

DMD Gene Analysis in Dystrophinopathies (Duchenne & Becker Muscular Dystrophy)

CLINICAL FEATURES

The dystrophinopathies are a group of diseases with overlapping clinical features that are caused by mutations in the X-linked DMD gene. The DMD gene encodes dystrophin, which is an important component of the dystrophin-associated protein complex (DAPC) and plays a structural role in ensuring membrane stability, regulation of signaling processes and forcing transduction during muscle contraction. Dystrophin is mainly expressed in the skeletal and cardiac muscles and in the brain. Pathogenic variants in the DMD gene can lead to reduced or absent dystrophin, which can cause fragility of the muscle fiber and ineffective regeneration of muscle tissue.

The age-of-onset ranges from early childhood to adulthood. The mild end of the spectrum includes elevated serum creatine phosphokinase (CK) concentration, muscle cramps, quadriceps myopathy, and myoglobinuria. The more severe end of the spectrum includes progressive Duchenne/Becker muscular dystrophy and DMD-associated dilated cardiomyopathy (DCM). Duchenne muscular dystrophy (DMD) can present in early childhood with motor developmental delay, symmetric proximal weakness, waddling gait, difficulty climbing, calf hypertrophy and a highly elevated serum creatine phosphokinase (CK) concentration. As the disorder progresses, respiratory complications or dilated cardiomyopathy (DCM) can occur (PMID: 20301298). Becker muscular dystrophy (BMD) typically presents as a later-onset disorder with a similar phenotype to DMD including progressive symmetric muscle weakness and atrophy, elevated serum CK, quadriceps weakness and DCM, and it may also cause activity-induced cramping and flexion contractures of the elbow. Heterozygous carriers for a pathogenic variant in the DMD gene causing DMD/BMD are at an increased risk for DCM (PMID: 20301298). In some individuals with pathogenic *DMD* variants, the heart muscle is primarily affected, resulting in DMD-associated DCM with little or no clinical evidence of skeletal muscle involvement. DMD-associated DCM typically presents in hemizygous individuals in young adulthood and in heterozygous individuals in the fourth or fifth decade with one or more of the following: i) heart failure with symptoms of congestion, ii) reduced cardiac output resulting in fatigue or dyspnea on exertion, arrhythmias and/or conduction system disease, iii) thromboembolic disease or stroke, iv) elevated serum CK, and/or v) mild skeletal muscle weakness (PMID: 20370590, 20301298, 20301486). Dystrophinopathies are common neuromuscular disorders with a reported incidence of 1 in 3,900–4,700 live male births (PMID: 1673177, 20080524, 2784019).

GENETICS

Dystrophinopathies are inherited in an X-linked manner. Sporadic pathogenic variants occur in approximately 25% of cases, while 75% are maternally inherited (PMID: 2338336). Penetrance of dystrophinopathies is complete in hemizygous individuals; however, penetrance in heterozygous carriers can vary and may depend on X-chromosome inactivation.

Deletions or duplications of one or more exons of the DMD gene account for ~65–70% of all disease causing pathogenic variants (PMID: 16770791, 19367636). In the absence of a family history, the type of deletion/duplication predicts the DMD/BMD phenotype with approximately 90% accuracy; deletions/duplications that alter the reading frame of the protein typically correlate with the more severe

DMD phenotype, whereas those that maintain the reading frame are associated with the milder BMD phenotype (PMID: 16770791).

CLINICAL SENSITIVITY

The clinical sensitivity of this test depends in part on the patient's clinical presentation and is expected to be highest for individuals with a clearly defined phenotype and/or family history. Interpretations are made with the assumption that any clinical information provided, including familial relationships, are accurate.

Approximately 65–70% of individuals with a dystrophinopathy have an exon-level deletion or duplication in the DMD gene (PMID: 20301298, 18752307). Sequence variants, including single nucleotide changes and small rearrangements, account for ~25–30% of disease-causing pathogenic variants (PMID: 25037084). Approximately 3–7% of individuals with a dystrophinopathy do not have a pathogenic variant that is identifiable by the combined methods of sequencing and deletion/duplication testing (PMID: 25037084, 18059005). If other neuromuscular disorders are under consideration, the Neuromuscular Disorder Panel is also available at GeneDx.

TEST METHODS

Genomic DNA is extracted directly from the submitted specimen or, if applicable, from cultured fibroblasts. The DNA is enriched for the complete coding regions and splice junctions of the gene(s) tested using a proprietary targeted capture system developed by GeneDx for next-generation sequencing. The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants. Alternative sequencing methods are used to analyze or confirm regions with inadequate sequence data by NGS. Exon-level oligo array CGH (ExonArrayDx) is performed for most, if not all, of the coding exons of the requested gene(s). Exon-level array CGH can detect deletions and duplications greater than 250 bp. Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CGH analysis. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. Reportable variants include pathogenic variants, likely pathogenic variants, and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. Available evidence for variant classification may change over time and reported variant(s) may be reclassified according to the ACMG/AMP Standards and Guidelines (PMID: 25741868), which may lead to issuing a revised report.

Disclaimer:

Genetic testing using the methods applied at GeneDx is expected to be highly accurate. Normal findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable by this test. Unless otherwise indicated, the methods used cannot reliably detect deletions of 20bp to 500bp in size, or insertions of 10bp to 500bp in size. Sequencing cannot detect low-level mosaicism. Copy number assessment methods cannot reliably detect mosaicism and cannot identify balanced chromosome

aberrations. Regions of certain genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that yield suboptimal data, potentially impairing accuracy of the results.