Cardiovascular Diseases Genetic Testing Program

Inherited Arrhythmia Panels

The Inherited Arrhythmia Panels offer Next Generation Sequencing of genes associated with heart rhythm disorders, including Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), familial atrial fibrillation, familial AV block, long QT syndrome, short QT syndrome, as well as a comprehensive cardiac channelopathies panel, which is best suited for patients without a clear diagnosis but are suspected to have a cardiac channelopathy.

Atrial Fibrillation (Familial)

Familial Atrial Fibrillation (FAF) is an inherited electrical disorder of the heart which is characterized by rapid and irregular electrical activation of the atria. Atrial Fibrillation (AF) is the most common type of sustained abnormal heart rhythm and can be associated with an increased risk of stroke, heart failure, dementia, and death. The incidence of the FAF is unknown; however, up to 30% of patients with AF may have a family history of AF. FAF appears to be inherited in an autosomal dominant pattern.

AV Block (Familial)

Atrioventricular (AV) Block occurs when the electrical signaling between the upper and lower chambers of the heart becomes obstructed. In cases of familial AV block, the condition generally worsens over time. Most of familial AV block is inherited in an autosomal dominant pattern with reduced penetrance and variable expressivity.

Brugada syndrome

Brugada syndrome (BS) is characterized by ST segment elevation in the right precordial leads on electrocardiogram and susceptibility to ventricular tachyarrhythmia and sudden death. BS is typically inherited in an autosomal dominant manner and is more prevalent among males, but affects female too. *SCN5A* is the most common gene associated with BS. Other genes have also been reported. Current genetic testing will identify a disease causing mutation in approximately 40% of cases.

CPVT

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an inherited arrhythmia characterized by cardiac calcium channel dysfunction that can be triggered by the release of catecholamines during times of stress. CPVT can display autosomal dominant or autosomal recessive transmission. The most common gene associated with CPVT is *RYR2* which accounts for up to 55% of cases.

Long QT syndrome

Long QT syndrome (LQTS) is characterized by prolongation of the QT interval on electrocardiogram. LQTS is associated with increased risk for syncope, ventricular arrhythmias, and sudden cardiac death. There are currently more than 14 types of LQTS. LQTS is inherited in an autosomal dominant manner with reduced penetrance. An exception is LQTS associated with sensorineural deafness (Jervell and Lange-Nielsen syndrome), which is inherited in an autosomal recessive manner. Disease causing mutations can be identified in approximately 75% of cases.

Short QT syndrome

Short QT syndrome (SQTS) is a rare condition characterized by shortening of the QT interval on electrocardiogram. SQTS can be associated with paroxysmal atrial and ventricular tachyarrhythmia, risk of atrial fibrillation, and sudden death. There are currently 6 types of SQTS which display autosomal dominant inheritance. The current yield of genetic testing for SQTS is unknown.

Indication

This test is indicated for individuals with suspected arrhythmias in the absence of predisposing cardiac/cardiovascular conditions or other identifiable acquired causes.

Genes on the Arrhythmia Panels

- Cardiac Channelopathy Panel – 32 genes
- Atrial Fibrillation Panel – 16 genes
- AV Block Panel – 7 genes
- Brugada Syndrome Panel – 15 genes
- CPVT Panel – 6 genes
- LQTS Panel – 14 genes
- SQTS Panel – 6 genes

Molecular Genetics Laboratory

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Molecular Genetics Lab
Cincinnati Children's Hospital
3333 Burnet Ave. NRB 1042
Cincinnati, OH 45229

Phone: 513-636-4474
Fax: 513-636-4373

Methodology:

Next Generation Sequencing: All coding exons, as well as their 15-bp flanking regions, of the genes listed in the panels are enriched from the patient's genomic DNA and sequenced using a solid-state sequencing-by-synthesis process. DNA sequences are assembled and compared to the published genomic reference sequences in Genome Reference Consortium Build 37. Dideoxy DNA sequencing is used to provide data for bases with insufficient coverage and to confirm the reported variants from next-generation sequencing. This assay does not detect variants in the promoter regions, deep intronic regions, or other regulatory elements, and does not detect large deletions or mosaicisms. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

Sensitivity & Accuracy:

Validation testing indicates an analytic sensitivity of greater than 99% and an analytic specificity of 100%.

References:

1. Campuzano O, et al. Genetics and cardiac channelopathies. Genet Med. 2010 May;12(5):260-7.
2. Amin AS, et al. Cardiac sodium channelopathies. Pflugers Arch. 2010 Jul;460(2):223-37
3. Kim JB. Channelopathies. Korean J Pediatr. 2014 Jan;57(1):1-18.
4. Bai R, et al. Yield of genetic screening in inherited cardiac channelopathies: how to prioritize access to genetic testing. Circ Arrhythm Electrophysiol. 2009 Feb;2(1):6-15.
5. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) J. Am. Coll. Cardiol 2006; 48:e247-e346.
6. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm 2011 8(8):1308-1339.
7. Wilde, AAM, et al. Genetic testing for inherited cardiac disease. Nat Rev Cardiol. 2013 Oct; 10(10): 571–83.
8. Spears DA, et al. Genetics of inherited primary arrhythmia disorders. Appl Clin Genet. 2015 Sep 18;8:215-33.
9. Napolitano C, et al. (Updated [3/6/2014]). Catecholaminergic Polymorphic Ventricular Tachycardia. In: *GeneReviews* at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [10/21/15].
10. Brugada R, et al. (Updated [4/10/2014]). Brugada Syndrome. In: *GeneReviews* at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [10/21/15].
11. Alders M, et al. (Updated [6/18/2015]). Long QT Syndrome. In: *GeneReviews* at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [10/21/15].
12. Statland JM, et al. (Updated [9/3/2015]). Andersen-Tawil Syndrome. In: *GeneReviews* at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [10/21/15].
13. Napolitano C, et al. (Updated [7/16/2015]). Timothy Syndrome. In: *GeneReviews* at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [10/21/15].
14. Tranebjaerg L, et al. (Updated [11/24/2014]). Jervell and Lange-Nielsen Syndrome. In: *GeneReviews* at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [10/21/15].
15. Ishikawa T, et al. A novel disease gene for Brugada syndrome: sarcolemmal membrane-associated protein gene mutations impair intracellular trafficking of hNav1.5. Circ Arrhythm Electrophysiol. 2012 Dec;5(6):1098-107.
16. Antzelevitch C, et al. Brugada syndrome. Report of the Second Consensus Conference. Heart Rhythm 2005;2:429–440.
17. Arbustini E, et al. Desmin accumulation restrictive cardiomyopathy and atrioventricular block associated with desmin gene defects. Eur J Heart Fail. 2006 Aug;8(5):477-83.
18. Stallmeyer B, et al. Mutational Spectrum in the Ca2+-Activated Cation Channel Gene *TRPM4* in Patients with Cardiac Conductance Disturbances Hum Mutat. 2012 Jan;33(1):109-17.
19. Benson DW. Genetics of atrioventricular conduction disease in humans. Anat Rec A Discov Mol Cell Evol Biol. 2004 Oct;280(2):934-9.
20. Probst V, et al. Haploinsufficiency in combination with aging causes *SCN5A*-linked hereditary Lenegre disease. J Am Coll Cardiol 2003;41:643–652.

Specimen:

Peripheral blood in EDTA tube
Adult: 3-5mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact us at 636-4474

Turnaround Time:

Full panel analysis 8-10 weeks
Known Mutation Analysis 1-2 weeks

Molecular Genetics Laboratory | Cincinnati Children's Hospital
3333 Burnet Ave. | Cincinnati, OH 45229
Phone: 513-636-4474 | Fax: 513-636-4373

Cardiovascular Diseases Genetic Testing Program

Arrhythmia Panel Gene List

Gene	A Fib Panel	AV Block Panel	Brugada Panel	CPVT Panel	Long QT Panel	Short QT Panel	Cardiac Channelopathy Panel
ABCC9	x						x
AKAP9					x		x
ANK2				x	x		x
CACNA1C			x		x	x	x
CACNA2D1			x			x	x
CACNB2			x			x	x
CALM1				x	x		x
CASQ2				x			x
CAV3					x		x
DES		x					
EMD		x					
GJA5	x						
GPD1L			x				x
HCN4			x				x
KCNA5	x						x
KCND3	x		x				x
KCNE1	x				x		x
KCNE2	x				x		x
KCNE3			x				x
KCNH2	x				x	x	x
KCNJ2	x			x	x	x	x
KCNJ5					x		x
KCNJ8			x				x
KCNQ1	x				x	x	x
LMNA	x	x					
NKX2.5		x					
NPPA	x						
NUP155	x						
RANGRF			x				x
RYR2				x			x
SCN1B	x	x	x				x
SCN2B	x		x				x
SCN3B	x		x				x
SCN4B					x		x
SCN5A	x	x	x		x		x
SLMAP			x				x
SNTA1					x		x
TRDN				x			x
TRPM4		x	x				x

Molecular Genetics Laboratory

Cincinnati Children's Hospital
3333 Burnet Ave.
Cincinnati, OH 45229

Phone: 513-636-4474
Fax: 513-636-4373