Marfan Panel

The Blueprint Genetics Marfan Panel is a powerful diagnostic and differential diagnostic tool with patients manifesting a connective-tissue disorder with phenotypic features of Marfan syndrome. The diagnosis of Marfan syndrome can be difficult as many of the features are also identified in normal population, features appear in an age-dependent manner and there is substantial phenotypic variability between diseased individuals. There is also considerable overlap with other connective-tissue disorders such as congenital contractural arachnodactyly (CCA), Loeys-Dietz syndrome (LDS), Ehlers-Danlos syndrome type 4 (vascular type), arterial tortuosity syndrome and Shprintzen-Goldberg syndrome, which are covered by the Marfan Panel. If the patient has an isolated aortic aneurysm with no other Marfan-like organ manifestations, we recommend to use the Blueprint Genetics Aorta Panel, which covers all syndromic and non-syndromic forms of aortic aneurysm disease.

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

Genes Covered by Panel

*FBN1, FBN2, TGFBR1, TGFBR2, SKI, SMAD3, TGFB2, COL3A1, SLC2A10*

The test covers 9 genes with evidence of association with Marfanoid syndromes. 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 Marfan syndrome gene test panel that covers the genes associated with Marfanoid syndromes. The genes are carefully selected based on the existing scientific evidence, our experience and existing mutation databases. Candidate genes are excluded from this first-line diagnostic test.

Coverage

In our latest validation of the Marfan 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 Marfan 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 Marfan Panel is currently 23.7%. The relatively low yield is caused by the large variety of connective-tissue disorder patients analyzed with the Panel. 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 Marfanoid syndromes. 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 connective tissue disorders 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

The diagnosis of Marfan syndrome can be difficult as many of the features are also identified in normal population, features appear in an age-dependent manner and there is substantial phenotypic variability between the patients. There is also considerable overlap with other connective-tissue disorders such as congenital contractural arachnodactyly (CCA), Loeys-Dietz syndrome (LDS), Ehlers-Danlos syndrome type 4 (vascular type), arterial tortuosity syndrome and Shprintzen-Goldberg syndrome (Cañadas et al. 2010). The BpG Marfan Panel is designed as a genetic diagnostic tool for patients suffering from clinical features of Marfan syndrome (Table 1). Genetic diagnosis has substantial significance for the patient and his family as it forms the basis for genetic counseling and can be used to determine risk of vascular complications and assessment of treatment strategies.

References

