Aorta Panel

The Blueprint Genetics Aorta Panel is an efficient genetic diagnostic tool targeted for aortic dilatation and aortic aneurysm diseases. The Aorta Panel covers 18 genes associated with non-syndromic and syndromic aortic disease. Most of the aortic aneurysms associate to non-syndromic dilatation. However, at least 20% of aortic aneurysms are in context of syndromic diseases such as Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), Shprintzen-Goldberg syndrome (SGS) and vascular and other Ehlers-Danlos syndromes (EDS), which are also covered by the Aorta Panel. In clear syndromic cases we recommend to use the Blueprint Genetics Marfan Panel targeting only the syndromic forms of the disease.

The Aorta Panel provides a high quality read-out of all genes with well-established association to aortic aneurysms or dissection. Our OS-Seq™ technology provides high coverage clinical grade sequencing and enables reliable diagnostics for aortic disease patients with significantly lower costs and faster turnaround time (basic service TAT 21 days and express service TAT 7-10 days). The Aorta Panel has undergone rigorous validation process during its evolution at Blueprint Genetics. Our unique sequencing technology combined with in-house built bioinformatics pipeline and aortic disease mutation and knowledge databases, together with our experienced team of geneticists and clinicians, forms the most efficient aortic 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 aorta 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 aorta patients and their families.

Genes Covered by Panel

- ACTA2, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, GATA5, MYH11, MYLK, NOTCH1, PRKG1, SIK1, SLC2A10, SMAD3, TGFB2, TGFBR1, TGFBR2

The test covers 18 genes with evidence of association with non-syndromic and syndromic form of aortic aneurysm disease. All protein coding exons and exon-intron boundaries are covered. Sequencing is also targeted to other regions if reported mutations exist.

Description of Test

Blueprint Genetics offers a comprehensive aortic disease gene test panel that covers the genes associated with aortic aneurysms and dissection. The genes are carefully selected based on the existing scientific evidence, our experience and existing mutation databases.

Coverage

In our latest validation of the Aorta Panel, median sequencing depth in the target region was 757x on a nucleotide level and 100.00% 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 each modification is followed by our standardized validation process. In our latest validation the Aorta Panel had sensitivity of 1.000 and specificity of 1.000 to detect single nucleotide polymorphisms. Our panel had also good performance to detect insertions and deletions. Sensitivity was 0.963 for indels ranged 1-5 bp. This panel has not been validated to identify larger deletions, insertions or complex rearrangements.
Yield

Blueprint Genetics provides genetic diagnostics for hundreds of hospitals and clinics around the world. The diagnostic yield varies substantially between hospitals and countries. At Blueprint Genetics, diagnostic yield (detecting a pathogenic or likely pathogenic mutation) with Aorta Panel is currently 18.9%. Please review our variant interpretation strategy here.

Bioinformatics

We have developed a unique aortic disease sequence analyzer and interpretation pipeline. In the core of our bioinformatics lies our in-house created and curated aortic disease database, which is a synthesis of hundreds of original publications of aortic disease associated and validated mutations. 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 aortic diseases. At Blueprint Genetics the clinical statement is prepared by 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. 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 aortic 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.
Aortic dilatation is defined by a diameter larger than 110% of reference value determined by age, sex, and body surface area. Progressing aortic dilatation eventually fulfills the definition of aortic aneurysm, which is a local aortic diameter higher than 150% of reference value. Usually aortic aneurysm formation is driven by reduced elastin content and its fragmentation with concomitant smooth muscle cell loss, a process called cystic medial degeneration. Although this process is seen normally as a consequence of aging, it is accelerated in aortic aneurysm diseases. Most of the aortic aneurysms associate to non-syndromic dilatation. However, at least 20% of aortic aneurysms are in context of syndromic diseases such as Marfan syndrome (MfS), Loeys-Dietz syndrome (LDS), Shprintzen-Goldberg syndrome (SGS) and vascular and other Ehlers-Danlos syndromes (EDS). Aortic aneurysms lead frequently to sudden cardiac death due to rupture and dissection that may also rarely exist without earlier aneurysm or dilatation. In Sweden, incidence of ascending aortic aneurysm and dissection was 16.3/100,000 in men and 9.1/100,000 in women in 2002 and it is increasing in both genders due to larger aging population and improved imaging methods (Olsson et al. 2006). The most common syndromic aortic disease, Marfan syndrome, has an incidence of 20/100,000 with equal gender distribution.

According to recent guideline, surgical aneurysm treatment is indicated in adults at the latest when aortic diameter reaches 55 mm (Davies et al. 2002; H. J. Patel & Deeb 2008). This criterion seems to give much emphasis to operative risk as 62% of the patients suffer from dissection before aortic diameter exceeds 55 mm (Parish et al. 2009). Number of operations for thoracic aorta has increased substantially, 7-15 fold in Sweden between years 1987 and 2002 (Olsson et al. 2006). There is no full consensus on the optimal timing of treatment as many hospitals apply different criteria for patients with Loeys-Dietz syndrome, Marfan syndrome, familial thoracic aortic aneurysm and aortic dissection (TAAD) or bicuspid aortic valve. Optimal treatment thresholds have been challenging to determine due to several limitations, of which the most important is that diverse group of diseases predispose to dissection. An aortic surgery cohort of 675 MfS patients from Johns Hopkins showed 1.5% mortality within 30 days from surgery in patients with elective surgery (455 pts) compared to 11.7% in patients undergoing emergency repair (103 pts) (Gott et al. 1999). Although many patients with dissection die before reaching operating room, significant difference in peri- and post-operative mortality underscores the importance of developing molecular genetic approaches to determine personalized dissection risk.

Non-syndromic aortic dilatation associates to mutations in ACTA2, COL3A1, EFEMP2, FBN2, MYH11, MYLK, PRKG1, SLC2A10, and SMAD3. Molecular genetics of syndromic aortic dilatation is well characterized; MfS is caused generally by FBN1 and rarely by FBN2 mutations, LDS by SMAD3, TGFB2, TGFB1 or TGFB2 mutations, SGS by SKI mutations and EDS by COL3A1, COL5A1, and COL5A2 mutations. Dilatation of ascending aorta is also associated with bicuspid aortic valve which is genetically linked to mutations in NOTCH1 and GATA5 genes. Families carrying mutations in these genes can manifest as aortic disease even without the presence of bicuspid aortic valve. So far, over 2400 mutations from 18 genes have been identified behind inherited dilated aortic diseases (Table 1).

The benefits of genetic diagnostics in aortic disease are clear when noting marked heterogeneity in progression rate of the diseases with potentially catastrophic outcomes. Definitive Marfan syndrome diagnosis is still lacking in many patients in clinical practice due to insufficient use of molecular genetic testing (Caglayan & Dundar 2009). Utilizing efficient gene diagnostics has provided a specific gene diagnosis for over 85% of patients in a pediatric MfS population (Fairve et al. 2009). In Marfan syndrome, mutation type and location can predict disease severity. Mutation location in exons 24-32 of FBN1 gene associates with a more severe and complete phenotype including younger age at diagnosis and higher probability for aortic surgery (Fairve et al. 2007). Conversely, the mean age of LDS patients was only 16 years in 31 consecutive patients who underwent aortic root surgery due to very advanced (z-score 7.0±2.9) aortic aneurysm (Patel et al. 2011). Sequencing both TGFB1 and TGFB2 genes makes it possible to find gene diagnosis in 95% of the patients with LDS. It has direct effects on follow-up and treatment decisions because aortic dissection develops in narrower aorta and at younger age in LDS compared to MfS (Van Hemelrijk et al. 2010). Unfortunately, another major vascular disease, vascular EDS (type 4) is still diagnosed mostly after major vascular complications (Pepin et al. 2000).

Undisputed evidence shows that aortic aneurysm diseases advance with variable progression rate. Thus, gene diagnostics offers help for differential diagnostics but also improves risk evaluation within the same disease. Gene diagnostics has an increasing role in determining timing of interventions. It is likely that variations in other aneurysm genes may modify the disease phenotype but further investigations are needed to clarify this. Gene diagnosis enables efficient screening of first-degree relatives and identification of family members at higher risk for catastrophic complications of aortic aneurysm diseases.
References


