The Blueprint Genetics Periodic Fever Syndrome Panel is a comprehensive and efficient diagnostic tool for patients with periodic fever. Periodic fever syndromes are a group of monogenic autoinflammatory diseases characterized by recurrent fever attacks and serosal inflammation. The panel covers 9 genes associated with the phenotype.

The Periodic Fever Syndrome Panel provides a high quality read-out of all clinically relevant genes associated with hereditary fever. 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 Periodic Fever Syndrome Panel has undergone rigorous validation process during its evolution at Blueprint Genetics. Our unique sequencing technology combined with in-house built bioinformatics pipeline with periodic fever mutation and knowledge database, together with our experienced team of geneticists and clinicians, forms the most efficient periodic fever diagnostics service in the market. Our variant classification schemes and clinical interpretation processes have been developed and validated with thousands of patients with hereditary disease. Blueprint Genetics publically shares all classified variants identified in periodic fever 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 periodic fever syndrome patients and their families.

Genes Covered by Panel

*NLRP3, NLRP12, ELANE, HAX1, MVK, LPIN2, MEFV, PSTPIP1, TNFRSF1A*

The test covers 9 genes with evidence of association with periodic fever 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 Periodic Fever Syndrome Panel that covers the genes associated with periodic fever syndromes. The genes are carefully selected based on the existing scientific evidence, our experience and existing mutation databases.

Coverage

In our latest validation of the Periodic Fever Syndrome Panel, median sequencing depth in the target region was 662x on a nucleotide level and 99.93% 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 Periodic Fever Syndrome 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.

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 periodic fever syndrome cannot be reliably estimated as the Panel is the latest diagnostic panel developed and the number of patients analyzed, to date, is not enough. Please review our variant interpretation strategy here.

Bioinformatics

We have developed a unique periodic fever syndrome sequence analyzer and interpretation pipeline. In the core of our bioinformatics lies our in-house created and curated periodic fever syndrome mutation database, which is a synthesis of original publications on periodic fever syndrome 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 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 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 periodic fever syndrome 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

Periodic fever syndromes (PFS) are a group of monogenic autoinflammatory diseases characterized by recurrent fever attacks and serosal inflammation. These diseases arise from defective genes regulating innate immunity mainly by affecting proinflammatory cytokines and apoptosis pathways. PFS include familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), hyper-IgD syndrome (HIDS, also known as mevalonate kinase deficiency, MKD), severe congenital neutropenia types 1 and 3, cyclic neutropenia and a spectrum of diseases known as the cryopyrin-associated periodic syndromes (CAPS) or cryopyrinopathies namely familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurologic cutaneous articular (CINCA, also known as neonatal-onset multisystem inflammatory disease, NOMID). Periodic fevers typically present in children but disease onset in adult age is not a rare occasion in some of the conditions.

Although each PFS has some characteristic features, patients often display overlapping inflammatory symptoms in abdomen, chest, skin and musculoskeletal system. Certain clinical signs may help differentiation; attack duration and interval, rash type, central nervous system involvement (frequently observed in CAPS), and pleural effusion (common in FMF and TRAPS, but rare in HIDS or CAPS). However, in clinical practice definitive diagnosis is often hard to establish due to individual variability in symptom intensity and localization. An algorithm has been established to guide the use of genetic testing in FMF by family history, age of onset, presence of abdominal or chest pain, and diarrhea (Gattorno et al. 2008). However, the algorithm has only moderate accuracy (87% sensitivity and 72% specificity) in identifying the genetic origin of FMF. Corresponding algorithms have never been created for adult patients or large populations of other periodic fevers. Nonspecific manifestations of the PFS mimic many common acquired disorders such as infections, acute appendicitis, cholecystitis, and arthritis. This can delay diagnosis for many years and subject patients to diagnostic odyssey and even unnecessary surgery. Untreated PFS can result in serious complications such as end-stage renal disease, malabsorption, kidney failure, infertility and growth retardation. Molecular analysis of periodic fever patients can improve their quality of life by providing early and accurate diagnosis and allowing the administration of appropriate treatment.

There are no universally accepted clinical diagnostic criteria or guidelines for genetic diagnostics of PFS. However, the field is evolving and some national and even international guidelines have been published trying to guide genetic diagnostics of PFS (Samuels et al. 2006, Timmann et al. 2009, Shinar et al. 2012, Marcuzzi et al. 2013). Genetic testing of PFS is indicated when patient has clinical symptom pattern consistent with one or more of the periodic fever syndromes (Shinar et al. 2012). Presymptomatic genetic testing may be recommended also for asymptomatic family members when a severe genotype has been found in a relative with an overt disease, or if there is a family history of amyloidosis (Shinar et al. 2012). Moreover, carrier status testing may be reasonable in healthy relatives to phase two known disease causing or new mutations identified in an index patient.

Colchicine has been used for a long time as standard treatment for FMF, due to its microtubule stabilizing abilities. Corticosteroids are still used commonly as initial therapy. Accumulating knowledge on pathways controlling immunity and inflammation along with the molecular characterization of major PFS has enabled development of targeted therapies. Anakinra, a specific IL-1 receptor antagonist, was a breakthrough in therapeutics of the most severe cryopyrinopathy (CINCA), with dramatic effects not only on the rash and acute-phase proteins, but also on the aseptic meningitis and cochlear inflammation that often lead to severe disability (Goldbach-Mansky et al. 2006). Other novel biological treatments, such as IL-1 inhibitors canakinumab and rilonacept, and anti-TNF-α agents adalimumab, etanercept, and infliximab, have also become available (Marcuzzi et al 2013). Utilization of these treatments has increased with precision diagnostics. Long-term treatments are designed to reduce the number and severity of the inflammatory attacks, as well as to prevent severe disease complications.

Until to date over 900 variants have been identified in genes encoding proteins involved in PFS. Some of the variants are clearly pathogenic but most variants are of unknown significance or clearly non-pathogenic. Genetic testing of PFS with NGS strategies is recognized as a logical and feasible way to corroborate clinical diagnosis due to high diagnostic yield. More than 93% of the reported sequence variants in the underlying genes are single nucleotide variants, whereas less than 1% are indels >50bp. Therefore, high quality NGS is optimal genetic diagnostic tool in this disease group. Recently, somatic NLRP3/CIA51 mosaicism has been reported as a major cause of CINCA/NOMID after an international case-control study revealed mosaicism in 18 of the 26 patients (69%) and none of their healthy control relatives (Tanaka et al. 2011). This should be noted when establishing a bioinformatic pipeline for NLRP3.
References


