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 50 or more repeats.[4] Premutation alleles with 35-49 CTG repeats are not associated with symptoms of DM1, however all alleles with 35 or more 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] Repeat expansions of <250 generally result in mild DM1; however, larger repeat expansions do not appear to have the same linear correlation with age-of-onset and disease severity.[5,6,7] Although anticipation is well documented for DM1, multiple studies have shown considerable phenotypic variation among individuals with similar repeat numbers, including classically affected individuals with >1000 repeats and congenitally affected individuals with <1000 repeats.[8-12] It's estimated that Congenital DM1 is only strongly associated with repeat lengths in excess of 2000.[8,11] Therefore, a repeat number of 50 or more is sufficient to make a diagnosis of DM1 and use of repeat number to predict disease subtype or prognosis is not recommended by multiple guidelines.[11,12] Clinical correlation is necessary to determine the

specific DM1 subtype and is especially relevant for prenatal and carrier testing of asymptomatic individuals.

Test Methods:
Using genomic DNA obtained from the submitted specimen, repeat analysis is performed via standard PCR fragment analysis to identify alleles with 100 or fewer repeats and the Asuragen AmplideX PCR/CE DMPK kit to identify alleles with >100 repeats. Nucleotide repeat numbers up to 50 are reported with an accuracy of +/- 2 repeats and repeat numbers from 50-200 are reported with an accuracy of +/- 5 repeats. The exact number of repeats cannot be determine for alleles with >200 repeats. Internal standards are analyzed along with clinical samples to evaluate assay performance. Southern blot analysis is required to determine the number of repeats in alleles larger than this, but is not completed as part of this test. If desired, Southern blot can be ordered from GeneDx, however it is not available for prenatal analysis or 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 200 repeats. The technical sensitivity of fragment analysis is estimated to be greater than 95%.

References:
1. Bird T (Updated 2018). Myotonic Dystrophy Type 1. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2012. Available at http://www.genetests.org;
2. Yotova et al. (2005) Anatomy of a founder effect: myotonic dystrophy in Northeastern Quebec. Hum Genet 117:177-87
3. Arsenault et al. (2006) Clinical characteristics of myotonic dystrophy type 1 patients with small CTG expansions. Neuro 66:1248-50.
4. Martorell et al., (2001) Frequency and stability of the myotonic dystrophy type 1 premutation. Neurology 56 (3): 328-335 (PMID: 11171897)
5. Savic et al. (2002) Human Mutation 19 (2):131-9 (PMID: 11793472)
6. Hamshere et al. (1999) J. Med. Genet. 36 (1):59-61 (PMID: 9950368)
7. Thornton et al. (2014) Neurol Clin 32 (3):705-19, viii (PMID: 25037086)
8. Meola et al. (2015) Biochimica Et Biophysica Acta 1852 (4):594-606 (PMID: 24882752)
9. Tsilfidis et al. (1992) Nat. Genet. 1 (3):192-5 (PMID: 1303233)
10. Lavedan et al. (1993) Am. J. Hum. Genet. 52 (5):875-83 (PMID: 8098180)
11. The International Myotonia Dystrophy Consortium (2000) Neurology 54 (6): 1218-1221 (PMID: 10746587)
12. Kamsteeg et al. (2012) Eur. J. Hum. Genet. 20 (12):1203-8 (PMID: 22643181)