CNBP Gene Analysis for Myotonic Dystrophy Type 2

Disorder Also Known As: Myotonic Dystrophy 2 (DM2): Dystrophia myotonica 2; proximal myotonic myopathy; PROMM; Ricker syndrome

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 2 (DM2) typically presents in the third decade or later with myotonia and muscle weakness or stiffness, but may also include generalized proximal weakness, cardiac conduction defects, cataracts, insulin-insensitivity, or testicular failure.[2,7] Histological findings include atrophic fibers with pyknotic myonuclei, and marked proliferation of fibers with central nuclei.[2] The myotonic dystrophies have a prevalence of 1 in 8000, with a higher prevalence of DM2 in German, Finnish, and Polish populations.[9,11]

Inheritance Pattern/Genetics:
DM2 is an autosomal dominant disorder caused by an expansion of the CCTG tetranucleotide repeat within the complex repeat motif [TG(n)TCTG(n)CCTG(n)] in intron 1 of the CNBP (also known as ZNF9) gene.[2] The three repeating units (TG, TCTG, CCTG) within this motif are all highly variable in both individuals with DM2 and the general population.[6] The CCTG repeat is the only repeat that expands to pathogenic lengths, although the highly polymorphic TG and TCTG repeats contribute to the overall length of the expansion. Consequently, the exact number of CCTG repeats cannot be determined as the TG and TCTG repeats make up a significant and unknown proportion of the overall length of the expansion.[4] Normal alleles have 11-26 CCTG repeats and disease alleles have greater than 75 repeats. Disease alleles can contain more than 11,000 repeats, with an average of 5,000 repeats[2]. Alleles in the range of 27-74 repeats are not well characterized and their pathogenicity and stability is unknown.[1] The tetranucleotide repeat displays somatic instability resulting in a heterogeneous population of expanded alleles. The repeat is also meiotically unstable, allowing for both expansions and contractions of disease alleles within the disease range during transmission from parent to offspring.[2,3,5]

Test Methods:
Using genomic DNA obtained from blood (2-5 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 normal alleles. 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 determined for those alleles that have greater than 75 repeats in *CNBP*.

Test Sensitivity:

The clinical sensitivity for analysis of the repeat region in CNBP depends on the clinical phenotype of the patient. All individuals with DM2 have an expansion of greater than 75 repeats in intron 1 of the CNBP gene, which is detectable by this targeted analysis.[2] The technical sensitivity of fragment analysis is estimated to be greater than 95%.

References:

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