Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication

Inherited cardiomyopathy and arrhythmia disorders are genetically and phenotypically heterogeneous. Phenotypes include arrhythmogenic right ventricular cardiomyopathy (ARVC), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), left ventricular noncompaction (LVNC), long QT syndrome (LQTS), and short QT syndrome (SQTS). Genetic testing is used to confirm diagnosis.

Tests to Consider

Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication 2010183

Method: Massively Parallel Sequencing

Use to confirm hereditary form of cardiomyopathy or arrhythmia.

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

- Recommended test for a known familial sequence variant previously identified in a family member.
- A copy of the family member's test result documenting the familial variant is required.

See Related Tests.

DISEASE OVERVIEW

See Common Disorders table below.

TEST DESCRIPTION

See Genes Tested table for genes included in the panel.

Clinical Sensitivity

Variable, dependent on phenotype/condition

- ARVC: 50 percent[1]
- BrS: 15-30 percent[2]
- CPVT: 60 percent[3]
- DCM: 30-40 percent[4]
- HCM (nonsyndromic familial): 50-60 percent[5]
- LQTS: 60-75 percent[6]

Limitations

- A negative result does not exclude a heritable form of cardiomyopathy or arrhythmia.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Variants in the mitochondrial genome
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *BAG3, CRYAB, EMD, FHL1, GATAD1, TAZ, TRDN*
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *TTN* (NM_001267550) 172, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 215
    - *TTN* (NM_133378) 153, 154, 155
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

- Single exon deletions/duplications in the following exons:

Gene	Exon(s)
ACTN2	(NM_001103) 17
CACNB2	(NM_001167945) 7
DMD	(NM_000109) 1
DSC2	(NM_024422) 1
DTNA	(NM_001390) 16, 21
KCNH2	(NM_000238) 13
KCNQ1	(NM_000218) 16
KCNQ1	(NM_181798) 1
MYBPC3	(NM_000256) 10, 24
MYH6	(NM_002471) 24, 28
MYH7	(NM_000257) 29
PKP2	(NM_004572) 6
PRKAG2	(NM_001304527) 1
PRKAG2	(NM_001304531) 2
PRKAG2	(NM_016203) 5
SGCB	(NM_000232) 1
SGCG	(NM_000231) 8
TGFB3	(NM_003239) 7
TRPM4	(NM_001321285) 4
TRPM4	(NM_017636) 7
TTN	(NM_001267550) 158, 173, 176, 185, 191, 194
TTN	(NM_133378) 114, 148, 155, 156, 167, 170

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	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	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

Common Disorders

Disorder	Clinical Characteristics	Prevalence	Inheritance	Comments
ARVC	Progressive fibrofatty replacement of the myocardium predisposing to ventricular tachycardia and sudden death	1/1,000	AD	Commonly implicated genes include *PKP2, DSP, DSG2*
BrS	Cardiac conduction abnormalities that can result in sudden death	Unknown	AD, 1% de novo	Variants in *SCN5A* account for 15-30% of BrS
CPVT	Episodic syncope or ventricular arrhythmias occurring during exercise or acute emotion without presence of structural cardiac abnormalities	1/10,000	AD or AR	Variants in *RYR2* account for 50-55% of all CPVT
DCM	Left ventricular enlargement and systolic dysfunction	~1/500	Typically AD; AR/XL/Mitochondrial less common	~20-35% of isolated DCM is familial Variants in *TTN* account for 10-20% of isolated DCM
HCM	Left ventricular hypertrophy with absence of other cardiovascular causes	1/500	AD	Variants in *MYH7* and *MYBPC3* account for majority of familial HCM. Variants in genes encoding for components of the sarcomere account for 55-70% of HCM with no multisystem involvement.
LVNC	Hypertrophic and hypokinetic left ventricle with distinctive morphology	Unknown	Typically AD	*MYH7* and *MYBPC3* commonly implicated genes
LQTS	Cardiac electrophysiologic disease with prolonged QT- and T-wave abnormalities on ECG associated with ventricular tachycardia (torsade de pointes)	1/3,000	AD	Incomplete penetrance
SQTS	Cardiac arrhythmia with short QT interval on ECG	Unknown	AD	Associated genes: *KCNH2, KCNJ2, KCNQ1*

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ABCC9	601439	Cantu syndrome Dilated cardiomyopathy, 1O Familial atrial fibrillation, 12	AD
ACTC1	102540	Familial hypertrophic cardiomyopathy, 11 Atrial septal defect 5 Dilated cardiomyopathy, 1R Left ventricular noncompaction 4	AD
ACTN2	102573	Dilated cardiomyopathy, 1AA, with or without LVNC Hypertrophic cardiomyopathy, 23, with or without LVNC	AD
ANK2	106410	Cardiac arrhythmia, ankyrin-B-related Long QT syndrome 4	AD
ANKRD1	609599	Dilated cardiomyopathy	AD
BAG3	603883	Myofibrillar myopathy, 6 Dilated cardiomyopathy, 1HH	AD
CACNA1C	114205	Timothy syndrome Brugada syndrome 3	AD
CACNB2	600003	Brugada syndrome 4	AD
CASQ2	114251	Catecholaminergic polymorphic ventricular tachycardia, 2	AR
CAV3	601253	Familial hypertrophic cardiomyopathy, 1 Long QT syndrome 9	AD
CRYAB	123590	Myofibrillar myopathy, 2 Dilated cardiomyopathy, 1II	AD
		Myofibrillar myopathy, fatal infantile hypertonic, alpha-B crystallin-related	AR
CSRP3	600824	Dilated cardiomyopathy, 1M Familial hypertrophic cardiomyopathy, 12	AD
DES	125660	Myofibrillar myopathy, 1 Dilated cardiomyopathy, 1I	AD
		Myofibrillar myopathy, 1	AR
DMD	300377	Becker muscular dystrophy Dilated cardiomyopathy, 3B Duchenne muscular dystrophy	XL

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Gene	MIM Number	Disorder	Inheritance
DSC2	125645	Arrhythmogenic right ventricular dysplasia, 11	AD
		Arrhythmogenic right ventricular dysplasia 11 with mild palmoplantar keratoderma and woolly hair	AR
DSG2	125671	Arrhythmogenic right ventricular dysplasia, 10 Dilated cardiomyopathy, 1BB	AD
DSP	125647	Arrhythmogenic right ventricular dysplasia, 8 Dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis	AD
		Dilated cardiomyopathy with woolly hair and keratoderma	AR
DTNA	601239	Left ventricular noncompaction 1	AD
EMD	300384	Emery-Dreifuss muscular dystrophy 1	XL
EYA4	603550	Dilated cardiomyopathy, 1J	AD
FHL1	300163	Uruguay faciocardiomusculoskeletal syndrome Scapuloperoneal myopathy Myopathy with postural muscle atrophy Emery-Dreifuss muscular dystrophy 6 Reducing body myopathy 1B, with late childhood or adult onset	XL
FKRP	606596	Muscular dystrophy-dystroglycanopathy, type A, 5 Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 5	AR
FKTN	607440	Dilated cardiomyopathy, 1X Muscular dystrophy-dystroglycanopathy, type A, 4	AR
GAA	606800	Glycogen storage disease II	AR
GATAD1	614518	Dilated cardiomyopathy, 2B	AR
GLA	300644	Fabry disease	XL
GPD1L	611778	Brugada syndrome 2	AD
JPH2	605267	Hypertrophic cardiomyopathy, 17	AD
JUP	173325	Arrhythmogenic right ventricular dysplasia, 12	AD
		Naxos disease	AR
KCNE1	176261	Long QT syndrome 5	AD

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Gene	MIM Number	Disorder	Inheritance
		Jervell and Lange-Nielsen syndrome 2	AR
KCNE2	603796	Atrial fibrillation, familial, 4 Long QT syndrome 6	AD
KCNE3	604433	Brugada syndrome 6	AD
KCNH2	152427	Long QT syndrome 2 Short QT syndrome 1	AD
KCNJ2	600681	Andersen syndrome Short QT syndrome 3 Atrial fibrillation, familial, 9	AD
KCNQ1	607542	Long QT syndrome 1 Atrial fibrillation, familial, 3 Short QT syndrome 2	AD
		Jervell and Lange-Nielsen syndrome 1	AR
LAMA4	600133	Dilated cardiomyopathy, 1JJ	AD
LAMP2	309060	Danon disease	XL
LDB3	605906	Dilated cardiomyopathy, 1C, with or without LVNC Hypertrophic cardiomyopathy, 24 Myofibrillar myopathy, 4	AD
LMNA	150330	Dilated cardiomyopathy, 1A Emery-Dreifuss muscular dystrophy 2 Heart-hand syndrome, Slovenian type Muscular dystrophy, congenital Malouf syndrome	AD
		Emery-Dreifuss muscular dystrophy 3	AR
MYBPC3	600958	Hypertrophic cardiomyopathy, 4 Dilated cardiomyopathy, 1MM Left ventricular noncompaction 10	AD
MYH6	160710	Dilated cardiomyopathy, 1EE Hypertrophic cardiomyopathy, 14	AD

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Gene	MIM Number	Disorder	Inheritance
MYH7	160760	Laing distal myopathy Hypertrophic cardiomyopathy 1 Dilated cardiomyopathy, 1S Left ventricular noncompaction 5	AD
		Myopathy, myosin storage	AR
MYL2	160781	Hypertrophic cardiomyopathy, 10	AD
MYL3	160790	Hypertrophic cardiomyopathy, 8	AD/AR
MYLK2	606566	Hypertrophy cardiomyopathy, 1	AD
MYOT	604103	Myofibrillar myopathy, 3	AD
MYOZ2	605602	Hypertrophic cardiomyopathy, 16	AD
MYPN	608517	Dilated cardiomyopathy, 1KK Familial restrictive cardiomyopathy 4 Hypertrophic cardiomyopathy 22	AD
		Nemaline myopathy 11	AR
NEXN	613121	Dilated cardiomyopathy, 1CC Hypertrophic cardiomyopathy, 20	AD
PKP2	602861	Arrhythmogenic right ventricular dysplasia, 9	AD
PLN	172405	Dilated cardiomyopathy, 1P Hypertrophic cardiomyopathy, 18	AD
PRKAG2	602743	Hypertrophic cardiomyopathy, 6 Glycogen storage disease of the heart, lethal congenital Wolff-Parkinson-White syndrome	AD
RBM20	613171	Dilated cardiomyopathy, 1DD	AD
RYR2	180902	Arrhythmogenic right ventricular dysplasia, 2 Catecholaminergic polymorphic ventricular tachycardia, 1	AD
SCN1B	600235	Brugada syndrome 5 Cardiac conduction defect, nonspecific Atrial fibrillation, familial, 13	AD
SCN2B	601327	Atrial fibrillation, familial, 14	AD

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Gene	MIM Number	Disorder	Inheritance
SCN3B	608214	Brugada syndrome 7 Atrial fibrillation, familial, 16	AD
SCN4B	608256	Long QT syndrome 10 Atrial fibrillation, familial, 17	AD
SCN5A	600163	Heart block, progressive, type IA Heart block, nonprogressive Brugada syndrome 1 Cardiomyopathy, dilated, 1E Ventricular fibrillation, paroxysmal familial, 1 Long QT syndrome 3 Atrial fibrillation, familial, 10	AD
		Sick sinus syndrome 1	AR
SGCA	600119	Muscular dystrophy, limb-girdle, type 2D	AR
SGCB	600900	Muscular dystrophy, limb-girdle, type 2E	AR
SGCD	601411	Muscular dystrophy, limb-girdle, type 2F	AR
		Dilated cardiomyopathy, 1L	AD
SGCG	608896	Muscular dystrophy, limb-girdle, type 2C	AR
SLC25A4	103220	Mitochondrial DNA depletion syndrome 12A	AD
		Mitochondrial DNA depletion syndrome 12B	AR
SNTA1	601017	Long QT syndrome 12	AD
TAZ	300394	Barth syndrome	XL
TCAP	604488	Hypertrophic cardiomyopathy, 25	AD
		Muscular dystrophy, limb-girdle, type 2G	AR
TGFB3	190230	Arrhythmogenic right ventricular dysplasia, 1	AD
TMEM43	612048	Arrhythmogenic right ventricular dysplasia, 5 Emery-Dreifuss muscular dystrophy 7	AD
TNNC1	191040	Dilated cardiomyopathy, 1Z Hypertrophic cardiomyopathy, 13	AD

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Gene	MIM Number	Disorder	Inheritance
TNNI3	191044	Dilated cardiomyopathy, 1FF Cardiomyopathy, familial restrictive, 1 Hypertrophic cardiomyopathy, 7	AD
		Dilated cardiomyopathy, 2A	AR
TNNT2	191045	Hypertrophic cardiomyopathy, 2 Dilated cardiomyopathy, 1D Left ventricular noncompaction 6 Cardiomyopathy, familial restrictive, 3	AD
TPM1	191010	Hypertrophic cardiomyopathy, 3 Dilated cardiomyopathy, 1Y Left ventricular noncompaction 9	AD
TRDN	603283	Catecholaminergic polymorphic ventricular tachycardia, 5, with or without muscle weakness	AR
TRPM4	606936	Progressive familial heart block, type IB	AD
TTN	188840	Dilated cardiomyopathy, 1G Hypertrophic cardiomyopathy, 9	AD
		Salih myopathy	AR
TTR	176300	Amyloidosis, hereditary, transthyretin-related	AD
VCL	193065	Hypertrophic cardiomyopathy, 15 Dilated cardiomyopathy, 1W	AD

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References

1. McNally E, MacLeod H, Dellefave-Castillo L. Arrhythmogenic Right Ventricular Cardiomyopathy. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: May 2017; Accessed: Feb 2020]

2. Brugada R, Campuzano O, Sarquella-Brugada G, et al. Brugada Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Nov 2016; Accessed: Feb 2020]

3. Napolitano C, Priori SG, Bloise R. Catecholaminergic Polymorphic Ventricular Tachycardia. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Oct 2016; Accessed: Feb 2020]

4. 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]

5. Cirino AL, Ho C. Hypertrophic cardiomyopathy overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last Update: Jun 2019; Accessed: Feb 2020]

6. Alders M, Bikker H, Christiaans I. Long QT syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2021. [Last Update: Feb 2018; Accessed: Feb 2021]

Related Tests

Dilated Cardiomyopathy Panel, Sequencing 3001581

Method: Massively Parallel Sequencing

Hypertrophic Cardiomyopathy Panel, Sequencing 3001579

Method: Massively Parallel Sequencing

Long QT Panel, Sequencing and Deletion/Duplication 3001603

Method: Massively Parallel Sequencing / Exonic Oligonucleotide-based CGH Microarray

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