Helix Family Variant Testing

Item	Description
Test Name	Helix Family Variant Testing
Test Type	Target Analysis
Catalog Number	FAVT1
Procedure Code	H00724-6 (Helix)
Test Description	Helix Family Variant Testing is a targeted test to identify the presence or absence of one or more specific variants previously identified as being present in a family member. The entire gene will be evaluated and therefore additional variants determined to be pathogenic or likely pathogenic within the gene ordered will also be included in the report. Variants of uncertain significance (VUS) will not be included except in cases where the variant specified in the order is determined to be a VUS. A separate order is required for variants in separate genes.
Genes Tested	Based on order.
Genetics Information	This test utilizes next-generation sequencing to detect single nucleotide variants, insertions and deletions up to 20 bp, and copy number variants. This test includes the targeted variant or variants ordered for a given gene, along with any other pathogenic or likely pathogenic variants detected in the gene.
Indications For Testing	A family member of a proband who has received a genetic test result with a pathogenic or likely pathogenic variant.
Clinical Descriptions	Useful for diagnostic testing when a variant associated with a specific condition has been previously identified in a family member.
Conditions	Dependent upon the specific gene(s) ordered.
Interpretation	All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity; however, this test only reports pathogenic and likely pathogenic variants along with interpretive comments detailing the evidence applied towards classification. Variants of uncertain significance are not reported.
Reclassification of Variants	Helix does not systematically review their variant database looking for classification changes. Helix will review the classification of previously reported variants upon request of the ordering physician/provider. Ordering physicians/providers may contact Helix Customer Support or their Dedicated Advisor and request a review of the variant classification to be performed. At the discretion of the laboratory director, the frequency of reclassification requests may be limited to once per year, no earlier than 12 months after initial variant interpretation has been performed.
Variant Evaluation	Variant classification is performed using the guidelines set forth by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, with modifications as suggested by domain specific Expert Panels of the Clinical genome Resource (ClinGen) when available. Variant pathogenicity is categorized as benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, or pathogenic.
Turnaround Time	7 to 24 days
Available in NY State	No

Item	Description
Test Classification	This test was developed, and its performance characteristics determined, by Helix, Inc. in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.
Performing Laboratory Information	CLIA Laboratory Number: 05D2117342 Laboratory Hours of Operation: Monday-Saturday (7AM-10:30PM PST) Address: 10170 Sorrento Valley Road, Suite 100, San Diego, CA 92121 Helix Customer Service: (844) 211-2070 Email: support@helix.com
Regulatory Information	CLIA Complexity: High Test Classification: Non-Waived/ Laboratory Developed Test
CLIA Category	Chemistry / Routine Chemistry

Methods & Limitations for Helix Family Variant Testing

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. Reportable variants in *PMS2* exons 12-15 are confirmed by PacBio long reads. The *MSH2* Boland inversion (exons 1-7) is detected by identifying discordant read-pairs spanning the presumed breakpoint. 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.

Results do not rule out the presence of other variants related to this condition. Results may include incidental findings within the gene that are determined to be pathogenic or likely pathogenic.

Gene Specific Notes:
N/A

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.

Targeted Genes & Methodology for Helix Family Variant Testing

The following applies to the Helix Family Variant Testing. Testing is performed to evaluate for the presence of variants in coding regions and extending to +/- 10 base pairs of adjacent intronic sequences on either side of the coding exons of the genes analyzed. In addition, the analysis will cover select non-coding variants, as listed below. Next-generation sequencing is performed to test for the presence of small variants and copy number variants in the genes analyzed. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

This list is current from November 2024 to the present. This document is intended to highlight additional evaluations for variants of high clinical interest as well as technical limitations. For questions regarding genes, reference transcripts, or specific regions covered, contact Helix Customer Service at (844) 211-2070.

Genomic Build: GRCh38
Catalog Number: FAVT1

Gene	Transcript	Additional Evaluations	Technical Limitations
ABCC9	NM_020297.4	–	–
ACAD9	NM_014049.5	–	–
ACADVL	NM_000018.4	–	–
ACTA2	NM_001613.4	–	–
ACTC1	NM_005159.5	–	–
ACTN2	NM_001103.4	–	–
ADAMTS10	NM_030957.4	–	–
AGL	NM_000642.3	Chr1: 99916398 (c.4260-12A>G)	–
AIP	NM_003977.4	–	–
ALK	NM_004304.5	–	–
ALMS1	NM_001378454.1	–	–
ALPK3	NM_020778.5	–	Sensitivity in ALPK3 exon1 may be reduced
APC	NM_000038.6	Includes CNV detection of Promoters 1A and 1B and sequencing of Promoter 1B	–
APOB	NM_000384.3	–	–
ATM	NM_000051.4	–	–
AXIN2	NM_004655.4	–	–
BAG3	NM_004281.4	–	–
BAP1	NM_004656.4	–	–
BARD1	NM_000465.4	–	–
BGN	NM_001711.6	–	–
BLM	NM_000057.4	–	–
BMP10	NM_014482.3	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
BMPR1A	NM_004329.3	Includes CNV detection in the promoter	–
BRAF	NM_004333.6; NM_001374258.1	–	Sensitivity to BRAF exon1 may be reduced
BRCA1	NM_007294.4	Sequencing analysis extends to CDS +/-20 bp	–
BRCA2	NM_000059.4	Sequencing analysis extends to CDS +/-20 bp	–
BRIP1	NM_032043.3	–	–
CBS	NM_000071.3	–	–
CDC73	NM_024529.5	–	–
CDH1	NM_004360.5	–	–
CDH2	NM_001792.5	–	Sensitivity in CDH2 exon1 may be reduced
CDK4	NM_000075.4	–	–
CDKN1B	NM_004064.5	–	–
CDKN2A	NM_000077.5; NM_058195.4	Includes analysis of both the p16 (p16INK4a) and p14 (p14ARF) transcripts	–
CHEK2	NM_007194.4	–	–
COL3A1	NM_000090.4	–	–
COL5A1	NM_000093.5	–	–
COL5A2	NM_000393.5	–	–
CPT2	NM_000098.3	–	–
CRYAB	NM_001289808.2	–	–
CSRP3	NM_003476.5	–	–
CTNNA1	NM_001903.5	–	–
DES	NM_001927.4	–	–
DICER1	NM_177438.3	–	–
DMD	NM_004006.3	ChrX:33174335 (c.31+36947G>A) ChrX:31261663 (c.9225-647A>G) ChrX:31261301 (c.9225-285A>G)	–
DNAJC19	NM_145261.4	–	–
DOLK	NM_014908.4	–	–
DSC2	NM_024422.6	–	–
DSG2	NM_001943.5	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
DSP	NM_004415.4	–	–
DTNA	NM_001386795.1	–	–
EFEMP2	NM_016938.5	–	–
EGFR	NM_005228.5	–	Results limited to NM_005228(EGFR): c.2369C>T (p.Thr790Met)
ELAC2	NM_018127.7	–	–
EMD	NM_000117.3	–	–
EPCAM	NM_002354.3	–	Results limited to CNV and limited to exons 8 and 9
FBN1	NM_000138.5	–	–
FBN2	NM_001999.4	–	–
FH	NM_000143.4	–	–
FHL1	NM_001159699.2; NM_001159702.3	–	–
FKRP	NM_024301.5	–	–
FKTN	NM_001079802.2	Chr9:105606576 (c.648-1243G>T)	–
FLCN	NM_144997.7	–	–
FLNA	NM_001110556.2	–	–
FLNC	NM_001458.5	–	–
F0XE3	NM_012186.3	–	Analysis begins at chr1:47416567 (GRCh38) and excludes the first quarter of exon 1
GAA	NM_000152.5	Chr17:80104542 (c.-32-13T>G) Chr17:80104552 (c.-32-3C>A) Chr17:80104554 (c.-32-1G>C) Chr17:80108467 (c.1076-22T>G)	–
GLA	NM_000169.3	ChrX: 101399747 (c.640-801G>A)	–
GREM1	NM_013372.7	–	Results limited to CNV of promoter region
HCN4	NM_005477.3	–	–
HOXB13	NM_006361.6	–	Results limited to NM_006361.6(HOXB13): c.251G>A (p.Gly84Glu)
HRAS	NM_005343.4; NM_176795.5	–	–
JPH2	NM_020433.5	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
JUP	NM_002230.4	–	–
KIT	NM_000222.3	–	–
KRAS	NM_004985.5; NM_033360.4	–	–
LAMP2	NM_002294.3	–	–
LDLR	NM_000527.5	Chr19: 11117009 (c.1845+11C>G) Chr19: 11089400 (c.-149C>A) Chr19: 11089414 (c.-135C>G) Chr19: 11089413 (c.-136C>T) Chr19: 11110640 (c.941-12G>A)	–
LDLRAP1	NM_015627.3	Chr1: 25564565 (c748-608G>A)	–
LMNA	NM_170707.4; NM_005572.4	–	–
LOX	NM_002317.7	–	–
LZTR1	NM_006767.4	–	–
LZTR1	NM_006767.4	–	–
MAP2K1	NM_002755.4	–	–
MAP2K2	NM_030662.4	–	Sensitivity in MAP2K2 exon 1 may be reduced
MAX	NM_002382.5	–	–
MBD4	NM_001276270.2	–	–
MED12	NM_005120.3	–	–
MEN1	NM_001370259.2	–	–
MET	NM_000245.4	–	–
MFAP5	NM_003480.4	–	–
MITF	NM_000248.4	–	Results limited to NM_000248.4(MITF): c.952G>A (p.Glu318Lys)
MLH1	NM_000249.4	Includes CNV detection in the promoter	–
MRAS	NM_001085049.3	–	–
MSH2	NM_000251.3	Includes detection of the exon 1-7 rearrangement known as the Boland Inversion and of c.942+3A>T	–
MSH3	NM_002439.5	–	Excludes known repeat region in MSH3 exon 1
MSH6	NM_000179.3	–	–
MTO1	NM_012123.4	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
MUTYH	NM_001048174.2; NM_001128425.2	–	–
MYBPC3	NM_000256.3	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) Chr11:47340403 (c.1927+600C>T)	–
MYH11	NM_002474.3; NM_001040113.2	–	–
MYH7	NM_000257.4	–	–
MYL2	NM_000432.4	–	–
MYL3	NM_000258.3	–	–
MYLK	NM_053025.4	–	–
MYLK3	NM_182493.3	–	–
MYPN	NM_032578.4	–	–
NEXN	NM_144573.4	–	–
NF1	NM_001042492.3	–	–
NF2	NM_000268.4	–	–
NKX2-5	NM_004387.4	–	–
NOTCH1	NM_017617.5	–	–
NRAS	NM_002524.5	–	–
NTHL1	NM_002528.7	–	–
PALB2	NM_024675.4	–	–
PCCA	NM_000282.4	–	–
PCCB	NM_000532.5	–	–
PCSK9	NM_174936.4	–	–
PDGFRA	NM_006206.6	–	–
PKP2	NM_001005242.3	–	–
PLN	NM_002667.5	–	–
PLOD1	NM_000302.4	–	–
PMS2	NM_000535.7	–	–
POLD1	NM_002691.4	–	CNVs not reported, and sequencing isolated to the exonuclease domain

Gene	Transcript	Additional Evaluations	Technical Limitations
POLE	NM_006231.4	–	CNVs not reported, and sequencing isolated to the exonuclease domain
POT1	NM_015450.3	–	–
PPA2	NM_176869.3	–	–
PPCS	NM_024664.4	–	–
PRDM16	NM_022114.4	–	Analysis for exon 1 will not be performed
PRKAG2	NM_016203.4	–	Sensitivity in PRKAG2 exon 5 may be reduced
PRKAR1A	NM_002734.5	–	–
PRKG1	NM_006258.4	–	–
PTCH1	NM_000264.5; NM_001083603.3	–	Sensitivity in PTCH1 exon 1 may be reduced
PTEN	NM_000314.8	Includes CNV detection in the promoter	–
PTPN11	NM_002834.5	–	–
RAD51C	NM_058216.3	–	–
RAD51D	NM_002878.4	–	–
RAF1	NM_002880.4	–	–
RB1	NM_000321.3	–	–
RBM20	NM_001134363.3	–	–
RET	NM_020975.6	–	–
RIT1	NM_006912.6	–	–
RYR2	NM_001035.3	–	–
SCN5A	NM_000335.5; NM_001099404.2	–	–
SDHA	NM_004168.4	–	CNVs not reported
SDHAF2	NM_017841.4	–	–
SDHB	NM_003000.3	–	–
SDHC	NM_003001.5	–	–
SDHD	NM_003002.4	–	–
SGCD	NM_000337.6	–	–
SHOC2	NM_007373.4	–	–
SKI	NM_003036.4	–	–
SLC22A5	NM_003060.4	Chr5:132369824 (c.-149G>A) Chr5:132378362 (c.394-16T>A) Chr5:132386973 (c.825-52G>A)	–

Gene	Transcript	Additional Evaluations	Technical Limitations
SLC2A10	NM_030777.4	–	–
SMAD2	NM_005901.6	–	–
SMAD3	NM_005902.4	–	–
SMAD4	NM_005359.6	–	–
SMAD4	NM_005359.6	–	–
SMARCA4	NM_003072.5; NM_001387283.1	–	–
SMARCB1	NM_003073.5	–	–
SMARCE1	NM_003079.5	–	–
SOS1	NM_005633.4	–	–
SOS2	NM_006939.4	–	Sensitivity in SOS2 exon 1 may be reduced
STK11	NM_000455.5	–	Sensitivity in STK11 exon 3 may be reduced
SUFU	NM_016169.4	–	–
SYNE2	NM_182914.3	–	–
TAFAZZIN	NM_000116.5	–	–
TBX20	NM_001077653.2	–	–
TCAP	NM_003673.4	–	–
TGFB2	NM_003238.6	–	–
TGFB3	NM_003239.5	–	–
TGFBR1	NM_004612.4	–	Analysis for exon 1 will not be performed
TGFBR2	NM_003242.6	–	–
TMEM127	NM_017849.4	–	–
TMEM43	NM_024334.3	–	–
TMEM70	NM_017866.6	–	–
TNNC1	NM_003280.3	–	–
TNNI3	NM_000363.5	–	–
TNNI3K	NM_015978.3	–	–
TNNT2	NM_001276345.2	–	–
TP53	NM_000546.6	Includes CNV detection in the promoter	–
TPM1	NM_001018005.2	–	–
TRIM63	NM_032588.4	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
TSC1	NM_000368.5	–	Sensitivity in TSC1 exon 21 may be reduced
TSC2	NM_000548.5	–	–
TTN	NM_001267550.2; NM_133379.5	–	Analysis for exons 172 to 197 will not be performed
TTR	NM_000371.4	–	–
VCL	NM_014000.3	–	–
VHL	NM_000551.4	–	Excludes coverage of cryptic exon E1' (chr3:10142758-10143009)