Heart Panel

The Blueprint Genetics Heart Panel is a comprehensive 133 genetic diagnostic tool developed to cover a wide spectrum of cardiomyopathy and channelopathy diagnostics. It is a combination of Blueprint Genetics Pan Cardiomyopathy and Arrhythmia Panels. It can be used as a primary tool for patients with complex phenotype or family history. Typically there is a difficulty to distinguish if the patient has a cardiomyopathy or channelopathy. In some occasions the patient can actually have both conditions. The Heart Panel is also an excellent diagnostic tool in cases of sudden cardiac death (SCD).

The Heart Panel provides a high quality read-out of all clinically relevant genes associated with cardiomyopathies and channelopathies. 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 Heart Panel has undergone rigorous validation process during its evolution at Blueprint Genetics. Our unique sequencing technology combined with in-house built bioinformatics pipeline with cardiomyopathy and 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 cardiac patients and their families.

Genes Covered by Panel

The test covers 133 genes with evidence of association with cardiomyopathies and channelopathies. All protein coding exons and exon-intron boundaries are covered. Sequencing is also targeted to other regions with reported pathogenic or likely pathogenic cardiomyopathy mutations.

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Description of Test

Blueprint Genetics offers a comprehensive Heart Panel that covers the genes associated with cardiomyopathies and channelopathies. The genes are carefully selected based on the existing scientific evidence, our experience and existing mutation databases.
Coverage

In our latest validation of the Heart Panel, median sequencing depth in the target region was 441x on a nucleotide level and 99.49% 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 Heart 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 Heart Panel is currently 25.0% in our laboratory. Please review our variant interpretation strategy here.

Disorders and diagnoses where Heart Panel can be applied

I42.0 Dilated cardiomyopathy
I42.1 Hypertrophic cardiomyopathy
I42.1 Obstructive hypertrophic cardiomyopathy
I42.2 Other hypertrophic cardiomyopathy
I42.4 Endocardial fibroelastosis
I42.5 Other restrictive cardiomyopathy
I42.8 Other cardiomyopathies
I42.8 Arrhythmogenic right ventricular cardiomyopathy
I42.9 Cardiomyopathy unspecified
E74.0 Glycogen storage disease
E74.00 Unspecified glycogen storage disease
E74.02 Pompe disease
E74.03 Cori disease
E74.09 Other glycogen storage disease
E75.10 Unspecified gangliosidosis
E78.71 Barth syndrome
E75.21 Anderson-Fabry disease
E76.29 Beta-gluduronidase deficiency
E83.11 Hemochromatosis
E83.110 Hereditary hemochromatosis
E83.118 Other hemochromatosis
E83.119 Unspecified hemochromatosis
E85.0 Non-neuropathic heredofamilial amyloidosis
E85.1 Neuropathic heredofamilial amyloidosis
E85.2 Heredofamilial amyloidosis unspecified
E85.4 Organ-limited amyloidosis
E85.8 Other amyloidosis
E85.9 Amyloidosis unspecified
G11.1 Friedreich’s ataxia
G71.0 Duchenne’s muscular dystrophy
G71.0 Becker’s muscular dystrophy
G71.0 Emery-Dreifuss muscular dystrophy
Q87.1 Noonan’s syndrome
Q87.1 Costello syndrome
Q87.1 Leopard syndrome
Q87.89 Cardiofaciocutaneous syndrome
I50 Heart failure
I50.1 Left ventricular failure
I50.2 Systolic (congestive) heart failure
I50.20 Unspecified systolic (congestive) heart failure
‘I50.21 Acute systolic (congestive) heart failure
I50.22 Chronic systolic (congestive) heart failure
I50.23 Acute on chronic systolic (congestive) heart failure
I50.3 Diastolic (congestive) heart failure
I50.30 Unspecified diastolic (congestive) heart failure
I50.31 Acute diastolic (congestive) heart failure
I50.32 Chronic diastolic (congestive) heart failure
I50.33 Acute on chronic diastolic (congestive) heart failure
I50.4 Combined systolic (congestive) and diastolic (congestive) heart failure
I50.40 Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
I50.41 Acute combined systolic (congestive) and diastolic (congestive) heart failure
I50.42 Chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.43 Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.9 Heart failure unspecified
I46 Cardiac arrest

I46.2 Cardiac arrest due to underlying cardiac condition

I46.8 Cardiac arrest due to other underlying condition

I46.9 Cardiac arrest cause unspecified

I49 Other cardiac arrhythmias

I49.0 Ventricular fibrillation and flutter

I49.01 Ventricular fibrillation

I49.5 Sick sinus syndrome

I49.8 Other specified cardiac arrhythmias

I49.9 Cardiac arrhythmia unspecified

I45.81 Long QT syndrome

R94.3 prolongation of QT interval

Bioinformatics

We have developed a unique cardiomyopathy 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 5000 original publications on cardiomyopathies and channelopathies 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 cornerstone 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 clinically relevant variants, 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

When a person dies suddenly and unexpectedly from a suspected cardiovascular cause, the term sudden cardiac death (SCD) is used to classify the mortal event. SCD is frequently caused by an abrupt change in heart rhythm (arrhythmia), most often ventricular tachycardia or ventricular fibrillation that impairs cardiac pumping, thereby depriving vital organs of oxygenated blood. A brief episode of VT or VF may cause only momentary loss of consciousness (syncope), but death is the inevitable result of sustained VF in the absence of emergent medical care.

Estimates of the annual SCD incidence vary but are generally in the range of 50–100 per 100,000 persons in industrialized nations. In the United States, previous estimates have been as high as 450,000 deaths per year, representing a large fraction of total mortality due to heart disease and a substantial public health burden. These statistics largely reflect adult deaths in the setting of ischemic heart disease or heart failure but children can also be susceptible to SCD in the context of certain genetic disorders. Genetic defects can also cause SCD among adult patients.

Typical genetic defects are detected in genes associated with channelopathies and cardiomyopathies. Differential diagnostics between ion channel disease and cardiomyopathies can be occasionally challenging as severe ventricular arrhythmias can manifest in cardiomyopathy patients with subclinical or no morphological cardiomyopathy. Sudden cardiac deaths have been described in genotype positive phenotype negative asymptomatic patients carrying sarcomere mutations associated to HCM (Christiaans et al. 2009). In 90’s McKenna and colleagues described two families with five premature sudden deaths (from 17 to 44 years) in patients without macroscopic hypertrophy but with widespread myocardial disarray on histological examination, ECG abnormalities in alive relatives and later studies showed segregating TNNT2 mutation (p.Arg94Leu) within these families (McKenna et al. 1990 and Varnava et al. 1999). The largest study to date with 339 mutation carriers without clinical HCM showed low mortality (0.13% / person-year) in MYBPC3 mutation carriers whereas TNNT2 mutation carriers were at much higher risk for mortality (0.93% person-year) suggesting a role for the mutated gene in the risk stratification even without clinical findings (Pasquale et al. 2012). Furthermore, hereditary channelopathy can be a significant cause of morbidity and mortality in a patient with myocardial abnormalities originating from any cause. In addition to certain complex clinical situations the Blueprint Genetics Heart Panel can be utilized in forensics when evaluating patients with sudden cardiac death. If the patient has a clear clinical suspicion of a certain disease entity, we recommend choosing smaller phenotype-specific BpG panels rather than the Heart Panel.

References


