

Comprehensive Cardiovascular: Deletion/Duplication Panel

Test Code: DCAR1

Turnaround time: 2 weeks

CPT Codes: 81414 x1

Condition Description

Arrhythmias

Arrhythmia is any change from the normal sequence of electrical impulses of the heart. These impulses may happen too fast (tachycardia), too slowly (bradycardia), or erratically. Types of arrhythmias include atrial fibrillation, conduction disorders, premature contraction, ventricular fibrillation, tachycardia, and bradycardia. Arrhythmias can present with a broad spectrum of symptoms including palpitation, a fluttering sensation, fatigue, dizziness, lightheadedness, syncope, rapid heartbeat, shortness of breath, chest pain, and sudden cardiac arrest.

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.

Brugada Syndrome

Brugada syndrome is characterized by cardiac conduction abnormalities. These cardiac abnormalities can result in sudden death. Often features such as syncope and/or arrhythmias present in adulthood; however, the age of diagnosis ranges from two days to 85 years. Pathogenic variants in eight genes are known to cause Brugada syndrome. Only 25% of individuals with Brugada syndrome have an identifiable pathogenic variant in one of the eight genes known to cause it. Most individuals with Brugada syndrome have an affected parent but approximately 1% of cases are the result of a de novo pathogenic variant.

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.

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.

Long QT Syndrome

Long QT syndrome (LQTS) is characterized by a QT interval that is prolonged on the surface electrocardiogram and a predisposition to early after depolarizations and torsades de pointes. LQTS can present clinically with palpitations, presyncope, syncope, or sudden cardiac death.

Marfan Syndrome, Thoracic Aortic Aneurysm & Dissection (TAAD), and Related Disorders

Thoracic aortic aneurysm and dissection (TAAD) has a highly variable presentation and age of onset. It is characterized by dilation and dissections of the ascending thoracic aorta and/or ascending aorta. An aneurysm involving the descending thoracic aorta is observed rarely. Without surgical repair of the ascending aorta, individuals with TAAD have continual enlargement of the ascending aorta that leads to an acute aortic dissection. Isolated TAAD is typically inherited in an autosomal dominant manner with variable expression and reduced penetrance. Only about 20% of familial non-syndromic TAAD is attributed to pathogenic variants in known genes.

TAAD can also be present as part of a genetic syndrome. Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome vascular type, multisystemic smooth muscle dysfunction syndrome, and congenital contractural arachnodactyly all have TAAD as part of their clinical spectrum.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is increased pulmonary artery pressure in the absence of common causes of pulmonary hypertension, such as lung, heart, or thromboembolic chronic diseases. It is thought that both genetic and environmental factors that alter vascular structure and function contribute to the pathogenesis of PAH.

Familial cases of PAH are usually inherited in an autosomal dominant manner. With the identification of pathogenic variants in genes known to cause PAH, what was previously thought to be idiopathic PAH is now known to be genetic. A pathogenic variant in the *BMPR2* gene causes ~70% of hereditary cases of PAH and in 10-40% of idiopathic PAH. Pathogenic variants in the *CAV1* gene cause PAH.

Heterozygous pathogenic variants in the *ENG* and *ACVRL1* (previously known as *ALK1*) genes cause hereditary hemorrhagic telangiectasia (HHT). HHT is an autosomal dominant vascular disorder characterized by acquired cutaneous telangiectasias and arteriovenous malformations that can lead to the development of PAH.

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 adult hood. 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.

Short QT Syndrome

Short QT syndrome (SQTS) is characterized by an abnormally short QT interval and susceptibility to both ventricular tachyarrhythmias and atrial fibrillation.

Sudden Cardiac Arrest

Sudden cardiac arrest is the abrupt loss of heart function due to a malfunction in the heart's electrical system, such as an arrhythmia. The individual may or may not have been diagnosed with heart disease.

References:

- American Heart Association.
- GeneReviews.
- Ma and Chung. (2014). *Hum Genet.* [Epub ahead of print]
- OMIM.
- 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](#), [ACTA2](#), [ACTC1](#), [ACTN2](#), [ACVRL1](#), [AKAP9](#), [ANK2](#), [ANKRD1](#), [BAG3](#), [BMPR2](#), [BRAF](#), [CACNA1C](#), [CACNB2](#), [CASQ2](#), [CAV1](#), [CAV3](#), [CBS](#), [COL3A1](#), [COL5A1](#), [COL5A2](#), [CRYAB](#), [CSRP3](#), [DES](#), [DMD](#), [DSC2](#), [DSG2](#), [DSP](#), [DTNA](#), [EMD](#), [ENG](#), [FBN1](#), [FBN2](#), [FHL2](#), [FKTN](#), [FLNA](#), [GAA](#), [GATAD1](#), [GLA](#), [GPD1L](#), [HCN4](#), [HRAS](#), [JPH2](#), [JUP](#), [KCNE1](#), [KCNE2](#), [KCNE3](#), [KCNH2](#), [KCNJ2](#), [KCNJ5](#), [KCNJ8](#), [KCNQ1](#), [KRAS](#), [LAMA4](#), [LAMP2](#), [LDB3](#), [LMNA](#), [MAP2K1](#), [MAP2K2](#), [MED12](#), [MYBPC3](#), [MYH11](#), [MYH6](#), [MYH7](#), [MYL2](#), [MYL3](#), [MYLK](#), [MYLK2](#), [MYOZ2](#), [MYPN](#), [NEBL](#), [NEXN](#), [NKX2-5](#), [NRAS](#), [PKP2](#), [PLN](#), [PRKAG2](#), [PTPN11](#), [RAF1](#), [RANGRF](#), [RBM20](#), [RIT1](#), [RYR2](#), [SCN1B](#), [SCN3B](#), [SCN4B](#), [SCN5A](#), [SGCD](#), [SKI](#), [SLC2A10](#), [SMAD3](#), [SNTA1](#), [SOS1](#), [TAZ](#), [TCAP](#), [TGFB2](#), [TGFB1](#), [TGFB2](#), [TMEM43](#), [TMPO](#), [TNNC1](#), [TNNI3](#), [TNNT2](#), [TPM1](#), [TTN](#), [TTR](#), [VCL](#)

Indications

This test is indicated for:

- Individuals with a cardiovascular condition.

Methodology

Deletion/Duplication Analysis: DNA isolated from peripheral blood is hybridized to a gene-targeted CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes that cover the entire genomic region.

Detection

Deletion/Duplication Analysis: Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

Type: DNA, Isolated

Specimen Requirements:

Microtainer

3µg

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.

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.

Related Tests

- Individual gene sequencing analysis and deletion duplication analysis are available for the *CAV3*, *DES*, *DMD*, *EMD*, *GAA*, *GLA*, *LAMP2*, *LMNA*, *RYR2*, *SGCD*, and *TCAP* genes.
- 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.
- Comprehensive Cardiovascular: Sequencing Panel.