CNBP Gene Analysis for Myotonic Dystrophy Type 2

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.[1,2] Histological findings include atrophic fibers with pyknotic myonuclei, and marked proliferation of fibers with central nuclei.[1] The myotonic dystrophies have a prevalence of 1 in 8000, with a higher prevalence of DM2 in German, Finnish, and Polish populations.[3]

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.[1] The three repeating units (TG, TCTG, CCTG) within this motif are all highly variable in both individuals with DM2 and the general population.[4]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.[5] Normal alleles have 26 or less CCTG repeats and disease alleles have 75 or more repeats. Disease alleles can contain more than 11,000 repeats, with an average of 5,000 repeats.[1] Alleles in the range of 27-74 repeats are not well characterized and their pathogenicity and stability is unknown.[6] 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 tooffspring.[1,7,8]

TEST METHODS

Using genomic DNA obtained from the submitted specimen, repeat analysis is performed via standard PCR fragment analysis to identify alleles with 75 or fewer repeats and a laboratory developed repeat-primed PCR to identify alleles with >75repeats. Nucleotide repeat numbers up to 26 are reported with an accuracy of +/- 2 repeats and repeat numbers from 27-75 are reported with an accuracy of +/- 5 repeats. The exact number of repeats cannot be determine for alleles with >75 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.

CLINICAL 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.1 The technical sensitivity of fragment analysis is estimated to be greater than 95%.

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