CACNA1C-related Disorders: CACNA1C Gene Deletion/Duplication

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 syncpe 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

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of CACNA1C-related disorders in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of CACNA1C-related disorders in whom sequence analysis was negative.

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

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

* 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.

**Special Instructions**

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequence analysis of the *CACNA1C* gene is available and is required before deletion/duplication analysis.
- 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.