Athena Diagnostics

DMPK DNA Test (DM1)

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Testing that Makes a Difference.

Patient		Requesting Physician	Accession Number
REPORT, SAMPLE		Not Provided	12345678
Date of Birth	Sex	Report to	Family Number/Kindred Number
04/15/2015	F	QUEST DIAGNOSTICS	
Specimen Type		Address	Patient Number
Whole Blood		200 FOREST STREET	
Test Category			Specimen Collection Date
Diagnostic (Symptomatic)		2ND FLOOR	08/28/2020
Test Requested			Date Received
DMPK DNA Test (DM1)		MARLBOROUGH, MA 01752	08/29/2020
		Additional Reports to:	Report Date
			09/13/2020

DMPK DNA Test (DM1)

POSITIVE

This test identified a pathogenic variant in the *DMPK* gene.

INTERPRETIVE RESULTS TABLE

	Gene/Test	Technical Result	Variant Type	Inheritance	Clinical Relevance	Pub Med ID
Positive	**DMPK**	**953 and 5 repeats**	**Repeat Expansion**	**Autosomal Dominant**	**Pathogenic**	

DMPK CTG Repeat Ranges: Normal (5-34) Premutation (35-49) Mildly Affected (50-99) Classic (100-1000) Congenital (>1000)

Comments: This test result is consistent with a diagnosis of, or a predisposition to develop, myotonic dystrophy type 1 (DM1) associated with pathogenic variants in the *DMPK* gene.

Recommendations: This individual's family members are at risk for possessing or inheriting this variant. Careful reconciliation of this molecular data with this individual's clinical presentation, family history, and other laboratory results, in conjunction with genetic counseling, is highly recommended.

Health care providers, please contact the Athena Diagnostics Client Services Department at 1-800-394-4493 if you wish to consult with a Laboratory Director or a Genetic Counselor regarding this test result.

Background information: Myotonic dystrophies are clinicaly hetergeneous multisystem disorders characterized by myotonic myopathy and other systemic defects (1, 2, 3). Cardiac defects may be present in the form of arrhythmias (2). Endocrine affects include varying degrees of hypogonadism (2). Muscle weakness, both severity and particular muscles involved, varies greatly depending on the type of myotonic dystrophy and posterior iridescent cataracts are typically present later in life (2). Myotonic dystrophies are classified as either myotonic dystrophy type 1 (DM1), also known as Steinert disease, or type 2 (DM2) based on the causative gene and clinical features (2, 3).

DM1 is characterized by EMG myotonia, cataracts, facial, bulbar, respiratory, distal limb, and neck weakness, muscle atrophy, behavioral and cognitive impairments, and frontal balding (2, 4). DM1 can be further broken down into 4 distinct clinical subtypes (2, 3, 4). The earliest onset type of DM1, congenital myotonic dystrophy (CDM) is additionally characterized by low fetal movement, facial deformities that may interfere with crying and sucking, and in some cases, bilateral talipes (2). The classic or childhood-onset form of DM1 is less severe than CDM and predominantly characterized by basic DM1 degenerative features that develop before adulthood (2). The defining features of the mild or adult-onset form of DM1 are distal muscle weakness, abnormal sleep patterns, and intellectual deficits that are minor compared to earlier onset forms (2). Individuals with the late onset form of DM1 are often asymptomatic with the exception of the presence of cataracts (2). The prevalence of DM1 is approximately 1 in 8,000 (2, 4).

Expansion of an unstable CTG nucleotide repeat in the 3' untranslated region of the *DMPK* gene has been associated with DM1 (1, 2, 4, 5). DM1 exhibits anticipation, in which the offspring of mildly affected individuals may have a larger repeat expansion, especially if inherited from the mother. In these cases, the offspring may be more severely affected (1, 2). DM1 resulting from mutations in this gene is inherited as an autosomal dominant disorder (1, 2, 4, 5).

DMPK gene information: MIM ID: *605377; Chromosome Location: 19q13.3; NCBI Reference Sequence: NM_001081563.1; Phenotype information: MIM ID: #160900 for myotonic dystrophy type 1 (DM1)

Methods:

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Direct testing for the repeat expansion mutation was performed by PCR amplification of the repeat region followed by high-resolution electrophoresis to determine the number of tandem repeats in each allele. Southern blot analysis is used, as necessary, to confirm homozygosity of normal alleles and to detect the number of repeats in expanded alleles. Southern blot analysis is performed using *Nco I.* restriction digestion of genomic DNA and hybridization with a gene specific probe. This methodology is greater than 99% accurate for the detection of repeat expansion mutations.

Limitations of analysis: The accuracy of the determination of repeat number is ± 2 repeats for repeat numbers less than 51, ± 5 repeats for repeat numbers between 51-200 repeats, and ± 10% for expanded alleles greater than 200 on southern blots. This test does not detect mutations in the regions of the gene not analyzed. Additionally, this test does not detect large deletions or insertions, point mutations, and may not detect mutations in patients exhibiting mosaicism or allele dropout. Although rare, false positive or false negative results may occur. All results should be interpreted in the context of clinical findings, relevant history, and other laboratory data.

Background References

1. Singh, S, et al. (2014) Front Genet 5: 94. (PMID: 24795756)
2. Meola, G. (2013) Acta Myol 32: 154-65. (PMID: 24803843)
3. Timchenko, L. (2013) Int J Biochem Cell Biol 45: 2280-7. (PMID: 23796888)
4. Musova, Z, et al. (2009) Am J Med Genet A 149A: 1365-74. (PMID: 19514047)
5. Harmon, EB, et al. (2011) J Biol Chem 286: 40296-306. (PMID: 21949239)

This test was developed and its analytical performance characteristics have been determined by Athena Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

Laboratory results and submitted clinical information reviewed by,

Sat Dev Batish, PhD, FACMG

Chief Director, Genetics

Laboratory oversight provided by Vivekananda Datta, M.D., Ph.D., CLIA license holder, Athena Diagnostics (CLIA# 22D0069726)