Helix THIS IS A DIAGNOSTIC TEST

Helix Comprehensive Cardiomyopathy and Arrhythmias Panel

Patient Name: John Doe	**Patient ID:** 0123456	**Collection Date:** 12-20-2024
Date of Birth: 02-20-1975	**Helix ID:** TST12345	**Order Date:** 12-20-2024
Sex Assigned at Birth: MALE	**Provider Name:** Client Client	**Report Date:** 01-03-2025
Specimen Type: WHOLE BLOOD	**Provider Address:** -	

Results POSITIVE

Classification	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	MYH7	c.2389G>A	p.Ala797Thr	Heterozygous	AD

One Pathogenic variant was detected in the MYH7 gene.
These results indicate a predisposition to, or diagnosis of autosomal dominant MYH7-related conditions.

The MYH7 gene is associated with the following condition(s):
- autosomal dominant dilated cardiomyopathy (DCM) (MedGen UID: 371831)
- autosomal dominant hypertrophic cardiomyopathy (HCM) (MedGen UID: 501195)
- autosomal dominant and autosomal recessive MYH7-related skeletal myopathy (MedGen UID: 1647391)

DCM causes enlargement of the heart's left ventricle resulting in a reduced efficiency and function. HCM is characterized by increased thickness of the muscle of heart's left ventricle (left ventricular hypertrophy). While some individuals with DCM or HCM can be asymptomatic, others develop symptoms of heart failure and heartbeat irregularities (arrhythmias) including shortness of breath (dyspnea), chest pain due to reduced blood flow to the heart (angina), swelling due to retained body fluids (edema), palpitations, fainting (syncope), and blood clots (thromboembolism). DCM and HCM are primarily adult-onset conditions, although age of onset and symptoms can be variable, even among affected individuals from the same family.

MYH7-related skeletal myopathy is characterized by early-onset weakness (usually before 5 years of age) that initially involves the dorsiflexors of the ankles and great toes and then the finger extensors, especially those of the third and fourth fingers. Weakness of the neck flexors is seen in most affected individuals and mild facial weakness is often present. After distal weakness has been present for more than ten years, mild proximal weakness may be observed. Life expectancy is normal.

Individuals with pathogenic variants in MYH7 may develop DCM, HCM, or skeletal myopathy; clinical correlation is advised.

MEDICAL MANAGEMENT recommendations and/or guidelines are available for MYH7-related conditions: PMID: 35086661, 33215938, 25173338, 34153989

Biological family members may be at risk for developing autosomal dominant MYH7-related condition(s).

The Variant Interpretation section below may provide additional details regarding the reported variant(s). Genetic test results should be interpreted in the context of an individual's personal medical and family history. It is important to note that this assay cannot detect all variants known to increase disease risk. Genetic counseling is recommended. Clinical correlation is advised.

Test Description

This panel evaluates 103 genes associated with cardiomyopathy and arrhythmia, and several syndromic conditions associated with cardiomyopathy and arrhythmia.

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Genes Tested

ABCC9, ACAD9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ALPK3, ANK2, BAG3, BMP10, BRAF, CACNA1C, CACNA1D, CALM1, CALM2, CALM3, CASQ2, CAV3, CDH2, CPT2, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, DTNA, ELAC2, EMD, FHL1, FKRP, FKTN, FLNC, GAA, GLA, HCN4, HRAS, JPH2, JUP, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, KRAS, LAMP2, LMNA, LZTR1, MAP2K1, MAP2K2, MRAS, MTO1, MYBPC3, MYH7, MYL2, MYL3, MYL4, MYLK3, MYPN, NEXN, NKX2-5, NRAS, PCCA, PCCB, PKP2, PLN, PPA2, PPCS, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RIT1, RYR2, SCN5A, SGCD, SHOC2, SLC22A5, SLC4A3, SOS1, SOS2, SYNE2, TAFAZZIN, TBX20, TCAP, TECRL, TMEM43, TMEM70, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRDN, TRIM63, TTN, TTR, VCL

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PATHOGENIC	MYH7	c.2389G>A	p.Ala797Thr	Heterozygous	AD

Transcript: NM_000257.4

Genomic Change: NC_000014.9:g.23425316C>T

Variant Interpretation

This variant (NM_000257.4:c.2389G>A p.Ala797Thr) results in the substitution of alanine with threonine at codon 797 in the MYH7 protein. It is present in the gnomAD population database (PMID: 32461654) at the highest allele frequency in the African/African American subpopulation (2/16256 alleles, 0.0123%). This has been described as a founder variant in the South African subpopulation (PMID: 11186938). This variant has been observed in numerous individuals affected with hypertrophic cardiomyopathy (HCM) (PMID: 23299917, 33673806, 35288587, 37728764). In silico prediction from REVEL (PMID: 27666373) is indeterminate. This is a missense variant that occurs in the myosin motor domain, a region enriched for missense variants in individuals with HCM (PMID: 30696458). Clinical laboratory interpretations available in ClinVar are in broad agreement that this variant is Pathogenic (ClinVar Variation ID: 42901). The most relevant articles have been cited but the list is not exhaustive. In conclusion, this variant has been classified as Pathogenic.

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Methods & Limitations

Extracted DNA is enriched for targeted regions and then sequenced using the Helix Exome+ (R) assay on an Illumina DNA sequencing system. Data is then aligned to a modified version of GRCh38 and all genes are analyzed using the MANE transcript and MANE Plus Clinical transcript, when available. Small variant calling is completed using a customized version of Sentieon's DNAseq software, augmented by a proprietary small variant caller for difficult variants. Copy number variants (CNVs) are then called using a proprietary bioinformatics pipeline based on depth analysis with a comparison to similarly sequenced samples. Interpretation is based upon guidelines published by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) or their modification by ClinGen Variant Curation Expert Panels when available. Interpretation is limited to the transcripts indicated on the report, +/- 10 bp into intronic regions, except as noted below. Helix variant classifications include pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. Variants classified as pathogenic, likely pathogenic, or VUS are included in the report. All reported variants (except for VUSs with limited evidence of pathogenicity) are confirmed through secondary manual inspection of DNA sequence data or orthogonal testing. Benign and likely benign variants are not reported but are available upon request. Risk estimations and management guidelines included in this report are based on analysis of primary literature and recommendations of applicable professional societies, and should be regarded as approximations.

Based on validation studies, this assay delivers > 99% sensitivity and specificity for single nucleotide variants and insertions and deletions (indels) up to 20 bp. Larger indels and complex variants are also reported but sensitivity may be reduced. Based on validation studies, this assay delivers > 99% sensitivity to multi-exon CNVs and > 90% sensitivity to single-exon CNVs. This test may not detect variants in challenging regions (such as short tandem repeats, homopolymer runs, and segment duplications), sub-exonic CNVs, chromosomal aneuploidy, or variants in the presence of mosaicism. Phasing will be attempted and reported, when possible. Structural rearrangements such as inversions, translocations, and gene conversions are not tested in this assay unless explicitly indicated. Additionally, deep intronic, promoter, and enhancer regions may not be covered. It is important to note that this assay cannot detect all variants known to increase disease risk, and that a negative result does not guarantee that the tested individual does not carry a rare, undetectable variant in genes analyzed. Any potential incidental findings outside of these genes and conditions will not be identified, nor reported. The results of a genetic test may be influenced by various factors, including bone marrow transplantation, blood transfusions, or in rare cases, hematolymphoid neoplasms.

Gene Specific Notes: AGL: Evaluation of chr1: 99916398 (c.4260-12A>G) will be performed. ALPK3: Sensitivity in exon 1 may be reduced. BRAF: Sensitivity in exon 1 may be reduced. CDH2: Sensitivity in exon 1 may be reduced. DMD: Evaluation of chrX:33174335 (c.31+36947G>A), chrX:31261663 (c.9225-647A>G), and chrX:31261301 (c.9225-285A>G) will be performed. FKTN: Evaluation of chr9:105606576 (c.648-1243G>T) will be performed. GAA: Evaluation of chr17:80104542 (c.-32-13T>G), chr17:80104552 (c.-32-3C>A), chr17:80104554 (c.-32-1G>C), and chr17:80108467 (c.1076-22T>G) will be performed. GLA: Evaluation of chrX: 101399747 (c.640-801G>A) will be performed. KCNH2: Evaluation of Chr7:150958048-150958065 (c.910_916+11del) will be performed. KCNQ1: Evaluation of Chr11:2461715 (c.386+16231G>A), Chr11:2585210-2585211 (c.1033-1_1117dup) will be performed and sensitivity in KCNQ1 exon 1 may be reduced. MAP2K2: Sensitivity in exon 1 may be reduced. MYBPC3: Evaluation of chr11:47332275-47332299 (c.3628-41_2628-17del25), chr11:47347065 (c.906-36G>A), chr11:47346372 (c.927-2A>G), chr11:47343281 (c.1224-19G>A), chr11:47343314 (c.1224-52G>A), chr11:47343158 (c.1227-13G>A), and chr11:47340403 (c.1927+600C>T) will be performed. PRDM16: Analysis for exon 1 will not be performed. PRKAG2: Sensitivity in exon 5 may be reduced. SLC22A5: Evaluation of chr5:132369824 (c.-149G>A), chr5:132378362 (c.394-16T>A), and chr5:132386973 (c.825-52G>A) will be performed. SOS2: Sensitivity in exon 1 may be reduced. TRDN: Evaluation of Chr6:123636725 (c.22+29A>G) will be performed. TTN: Analysis for exons 172 to 197 will not be performed.

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Disclaimer

This test was developed and validated by Helix, Inc. This test has not been cleared or approved by the United States Food and Drug Administration (FDA). The Helix laboratory is accredited by the College of American Pathologists (CAP) and certified under the Clinical Laboratory Improvement Amendments (CLIA #: 05D2117342) to perform high-complexity clinical tests. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Reports Signed By

Philip D Cotter, PhD, FACMG, FFSC (RCPA)

Helix's Sequence Once, Query Often ® Model

When your provider first orders a genetic test through Helix, Helix leverages its proprietary Sequence Once, Query Often ® model to perform whole exome sequencing and interpret the specific genes related to the test being ordered. Helix will then continue to store your genetic information for future clinical use. This means that, with your permission, your health care providers can order future medically necessary genetic tests from Helix without the need for you to submit another sample in most cases. Instead, future tests will be performed through digital analysis of your genetic information that is stored by Helix.

When you receive a genetic test performed by Helix, you are in control of how and when your genetic information is used. To manage your genetic information and understand your rights, please visit https://www.helix.com/privacy-and-policy-highlights.