Myotonic Dystrophy Type 1 (DMPK)

Myotonic dystrophy type 1 (DM1) is an inherited genetic disorder caused by an expanded number of CTG repeats in the *DMPK* gene. Disease onset and severity is variable ranging from mild adult-onset to prenatal/congenital onset. Classic DM1 is characterized by progressive muscle wasting and weakness, particularly in the lower legs, hands, neck, and face, myotonia, cataracts, GI disturbances, and cardiac conduction abnormalities. DM1 symptoms may occur at early ages and increase in severity with each succeeding generation. Genetic testing confirms diagnosis and aids in classification of DM1.

Tests to Consider

Myotonic Dystrophy Type 1 (DMPK) CTG Expansion 3001907

Method: Polymerase Chain Reaction/Capillary Electrophoresis

Diagnostic testing in children or adults with a suspected clinical diagnosis of DM1. Predictive testing for adults with a family history of DM1. Specific allele sizing estimates cannot be determined for CTG repeats of greater than 150. Prenatal samples are not accepted.

Disease Overview

Prevalence

Estimated at 1/20,000 births worldwide

Clinical Presentation

Clinical phenotypes span a continuum from mild to severe.

CTG repeat length is unstable in individuals with DM1, which often leads to somatic mosaicism for CTG repeat size.

- Correlation between CTG repeat size observed in one tissue with disease severity may not be possible.
- Larger CTG repeat expansions are associated with more severe and earlier-onset disease; however, significant overlap exists.
  - Predicting age of onset, severity, and rate of progression based on the number of CTG repeats is not possible.

DM1 Type	CTG Repeats	Clinical Phenotype
Mild	50-150	Adult onset with normal lifespan Symptoms include mild myotonia, cataracts, premature baldness
Classic	~100-1,000	Onset typically 10-30 years, lifespan may be reduced Symptoms include muscle weakness and wasting, myotonia, cataracts, cardiac conduction abnormalities, insulin resistance, gastrointestinal disease, premature balding
Congenital	>1,000	Onset in prenatal period or infancy with increased mortality in neonatal period: • Infants who survive have improvement in motor function, but later experience progressive myopathy and typical features of classic DM1. • Prenatal findings include polyhydramnios and reduced fetal movement. • Symptoms in infancy include hypotonia, generalized weakness, facial muscle weakness, respiratory insufficiency, and intellectual disability.

Genetics

Gene

DMPK

Inheritance

- Autosomal dominant
- Exhibits anticipation:
  - Premutation and full-penetrance disease alleles are unstable and have the ability to expand during transmission.

- Allele expansion may result in increasing disease severity and decreasing age of onset over generations.
- Expansion to allele sizes associated with congenital DM1 is more common when maternally transmitted.

Variants

Allele sizes are classified by the number of CTG repeats.

Allele Size	CTG Repeats	Result
Normal	5-34	Individual not at risk for developing or transmitting DM1
Premutation	35-49	Individual unaffected with DM1, but at risk for offspring with CTG expansion in disease-causing range
Full penetrance	≥50	Disease causing Clinical manifestations highly variable and age related; penetrance is 100% by age 50 Offspring at risk for DM1

Test Description

- Triplet repeat-primed polymerase chain reaction (PCR) followed by size analysis using capillary electrophoresis to assess the CTG repeat in the *DMPK* 3′ untranslated region
- Repeat sizing precision is approximately +/- 2 repeats for alleles with 5-24 repeats and +/- 4 repeats for alleles with 77 to 150 repeats.

Sensitivity/Specificity

- Clinical sensitivity is greater than 99% for DM1.[1]
- Analytical sensitivity/specificity is 99%.

Limitations

- Diagnostic errors can occur due to rare sequence variations.
- Specific allele sizing estimates cannot be determined for expanded alleles with greater than 150 CTG repeats.

References

1. Bird TD. Myotonic dystrophy type 1. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews, University of Washington; 1993-2020. [Last Revision: Oct 2019; Accessed: Feb 2020]

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