

HEARTGENE CARDIOMYOPATHY AND CHANNELOPATHY PANEL (57 GENES):

The Heartgene Cardiomyopathy and Channelopathy Panel includes genetic testing of 57 genes with known association to cardiomyopathies and channelopathies and is performed by next generation sequencing.

Testing strategy

This genetic test is intended for individuals with a personal or family history of inherited cardiomyopathies or cardiac channelopathies. These are a group of genetically heterogeneous disorders with a well-established genetic component and an association with sudden cardiac death. Cardiomyopathies primarily involve structural and functional abnormalities of the myocardium (the muscular tissue of the heart), while channelopathies affect cardiac conduction and arise from dysfunction of cardiac ion channels, leading to electrical instability, often in the absence of overt structural heart disease. Familial inheritance typically follows an autosomal dominant pattern, though autosomal recessive, and X-linked inheritance have been reported for some genes. The predominant cardiomyopathy subtypes include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC), while major channelopathies include long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT). Collectively, these conditions are relatively common, with cardiomyopathies affecting an estimated 1 in 250 to 1 in 500 individuals, and channelopathies affecting approximately 1 in 2,000 to 1 in 5,000 individuals, making them among the most common genetic heart disorders.

Despite their prevalence and the associated risk of sudden cardiac death, access to genetic testing remains limited—especially for individuals who are uninsured or those who face financial barriers to accessing available testing. This test is in part designed to support these individuals who encounter challenges to accessing care through traditional healthcare channels.

The initial DNA extraction and sequencing component of this test is performed by the Broad Clinical Laboratories (BCL; 27 Blue Sky Drive, Burlington, MA 01803; CLIA#22D2055652), and interpretive algorithms, clinical reports and Sanger confirmation when applicable, are generated by the Laboratory for Molecular Medicine at Mass General Brigham Personalized Medicine (LMM, 65 Landsdowne St, Cambridge, MA 02139; 617-768-8500; CLIA#22D1005307).

Gene information

Gene	Protein	OMIM#	Locus	Reported Associated Disorder(s); (cardiomyopathy)^	Inheritance*
<i>ACTC1</i>	Actin, Alpha, Cardiac Muscle	102540	15q14	HCM, DCM	AD
<i>ACTN2</i>	Actinin, Alpha-2	102573	1q43	HCM, DCM	AD
<i>ALPK3</i>	Alpha Kinase 3	617608	15q25.3	HCM	AD/AR
<i>BAG3</i>	Bag Cochaperone 3	603883	10q26.11	DCM	AD
<i>BRAF</i>	B-RAF Protooncogene, Serine/Threonine Kinase	164757	7q34	RASopathy (HCM and other cardiac issues)	AD
<i>CALM1</i>	Calmodulin 1	114180	14q32.11	LQTS, CPVT	AD
<i>CALM2</i>	Calmodulin 2	114182	2p21	LQTS, CPVT	AD
<i>CALM3</i>	Calmodulin 3	114183	19q13.32	LQTS, CPVT	AD
<i>CASQ2</i>	Calsequestrin 2	114251	1p13.1	CPVT	AR
<i>CSRP3</i>	Cysteine- And Glycine-Rich Protein 3	600824	11p15.1	HCM	AD/AR (Semi-dominant)
<i>DES</i>	Desmin	125660	2q35	DCM, ARVC, Desminopathy	AD
<i>DSC2</i>	Desmocollin 2	125645	18q12.1	ARVC	AD
<i>DSG2</i>	Desmoglein 2	125671	18q12.1	ARVC	AD
<i>DSP</i>	Desmoplakin	125647	6p24.3	DSP-related cardiocutaneous disease (Arrhythmogenic cardiomyopathy/DCM-like, Carvajal syndrome)	AD/AR
<i>EMD</i>	Emerin	300384	Xq28	Emery-Dreifuss muscular dystrophy (HCM)	XL
<i>FHL1</i>	Four-And-A-Half Lim Domains 1	300163	Xq26.3	Emery-Dreifuss muscular dystrophy (HCM/DCM)	XL
<i>FLNC</i>	Filamin C	102565	7q32.1	DCM	AD
<i>GAA</i>	Glucosidase, Alpha, Acid	606800	17q25.3	Glycogen storage disease II (HCM)	AR
<i>GLA</i>	Galactosidase, Alpha	300644	Xq22.1	Fabry disease (HCM and other cardiac issues including LVH)	XL
<i>HRAS</i>	HRAS Protooncogene, GTPase	190020	11p15.5	RASopathy (HCM and other cardiac issues)	AD
<i>JPH2</i>	Junctophilin 2	605267	20q13.12	HCM, DCM	AD, AD/AR (Semi-dominant)
<i>JUP</i>	Junction Plakoglobin	173325	17q21.2	ARVC, Naxos disease (ARVC)	AD AR
<i>KCNH2</i>	Potassium Channel, Voltage-Gated, Subfamily H, Member 2	152427	7q36.1	LQTS, SQTS	AD
<i>KCNQ1</i>	Potassium Channel, Voltage-Gated, KQT-Like Subfamily, Member 1	607542	11p15.5-p15.4	LQTS, SQTS, Jervell and Lange Nielsen Syndrome (JLNS)	AD AR
<i>KRAS</i>	KRAS Protooncogene, GTPase	190070	12p12.1	RASopathy (HCM and other cardiac issues)	AD
<i>LAMP2</i>	Lysosome-Associated Membrane Protein 2	309060	Xq24	Danon disease (HCM)	XL

<i>LMNA</i>	Lamin A/C	150330	1q22	DCM, Laminopathies with cardiac involvement (e.g. muscular dystrophies)	AD
<i>LZTR1</i>	Leucine Zipper-Like Transcriptional Regulator 1	600574	22q11.21	RASopathy (HCM and other cardiac issues)	AD/AR
<i>MAP2K1</i>	Mitogen-Activated Protein Kinase Kinase 1	176872	15q22.31	RASopathy (HCM and other cardiac issues)	AD
<i>MAP2K2</i>	Mitogen-Activated Protein Kinase Kinase 2	601263	19p13.3	RASopathy (HCM and other cardiac issues)	AD
<i>MYBPC3</i>	Myosin-Binding Protein C, Cardiac	600958	11p11.2	HCM	AD
<i>MYH7</i>	Myosin, Heavy Chain 7, Cardiac Muscle, Beta	160760	14q11.2	HCM, DCM	AD
<i>MYL2</i>	Myosin, Light Chain 2, Regulatory, Cardiac, Slow	160781	12q24.11	HCM	AD
<i>MYL3</i>	Myosin, Light Chain 3, Alkali, Ventricular, Skeletal, Slow	160790	3p21.31	HCM	AD
<i>NEXN</i>	Nexilin F-Actin-Binding Protein	613121	1p31.1	DCM	AD
<i>NRAS</i>	NRAS Protooncogene, GTPase	164790	1p13.2	RASopathy (HCM and other cardiac issues)	AD
<i>PKP2</i>	Plakophilin 2	602861	12p11.21	ARVC	AD
<i>PLN</i>	Phospholamban	172405	6q22.31	HCM, DCM, ARVC	AD
<i>PRKAG2</i>	Protein Kinase, AMP-Activated, Noncatalytic, Gamma-2	602743	7q36.1	PRKAG2-related cardiomyopathy (HCM and other cardiac issues)	AD
<i>PTPN11</i>	Protein-Tyrosine Phosphatase, Nonreceptor-Type, 11	176876	12q24.13	RASopathy (HCM and other cardiac issues)	AD
<i>RAF1</i>	RAF1 Protooncogene, Serine/Threonine Kinase	164760	3p25.2	RASopathy (HCM and other cardiac issues)	AD
<i>RBM20</i>	RNA-Binding Motif Protein 20	613171	10q25.2	DCM	AD
<i>RIT1</i>	RIC-Like Protein Without Caax Motif 1	609591	1q22	RASopathy (HCM and other cardiac issues)	AD
<i>RRAS2</i>	Related RAS Viral Oncogene Homolog 2	600098	11p15.2	RASopathy (HCM and other cardiac issues)	AD
<i>RYR2</i>	Ryanodine Receptor 2	180902	1q43	CPVT	AD
<i>SCN5A</i>	Sodium Channel, Voltage-Gated, Type V, Alpha Subunit	600163	3p22.2	SCN5A – channelopathy (DCM and other conduction disorders; Brugada and Long QT syndrome)	AD
<i>SOS1</i>	SOS RAS/RAC Guanine Nucleotide Exchange Factor 1	182530	2p22.1	RASopathy (HCM and other cardiac issues)	AD
<i>SOS2</i>	SOS RAS/RAC Guanine Nucleotide Exchange Factor 2	601247	14q21.3	RASopathy (HCM and other cardiac issues)	AD
<i>TAFAZZIN</i>	Tafazzin, Phospholipid-Lysophospholipid Transacylase	300394	Xq28	Barth Syndrome (DCM)	XL
<i>TMEM43</i>	Transmembrane Protein 43	612048	3p25.1	ARVC	AD
<i>TNNC1</i>	Troponin C, Slow	191040	3p21.1	HCM, DCM	AD
<i>TNNI3</i>	Troponin I, Cardiac	191044	19q13.42	HCM, DCM	AD
<i>TNNT2</i>	Troponin T2, Cardiac	191045	1q32.1	HCM, DCM	AD
<i>TPM1</i>	Tropomyosin 1	191010	15q22.2	HCM, DCM	AD
<i>TTN</i>	Titin	188840	2q31	DCM	AD

<i>TTR</i>	Transthyretin	176300	18q12.1	Hereditary transthyretin amyloidosis (HCM)	AD
<i>VCL</i>	Vinculin	193065	10q22.2	DCM	AD

^ HCM = Hypertrophic cardiomyopathy; DCM = Dilated cardiomyopathy; ARVC = Arrhythmogenic right ventricular cardiomyopathy; LVH = Left ventricular hypertrophy; LQTS = Long QT syndrome; SQTS = Short QT syndrome; CPVT = Catecholaminergic polymorphic ventricular tachycardia

*AD = Autosomal dominant; AR = Autosomal recessive; XL = X-Linked

Methodology:

Cardiomyopathy panel: This panel includes 57 genes: ACTC1 (NM_005159.5), ACTN2 (NM_001103.4), ALPK3 (NM_020778.5), BAG3 (NM_004281.4), BRAF (exons 01-18: NM_004333.6, exon 10A: NM_001374258.1), CALM1 (NM_006888.6), CALM2 (NM_001743.6), CALM3 (NM_005184.4), CASQ2 (NM_001232.4), CSRP3 (NM_003476.5), DES (NM_001927.4), DSC2 (NM_024422.6), DSG2 (NM_001943.5), DSP (NM_004415.4), EMD (NM_000117.3), FHL1 (exons 01-06: NM_001159699.2, exon 7A: NM_001159702.3), FLNC (NM_001458.5), GAA (NM_000152.5), GLA (NM_000169.3), HRAS (exons 02-05: NM_005343.4, exon 05A: NM_176795.5), JPH2 (NM_020433.5), JUP (NM_002230.4), KCNH2 (NM_000238.4), KCNQ1 (NM_000218.3), KRAS (exons 02-05: NM_004985.5, exon 05A: NM_033360.4), LAMP2 (NM_002294.3), LMNA (exons 01-12: NM_170707.4, exon 10A: NM_005572.4), LZTR1 (NM_006767.4), MAP2K1 (NM_002755.4), MAP2K2 (NM_030662.4), MYBPC3 (NM_000256.3), MYH7 (NM_000257.4), MYL2 (NM_000432.4), MYL3 (NM_000258.3), NEXN (NM_144573.4), NRAS (NM_002524.5), PKP2 (NM_001005242.3), PLN (NM_002667.5), PRKAG2 (NM_016203.4), PTPN11 (NM_002834.5), RAF1 (NM_002880.4), RBM20 (NM_001134363.3), RIT1 (NM_006912.6), RRAS2 (NM_012250.6), RYR2 (NM_001035.3), SCN5A (exons 02-28: NM_000335.5, exons 06A and 18A: NM_001099404.2), SOS1 (NM_005633.4), SOS2 (NM_006939.4), TFAZZIN (NM_000116.5), TMEM43 (NM_024334.3), TNNC1 (NM_003280.3), TNNT1 (NM_000363.5), TNNT2 (NM_001276345.2, exon 04 (-3 to +15 bps)), TPM1 (NM_001018005.2), TTN (NM_001267550.2, except for exons 147, 149, 158-201 and 212-216 which are not present in any biological isoform), TTR (NM_000371.4), and VCL (NM_014000.3). Except when otherwise noted, sequencing is limited to coding regions and splice sites (+/- 15bp) of these genes. For additional information on reference sequences and exon coverage, please email imm@mgb.org

Genome sequencing and variant calling (from BCL validation document): The clinical Blended Genome Exome (cBGE) laboratory workflow utilized the New England Biolabs NEBNext Ultra II FS DNA Library Preparation kit and NEBNext Multiplex unique dual index adapter oligos set 1-4, which transformed genomic DNA extracted from blood or saliva into DNA libraries that are compatible with Illumina sequencing platforms. During the library construction workflow, gDNA was enzymatically fragmented, adapter-ligated, and barcoded to create a single PCR-free whole genome. Following PCR-free generation, an aliquot from the PCR-free whole genome library was taken through PCR amplification and exome selection. The PCR-free genome and whole exome were then rejoined and blended together pre-sequencing, to deliver an optimal coverage balance and combined sequencing output. Library fragments were sequenced (2x150 base paired-end)

using Sequencing-By-Synthesis (SBS) chemistry on the Illumina NovaSeq X Plus sequencer. Sequencing data were aligned to the GRCh38 assembly after discarding low-quality sequences. Illumina's DRAGEN (Dynamic Read Analysis for GENomics) platform was used for demultiplexing, read mapping, genome alignment, read sorting, duplicate marking, and variant calling. The DRAGEN pipeline generated the quality metrics that met the following thresholds: $\geq 90\%$ of exome bases at or greater than 20X, genome mean coverage $\geq 1X$, and mean target coverage $\geq 60X$. Other quality metrics that are reviewed are percent contamination ($\leq 2.5\%$), percent mapped ($\geq 75\%$), and percent exome callability ($\geq 95\%$). The DRAGEN pipeline also generated a CRAM file (compressed BAM file), and a hard-filtered VCF (Variant Call Format) file that contains SNPs/indels (single nucleotide variants and small insertions/deletions) with a target region of ± 16 base pairs into the introns.

Filtration Strategy and variant interpretation:

Variants in the 57 genes described above are subsequently filtered to identify:

- (1) variants classified as disease causing mutations in public databases (ClinVar and the Human Gene Mutation Database (HGMD)) that have a minor allele frequency $< 5.0\%$ in the Genome Aggregation Database (gnomAD, <http://gnomad.broadinstitute.org/>); and
- (2) nonsense, frameshift, and $\pm 1,2$ splice-site variants in disease associated genes with a minor allele frequency $\leq 1\%$ in gnomAD. The evidence for phenotype-causality is then evaluated for each variant identified from the filtering strategies listed above and variants are classified based on ACMG/AMP criteria (Richards et al. 2015) with ClinGen rule specifications (<https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/>). Variants are reported using the GRCh38 human genome reference sequence and according to HGVS nomenclature (<http://varnomen.hgvs.org/>).

Limitations and additional comments: Specific types of genetic variation, such as short tandem repeats (including triplet repeat expansions), structural variation, and large copy number events are currently not reliably detected by this assay. Additionally, while blended genome-exome (BGE)sequencing covers $\sim 95\%$ of the exome/genome; there are certain regions for which the assay may fail to adequately generate sequence information, such as regions of high homology or regions that are highly repetitive as well as regions with low coverage, mapping quality or base quality. No orthogonal assay will be used for fill-in for low coverage regions or bases. The sequencing data is limited to the cell-type (material) source used for DNA extraction. Additionally, not all variants identified have been analyzed. Variant interpretation may change over time if more information becomes available.

Only those variants with evidence for causing or contributing to disease are reported. Variants of uncertain significance are not reported but may be included in some instances. Variants on this report are confirmed via Sanger sequencing or another orthogonal technology if they fail to meet technical metrics and specifications as determined by the laboratory. Please contact the laboratory for additional information.

Analytic Sensitivity and Technical Positive Predictive Value:

Variant Class	Analytic Sensitivity *	Technical positive predictive value *
Single nucleotide variants	99.31% (95% CI = 99.22 – 99.40%)	99.87% (95% CI = 99.85 – 99.89%)
Insertions and Deletions	96.93% (95% CI = 96.64 – 97.21%)	97.28% (95% CI = 96.88 – 97.67%)

* Within covered regions
CI = Confidence interval

There is demonstrated reduced detection for larger indels, especially in low complexity regions with corresponding low sequence coverage and in regions with high homology.

Clinical sensitivity

Variable, depending on disease:

- Hypertrophic cardiomyopathy (HCM): 30 – >60%; higher sensitivity observed in familial HCM^{1,2}
- Dilated cardiomyopathy (DCM): 10 – 40%; higher sensitivity observed in familial DCM²
- Arrhythmogenic right ventricular cardiomyopathy (ARVC): 10 – >50%^{2,3}
- Long QT syndrome (LQTS): 60 – 80%^{4,7}
- Brugada syndrome (BrS): 15 – 30%; SCN5A accounts for the majority of genetically solved cases^{5,7}
- Catecholaminergic polymorphic ventricular tachycardia (CPVT): 60 – 70%; predominantly associated with RYR2 variants^{6,7}

The detection rate for the other cardiomyopathies and channelopathies is unknown.

References

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