Emery-Dreifuss Muscular Dystrophy (EDMD) Panel

The Blueprint Genetics EDMD Panel is an efficient diagnostic tool for patients with clinical features of Emery-Dreifuss muscular dystrophy. It covers all 7 genes associated with the disorder.

The EDMD Panel provides a high quality read-out of all clinically relevant genes associated with channelopathies and ARVC. 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 EDMD 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 and ARVC mutation and knowledge database, together with our experienced team of geneticists and clinicians, forms the most efficient Emery-Dreifuss muscular dystrophy 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 EDMD 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 muscular dystrophy patients and their families.

Genes Covered by Panel

**EMD, FHL1, LMNA, SYNE1, SYNE2, TMEM43, TTN**

The test covers 7 genes with evidence of association with Emery-Dreifuss muscular dystrophy. 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 EDMD Panel that covers the genes associated with Emery-Dreifuss muscular dystrophy. The genes are carefully selected based on the existing scientific evidence, our experience and existing mutation databases.

Coverage

In our latest validation of the EDMD Panel, median sequencing depth in the target region was 414x on a nucleotide level and 99.58% 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 EDMD 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 for EDMD cannot be reliably estimated as the disorder is extremely rare and only few cases, to date, have been analyzed. Please review our variant interpretation strategy here.

Bioinformatics

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

Emery-Dreifuss muscular dystrophy is a condition that affects mainly skeletal muscle and heart. Usually it presents in early childhood with joint deformities called contractures, which restrict the movement of certain joints – most often elbows,
ankles, and neck. Majority of the patients experience also slowly progressive muscle weakness and wasting, initiating from upper arm and lower leg muscles and progressing to shoulders and hips. Practically all patients with Emery-Dreifuss muscular dystrophy have cardiac involvement by adulthood. It presents clinically as cardiac conduction defects and/or arrhythmias. Cardiomyopathy phenotype is usually classified as dilated cardiomyopathy but also ARVC and hypertrophic cardiomyopathies have been described. Different types of Emery-Dreifuss muscular dystrophy are classified by their pattern of inheritance: X-linked, autosomal dominant, and autosomal recessive. Although the three types have similar signs and symptoms, researchers believe that the features of autosomal dominant Emery-Dreifuss muscular dystrophy are more variable than the other types. A small proportion of patients with the autosomal dominant type experience cardiac manifestation without any skeletal muscle weakness or wasting.

It is estimated that 45% of patients do not carry mutations in \textit{EMD} and \textit{LMNA} that are the most common defective genes causing EDMD (Orphanet #261). Mutation in seven genes are involved in the pathogenesis of EDMD (Table 1). It is probable that some genes causing EDMD have not been discovered yet. The main differential diagnoses include other forms of skeletal muscle myopathy with contractures, with or without cardiac involvement such as Bethlem myopathy, \textit{SEPN1} and \textit{FKRP}-related myopathies, desmin-related myopathies, proximal myotonic myopathy, and certain forms of limb-girdle muscular myopathies with cardiac involvement.

In February 2014, \textit{TTN} gene was added into the EDMD panel and the justification for this is discussed shortly below. Especially recessive \textit{TTN} mutations are linked to neuromuscular diseases such as 1) early-onset myopathy with fatal cardiomyopathy (\textit{OMIM} #611705) and 2) limb-girdle type 2J muscular dystrophy (also heterozygotes have mild, late-onset disease, \textit{OMIM} #608807). However, the pathophysiological role of titin in skeletal muscle conditions and cardiomyopathies is incompletely understood, due to limited number of studies where titin gene has been fully sequenced in respective patients groups. In 2014, Chauveau and colleagues published a study of 23 families with congenital core myopathy (main non-dystrophic myopathy in childhood) and primary heart disease using partial \textit{TTN} sequencing followed by functional studies (Chauveau et al. 2014). They identified recessive \textit{TTN} mutations (homozygous and compound heterozygous) in 17% of the patients. In their study, phenotype analysis identified four novel titinopathies including Emery-Dreifuss muscular dystrophy, cardiac septal defects, left ventricular non-compaction and arthrogryposis. Parents with a single heterozygous mutation were healthy. Based on this novel finding, BpG has added the \textit{TTN} gene into our EDMD Panel, even though the role of \textit{TTN} in EDMD needs still further confirmation. We believe that evaluation of all coding exons of the \textit{TTN} gene can help differential diagnostics in patients with early onset non-dystrophic myopathy.

References


Orphanet #261, Emery-Dreifuss Muscular Dystrophy. \textbf{Link}.