Short QT Syndrome (SQTS) Panel

The Blueprint Genetics SQTS panel represents an efficient genetic diagnostic tool for short QT syndrome (SQTS). SQTS is a rare heart disease caused by abnormal functions of cardiac ion-channel proteins that lead to accelerated atrial and ventricular repolarization characterized by shortening of the QT interval on electrocardiogram (ECG). In the case of atypical features or unclear clinical diagnosis we recommend using the BpG Arrhythmia Panel, which covers other hereditary arrhythmias that have overlapping features with SQTS.

The SQTS Panel provides a high quality read-out of all clinically relevant genes associated with short QT syndrome. Our OS-Seq™ technology provides high coverage clinical grade sequencing and enables reliable diagnostics for patients with significantly lower costs and faster turnaround time (basic service TAT 21 days and express service TAT 7-10 days). The SQTS Panel has undergone rigorous validation process during its evolution at Blueprint Genetics. Our unique sequencing technology combined with in-house built bioinformatics pipeline with channelopathy mutation and knowledge database, together with our experienced team of geneticists and clinicians, forms the most efficient hereditary cardiovascular disease diagnostics service in the market. Our variant classification schemes and clinical interpretation processes have been developed and validated with thousands of patients with hereditary cardiovascular disease. Blueprint Genetics publically shares all classified variants identified in cardiomyopathy and channelopathy patients to improve future diagnostics (ClinVar; http://www.ncbi.nlm.nih.gov/clinvar/). Our mission is to improve the quality of diagnostics and management of hereditary arrhythmia disorder patients and their families.

Genes Covered by Panel

CACNA1C, CACNA2D1, CACNB2, KCNH2, KCNJ2, KCNQ1

The test covers 6 genes with evidence of association with short QT syndrome. All protein coding exons and exon-intron boundaries are covered. Sequencing is also targeted to other regions with reported pathogenic or likely pathogenic mutations.

Description of Test

Blueprint Genetics offers a comprehensive SQTS Panel that covers the genes associated with short QT syndrome. The genes are carefully selected based on the existing scientific evidence, our experience and existing mutation databases.

Coverage

In our latest validation of the SQTS Panel, median sequencing depth in the target region was 462x on a nucleotide level and 99.65% of the nucleotides had at least 15x coverage.

Analytical validity

Analytical validation is a continuous process at Blueprint Genetics. Our mission is to improve the quality of the sequencing process and our standardized validation process follows each modification. In our latest validation the SQTS Panel had sensitivity of 0.991 and specificity of 1.000 to detect single nucleotide polymorphisms. Our panel had also good performance to detect insertions and deletions. Sensitivity was 1.000 for both indels ranged 1-5 bp and 6-19 bp. This panel has not been validated to identify larger deletions, insertions or complex rearrangements.

Diagnostic yield

Blueprint Genetics provides genetic diagnostics for hundreds of hospitals and clinics around the world. The diagnostic yield
varies substantially between hospitals and countries. Diagnostic yield for SQTS cannot be reliably estimated as the disorder is extremely rare and only few cases, to date, have been analyzed. Please review our variant interpretation strategy here.

**Bioinformatics**

We have developed a unique ventricular arrhythmia sequence analyzer and interpretation pipeline. In the core of our bioinformatics lies our in-house created and curated cardiomyopathy and channelopathy mutation database, which is a synthesis of over 2000 original publications on hereditary arrhythmia disorders and existing mutation databases. The analysis pipeline includes rigorous quality control steps to ensure validity and consistency of results, and incorporates gene variability data from thousands of publicly available human reference sequences in order to eliminate false positive findings and deliver data of the highest relevance. Reference databases currently used are 1000 Genomes (http://www.1000genomes.org), NHLBI GO Exome Sequencing Project (ESP; http://evs.gs.washington.edu/EVS), Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org). In addition, we apply the following *in silico* variant prediction tools in our analyses: SIFT (http://sift.jcvi.org), Polyphen (http://genetics.bwh.harvard.edu/pph2/) and Mutation Taster (http://www.mutationtaster.org).

Through our online ordering and statement system, Nucleus, the customer can access specific details of the analysis of the patient. This includes coverage and quality specifications and other information on the analysis. This represents our mission to build fully transparent diagnostics where customer has easy access to the details of the analysis.

**Clinical Interpretation**

In addition to our cutting-edge proprietary sequencing technology and bioinformatics pipeline, BpG also provides the customers with the best-informed clinical statement on the market. Clinical interpretation requires fundamental clinical and genetic understanding on hereditary cardiovascular diseases. At Blueprint Genetics our geneticists and cardiologists, who together, evaluate the results from the sequence analysis pipeline in the context of phenotype information provided in the requisition form, prepare the clinical statement. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals, even without training in genetics.

Variants reported in the statement are always classified using the Blueprint Genetics Classification Scheme modified from the ACMG guidelines (Richards et al. 2015), which has been developed by evaluating existing literature, databases and with thousands of clinical cases analyzed in our laboratory. Variant classification forms the corner stone of clinical interpretation and following patient management decisions. Our statement also provides allele frequencies in existing databases and *in silico* predictions. We also provide PubMed IDs to the articles or submission numbers to public databases that have been used in the interpretation of the detected variants. In our conclusion, we summarize all the existing information and provide our rationale for the classification of the variant.

A final component of the analysis is the Sanger confirmation of variants classified as likely pathogenic or pathogenic. This does not only bring confidence to the results obtained by our NGS solution but establishes the mutation specific test for family members. Sanger sequencing is also used occasionally with other variants reported in the statement. In the case of variant of unknown significance (VUS) we do not recommend risk stratification based on the genetic finding. Furthermore, in the case of VUS we do not recommend use of genetic information in patient management or genetic counseling. For some cases Blueprint Genetics offers a special service to investigate the role of identified VUS.

We constantly follow the development on the field of hereditary cardiovascular diseases and adapt new relevant information and findings to our diagnostics. Relevant novel discoveries can be rapidly translated and adopted into our diagnostics without delay. These processes ensure that our diagnostic panels and clinical statements remain the most up-to-date and relevant on the market.

**Sample Requirements**

- 3ml of EDTA blood
- Purified DNA 10μg
- Saliva (Oragene DNA OG-500 or OGD-500 kit, DNA Genotek)

Details for sample preparations and sending are found [here](#).
About the Disorder

Short QT syndrome is a rare heart disease caused by abnormal functions of cardiac ion-channel proteins that lead to accelerated atrial and ventricular repolarization characterized by shortening of the QT interval on electrocardiogram (ECG). This recent addition to the growing list of channelopathies is associated with increased risk for paroxysmal atrial and ventricular tachyarrhythmias, and sudden cardiac death (SCD). Cardiac arrest is the most commonly reported symptom among SQTS patients and it is the first symptom in as many as 28% of patients (Giustetto et al. 2006). SQTS can manifest in any stage of life even in infancy and has been suggested as one potential cause for sudden infant death syndrome (Giustetto et al. 2006). Similarly to long QT syndrome (LQTS), the diagnosis of SQTS is based on patient’s clinical history, ECG findings, and family history. Implantable cardioverter-defibrillator (ICD) is the first-line treatment for secondary prevention of SCD and could be used also in primary prevention (Patel et al. 2010).

SQTS is a dominantly inherited genetically heterogeneous disease. To date mutations in six genes have been reported to associate with SQTS: KCNH2, KCNQ1, KCNJ2,CACNA1C, CACNA2D1 and CACNB2. They have been labeled SQT1-SQT5 based on the chronology of their discovery. Interestingly, SQT1-3 are associated with the same genes causing also LQTS subtypes 1, 2, and 7. In contrast to the loss-of-function mutations in LQTS, the SQTS mutations cause a gain-of-function phenotype. SQT1 caused by mutations in KCNH2 is currently the most common form of the SQTS. Importantly, SQT mutations in KCNH2 dramatically decrease the affinity of class III anti-arrhythmic drugs such as d-sotalol and thus explain the poor efficacy of class III drugs in SQTS. In studies with small patient numbers, 25% of SQTS patients had mutations in KCNH2 (Giustetto et al. 2006). To date mutations in KCNQ1 and KCNJ2 are only rarely been reported (Bellocq 2004; Priori 2005).

Loss-of-function mutations of CACNA1C and CACNA2B, encoding cardiac L-type calcium channel, have been reported in families with SQTS and ECG characteristics of both Brugada syndrome and short QT interval (Antzelevitch et al. 2007). Similar phenotype has been described in patients carrying mutations in CACNA2D1, which is also a component of cardiac L-type calcium channel (Burashnikov et al. 2010).

References

Ackerman, M.J. et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace 2011, 13(8), 1077–1109. Link.


