Helix

THIS IS A SCREENING TEST

Helix Hereditary Actionable Disorders Screen

Patient Name: Jane Doe	**Patient ID:** 96138	**Provider Name:** Client Client	**Order Date:** 06-05-2024
Date of Birth: 01-01-1990	**Helix ID:** Test12345	**Collection Date:** 06-05-2024	**Report Date:** 10-22-2025

Results POSITIVE

Classification	Gene	DNA Change	Protein Change	Zygosity	Inheritance
PATHOGENIC	F2	c.*97G>A	p.(=)	Heterozygous	AD

One Pathogenic Risk Allele was detected in the F2 gene.
These results indicate a predisposition to, or diagnosis of, autosomal dominant F2-related conditions. These results also indicate carrier status for autosomal recessive F2-related conditions.

The F2 gene is associated with the following condition(s):
- autosomal dominant prothrombin-related thrombophilia (MedGen UID: 463623)
- autosomal recessive congenital prothrombin deficiency (MedGen UID: 124425)

Having one pathogenic variant in the F2 gene is associated with autosomal dominant prothrombin-related thrombophilia, a condition that increases the risk of developing abnormal blood clots (thrombosis). Prothrombin is a protein essential for blood clotting. This condition is characterized by excessive clotting, especially in veins, which can cause serious complications like deep vein thrombosis (DVT) or pulmonary embolism (PE). While many affected individuals may never develop blood clots, certain factors like pregnancy, surgery, or long periods of immobility can increase the risk.

Having two pathogenic variants in the F2 gene is associated with autosomal recessive congenital prothrombin deficiency, a condition in which an individual is born with lower levels of prothrombin. Without enough prothrombin, an individual's blood may not clot properly, which increases the risk of excessive bleeding, especially after injuries or surgery. Symptoms can include easy bruising, prolonged bleeding from cuts, or heavy menstrual periods.

The age of onset, severity, and types of symptoms associated with F2-related conditions can vary widely, even among affected individuals from the same family.

MEDICAL MANAGEMENT recommendations and/or guidelines are available for F2-related condition(s): PMID: 38453604, 37195076, 28969316

Biological family members may be at risk for developing autosomal dominant F2-related condition(s) and are at risk for, or may be carriers of, autosomal recessive F2-related conditions.

Genetic test results should be interpreted in the context of an individual's personal medical and family history. Genetic counseling is recommended. Clinical correlation is advised.

Additional Considerations

- This is a screening test; individuals may still carry pathogenic or likely pathogenic variant(s) in the tested genes that are not detected by this test.
- For individuals at risk for these or other related conditions based on factors including personal or family history, diagnostic testing is recommended.
- The Variant Interpretation section below may provide additional details regarding the reported variant(s).
- The absence of pathogenic or likely pathogenic variant(s) in any of the other analyzed genes, while reassuring, does not eliminate

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the possibility of a hereditary condition; there are other variants and genes associated with heart disease and hereditary cancer that are not included in this test.

Test Description

Helix Hereditary Actionable Disorders Screen is a screening test that analyzes 89 genes related to hereditary predisposition to cancer, cardiac disease, metabolic disorders, muscular disorders, and blood clotting disorders; analysis of the PMS2 gene excludes exons 11-15, which overlap with a known pseudogene (PMS2CL) and analysis of the F2, F5, HFE, and SERPINA1 genes is limited to specific targeted variants. This test only reports clinically significant pathogenic and likely pathogenic variants but does not report variants of uncertain significance (VUS).

Genes Tested

ABCD1, ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, COL3A1, CYP27A1, DES, DSC2, DSG2, DSP, ENG, EPCAM, F2, F5, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LDLRAP1, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH7, MYH11, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PLN, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SERPINA1, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1

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Transcript:	Genomic Change:
NM_000506.5	NC_000011.10:g.46739505G>A

Variant Interpretation

This variant (NM_000506.5:c.*97G>A p.(=)) results in a nucleotide substitution in the 3' untranslated region of the F2 gene. This variant is also known as c.20210G>A. It is present in the gnomAD population database (v4.1, https://gnomad.broadinstitute.org) at the highest allele frequency in the Middle Eastern subpopulation among non-founder subpopulations (76/4238 alleles, 1.8%) with 2 homozygotes; it was also found at a frequency of 1.3% in the European (non-Finnish) subpopulation (13811/1070898 alleles with 92 homozygotes). Case-control studies and meta-analyses have demonstrated that this variant is associated with an increased risk of venous thromboembolism with odds ratios of 2.8-3.2 (OR 2.8 [95%CI 2.3-3.5] in PMID: 23900608; OR 3.2 [95%CI 2.2-3.5] in PMID: 19652888); homozygotes appear to present at an earlier age and have even greater risk, with odds ratios ranging from 5-6.7 (OR 5 [95%CI 2.1-11.9] in PMID: 28707429; OR 6.7 [95%CI 2.2-20.7] in PMID: 23900608). Functional studies suggest that this variant may affect protein function (PMID: 8916933, 11443298, 15059842). It has been reported in individuals with venous thromboembolism but is also found at a relatively high frequency in the general population; taken together, this evidence suggests this variant is a risk factor. The most relevant articles have been cited but the list is not exhaustive. This variant is present in ClinVar (Variation ID: 13310). In conclusion, this variant has been classified as a Pathogenic Risk Allele.

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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. Analysis of the PMS2 gene is limited to exons 1-10. Both the MSH2 Boland inversion (exons 1-7) and the BRCA2 Alu insertion are detected by identifying discordant read-pairs spanning the breakpoints. The interpretation and reporting of variants in APOB, PCSK9, and LDLR is specific to familial hypercholesterolemia; variants associated with hypobetalipoproteinemia are not included. Interpretation is based upon guidelines published by the American College of Medical Genetics and Genomics (ACMG), the Association for Molecular Pathology (AMP) or their modification by ClinGen Variant Curation Expert Panels when available and/or review of previous clinical assertions available in the ClinVar database. Interpretation is limited to the transcripts indicated on the report and +/- 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. Only variants classified as pathogenic and likely pathogenic are included in the report. All reported variants are confirmed through secondary manual inspection of DNA sequence data or orthogonal testing. 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, complex rearrangements, 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 is a screening test and cannot detect all disease-causing variants. A negative result does not guarantee the absence of a rare, undetectable variant in the genes analyzed; consider using a diagnostic test if there is significant personal and/or family history of one of the conditions analyzed by this test. 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:
APC: analysis includes CNV of promoters 1A and 1B and sequencing of promoter 1B; APOB: analysis is limited to c.10580G>A and c.10579C>T; BMPR1A: analysis includes CNV of promoter; BRCA1: sequencing analysis extends to CDS +/-20 bp; BRCA2: analysis includes detection of c.156_157insAlu and sequencing analysis extends to CDS +/-20 bp. EPCAM: analysis is limited to CNV of exons 8-9; F2: analysis is limited to c.*97G>A; F5: analysis is limited to c.1601G>A (p.Arg534Gln); HFE: Analysis is limited to c.845G>A (p.Cys282Tyr) and c.187C>G (p.His63Asp); KCNQ1: Sensitivity in KCNQ1 exon 1 may be reduced; LDLR: analysis includes CNV of the promoter; MLH1: analysis includes CNV of the promoter; MSH2: analysis includes detection of the Boland inversion (inversion of exons 1-7) and detection of c.942+3A>T; PMS2: analysis is limited to exons 1-10; PTEN: analysis includes CNV of the promoter; SERPINA1: analysis is limited to c.1096G>A and c.863A>T; STK11: Sensitivity in STK11 exon 3 may be reduced; TP53: analysis includes CNV of the promoter; TSC1: Sensitivity in TSC1 exon 21 may be reduced; TTN: analysis is limited to exons 1-10, 14-44, 47, 49-50, 101, 104-114, 220-224, 226-242, and 244-363; VHL: analysis excludes coverage of the cryptic E1' exon (chr3:10142758-10143009)

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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 use only or for research use only.

Reports Signed By

Matthew J Ferber, PhD, FACMGG

Helix's Sequence Once, Query Often® Model

When your provider orders a genetic test through Helix, we use our proprietary Sequence Once, Query Often®model to perform whole exome sequencing and analyze the specific genes related to the test. Helix securely stores your whole exome for future clinical use. With your permission, this allows your health care providers to order future medically necessary genetic tests from Helix without needing another sample. Instead, these tests are conducted through digital analysis of your stored genetic information.

To learn more about how Helix protects the privacy and security of your genetic information and learn more about your rights, please visit https://www.helix.com/privacy-and-policy-highlights