**Condition Description**

**Timothy Syndrome**
Timothy syndrome is characterized by cardiac abnormalities such as long QT interval and congenital heart defects, hand/foot syndactyly, and neuropsychiatric involvement such as developmental delays and autism spectrum disorder. Characteristic facial features include flat nasal bridge, low-set ears, thin upper lip, and a round face. Timothy syndrome is an autosomal dominant disorder with death occurring on average by two and a half years of age. Mutation of the CACNA1C gene (12p13.3) is reported to cause Timothy syndrome. There are two types; type 1 a classic form and type 2 a rare form. Most cases of Timothy syndrome result from a de novo mutation and only three different mutations have been identified at this time. The common mutation p.Gly406Arg in the CACNA1C gene confirms the diagnosis of Timothy syndrome type 1 while the p.Gly406Arg or p.Gly402Ser mutations in the alternatively spliced transcript of the CACNA1C gene result in Timothy syndrome type 2.

**Brugada Syndrome**
Mutation of the CACNA1C gene also causes Brugada syndrome, which 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. In addition to the CACNA1C gene, mutation of seven other genes cause Brugada syndrome. Only 25% of individuals with Brugada syndrome have an identifiable mutation 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 mutation.

Please note that this test is for the CACNA1C gene only.

For patients with suspected CACNA1C-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 #114205: CACNA1C gene
- OMIM #601005: Timothy syndrome
- OMIM #611875: Brugada syndrome

**Genes**

CACNA1C

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of CACNA1C-related disorders.
- Carrier testing in adults with a family history of CACNA1C-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: Sequencing analysis will detect 100% of individuals with Timothy syndrome type 1. The detection rates for Timothy syndrome type 2 and Brugada syndrome are currently 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) or ACD (yellow 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 CACNA1C 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.