Cardiomyopathy and Arrhythmia Gene Panel

Indication for Ordering

Confirm hereditary form of cardiomyopathy or arrhythmia

Test Description

- 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

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

Mitochondrial Disorders Panel (mtDNA by Sequencing and Deletion/Duplication, 121 Nuclear Genes by Sequencing, 119 Nuclear Genes by Deletion/Duplication) 2006054

- Comprehensive test to confirm a suspected diagnosis of a mitochondrial disorder

Familial Mutation, Targeted Sequencing 2001961

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

Disease Overview

See Table 1

Genetics

See Table 2

Test Interpretation

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)	• Left ventricular hypertrophy with absence of other cardiovascular causes • Variable presentation o Asymptomatic to sudden death • Common symptoms o Shortness of breath o Chest pain o Palpitation o Orthostasis o Syncope • Doppler echocardiographic imaging result consistent with hypertrophy	*ACTC1, ACTN2, CAV3, COX15, CSRP3, 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*	1/500	• AD • Variants in genes encoding for components of the sarcomere account for 55-70% of HCM with no multisystem involvement • Variants in *MYH7* and *MYBPC3* account for majority of familial HCM
Dilated cardiomyopathy (DCM)	• Left ventricular enlargement and systolic dysfunction • Variable presentation • Heart failure with symptoms of congestion and/or reduced cardiac output o Edema o Orthopnea o Paroxysmal dyspnea o Fatigue o Dyspnea on exertion • Arrhythmias and/or conduction system disease • Thromboembolic disease or stroke	*ABCC9, ACTC1, ACTN2, ANKRD1, CSRP3, 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*	Unknown – estimated to be >1/500	• Typically AD o AR, X-linked, and mitochondrial less common • ~20-35% of isolated DCM is familial • Variants in *TTN* account for ~20% of isolated DCM
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	• Progressive fibrofatty replacement of the myocardium predisposing to ventricular tachycardia and sudden death • Heart palpitations • Syncope • Sudden death • Variable presentation o Some affected individuals do not meet established clinical criteria	*DSC2, DSG2, DSP, JUP, PKP2, RYR2, TGFB3, TMEM43*	1/1,000	• AD
Left ventricular noncompaction (LVNC)	• Hypertrophic and hypokinetic left ventricle with distinctive morphology • Often present with additional cardiac abnormalities • Variable presentation • Asymptomatic to sudden death	*ACTC1, DTNA, LDB3, MYBPC3, MYH7, TAZ, TPM1, TNNT2*	Unknown	• AD
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	• Episodic syncope or ventricular arrhythmias occurring during exercise or acute emotion without presence of structural cardiac abnormalities • Variable presentation o Asymptomatic to sudden death	*CASQ2, RYR2*	1/10,000	• AD for *RYR2* • AR for *CASQ2* • Variants in *RYR2* account for 50-55% of all CPVT
Brugada syndrome (BrS)	• Variable cardiac conduction abnormalities that can result in sudden death	*CACNA1C, CACNB2, GPD1L, KCNE3, SCN1B, SCN3B, SCN5A, TRPM4*	Unknown	• AD o 1% de novo • Variants in *SCN5A* account for 15-30% of BrS
Long QT syndrome (LQTS)	• Electrophysiological cardiac disease o Prolonged QT- and T-wave abnormalities on ECG o Ventricular tachycardia (torsades de pointes) ▪ Syncope ▪ Cardiac arrest ▪ Sudden death	*AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNQ1, SCN4B, SCN5A, SNTA1*	Estimated >1/3,000	• AD • Commonly incomplete penetrance
Short QT syndrome (SQTS)	• Cardiac arrhythmia o Short QT interval on ECG • Variable presentation o Asymptomatic o Syncope o Cardiac arrest o Sudden death	*KCNH2, KCNJ2, KCNQ1*	Unknown	• AD

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

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ILK	Integrin-linked kinase	004517	602366	AD	DCM	Unknown
JPH2	Junctophilin 2	020433	605267	AD	HCM	Unknown
JUP	Junction plakoglobin	002230	173325	AD/AR	ARVC, Naxos disease	Rare
KCNE1	Potassium voltage-gated channel, Isk-related family, member 1	000219	176261	AD/AR	LQTS, Jervell and Lange-Nielsen syndrome (JLNS)	2% LQTS; 10% JLNS
KCNE2	Potassium voltage-gated channel, Isk-related family, member 2	172201	603796	AD	LQTS	1% LQTS
KCNE3	Potassium voltage-gated channel, Isk-related family, member 3	005472	604433	AD	BrS	<5% BrS
KCNH2	Potassium voltage-gated channel, subfamily H (eag-related), member 2	000238	152427	AD	LQTS, SQTS	40% LQTS
KCNJ2	Potassium inwardly-rectifying channel, subfamily J, member 2	000891	600681	AD	Andersen syndrome, SQTS, ATFB	60% Andersen syndrome
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1	000218	607542	AD/AR	ATFB, LQTS, SQTS, JLNS	45% LQTS; 90% JLNS
KLHL3	Kelch-like family member 3	017415	605775	AD/AR	Pseudohypoaldosteronism	Unknown
LAMA4	Laminin, alpha 4	002290	600133	AD	DCM	Unknown
LAMP2	Lysosomal-associated membrane protein 2	002294	309060	XL	Danon disease	Unknown
LDB3	LIM domain binding 3	001080116	605906	AD	DCM, myofibrillar myopathy, LVNC	1% DCM
LMNA	Lamin A/C	005572	150330	AD/AR	DCM, EDMD, LGMD	45% dominant EDMD
MYBPC3	Myosin binding protein C, cardiac	000256	600958	AD	HCM, DCM, LVNC	40% HCM
MYH6	Myosin, heavy chain 6, cardiac muscle, alpha	002471	160710	AD	HCM, DCM, CHD	Unknown
MYH7	Myosin, heavy chain 7, cardiac muscle, beta	000257	160760	AD	HCM, DCM, Laing distal myopathy, LVNC	40% HCM
MYH10	Myosin, heavy chain 10, non-muscle	001256012	160776	Unknown	Unknown	Unknown
MYL2	Myosin, light chain 2, regulatory, cardiac, slow	000432	160781	AD	HCM	Unknown
MYL3	Myosin, light chain 3, alkali; ventricular, skeletal, slow	000258	160790	AD/AR	HCM	1% HCM
MYLK2	Myosin light chain kinase 2	033118	606566	Unknown	HCM	Unknown
MYOT	Myotilin	006790	604103	AD	LGMD, myofibrillar myopathy	Rare
MYOZ2	Myozenin 2	016599	605602	AD	HCM	Unknown
MYPN	Myopalladin	032578	608517	AD	DCM, HCM, restrictive cardiomyopathy	Unknown
NEXN	Nexilin (F actin binding protein)	144573	613121	AD	DCM, HCM	<1% DCM
OBSCN	Obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF	052843	608616	Unknown	HCM	Unknown
PKP2	Plakophilin 2	004572	602861	AD	ARVC	10-40% ARVC
PLN	Phospholamban	002667	172405	AD	HCM, DCM	Unknown
PRKAG2	Protein kinase, AMP-activated, gamma 2 non-catalytic subunit	016203	602743	AD	HCM, Wolff-Parkinson-White syndrome	Rare
RBM20	RNA binding motif protein 20	001134363	613171	AD	DCM	2% DCM
RYR2	Ryanodine receptor 2 (cardiac)	001035	180902	AD	CPVT, ARVC	~50% CPVT, Rare ARVC
SCN1B	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
SCN2B	Sodium channel, voltage-gated, type II, beta subunit	004588	601327	AD	ATFB	Unknown
SCN3B	Sodium channel, voltage-gated, type III, beta subunit	018400	608214	AD	BrS, ATFB	<5% BrS
SCN4B	Sodium channel, voltage-gated, type IV, beta subunit	174934	608256	AD	LQTS	Rare
SCN5A	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
SCO2	SCO2 cytochrome c oxidase assembly protein	005138	604272	AR	fatal infantile cardioencephalomyopathy	Unknown
SGCA	Sarcoglycan, alpha (50kDa dystrophin-associated glycoprotein)	000023	600119	AR	LGMD	~35% childhood onset AR LGMD
SGCB	Sarcoglycan, beta (43kDa dystrophin-associated glycoprotein)	000232	600900	AR	LGMD	~15% childhood onset AR LGMD
SGCD	Sarcoglycan, delta (35kDa dystrophin-associated glycoprotein)	000337	601411	AR/digenic	LGMD, DCM	~8% childhood onset AR LGMD; <1% DCM
SGCG	Sarcoglycan, gamma (35kDa dystrophin-associated glycoprotein)	000231	608896	AR	LGMD	~4% childhood onset AR LGMD
SLC25A4	Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4	001151	103220	AR	Mitochondrial DNA depletion syndrome (HCM)	Unknown
SNTA1	Syntrophin, alpha 1	003098	601017	AD/digenic	LQTS, SIDS	Rare
SYNE1	Spectrin repeat containing, nuclear envelope 1	033071	608441	AD	EDMD	Unknown
TAZ	Tafazzin	000116	300394	XL	Barth syndrome, DCM, LVNC	Unknown
TCAP	Titin-cap	003673	604488	AD/AR	LGMD, DCM, HCM	3% AR LGMD; 1% DCM
TGFB3	Transforming growth factor, beta 3	003239	190230	AD	ARVC	Rare
TMEM43	Transmembrane protein 43	024334	612048	AD	ARVC, EDMD	Unknown
TMPO	Thymopoietin	003276	188380	AD	DCM	1% DCM
TNNC1	Troponin C type 1 (slow)	003280	191040	AD	DCM, HCM	1% DCM
TNNI3	Troponin I type 3 (cardiac)	000363	191044	AD/AR	HCM, DCM, restrictive cardiomyopathy (RCM)	5% HCM; 1% DCM
TNNT2	Troponin T type 2 (cardiac)	001001430	191045	AD	HCM, DCM, RCM, LVNC	5% HCM; 3% DCM
TPM1	Tropomyosin 1 (alpha)	001018005	191010	AD	HCM, DCM, LVNC	2% HCM; 1-2% DCM
TRPM4	Transient receptor potential cation channel, subfamily M, member 4	017636	606936	AD	Progressive familial heart block, BrS	Unknown
TTN	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
TTR	Transthyretin	000371	176300	AD	Transthyretin (TTR) cardiac amyloidosis	Only gene associated with TTR amyloidosis
VCL	Vinculin	014000	193065	AD	DCM, HCM	1% DCM

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