

Cardiomyopathy Panel: Sequencing and CNV Analysis

Test Code: MM520

Turnaround time: 6 weeks

CPT Codes: 81439 x1

Condition Description

Dilated Cardiomyopathy

Hereditary dilated cardiomyopathy (DCM) may be inherited in an autosomal dominant, autosomal recessive, or X-linked manner, depending on the gene involved. DCM is characterized by left ventricular enlargement and reduced myocardial contraction force. Typically, DCM presents with one of three features: heart failure, thromboembolic disease, or arrhythmias and/or conduction system disease. Approximately 20-50% of idiopathic dilated cardiomyopathy (those cases not due to acquired causes) are thought to have a genetic cause.

Hypertrophic Cardiomyopathy

Hereditary hypertrophic cardiomyopathy (HCM) is inherited in an autosomal dominant manner. HCM is characterized by left ventricular hypertrophy in the absence of a predisposing cardiac or cardiovascular condition. The manifestation of HCM is extremely variable, even within the same family, and can range from asymptomatic to progressive heart failure. Other features include syncope, presyncope, shortness of breath, chest pain, orthostasis, and palpitations. The onset of HCM is usually during adolescence or young adulthood; however, it can range from infancy to much later in adult life. The prevalence of HCM is approximately 1 in 500 and ~55-70% of cases are caused by a mutation in one of the genes that encode a part of the sarcomere.

Left Ventricular Noncompaction

Familial left ventricular noncompaction (LVNC) is an autosomal dominant or X-linked cardiomyopathy. The distinct diagnostic features of LVNC (a thick, bilayered myocardium, deep intertrabecular recesses, and prominent ventricular trabeculations) are secondary to an arrest of myocardial maturation during embryo development. Individuals with LVNC may be symptomatic or asymptomatic. Major complications of LVNC include heart failure, thromboembolic events, arrhythmias, and sudden cardiac death. Diagnosis can occur prenatally through late adulthood. The manifestation of LVNC is extremely variable, even within the same family. Approximately 30% of isolated LVNC are caused by a mutation in a sarcomere gene.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is a primary myocardial disorder in which the main feature, restrictive ventricular physiology, develops early in the disease. RCM is characterized by inadequate ventricular relaxation during diastole. Onset can range from childhood to late adulthood. Major complications of RCM can include congestive heart failure, cerebrovascular accidents, and arrhythmias. Cardiac restriction may occur secondary to many genetic syndromes, such as Pompe disease and Fabry disease.

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an autosomal dominant condition characterized by abnormalities in cardiac structure and rhythm. The fibrofatty replacement of myocardium can predispose affected individuals to ventricular tachycardia and sudden death in young individuals and athletes. Common presenting features include heart palpitation, syncope, and death. Other diagnostic criteria include right ventricular dilation and reduction of right ventricular function, and right ventricular aneurysms. The phenotype of ARVD/C is highly variable and while it primarily affects the right ventricle, it may involve the left ventricle as well.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by cardiac electrical instability. This instability can be exacerbated by acute activation of the adrenergic nervous system, such as during exercise or extreme emotional events. These episodes have an underlying cause of ventricular tachycardia, which may progress into ventricular fibrillation.

The Cardiomyopathy Panel offered at Emory Genetics Laboratory includes genes that cause each of the above cardiomyopathies, as well as genes that cause genetic syndromes, which have cardiomyopathy as a clinical feature. Syndromic conditions on this panel include Duchenne/Becker muscular dystrophy, Emery-Dreifuss muscular dystrophy, Pompe disease, Fabry disease, Danon disease, Charcot-Marie Tooth, congenital muscular dystrophy, limb girdle muscular dystrophy, Wolff-Parkinson-White syndrome, cardiac glycogenosis, Barth syndrome, familial transthyretin amyloidosis, myofibrillar myopathy, total anomalous venous return, rippling muscle disease, long QT syndrome, skin fragility and woolly hair syndrome, lethal acantholytic epidermolysis bullosa, Naxos disease, and progeria.

Note: This test does not detect the retrotransposon insertion in the 3' UTR of the *FKTN* gene common in some Asian populations. For patients with suspected Fukuyama congenital muscular dystrophy, testing for the *FKTN* insertion is recommended. Analysis for the *FKTN* insertion is available as a separate assay.

References:

- GeneReviews
- Paterick *et al.*, (2012), *J Am Soc Echocardiog*, 25:363-375.
- Peters and Khandheria, (2012), *Curr Cardiol Rep*, 14:381-388.
- Sen-Chowdhry *et al.*, (2010), *Heart Failure Clin*, 6:179-186.

Genes

[ABCC9](#), [ACTC1](#), [ACTN2](#), [ANKRD1](#), [BAG3](#), [BRAF](#), [CASQ2](#), [CAV3](#), [CRYAB](#), [CSRP3](#), [DES](#), [DMD](#), [DSC2](#), [DSG2](#), [DSP](#), [DTNA](#), [EMD](#), [FKTN](#), [GAA](#), [GATAD1](#), [GLA](#), [JPH2](#), [JUP](#), [KRAS](#), [LAMA4](#), [LAMP2](#), [LDB3](#), [LMNA](#), [MAP2K1](#), [MAP2K2](#), [MYBPC3](#), [MYH6](#), [MYH7](#), [MYL2](#), [MYL3](#), [MYOZ2](#), [MYPN](#), [NEBL](#), [NEXN](#), [NRAS](#), [PDLIM3](#), [PKP2](#), [PLN](#), [PRDM16](#), [PRKAG2](#), [PTPN11](#), [RAF1](#), [RBM20](#), [RIT1](#), [RYSR2](#), [SCN5A](#), [SGCD](#), [SLC22A5](#), [SOS1](#), [TAZ](#), [TCAP](#), [TMEM43](#), [TNNC1](#), [TNNI3](#), [TNNI2](#), [TPM1](#), [TTN](#), [TTR](#), [VCL](#)

Indications

This test is indicated for:

- Individuals with a cardiomyopathy.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Copy Number Analysis: Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

Detection

Next Generation Sequencing: Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

Copy Number Analysis: The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

Specimen Requirements

Submit only 1 of the following specimen types

Type: Whole Blood (EDTA)

Specimen Requirements:

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old): 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: DNA, Isolated

Specimen Requirements:

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Related Tests

- Individual gene sequencing analysis is available for *CAV3*, *DES*, *DMD*, *EMD*, *GAA*, *GLA*, *LAMP2*, *LMNA*, *RYR2*, *SGCD*, and *TCAP*.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the

- laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.
- Cardiomyopathy: Deletion/Duplication Panel.