuals are at risk for heart failure, arrhythmias or conduction disease, pregnancy-related cardiomyopathy, stroke, and sudden cardiac death. Symptoms may include dyspnea, chest pain, palpitations, fatigue, fainting, or edema. Some individuals remain asymptomatic. Syndromic forms of DCM include extracardiac manifestations, and identification of such disorders is important to enable appropriate management.

Molecular testing for individuals with DCM is recommended to determine if a genetic etiology can be identified, which can facilitate patient management and screening of at-risk relatives.

Tests to Consider

Dilated Cardiomyopathy Panel, Sequencing 3001581

Method: Massively Parallel Sequencing

- Use to determine etiology of DCM in symptomatic individuals.
- Useful for presymptomatic testing in individuals with family history of DCM or sudden cardiac death.

Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication 2010183

Method: Massively Parallel Sequencing

Preferred test to assess for hereditary form of cardiomyopathy or arrhythmia.

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

- Use to assess for a familial sequence variant previously identified in a family member.
- A copy of the relative's genetic laboratory report documenting the familial variant is required.

Disease Overview

Associated Disorders

Nonsyndromic Familial DCM

Should be considered if two or more individuals within a single family experience DCM or if a relative of an individual with DCM has experienced unexplained sudden death <35 years of age

Select Syndromes Associated with DCM

Syndrome	Gene	Clinical Features
Almstrom syndrome	*ALMS1*	Cone-rod dystrophy Obesity Progressive sensorineural hearing loss Type 2 diabetes mellitus Short stature
Barth syndrome	*TAZ*	Neutropenia Muscle weakness Growth delay Infantile/early childhood onset
Carvajal syndrome	*DSP*	Woolly hair Palmoplantar keratoderma

Syndrome	Gene	Clinical Features
Congenital disorder of glycosylation 1M	*DOLK*	Ichtyosiform skin Failure to thrive Seizures Developmental delay Hypotonia
Duchenne/Becker muscular dystrophy	*DMD*	Muscle weakness Isolated DCM in females
Emery-Dreifuss muscular dystrophy 1	*EMD*	Joint contractures Childhood-adult onset muscle weakness Conduction disease

Genetics

Genes

See table of Genes Tested.

Etiology

Pathogenic germline variants in genes associated with familial DCM:

- Genetically heterogeneous disease with unique or "private" variants being common[1]
- Genes implicated include those encoding components of the cytoskeleton, sarcomere, Z-disk, nuclear envelope, and those involved with calcium regulation/ion channels.

Other heritable forms of cardiomyopathy may have phenotypic overlap with DCM[2]:

- Cases of arrhythmogenic right ventricular cardiomyopathy (ARVC) with predominant left ventricular involvement
- Hypertrophic cardiomyopathy (HCM) progressing to end-stage disease with impaired systolic function and/or left ventricular dilation

Penetrance

Variable; influenced by gene, age, and nongenetic factors

Prevalence of DCM

- Estimated at 1:250 to 1:2,500
- 20-50% of cases are familial

Inheritance

- Familial DCM is typically autosomal dominant.
- Compound heterozygous or digenic heterozygous variants may result in severe and early onset disease.
- Genes with X-linked, autosomal recessive, or mitochondrial inheritance are also associated with DCM.
- De novo variation may be found in children or adults.

Test Description

Clinical Sensitivity

- 25-40% for familial DCM and 10-25% for isolated DCM[2]

- Core genes for HCM and ARVC are included on this DCM panel due to gene/phenotype overlap.

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a diagnosis of familial dilated cardiomyopathy.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes
  - Regulatory region and deep intronic variants
  - Large deletions/duplications/inversions in any of the tested genes (Large deletions/duplications account for <1% of causative variants for familial DCM.[3])
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *FLNC* (NM_001458) exons 47, 48
    - *PRKAG2* (NM_016203) exons 10, 13
    - *TTN* (NM_001267550) exons 172, 173, 175, 176, 177, 178, 179, 180, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 215
    - *TTN* (NM_133378) exons 153, 154, 155
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Genes Tested			
Gene	MIM #	Associated Disorder(s)	Inheritance
ABCC9	601439	Cantu syndrome Familial atrial fibrillation 12 DCM 1O	AD
ACTC1	102540	HCM 11 DCM 1R Atrial septal defect 5	AD
ACTN2	102573	DCM 1AA with or without LVNC	AD

Gene	MIM #	Associated Disorder(s)	Inheritance
ALMS1	606844	Alstrom syndrome	AR
BAG3	603883	Myofibrillar myopathy 6 DCM 1HH	AD
CRYAB	123590	DCM 1II Myofibrillar myopathy 2	AD
CSRP3	600824	HCM 12	AD
DES	125660	Myofibrillar myopathy 1	AD/AR
		DCM 1I	AD
DMD	300377	Becker muscular dystrophy Duchenne muscular dystrophy DCM 3B	XL
DOLK	610746	Congenital disorder of glycosylation 1M	AR
DSC2	125645	ARVC 11	AD
DSG2	125671	ARVC 10 DCM 1BB	AD
DSP	125647	ARVC 8 DCM with woolly hair, keratoderma, and tooth agenesis	AD
		DCM with woolly hair and keratoderma Lethal acantholytic epidermolysis bullosa	AR
EMD	300384	Emery-Dreifuss muscular dystrophy 1	XL
FKTN	607440	DCM 1X Muscular dystrophy-dystroglycanopathy A4 (congenital with brain and eye anomalies)	AR
FLNC	102565	Myofibrillar myopathy 5 HCM 26 Restrictive cardiomyopathy 5 Distal myopathy 4	AD
GLA	300644	Fabry disease	XL
JUP	173325	ARVC 12	AD
		Naxos disease	AR
LAMP2	309060	Danon disease	XL
LDB3	605906	DCM 1C with or without LVNC Myofibrillar myopathy 4	AD

Gene	MIM #	Associated Disorder(s)	Inheritance
LMNA	150330	Slovenian type heart-hand syndrome DCM 1A DCM with hypergonadotropic hypogonadism Emery-Dreifuss muscular dystrophy 2 Congenital muscular dystrophy	AD
		Emery-Dreifuss muscular dystrophy 3	AR
MYBPC3	600958	HCM 4 DCM 1MM	AD
MYH6	160710	DCM 1EE Atrial septal defect 3 Sick sinus syndrome 3	AD
MYH7	160760	HCM 1 DCM 1S	AD
		Myosin storage myopathy	AR
MYL2	160781	HCM 10	AD
MYL3	160790	HCM 8	AD
PKP2	602861	ARVC 9	AD
PLN	172405	HCM 18 DCM 1P	AD
PRDM16	605557	DCM 1LL	AD
PRKAG2	602743	Lethal congenital glycogen storage disease of the heart HCM 6 Wolff-Parkinson-White syndrome	AD
RAF1	164760	Noonan syndrome 5 DCM 1NN LEOPARD syndrome 2	AD
RBM20	613171	DCM 1DD	AD
RYR2	180902	CPVT 1 ARVC 2	AD
SCN5A	600163	Brugada syndrome 1 DCM 1E Familial atrial fibrillation 10 Familial heart block Familial paroxysmal ventricular fibrillation LQTS 3	AD

Gene	MIM #	Associated Disorder(s)	Inheritance
		Sick sinus syndrome 1	AR
SGCD	601411	DCM 1L	AD
		Limb-girdle muscular dystrophy 6	AR
TAZ	300394	Barth syndrome	XL
TCAP	604488	Limb-girdle muscular dystrophy 7	AR
TMEM43	612048	Emery-Dreifuss muscular dystrophy 7 ARVC 5	AD
TNNC1	191040	HCM 13 DCM 1Z	AD
TNNI3	191044	HCM 7 Restrictive cardiomyopathy 1 DCM 1FF	AD
		DCM 2A	AR
TNNT2	191045	HCM 2 Restrictive cardiomyopathy 3 DCM 1D	AD
TPM1	191010	HCM 3 DCM 1Y	AD
TTN	188840	DCM 1G Myofibrillar myopathy 9	AD
		Salih myopathy	AR
TTR	176300	Transthyretin-related amyloidosis	AD
VCL	193065	DCM 1W	AD

AD, autosomal dominant; AR, autosomal recessive; CPVT, catecholaminergic polymorphic ventricular tachycardia; LVNC, left ventricular noncompaction; XL, X-linked

References

1. Hershberger RE, Morales A. Dilated cardiomyopathy overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last Update: Aug 2018; Accessed: Mar 2020]

2. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy–a Heart Failure Society of America practice guideline. J Card Fail. 2018;24(5):281-302. PubMed

3. Ceyhan-Birsoy O, Pugh TJ, Bowser MJ, et al. Next generation sequencing-based copy number analysis reveals low prevalence of deletions and duplications in 46 genes associated with genetic cardiomyopathies. Mol Genet Genomic Med. 2015;4(2):143-151. PubMed

Related Information

Hypertrophic Cardiomyopathy Panel, Sequencing
Duchenne/Becker Muscular Dystrophy Deletion/Duplication with Reflex to Sequencing
Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication
Familial Transthyretin Amyloidosis (TTR) Sequencing

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
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