Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication

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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). Molecular testing is used to determine if a genetic etiology can be identified, which can facilitate patient management and screening of at-risk relatives.

Featured ARUP Testing

Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication 2010183

Method: Massively Parallel Sequencing

Use to confirm the hereditary form of cardiomyopathy or arrhythmia.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

See Common Disorders table below.

Genetics

See Genes Tested table for genes included in the panel.

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing, or NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for the detection of large deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

Variable, dependent on phenotype/condition

- ARVC: 50%[1]
- BrS: 15-30%[2]
- CPVT: 60%[3]
- DCM: 25-40% for familial DCM, 10-25% for isolated DCM[4]
- HCM: 50-60% for familial HCM, 20-30% for isolated HCM[5]
- LQTS: 60-75%[6]

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA)
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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

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 and deep intronic variants
  - Deletions/duplications in *PTPN11*
  - Breakpoints of large deletions/duplications
  - SNVs and small deletions/insertions will not be called in the following exons due to technical limitations of the assay:
    - *BRAF* (NM_004333) exon(s) 5,18
    - *BRAF* (NM_001354609) exon(s) 5,18,19
    - *BRAF* (NM_001374244) exon(s) 5,10,19
    - *BRAF* (NM_001374258) exon(s) 5,10,19,20
    - *BRAF* (NM_001378467) exon(s) 5,18,19
    - *BRAF* (NM_001378468) exon(s) 5,18
    - *BRAF* (NM_001378469) exon(s) 5,18
    - *BRAF* (NM_001378470) exon(s) 4,17,18
    - *BRAF* (NM_001378471) exon(s) 5,17,18
    - *BRAF* (NM_001378472) exon(s) 5,18,19
    - *BRAF* (NM_001378473) exon(s) 5,18
    - *BRAF* (NM_001378474) exon(s) 5,18
    - *BRAF* (NM_001378475) exon(s) 4,17,18
    - *CALM1* (NM_001363670) exon(s) 1
    - *CSRP3* (NM_001369404) partial exon(s) 5(Chr11:19204180-19204196)
    - *DES* (NM_001382712) exon(s) 9
    - *FKTN* (NM_001351497) exon(s) 6
    - *FKTN* (NM_001351498) partial exon(s) 9(Chr9:108382363-108382373)
    - *FLNC* (NM_001458) exon(s) 47,48
    - *FLNC* (NM_001127487) exon(s) 46,47
    - *PRKAG2* (NM_016203) exon(s) 13
    - *PRKAG2* (NM_001040633) exon(s) 13
    - *PRKAG2* (NM_001304527) exon(s) 11
    - *PRKAG2* (NM_001304531) exon(s) 10
    - *PRKAG2* (NM_001363698) exon(s) 11
    - *PRKAG2* (NM_024429) exon(s) 9
    - *RAF1* (NM_001354689) exon(s) 8
    - *RAF1* (NM_001354694) exon(s) 7
    - *SOS1* (NM_001382394) exon(s) 1
    - *TECRL* (NM_001363796) exon(s) 12
    - *TPM1* (NM_001365777) partial exon(s) 9(Chr15:63358119-63358186)
    - *TPM1* (NM_001365780) partial exon(s) 8(Chr15:63358119-63358186)
    - *TTN* (NM_001267550) exon(s) 172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197

    - *TTN* (NM_001256850) exon(s) 154,155,156
    - *TTN* (NM_133378) exon(s) 153,154,155
- The following may not be detected:
    - Deletions/duplications/insertions of any size by massively parallel sequencing
    - Large duplications less than 3 exons in size
    - Noncoding transcripts
    - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
    - Low-level somatic 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	1/250-1/2,500	Typically AD; AR/XL/Mitochondrial less common	~20-50% of cases are familial Variants in *TTN* account for 15-20% of nonsyndromic DCM
HCM	Left ventricular hypertrophy with absence of other cardiovascular causes	1/500	AD	Variants in *MYH7* and *MYBPC3* account for the majority of familial HCM[7]
LVNC	Hypertrophic and hypokinetic left ventricle with distinctive morphology	Unknown	Typically AD	*MYH7* and *MYBPC3* are commonly implicated genes
LQTS	Cardiac electrophysiologic disease with prolonged QT- and T-wave abnormalities on ECG associated with ventricular tachycardia (torsade de pointes)	1/2,500	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 DCM 10 Familial atrial fibrillation 12	AD
ACTC1	102540	HCM 11 Atrial septal defect 5 DCM 1R	AD
ACTN2	102573	DCM 1AA with or without LVNC HCM 23 with or without LVNC	AD
AGL	610860	Glycogen storage disease IIIa or IIIb	AR
ALMS1	606844	Alstrom Syndrome	AR
ALPK3	18052	HCM 27	AR
BAG3	603883	Myofibrillar myopathy 6	AD

Gene	MIM Number	Disorder	Inheritance
		DCM 1HH	
BRAF	164757	Cardiofaciocutaneous syndrome 1 Noonan syndrome 7	AD
CACNA1C	114205	Timothy syndrome LGTS 8	AD
CALM1	114180	LQTS 14 CPVT 4	AD
CALM2	114182	LQTS 15 CPVT	AD
CALM3	114183	LQTS 16 CPVT 6	AD
CASQ2	114251	CPVT 2	AR
CAV3	601253	Familial hypertrophic cardiomyopathy, 1 Long QT syndrome 9	AD
CRYAB	123590	Myofibrillar myopathy, 2 DCM 1II	AD
		Myofibrillar myopathy, fatal infantile hypertonic, alpha-B crystallin-related	AR
CSRP3	600824	HCM 12	AD
DES	125660	Myofibrillar myopathy, 1	AD/AR
		DCM 1I	AD
DMD	300377	Becker muscular dystrophy DCM 3B Duchenne muscular dystrophy	XL
DOLK	610746	Congenital disorder of glycosylation Im	AR
DSC2	125645	ARVC 11	AD
		ARVC 11 with mild palmoplantar keratoderma and woolly hair	AR
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	AR
EMD	300384	Emery-Dreifuss muscular dystrophy 1	XL
FHL1	300163	Uruguay faciocardiomusculoskeletal syndrome Scapuloperoneal myopathy Myopathy with postural muscle atrophy Emery-Dreifuss muscular dystrophy 6	XL

Gene	MIM Number	Disorder	Inheritance
		Reducing body myopathy 1B	
FKTN	607440	DCM 1X Muscular dystrophy-dystroglycanopathy Ad4	AR
FLNC	102565	Myofibrillar myopathy 5 HCM 26 Restrictive cardiomyopathy 5 Distal myopathy 4	AD
GAA	606800	Glycogen storage disease II	AR
GLA	300644	Fabry disease	XL
HCN4	605206	Sick sinus syndrome 2	AD
HRAS	190020	Costello syndrome	AD
JPH2	605267	HCM 17	AD
JUP	173325	ARVC 12	AD
		Naxos disease	AR
KCNE1	176261	LQTS 5	AD
		Jervell and Lange-Nielsen syndrome 2	AR
KCNE2	603796	Familial atrial fibrillation 4 LQTS 6	AD
KCNH2	152427	LQTS 2 SQTS 1	AD
KCNJ2	600681	Andersen syndrome SQTS 3 Familial atrial fibrillation 9	AD
KCNQ1	607542	LQT S 1 Familial atrial fibrillation 3 SQTS 2	AD
		Jervell and Lange-Nielsen syndrome 1	AR
KRAS	190070	Cardiofaciocutaneous syndrome 2 Noonan syndrome 3	AD
LAMP2	309060	Danon disease	XL
LDB3	605906	DCM 1C with or without LVNC Myofibrillar myopathy, 4	AD
LMNA	150330	DCM 1A Emery-Dreifuss muscular dystrophy 2 Slovenian type heart-hand syndrome Congenital muscular dystrophy Malouf syndrome	AD

Gene	MIM Number	Disorder	Inheritance
		Emery-Dreifuss muscular dystrophy 3	AR
MAP2K1	176872	Cardiofaciocutaneous syndrome 3	AD
MAP2K2	601263	Cardiofaciocutaneous syndrome 4	AD
MYBPC3	600958	HCM 4 DCM 1MM LVNC 10	AD
MYH6	160710	DCM 1EE Sick sinus syndrome 3 Atrial septal defect 3	AD
MYH7	160760	DCM 1S HCM 1 Laing distal myopathy	AD
		Myosin storage myopathy	AR
MYL2	160781	HCM 10	AD
MYL3	160790	HCM 8	AD/AR
NEXN	613121	DCM 1CC	AD
NKX2-5	600584	Atrial septal defect with or without AV conduction defects	AD
NRAS	164790	Noonan syndrome 6	AD
PKP2	602861	ARVC 9	AD
PLN	172405	DCM 1P HCM 18	AD
PRDM16	605557	DCM 1LL	AD
PRKAG2	602743	HCM 6 Glycogen storage disease of the heart, lethal congenital Wolff-Parkinson-White syndrome	AD
PTPN11	176876	Noonan syndrome 1 LEOPARD syndrome 1	AD
RAF1	164760	Noonan syndrome 5 DCM 1NN LEOPARD syndrome 2	AD
RBM20	613171	DCM 1DD	AD
RIT1	609591	Noonan syndrome 8	AD
RYR2	180902	ARVC 2 CPVT 1	AD
SCN5A	600163	Brugada syndrome 1 DCM 1E Familial atrial fibrillation 10	AD

Gene	MIM Number	Disorder	Inheritance
		Familial heart block Familial paroxysmal ventricular fibrillation LQTS 3	
		Sick sinus syndrome 1	AR
SOS1	182530	Noonan syndrome 4	AD
TAFAZZIN	300394	Barth syndrome	XL
TCAP	604488	Limb-girdle muscular dystrophy 2G	AR
TECRL	617242	CPVT 3	AR
TMEM43	612048	ARVC 5 Emery-Dreifuss muscular dystrophy 7	AD
TNNC1	191040	DCM 1Z HCM 13	AD
TNNI3	191044	DCM 1FF Restrictive cardiomyopathy 1 HCM 7	AD
		DCM 2A	AR
TNNI3K	613932	Cardiac conduction disease with or without DCM	AD
TNNT2	191045	HCM 2 DCM 1D Restrictive cardiomyopathy 3	AD
TPM1	191010	HCM 3 DCM 1Y	AD
TRDN	603283	Cardiac arrhythmia syndrome with or without skeletal muscle weakness	AR
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, XL, X-linked

References

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