Athena Diagnostics

CNBP DNA Test (DM2)

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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
04/15/1965	M	QUEST DIAGNOSTICS	
Specimen Type		Address	Patient Number
WHOLE BLOOD		200 FOREST STREET	00000000
Test Category			Specimen Collection Date
Not Available		2ND FLOOR	03/15/2020
Test Requested			Date Received
CNBP DNA Test (DM2)		MARLBOROUGH, MA 01752	03/16/2020
		Additional Reports to:	Report Date
			03/27/2020

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POSITIVE

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

INTERPRETIVE RESULTS TABLE

	Gene/Test	Technical Result	Variant Type	Inheritance	Clinical Relevance	Pub Med ID
Positive	**CNBP**	**Expansion (>15,600) and 136 base pairs**	**Repeat Expansion**	**Autosomal Dominant**	**Pathogenic**	

CNBP CCTG Ranges: Normal (<177 base pairs), Borderline (177-372 base pairs), Positive (>372 base pairs)

Comments: This test result is consistent with a diagnosis of, or a predisposition to develop, myotonic dystrophy type 2 (DM2) associated with pathogenic variants in the *CNBP* 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 clinically hetergeneous multisystem disorders characterized by myotonic myopathy and other systemic defects (1, 2, 3). Systemic defects may include arrhythmias, varying degrees of hypogonadism, and/or posterior iridescent cataracts that typically present later in life, and muscle weakness (2). Severity of, and particular muscles involved in muscle weakness vary greatly depending on the type of myotonic dystrophy (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). DM2 is characterized by proximal limb weakness, myalgic pain, cardio myopathy, and tremors (1, 2). The age of onset of DM2 ranges from the first to fifth decades of life (2). Expansions of an unstable CCTG nucleotide repeat in the *CNBP* (*ZNF9*) gene have been associated with myotonic dystrophy type 2 (DM2). DM2 resulting from mutations in this gene is inherited as an autosomal dominant disorder (2).

CNBP gene information: MIM ID: *116955; Chromosome Location: 3q21.3; NCBI Reference Sequence: NM_001127192.1; Phenotype information: MIM ID: #602668 for myotonic dystrophy type 2 (DM2)

Methods:
Direct testing for repeat expansion was performed by PCR amplification of the repeat region followed by high-resolution electrophoresis to determine the number of tandem repeats in each allele. Short Tandem Repeat-primed PCR (STR-PCR) is used, as necessary, to confirm homozygosity of normal alleles by detecting the presence of expanded alleles. Southern blot analysis is used, as necessary, to verify the number of repeats in expanded alleles. Southern blot analysis is performed using *EcoR1* restriction digestion of genomic DNA and hybridization with a gene specific probe. This methodology is greater than 99% accurate for the detection of repeat expansions in this gene.

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 variants in the regions of the gene not analyzed. Additionally, this test does not detect large deletions or insertions, substitution

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variants, and may not detect variants 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. Sammons, MA, et al. (2010) PLoS One 5: e9301. (PMID: 20174632)
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)

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,

Zhenyuan Wang, PhD, FACMG

Senior Director, Genetics

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