**Brugada Panel**

The Blueprint Genetics Brugada Panel is an effective diagnostic tool for patients manifesting Brugada syndrome or a Brugada-like disorder. The Panel covers 18 genes associated with the phenotype. It should be noted that clinical presentation in BrS overlap with many other inherited severe arrhythmia diseases that all carry a strong risk for SCD. These diseases include long QT syndromes (LQTS), short QT syndromes (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and arrhythmogenic right ventricular cardiomyopathy (ARVC). In addition to overlapping phenotypes, causative genes are often same. In the case of atypical features or failure to narrow reliably the exact diagnosis, we recommend BpG Arrhythmia Panel instead of Brugada Panel to cover other hereditary arrhythmias overlapping with Brugada syndrome.

The Brugada Panel provides a high quality read-out of all clinically relevant genes associated Brugada 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 Brugada 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**

ANK2, CACNA1C, CACNA2D1, CACNB2, CAV3, GPD1L, HCN4, KCND3, KCNE3, KCNH2, KCNJ8, RANGRF, SCN1B, SCN2B, SCN3B, SCN5A, SLMAP, TRPM4

The test covers 18 genes with evidence of association with Brugada or Brugada-like disorders. 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 Brugada Panel that covers the genes associated with Brugada 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 Brugada Panel, median sequencing depth in the target region was 635x on a nucleotide level and 99.78% 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 Brugada 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 (detecting a pathogenic or likely pathogenic mutation) with Brugada Panel is currently 36.0% in our laboratory. 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 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

In Brugada syndrome and Brugada-like disorders abnormal cardiac ion channel function leads to detectable ST changes in right precordial leads in a rest ECG in >20% of patients. It makes patients susceptible to fatal cardiac arrhythmia without having “structural” heart disease. Clinical manifestation varies from syncope to ventricular tachyarrhythmias and sudden cardiac death (SCD) that occur usually at rest, during sleep, or with high fever. Brugada syndrome is responsible for 4-12% of unexpected sudden deaths and for up to 20% of all sudden deaths occurring in individuals with apparently normal heart. Suspicion of Brugada syndrome arises when Brugada type ECG is found coincidentally from asymptomatic subject or from patient with arrhythmias. Brugada ECG pattern and SCD may be precipitated by electrolyte disturbances, cocaine use, fever, and certain medications such as ajmaline, flecainide, propafenone, antidepressants and propofol (www.brugadadrugs.org). However, Brugada syndrome may be present even in the absence of any clinical symptoms and in some patients SCD occurs without preceding symptoms and without an identifiable cause at autopsy. Prevalence of Brugada syndrome is 1:5,000 in Western countries but disease is believed to be more frequent in South Asia. Brugada syndrome is confirmed to be clinically and genetically same disorder as sudden unexpected nocturnal death syndrome (SUNDS), which has several synonyms throughout the world (Vatta et al. 2002; Hong et al. 2004). It has also been called as idiopathic ventricular fibrillation, although these mutations do not map entirely in the same genes.

Until to date, causative mutations have been characterized from 18 genes in Brugada syndrome (ANK2, CACNA1C, CACNA2D1, CACNB2 (CACNB2B), CAV3, GPD1L, HCN4, KCND3, KCNE3, KCNH2, KCNJ8, RANGRF (MOG1), SCN1B, SCN2B, SCN3B, SCN5A, SLMAP and TRPM4), of which SCN5A is the most important. In 2013, TRPM4 gene found to be the second (6%) most important cause of Brugada syndrome (Liu et al. 2013). Brugada syndrome has autosomal dominant pattern of inheritance. Disease penetrance is not yet well defined and prognosis is variable between Brugada syndrome cohorts, possible reflecting lack of easily interpretable diagnostic criteria and underuse of confirmatory molecular genetic testing. In near future, molecular genetics is likely to increase uniformity of Brugada syndrome patient cohorts.

Of all SCN5A mutation carriers, 25% have typical Brugada syndrome ECG finding and 80% will develop it during flecainide challenge, which is also predictive for SCD in Brugada syndrome (Kapplinge et al. 2010). In a patient level, molecular genetic testing has been recommend for all persons with type-1 Brugada ECG irrespective of symptoms (Ackerman et al. 2011). Genetic testing forms a basis of patient’s clinical evaluation and assessment of family members. Positive gene test in Brugada syndrome guides therapy towards ICD, the only good treatment option in Brugada syndrome (Cerrone & Priori 2011). All patients who undergo genetic testing should receive pre-test and post-test genetic counseling so that they can understand the implications of testing.

Early reports showed that only one fifth of the patients fulfilling Brugada syndrome clinical criteria had a positive gene test result. It is believed to reflect limited number of genes screened when evaluating this entity in clinical practice. Guidelines for molecular genetic testing have recommended sequencing only SCN5A in Brugada syndrome due to relatively low diagnostic yield of other genes and large size (high exon count) of other causative Brugada syndrome genes (Ackerman et al. 2011). However, recent technological discoveries have increased cost-effectiveness of panel based genetic testing. Large Brugada syndrome gene panels are now recommended diagnostic option for Brugada syndrome (Pagon et al. 2005).

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.


