CNBP Gene Analysis for Myotonic Dystrophy Type 2

Also known as:  Myotonic Dystrophy 2 (DM2); Dystrophia myotonica 2; proximal myotonic myopathy; PROMM; Ricker syndrome

Mendelian inheritance in Man Numbers:  602668  Myotonic Dystrophy 2; DM2

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 (Dalton et al., 2013; Meola et al., 2013). Histological findings include atrophic fibers with pyknotic myonuclei, and marked proliferation of fibers with central nuclei (Dalton et al., 2013). The myotonic dystrophies have a prevalence of 1 in 8000, with a higher prevalence of DM2 in German, Finnish, and Polish populations (Udd et al. 2003; Suominen et al. 2011).

Inheritance:  DM2 is inherited in an autosomal dominant manner.

Genetics:  DM2 is 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 (Dalton et al., 2013). The three repeating units (TG, TCTG, CCTG) within this motif are all highly variable in both individuals with DM2 and the general population (Liquori et al., 2003). 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 (Kamsteeg et al., 2012). 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 (Dalton et al, 2013). Alleles in the range of 27-74 repeats are not well characterized and their pathogenicity and stability is unknown (Bachinski et al., 2009). 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 (Dalton et al, 2013; Day et al, 2003; Liquori et al, 2001).

Reason for Referral:  
1. Molecular confirmation of a clinical diagnosis
2. Genetic counseling

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 (Dalton et al., 2013). The technical sensitivity of fragment analysis is estimated to be greater than 95%.

Specimen Requirements and Shipping/Handling:  
- Blood: Whole blood in EDTA. Adults: 2-5 ml; Children: 2-5 ml; Infants: 2-3 ml. Ship blood overnight at ambient temperature, using a cool pack in hot weather. Blood specimens may be refrigerated for up to 7 days prior to shipping.
- Extracted DNA: Submission of extracted DNA is discouraged; however, high quality extracted DNA can be accepted. This test requires a minimum of 20 ug of DNA at a concentration of 40 ng/ul of DNA with a minimum volume of 400 ul.
- Other specimens: Whole blood in EDTA is preferred. If any other sample is being considered, please contact us for specific information.

Required Forms:  
- Sample Submission (Requisition) Form -complete all pages.
- Payment Options Form or Institutional Billing Instructions.
For test and CPT codes, please refer to the Test Catalog “by Disorder” page on our website at http://www.genedx.com.

References:


