Name: Quest, Athena **DOB: 09/09/1999** **Accession: 14141414**

CMT Advanced Evaluation - Axonal

HSPB1 DNA Sequencing Test

This test identified a variant of unknown clinical significance (VUS) in the *HSPB1* gene.

INTERPRETIVE RESULTS TABLE

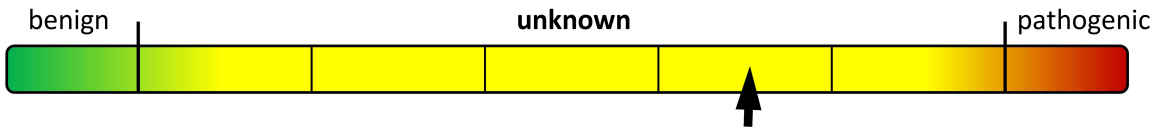
	Gene/Test	Technical Result	Mutation Type	Inheritance	Clinical Relevance	Pub Med ID
VUS	HSPB1	c.404C>G; p.Ser135Cys	Heterozygous Missense	Autosomal	Unknown	21149811

No other abnormal variants were detected.

Comments: The variant detected in this analysis has not been definitively demonstrated to be associated with Charcot-Marie-Tooth disease (CMT). This result does not confirm the diagnosis since the variant detected is of unknown clinical significance.

Athena Insight pathogenicity assessment

This test detected a DNA sequence variant of unknown clinical significance (HSPB1 c.404 C>G), but the following data indicate that this variant may be more likely pathogenic than benign:



Variant::	HSPB1 c.404 C>G (p.Ser135Cys)
Segregation Analysis: :	Inconclusive
Co-occurrence: :	Not enough information
General pop. freq.: :	0.000 (0 in 328 chromosomes)
Amino Acid Conservation: :	Moderately conserved across species
Grantham Score: :	112 [0-215] (radical difference)
SIFT: :	Predicted Tolerated
PolyPhen-2.2.2 (HumVar): :	Probably Damaging
Protein Domain: :	Alpha-crystallin domain
dbSNP Reference: :	None

- Published research does not provide sufficient evidence for classification of this variant as pathogenic or benign.
- Analysis of this variant's possible segregation with disease was inconclusive. Within the only affected family known to have the variant, a total of two affected individuals were genotyped, and both of these individuals have the variant. No unaffected family members were genotyped.
- One other missense mutation found at the same codon position is classified as pathogenic.
- There is not enough information regarding co-occurrence with known disease variants among index cases to be useful in characterizing this variant.
- SIFT and PolyPhen-2.2.2 (HumVar) predictions of the variant's effect on normal protein function disagree.
- This variant is predicted to result in the following change to the post-translational modification (PTM) of the HSPB1 protein: Loss of phosphorylation site. PTM is often important to normal protein function, but the effect of this predicted change (if any) is unknown.

References:
Benedetti, S, et al. (2010) Arch Neurol 67: 1498-505. (PMID: 21149811)

Recommendations: 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. Furthermore, testing of this individual's parents and family members is likely to improve the clinical utility of this test result.

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.