RYR2-related Disorders: RYR2 Gene Sequencing

**Condition Description**

**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. Two genes are known to cause CPVT. Mutation of the RYR2 gene cause autosomal dominant CPVT while mutations of the CASQ2 gene cause autosomal recessive CPVT.

**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 very variable and while it primarily affects the right ventricle, it may involve the left ventricle as well. Eight genes are known to cause ARVD/C; TGFB3, RYR2, TMEM43, DSP, PKP2, DSG2, DSC2, and JUP.

Please note that this is for the RYR2 (1q42.1-q43) gene only.

For patients with suspected RYR2-related disorders, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**References:**
- GeneReviews
- OMIM #180902: RYR2 gene
- OMIM #604772: CPVT
- OMIM #600996: ARVD/C

**Genes**

**RYR2**

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of RYR2-related disorders.
- Carrier testing in adults with a family history of RYR2-related disorders.

**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.

**Detection**

Clinical Sensitivity: CPVT – 50-55% and ARVD/C - unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type:** Whole Blood

Specimen Requirements:
In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Related Tests

- Deletion/duplication analysis of the *RYR2* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- 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.