

DMPK Gene Analysis for Myotonic Dystrophy Type 1

Disorder also known as: Myotonic Muscular Dystrophy type 1 (DM1): Dystrophia myotonica 1; Steinert Disease

Clinical Features:

Myotonic dystrophies are multisystem disorders that affect smooth and skeletal muscle and are one of the most common forms of muscular dystrophy. Myotonic dystrophy type 1 (DM1) can present with myotonia, cardiac abnormalities, muscle weakness, hypotonia, early-onset iridescent cataracts, hyperinsulinism, or early balding in males. Additionally, DM1 can also affect the central nervous and endocrine systems. Histological findings include atrophic fibers, with or without pyknotic myonuclei, and marked proliferation of fibers with central nuclei.² The age of onset and severity of symptoms is variable for DM1 leading to three clinical subtypes: mild, classic, and congenital. Mild DM1 is late onset (20-70 years) and presents with mild myotonia and cataracts. Classic DM1 has an age of onset from 10-30 years and is characterized by prominent facial weakness, drooping eyelids, distal muscle weakness, and gastrointestinal disturbances. Congenital DM1 presents with severe muscle weakness and hypotonia at birth. Additional features include feeding difficulties, positional malformations including club foot, and respiratory insufficiency that can lead to early death. Surviving infants typically have intellectual disability and developmental delays.² The myotonic dystrophies have a prevalence of 1 in 8000, with a higher prevalence of DM1 in Icelandic and French Canadian populations.⁷

Inheritance Pattern/Genetics:

DM1 is an autosomal dominant disorder caused by the expansion of a CTG trinucleotide repeat in the 3'UTR of the *DMPK* gene.² Normal alleles have 5-34 repeats, premutation (mutable normal) alleles have 35-49 repeats, and disease alleles have greater than 50 repeats.⁴ The clinical subtypes associated with disease alleles fall within a spectrum that is loosely based on CTG repeat number, where the mildest, latest onset form is associated with the smallest number of repeats (50-150) and the severe congenital onset form is associated with the greatest number of repeats (>1000).^{2,3} The trinucleotide repeat is meiotically unstable, leading to expansion of the repeat during transmission from parent to offspring. Therefore, premutation alleles are not associated with disease, but the offspring of individuals with premutation alleles have an increased risk for inheriting disease alleles. Furthermore, individuals may inherit disease alleles that are much longer than the parental allele, resulting in 'anticipation' or the occurrence of increasing severity and decreasing age of onset in subsequent generations. A child with early onset disease is more likely to have inherited the disease allele from the mother, and anticipation is more often associated with the transmission of an expanded

maternal allele. Overall, there is a negative correlation between CTG repeat length and age of onset, as well as a positive correlation between repeat length and disease severity, although this correlation is not absolute.^{1,3} Therefore, a repeat number of greater than 50 is sufficient to make a diagnosis of DM1 and repeat number alone should not be used for prognosis. Clinical correlation is necessary to determine if the finding is consistent with a specific DM1 subtype (Kamsteeg et al., 2012).

Test Methods:

Using genomic DNA obtained from blood (10-15 mL in EDTA), repeat analysis is performed using two complementary PCR assays. Each sample is evaluated by repeat-primed PCR to identify an expanded allele, and standard PCR fragment analysis is used to determine the number of repeats in normal alleles and small expansions. The combination of repeat-primed PCR and fragment analysis allows for the definitive identification of an expanded allele, although the exact number of repeats cannot be reported for those alleles that have greater than 150 repeats in *DMPK*. Southern blot analysis is required to determine the number of repeats in alleles larger than this and is not completed as part of this test. If desired, DM1 Southern blot analysis can be ordered from GeneDx. *DMPK* Southern blot analysis is not currently available for samples from New York State.

Test Sensitivity:

The clinical sensitivity for analysis of the repeat region in *DMPK* depends on the clinical phenotype of the patient. All individuals with DM1 have an expansion of the repeat in the 3' UTR the *DMPK* gene, which is detectable by this targeted analysis.² However, the exact number of repeats will not be determined for those alleles with more than 150 repeats. The technical sensitivity of fragment analysis is estimated to be greater than 95%.

References:

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