MAYO CLINIC
Mayo Medical Laboratories

TEST ID: PMARP

POSTMORTEM ARRHYTHMIA PANEL

USEFUL FOR

- Providing a postmortem genetic evaluation in the setting of sudden unexplained death and suspicion for long QT or Brugada syndrome
- Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

GENETICS TEST INFORMATION

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate the *AKAP9*, *ANK2*, *CACNA1C*, *CACNA2D1*, *CACNB2*, *CAV3*, *GPD1L*, *KCNE1*, KCNE2, *KCNE3*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNJ8*, *KCNQ1*, *SCN1B*, *SCN3B*, *SCN4B*, *SCN5A*, and *SNTA1* genes.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for all genes on this panel; see **KVAR1 / Known Variant Analysis-1 Variant**, **KVAR2 / Known Variant Analysis-2 Variants**, or **KVAR3 / Known Variant Analysis-3+ Variants**. Contact Mayo Medical Laboratories to confirm the appropriate test code for targeted testing if testing for a gene not included on this panel is needed.

CLINICAL INFORMATION

Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (ages 15–35), the incidence of SCD is between 1 to 2 per 100,000 young individuals. The reported incidence of SCD is likely an underestimate since more overt causes of death, such as car accidents and drownings, may result from arrhythmogenic events. In cases of sudden unexplained death where autopsy does not detect a structural basis for sudden death, a hereditary arrhythmia may be suspected. Brugada syndrome (BrS) and long QT syndrome (LQTS) are inherited forms of cardiac arrhythmia that may cause sudden cardiac death. Postmortem diagnosis of a hereditary arrhythmia may assist in confirmation of the cause and manner of death, as well as risk assessment in living family members.

REFERENCE VALUES

An interpretive report will be provided.

ANALYTIC TIME

6 weeks

SPECIMEN REQUIRED

PREFERRED

Type
Tissue

Container/Tube
Tissue block

ACCEPTABLE

Type
Blood spot

Container/Tube
Whatman FTA Classic Card or Whatman Protein Saver 903 Card

Specimen Volume
4–5 blood spots

01/2018

BrS is a genetic cardiac disorder characterized by ST segment elevation in leads V1-V3 on electrocardiography (EKG) with a high risk for ventricular arrhythmias that can lead to sudden cardiac death. BrS is inherited in an autosomal dominant manner and is caused by pathogenic variants in genes that encode cardiac ion channels. The diagnosis of BrS is established based on the characteristic EKG abnormality along with personal and family health history, and also requires exclusion of other causes including cardiac structural abnormalities, medications, and electrolyte imbalances. Genes associated with BrS include *CACNA1C*, *CACNA2D1*, *GPD1L*, *KCNE3*, *KCNJ8*, *SCN3B*, *CACNB2*, *SCN1B*, and *SCN5A*. Additional clinical information about BrS can be found in MML's **BRGGP / Brugada Syndrome Multi-Gene Panel, Blood** test.

LQTS is a genetic cardiac disorder characterized by QT prolongation and T-wave abnormalities on EKG, and may result in recurrent syncope, ventricular arrhythmia, and sudden cardiac death. Romano-Ward syndrome (RWS), which accounts for the majority of LQTS, follows an autosomal dominant inheritance pattern and is caused by pathogenic variants in genes that encode cardiac ion channels or associated proteins. The diagnosis of RWS is established by the prolongation of the QTc interval in the absence of other conditions or factors that may lengthen it, such as QT-prolonging drugs or structural heart abnormalities. Clinical factors such as a history of syncope and family history also contribute to the diagnosis of RWS. LQTS may also be associated with congenital profound bilateral sensorineural hearing loss, a condition known as Jervell and Lange-Nielsen syndrome (JLNS). JLNS is inherited in an autosomal recessive inheritance pattern and is caused by homozygous or compound heterozygous pathogenic variants in either the *KCNQ1* or *KCNE1* genes. Timothy syndrome (TS) is a multisystem disorder involving prolonged QT interval in association with congenital anomalies. TS is inherited in an autosomal dominant manner and usually occurs as a result of a de novo heterozygous variant in the *CACNA1C* gene. Genes associated with LQTS include *AKAP9*, *ANK2*, *CACNA1C*, *CAV3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNQ1*, *SCN4B*, *SCN5A*, and *SNTA1*. Additional clinical information about LQTS can be found in MML's **LQTGP / Long QT Syndrome Multi-Gene Panel, Blood** test.

INTERPRETATION

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

CLINICAL REFERENCE

1. Fishman GI, Chugh SS, DiMarco JP, et al: Sudden cardiac death prediction and prevention: report from the National Heart, Lung and Blood Institute and Heart Rhythm Society Workshop. Circulation 2010;122(22):2335-2348
2. Semsarian C, Ingles J: Molecular autopsy in victims of inherited arrhythmias. J Arrhythm 2016;32(5):359-365
3. Stattin EL, Westin IM, Cederquist K, et al: Genetic screening in sudden cardiac death in the young can save future lives. Int J Legal Med 2016;130(1):59-664. Ackerman MJ, Priori SG, Willems S, et al: HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm 2011;8:1308-1339

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