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.[1] 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.[1] 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.[1] Classic DM1 has an age of onset from 10-30 years and is characterized by myotonia, prominent facial weakness, muscle weakness and wasting, cataracts, and, often, cardiac conduction abnormalities.[1] Congenital DM1 can present before birth with polyhydramnios and reduced fetal movement or postnatally with severe muscle weakness, hypotonia, feeding difficulties, respiratory insufficiency, and intellectual disability.[1] The myotonic dystrophies have a prevalence of 1 in 8000, with a higher prevalence of DM1 in Icelandic and French Canadian populations.[2]

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.[3] Normal alleles have 5-34 repeats, premutation (mutable normal) alleles have 35-49 repeats, and disease alleles have greater than 50 repeats.[4] Repeat expansions of <250 generally result in the mild form of DM1; however, larger repeat expansions do not appear to have the same linear correlation with age-of-onset and disease severity.[5,6,7] Some studies do suggest that congenital DM1 is more commonly associated with repeats of greater than 2,000 repeats, but several studies have identified individuals with Classic DM1 and >1000 repeats.[8,9,10] 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.[11] Clinical correlation is necessary to determine if the finding is consistent with a specific DM1 subtype. Premutation alleles with 35-49 CTG repeats are not associated with symptoms of DM1, however all alleles with greater than 35 repeats are meiotically unstable and expansion of these alleles has been observed in their transmission from parent to offspring. Therefore, offspring of these individuals have an increased risk of inheriting an expanded allele and being affected with DM1.[4]

Test Methods:

Using genomic DNA, 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.[1] 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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