

# Cardiomyopathy and Arrhythmia Gene Panel

## Indication for Ordering

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Confirm hereditary form of cardiomyopathy or arrhythmia

## Test Description

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- Targeted capture of all coding exons and intron/exon boundaries followed by massively parallel sequencing
  - All clinically significant variants are confirmed by Sanger sequencing
- Deletion/duplication analysis by tiled, custom-designed array comparative genomic hybridization (CGH)
  - *EMD* and *TAZ* genes are not analyzed by array CGH

## Tests to Consider

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### Primary tests

[Cardiomyopathy and Arrhythmia Panel, Sequencing \(85 Genes\) and Deletion/Duplication \(83 Genes\) 2010183](#)

- Preferred test to assess for a hereditary form of cardiomyopathy or arrhythmia

### Related tests

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a pathogenic familial variant identifiable by sequencing is known

## Disease Overview

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See Table 1

## Genetics

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See Table 2

## Test Interpretation

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**Clinical sensitivity** – dependent on clinical phenotype

## Results

- Positive
  - Consistent with a diagnosis of a heritable cardiomyopathy or arrhythmia
    - Detection of one pathogenic variant in a gene with autosomal dominant (AD) inheritance
    - Detection of two pathogenic variants on opposite chromosomes in a gene with autosomal recessive (AR) inheritance
    - Detection of a single pathogenic variant in an X-linked gene (in males)
  - Consistent with carrier status
    - Detection of one pathogenic variant in an AR gene
    - Detection of one pathogenic variant in an X-linked gene (in females)
- Negative – no pathogenic variant detected
  - Reduces but does not exclude a heritable form of cardiomyopathy or arrhythmia
- Inconclusive – variants of uncertain clinical significance identified

## Limitations

- Only the genes listed in Table 2 will be analyzed
- Large deletions and duplications will not be detected in the *EMD* and *TAZ* genes
- Deep intronic and regulatory region variants will not be detected
- Small deletions or insertions may not be detected by massively parallel sequencing
- Breakpoints of large deletions/duplications will not be determined
- Diagnostic errors may occur due to rare sequence variations
- Lack of a detectable gene variant does not exclude a diagnosis of a hereditary form of myopathy or arrhythmia

**Table 1. Disease Overview**

Disorder	Major Clinical Features	Associated Genes	Prevalence	Inheritance/Comments
Hypertrophic cardiomyopathy (HCM)	<ul style="list-style-type: none"> <li>• Left ventricular hypertrophy with absence of other cardiovascular causes</li> <li>• Variable presentation                             <ul style="list-style-type: none"> <li>○ Asymptomatic to sudden death</li> </ul> </li> <li>• Common symptoms                             <ul style="list-style-type: none"> <li>○ Shortness of breath</li> <li>○ Chest pain</li> <li>○ Palpitation</li> <li>○ Orthostasis</li> <li>○ Syncope</li> </ul> </li> <li>• Doppler echocardiographic imaging result consistent with hypertrophy</li> </ul>	<i>ACTC1, ACTN2, CAV3, COX15, CSR3, FXN, GAA, GLA, JPH2, LAMP2, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEXN, OBSCN, PLN, PRKAG2, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL</i>	1/500	<ul style="list-style-type: none"> <li>• AD</li> <li>• Variants in genes encoding for components of the sarcomere account for 55-70% of HCM with no multisystem involvement</li> <li>• Variants in <i>MYH7</i> and <i>MYBPC3</i> account for majority of familial HCM</li> </ul>
Dilated cardiomyopathy (DCM)	<ul style="list-style-type: none"> <li>• Left ventricular enlargement and systolic dysfunction</li> <li>• Variable presentation</li> <li>• Heart failure with symptoms of congestion and/or reduced cardiac output                             <ul style="list-style-type: none"> <li>○ Edema</li> <li>○ Orthopnea</li> <li>○ Paroxysmal dyspnea</li> <li>○ Fatigue</li> <li>○ Dyspnea on exertion</li> </ul> </li> <li>• Arrhythmias and/or conduction system disease</li> <li>• Thromboembolic disease or stroke</li> </ul>	<i>ABCC9, ACTC1, ACTN2, ANKRD1, CSR3, CTF1, DES, DMD, DSG2, DSP, EYA4, FKTN, ILK, LDB3, LAMA4, LMNA, MYBPC3, MYH6, MYH7, MYPN, NEXN, PLN, RBM20, SCN5A, SGCD, TAZ, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, VCL</i>	Unknown – estimated to be >1/500	<ul style="list-style-type: none"> <li>• Typically AD                             <ul style="list-style-type: none"> <li>○ AR, X-linked, and mitochondrial less common</li> </ul> </li> <li>• ~20-35% of isolated DCM is familial</li> <li>• Variants in <i>TTN</i> account for ~20% of isolated DCM</li> </ul>
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	<ul style="list-style-type: none"> <li>• Progressive fibrofatty replacement of the myocardium predisposing to ventricular tachycardia and sudden death</li> <li>• Heart palpitations</li> <li>• Syncope</li> <li>• Sudden death</li> <li>• Variable presentation                             <ul style="list-style-type: none"> <li>○ Some affected individuals do not meet established clinical criteria</li> </ul> </li> </ul>	<i>DSC2, DSG2, DSP, JUP, PKP2, RYR2, TGFB3, TMEM43</i>	1/1,000	<ul style="list-style-type: none"> <li>• AD</li> </ul>
Left ventricular noncompaction (LVNC)	<ul style="list-style-type: none"> <li>• Hypertrophic and hypokinetic left ventricle with distinctive morphology</li> <li>• Often present with additional cardiac abnormalities</li> <li>• Variable presentation</li> <li>• Asymptomatic to sudden death</li> </ul>	<i>ACTC1, DTNA, LDB3, MYBPC3, MYH7, TAZ, TPM1, TNNT2</i>	Unknown	<ul style="list-style-type: none"> <li>• AD</li> </ul>
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	<ul style="list-style-type: none"> <li>• Episodic syncope or ventricular arrhythmias occurring during exercise or acute emotion without presence of structural cardiac abnormalities</li> <li>• Variable presentation                             <ul style="list-style-type: none"> <li>○ Asymptomatic to sudden death</li> </ul> </li> </ul>	<i>CASQ2, RYR2</i>	1/10,000	<ul style="list-style-type: none"> <li>• AD for <i>RYR2</i></li> <li>• AR for <i>CASQ2</i></li> <li>• Variants in <i>RYR2</i> account for 50-55% of all CPVT</li> </ul>
Brugada syndrome (BrS)	<ul style="list-style-type: none"> <li>• Variable cardiac conduction abnormalities that can result in sudden death</li> </ul>	<i>CACNA1C, CACNB2, GPD1L, KCNE3, SCN1B, SCN3B, SCN5A, TRPM4</i>	Unknown	<ul style="list-style-type: none"> <li>• AD                             <ul style="list-style-type: none"> <li>○ 1% de novo</li> </ul> </li> <li>• Variants in <i>SCN5A</i> account for 15-30% of BrS</li> </ul>
Long QT syndrome (LQTS)	<ul style="list-style-type: none"> <li>• Electrophysiological cardiac disease                             <ul style="list-style-type: none"> <li>○ Prolonged QT- and T-wave abnormalities on ECG</li> <li>○ Ventricular tachycardia (torsades de pointes)                                     <ul style="list-style-type: none"> <li>▪ Syncope</li> <li>▪ Cardiac arrest</li> <li>▪ Sudden death</li> </ul> </li> </ul> </li> </ul>	<i>AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNQ1, SCN4B, SCN5A, SNTA1</i>	Estimated >1/3,000	<ul style="list-style-type: none"> <li>• AD</li> <li>• Commonly incomplete penetrance</li> </ul>
Short QT syndrome (SQTS)	<ul style="list-style-type: none"> <li>• Cardiac arrhythmia                             <ul style="list-style-type: none"> <li>○ Short QT interval on ECG</li> </ul> </li> <li>• Variable presentation                             <ul style="list-style-type: none"> <li>○ Asymptomatic</li> <li>○ Syncope</li> <li>○ Cardiac arrest</li> <li>○ Sudden death</li> </ul> </li> </ul>	<i>KCNH2, KCNJ2, KCNQ1</i>	Unknown	<ul style="list-style-type: none"> <li>• AD</li> </ul>

Table 2. Genes Tested

Gene Symbol	Gene Description	NM #	OMIM #	Inh.	Associated Cardiac Disorder(s)	Frequency
<i>ABCC9</i>	ATP-binding cassette, subfamily C (CFTR/MRP), member 9	005691	601439	AD	Cantú syndrome, DCM, atrial fibrillation (ATFB)	Rare
<i>ACTC1</i>	Actin, alpha, cardiac muscle 1	005159	102540	AD	HCM, DCM, coronary heart disease (CHD), LVNC	<1% DCM
<i>ACTN2</i>	Actinin, alpha 2	001103	102573	AD	DCM, HCM	<1 % DCM
<i>AKAP9</i>	A kinase (PRKA) anchor protein 9	005751	604001	AD	LQTS	Rare
<i>ANK2</i>	Ankyrin 2, neuronal	001148	106410	AD	LQTS, ankyrin-B-related cardiac arrhythmia, CPVT, sinus node dysfunction, ATFB	Rare cause of LQTS
<i>ANKRD1</i>	Ankyrin repeat domain 1 (cardiac muscle)	014391	609599	AD	DCM	2% DCM
<i>CACNA1C</i>	Calcium channel, voltage-dependent, L type, alpha 1C subunit	000719	114205	AD	BrS, Timothy syndrome	<5% BrS; all cases of Timothy syndrome
<i>CACNB2</i>	Calcium channel, voltage-dependent, beta 2 subunit	201590	600003	AD	BrS	<5% BrS
<i>CASQ2</i>	Calsequestrin 2 (cardiac muscle)	001232	114251	AR	CPVT	1-2% CPVT
<i>CAV3</i>	Caveolin 3	033337	601253	AD/AR	Limb-girdle muscular dystrophy (LGMD), HCM, LQTS, rippling muscle disease, distal myopathy Tateyama type	1-2% LGMD
<i>CORIN</i>	Corin, serine peptidase	006587	605236	AD	Hypertension, preeclampsia	Unknown
<i>COX15</i>	Cytochrome c oxidase assembly homolog 15 (yeast)	004376	603646	AR	Fatal infantile cardiomyopathy, Leigh syndrome	Unknown
<i>CSRP3</i>	Cysteine and glycine-rich protein 3 (cardiac LIM protein)	003476	600824	AD	DCM, HCM	<1% DCM
<i>CTF1</i>	Cardiotrophin 1	001330	600435	Unknown	DCM	Unknown
<i>DES</i>	Desmin	001927	125660	AD/AR	DCM, myofibrillar myopathy, ARVC	<1% DCM
<i>DMD</i>	Dystrophin	004006	300377	XL	DCM	Unknown
<i>DSC2</i>	Desmocollin 2	024422	125645	AD/AR	ARVC, ARVC with palmoplantar keratoderma and woolly hair	Rare
<i>DSG2</i>	Desmoglein 2	001943	125671	AD/AR	ARVC, DCM	10-40% ARVC
<i>DSP</i>	Desmoplakin	004415	125647	AD/AR	ARVC, DCM, Carvajal syndrome	10% ARVC
<i>DTNA</i>	Dystrobrevin, alpha	032978	601239	AD	LVNC, LVNC with CHD	Unknown
<i>EMD</i>	Emerin	000117	300384	XL	Emery-Dreifuss muscular dystrophy (EDMD)	60% XL-EDMD
<i>EYA4</i>	Eyes absent homolog 4 (Drosophila)	004100	603550	AD	DCM	Unknown
<i>FKRP</i>	Fukutin-related protein	024301	606596	AR	LGMD	6% recessive LGMD
<i>FKTN</i>	Fukutin	001079802	607440	AR	DCM, LGMD, Fukuyama congenital muscular dystrophy (FCMD)	Only gene associated with FCMD
<i>FXN</i>	Frataxin	000144	606829	AR	Friedreich ataxia	~<2% pathogenic <i>FXN</i> variants
<i>GAA</i>	Glucosidase, alpha; acid	000152	606800	AR	Glycogen storage disease (GSD) II (Pompe disease)	Only gene associated with GSDII
<i>GLA</i>	Galactosidase, alpha	000169	300644	XL	Fabry disease	Only gene associated with Fabry
<i>GPD1L</i>	Glycerol-3-phosphate dehydrogenase 1-like	015141	611778	AD	BrS	<5% BrS

Gene Symbol	Gene Description	NM #	OMIM #	Inh.	Associated Cardiac Disorder(s)	Frequency
<i>ILK</i>	Integrin-linked kinase	004517	602366	AD	DCM	Unknown
<i>JPH2</i>	Junctophilin 2	020433	605267	AD	HCM	Unknown
<i>JUP</i>	Junction plakoglobin	002230	173325	AD/AR	ARVC, Naxos disease	Rare
<i>KCNE1</i>	Potassium voltage-gated channel, Isk-related family, member 1	000219	176261	AD/AR	LQTS, Jervell and Lange-Nielsen syndrome (JLNS)	2% LQTS; 10% JLNS
<i>KCNE2</i>	Potassium voltage-gated channel, Isk-related family, member 2	172201	603796	AD	LQTS	1% LQTS
<i>KCNE3</i>	Potassium voltage-gated channel, Isk-related family, member 3	005472	604433	AD	BrS	<5% BrS
<i>KCNH2</i>	Potassium voltage-gated channel, subfamily H (eag-related), member 2	000238	152427	AD	LQTS, SQTS	40% LQTS
<i>KCNJ2</i>	Potassium inwardly-rectifying channel, subfamily J, member 2	000891	600681	AD	Andersen syndrome, SQTS, ATFB	60% Andersen syndrome
<i>KCNQ1</i>	Potassium voltage-gated channel, KQT-like subfamily, member 1	000218	607542	AD/AR	ATFB, LQTS, SQTS, JLNS	45% LQTS; 90% JLNS
<i>KLHL3</i>	Kelch-like family member 3	017415	605775	AD/AR	Pseudohypoaldosteronism	Unknown
<i>LAMA4</i>	Laminin, alpha 4	002290	600133	AD	DCM	Unknown
<i>LAMP2</i>	Lysosomal-associated membrane protein 2	002294	309060	XL	Danon disease	Unknown
<i>LDB3</i>	LIM domain binding 3	001080116	605906	AD	DCM, myofibrillar myopathy, LVNC	1% DCM
<i>LMNA</i>	Lamin A/C	005572	150330	AD/AR	DCM, EDMD, LGMD	45% dominant EDMD
<i>MYBPC3</i>	Myosin binding protein C, cardiac	000256	600958	AD	HCM, DCM, LVNC	40% HCM
<i>MYH6</i>	Myosin, heavy chain 6, cardiac muscle, alpha	002471	160710	AD	HCM, DCM, CHD	Unknown
<i>MYH7</i>	Myosin, heavy chain 7, cardiac muscle, beta	000257	160760	AD	HCM, DCM, Laing distal myopathy, LVNC	40% HCM
<i>MYH10</i>	Myosin, heavy chain 10, non-muscle	001256012	160776	Unknown	Unknown	Unknown
<i>MYL2</i>	Myosin, light chain 2, regulatory, cardiac, slow	000432	160781	AD	HCM	Unknown
<i>MYL3</i>	Myosin, light chain 3, alkali; ventricular, skeletal, slow	000258	160790	AD/AR	HCM	1% HCM
<i>MYLK2</i>	Myosin light chain kinase 2	033118	606566	Unknown	HCM	Unknown
<i>MYOT</i>	Myotilin	006790	604103	AD	LGMD, myofibrillar myopathy	Rare
<i>MYO22</i>	Myozenin 2	016599	605602	AD	HCM	Unknown
<i>MYPN</i>	Myopalladin	032578	608517	AD	DCM, HCM, restrictive cardiomyopathy	Unknown
<i>NEXN</i>	Nexilin (F actin binding protein)	144573	613121	AD	DCM, HCM	<1% DCM
<i>OBSCN</i>	Obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF	052843	608616	Unknown	HCM	Unknown
<i>PKP2</i>	Plakophilin 2	004572	602861	AD	ARVC	10-40% ARVC
<i>PLN</i>	Phospholamban	002667	172405	AD	HCM, DCM	Unknown
<i>PRKAG2</i>	Protein kinase, AMP-activated, gamma 2 non-catalytic subunit	016203	602743	AD	HCM, Wolff-Parkinson-White syndrome	Rare
<i>RBM20</i>	RNA binding motif protein 20	001134363	613171	AD	DCM	2% DCM
<i>RYR2</i>	Ryanodine receptor 2 (cardiac)	001035	180902	AD	CPVT, ARVC	~50% CPVT, Rare ARVC
<i>SCN1B</i>	Sodium channel, voltage-gated, type I, beta subunit	001037	600235	AD	BrS, ATFB	<5% BrS

Gene Symbol	Gene Description	NM #	OMIM #	Inh.	Associated Cardiac Disorder(s)	Frequency
<i>SCN2B</i>	Sodium channel, voltage-gated, type II, beta subunit	004588	601327	AD	ATFB	Unknown
<i>SCN3B</i>	Sodium channel, voltage-gated, type III, beta subunit	018400	608214	AD	BrS, ATFB	<5% BrS
<i>SCN4B</i>	Sodium channel, voltage-gated, type IV, beta subunit	174934	608256	AD	LQTS	Rare
<i>SCN5A</i>	Sodium channel, voltage-gated, type V, alpha subunit	198056	600163	AD/AR	BrS, DCM, LQTS, ATFB, heart block, sudden infant death syndrome (SIDS), sick sinus syndrome	15-30% BrS; 2-4% DCM
<i>SCO2</i>	SCO2 cytochrome c oxidase assembly protein	005138	604272	AR	fatal infantile cardioencephalomyopathy	Unknown
<i>SGCA</i>	Sarcoglycan, alpha (50kDa dystrophin-associated glycoprotein)	000023	600119	AR	LGMD	~35% childhood onset AR LGMD
<i>SGCB</i>	Sarcoglycan, beta (43kDa dystrophin-associated glycoprotein)	000232	600900	AR	LGMD	~15% childhood onset AR LGMD
<i>SGCD</i>	Sarcoglycan, delta (35kDa dystrophin-associated glycoprotein)	000337	601411	AR/digenic	LGMD, DCM	~8% childhood onset AR LGMD; <1% DCM
<i>SGCG</i>	Sarcoglycan, gamma (35kDa dystrophin-associated glycoprotein)	000231	608896	AR	LGMD	~4% childhood onset AR LGMD
<i>SLC25A4</i>	Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4	001151	103220	AR	Mitochondrial DNA depletion syndrome (HCM)	Unknown
<i>SNTA1</i>	Syntrophin, alpha 1	003098	601017	AD/digenic	LQTS, SIDS	Rare
<i>SYNE1</i>	Spectrin repeat containing, nuclear envelope 1	033071	608441	AD	EDMD	Unknown
<i>TAZ</i>	Tafazzin	000116	300394	XL	Barth syndrome, DCM, LVNC	Unknown
<i>TCAP</i>	Titin-cap	003673	604488	AD/AR	LGMD, DCM, HCM	3% AR LGMD; 1% DCM
<i>TGFB3</i>	Transforming growth factor, beta 3	003239	190230	AD	ARVC	Rare
<i>TMEM43</i>	Transmembrane protein 43	024334	612048	AD	ARVC, EDMD	Unknown
<i>TMPO</i>	Thymopoietin	003276	188380	AD	DCM	1% DCM
<i>TNNC1</i>	Troponin C type 1 (slow)	003280	191040	AD	DCM, HCM	1% DCM
<i>TNNI3</i>	Troponin I type 3 (cardiac)	000363	191044	AD/AR	HCM, DCM, restrictive cardiomyopathy (RCM)	5% HCM; 1% DCM
<i>TNNT2</i>	Troponin T type 2 (cardiac)	001001430	191045	AD	HCM, DCM, RCM, LVNC	5% HCM; 3% DCM
<i>TPM1</i>	Tropomyosin 1 (alpha)	001018005	191010	AD	HCM, DCM, LVNC	2% HCM; 1-2% DCM
<i>TRPM4</i>	Transient receptor potential cation channel, subfamily M, member 4	017636	606936	AD	Progressive familial heart block, BrS	Unknown
<i>TTN</i>	Titin	133378	188840	AD/AR	DCM, HCM, temporomandibular joint dysfunction (TMD), LGMD, hereditary myopathy with early respiratory failure, Salih myopathy	20% DCM; only gene associated with TMD and Salih myopathy
<i>TTR</i>	Transthyretin	000371	176300	AD	Transthyretin (TTR) cardiac amyloidosis	Only gene associated with TTR amyloidosis
<i>VCL</i>	Vinculin	014000	193065	AD	DCM, HCM	1% DCM

Inh. = Inheritance; AD = autosomal dominant; AR = autosomal recessive; XL = X-linked