MAYO CLINIC LABORATORIES

Test Definition: SQTSG

Short QT Syndrome Gene Panel, Varies

Overview

Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of short QT syndrome

Establishing a diagnosis of short QT syndrome

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 4 genes associated with short QT syndrome (SQTS): *KCNH2, KCNJ2, KCNQ1,* and *SLC4A3*. See Targeted Genes and Methodology Details for Short QT Syndrome Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for SQTS.

Prior Authorization is available for this assay.

Special Instructions

- Informed Consent for Genetic Testing
- Hereditary Cardiomyopathies and Arrhythmias: Patient Information
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Short QT Syndrome Gene Panel
- Short QT Syndrome Gene Panel (SQTSG) Prior Authorization Ordering Instructions

Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This test is intended for genetic screening for and diagnosis of short QT syndrome.

For comprehensive inherited cardiac arrhythmia genetic testing, order CARGG / Comprehensive Arrhythmia Gene Panel, Varies.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

Prior Authorization is available, **but not required**, for this test. If proceeding with the prior authorization process, submit the required form with the specimen.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred)/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Hereditary Cardiomyopathies and Arrhythmias Patient Information (T725)
3. Short QT Syndrome Gene Panel (SQTSG) Prior Authorization Ordering Instructions
4. If not ordering electronically, complete, print, and send a Cardiovascular Test Request (T724) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Short QT syndrome (SQTS) is a genetic cardiac arrhythmia condition characterized by a shortened QT interval and T-wave abnormalities on electrocardiogram (ECG).(1) SQTS may result in or present with recurrent syncope, ventricular arrhythmia, sudden cardiac arrest, and sudden cardiac death.(1)

The prevalence of SQTS is unknown, but the condition is thought to be rare.(2) The overall diagnostic yield of genetic testing for SQTS is estimated to be 5% to 20%.(2,3) While disease-causing variants in several genes have been reported in association with SQTS, the strongest evidence of association is currently limited to gain-of- function variants in the cardiac ion change genes *KCNH2, KCNJ2,* and *KCNQ1*,(4) and loss-of-function variants in the *SLC4A3* gene.(5) Based on current knowledge, SQTS follows an autosomal dominant pattern of inheritance.

Genetic testing in SQTS is recommended to confirm the clinical diagnosis, assist with risk stratification, guide management, and identify at-risk family members. Even individuals with a normal QT interval may still be at risk for a cardiac event and sudden cardiac death; thus, ECG analysis alone is insufficient to rule out the diagnosis, and genetic testing is necessary to confirm the presence or absence of disease in at-risk family members.(1-5)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Refer to the Targeted Genes and Methodology Details for Short QT Syndrome Gene Panel for the most up to date list of genes included in this test. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

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 periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental

findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Campuzano O, Fernandez-Falgueras A, Lemus X, et al: Short QT syndrome: A comprehensive genetic interpretation and clinical translation of rare variants. J Clin Med. 2019 Jul 16;8(7):1035. doi:10.3390/jcm8071035
2. Mazzanti A, Underwood K, Nevelev D, Kofman S, Priori SG: The new kids on the block of arrhythmogenic disorders: Short QT syndrome and early repolarization. J Cardiovasc Electrophysiol. 2017 Oct;28(10):1226-1236. doi: 10.1111/jce.13265
3. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al; ESC Scientific Document Group: 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015 Nov 1;36(41):2793-2867. doi: 10.1093/eurheartj/ehv316
4. Walsh R, Adler A, Amin AS, et al: Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death. Eur Heart J. 2022 Apr 14:43(15):1500-1510. doi: 10.1093/eurheartj/ehab687
5. Thorsen K, Dam VS, Kjaer-Sorensen K, et al: Loss-of-activity-mutation in the cardiac chloride-bicarbonate exchanger AE3 causes short QT syndrome. Nat Commun. 2017 Nov 22;8(1):1696. doi: 10.1038/s41467-017-01630-0
6. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Short QT Syndrome Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *KCNH2, KCNJ2, KCNQ1,* and *SLC4A3*

PDF Report
Supplemental

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location
Rochester

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81403
81406 x 2
81479

Prior Auhtorization
Insurance preauthorization is available for this testing; forms are available.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
SQTSG	Short QT Syndrome Gene Panel	51966-0

Result ID	Test Result Name	Result LOINC® Value
617464	Test Description	62364-5
617465	Specimen	31208-2

617466	Source	31208-2
617467	Result Summary	50397-9
617468	Result	82939-0
617469	Interpretation	69047-9
617470	Additional Results	82939-0
617471	Resources	99622-3
617472	Additional Information	48767-8
617473	Method	85069-3
617474	Genes Analyzed	48018-6
617475	Disclaimer	62364-5
617476	Released By	18771-6