INVITAE

INVITAE PROACTIVE TESTING RESULTS

Patient name:	Charles D Warden	**Sample type:**	Saliva	**Report date:**	22-DEC-2023
DOB:	05-APR-1985	**Sample collection date:**	07-DEC-2023	**Invitae #:**	RQ5937338
Sex assigned at birth:	Male	**Sample accession date:**	11-DEC-2023	**Clinical team:**	Christina Mota
Gender:	Man				
Patient ID (MRN):					

Test performed

Sequence analysis and deletion/duplication testing of the 167 genes listed in the Genes Analyzed section.

- Invitae Genetic Health Screen

RESULT: POSITIVE

A clinically significant genetic change was found in the F5 gene, which is associated with a blood-related condition.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
F5	c.1601G>A (p.Arg534Gln)	heterozygous	PATHOGENIC

About this test

This test evaluates 167 genes for variants (genetic changes) that indicate a significantly increased risk of developing certain types of cancer, heart-related conditions, or other types of actionable medical genetic conditions. These are disorders for which effective medical interventions and preventive measures are known and available. Genetic changes of uncertain significance are not included in this report; however, if additional evidence becomes available to indicate that a previously uncertain genetic change is clinically significant, Invitae will update this report and provide notification.

Next steps

- This is a medically important result that should be discussed with an appropriate healthcare provider. Genetic counseling is recommended to discuss the implications of this result and potential next steps.
- Please see PMID: 19289024, 21707594, 26780744, 29939939, 11238089, 25634741, 33773040, and 28225426 for management guidelines regarding F5-related condition(s).
- Consider sharing this result with relatives as they may also be at risk. Details on our Family Variant Testing program can be found at www.invitae.com/family.
- Register your test at www.invitae.com/patients to download a digital copy of your results. You can also access educational resources about how your results can help inform your health.

Laboratory Director: Jeana DaRe, PhD, FACMG
Invitae 1400 16th Street, San Francisco, CA 94103 · clientservices@invitae.com · 800.436.3037

Clinical summary

A Pathogenic variant, c.1601G>A (p.Arg534Gln), was identified in F5.

- Certain genetic changes in one copy of the F5 gene significantly increase the risk for autosomal dominant factor V Leiden thrombophilia and autosomal dominant short FV bleeding disorder. If a person carries two other clinically significant genetic changes, one in each copy of the F5 gene, this may result in an autosomal recessive condition known as factor V deficiency.
- The specific genetic change in the F5 gene found in this individual is associated with a condition called factor V Leiden thrombophilia. This variant is not associated with factor V deficiency.
- Factor V Leiden thrombophilia is a condition that causes an increased risk for blood clots in the veins, known as venous thromboembolism (VTE). Individuals with a single genetic change in the F5 gene have a slightly increased risk to develop deep-vein thrombosis (DVT), which are blood clots in blood vessels deep within the body, as well as pulmonary embolism, which is the blockage of a blood vessel in the lungs caused by a blood clot, when compared to individuals in the general population. However, it is important to note that the majority of individuals with this genetic change will never develop a complication due to thrombophilia.
- Since genetic changes are often shared within families, there is a chance that biological relatives may be at risk as well and could consider testing.

Variant details

F5, Exon 10, c.1601G>A (p.Arg534Gln), heterozygous, PATHOGENIC

- This sequence change replaces arginine with glutamine at codon 534 of the F5 protein (p.Arg534Gln). The arginine residue is weakly conserved and there is a small physicochemical difference between arginine and glutamine.
- This variant is present in population databases (no rsID available, gnomAD 3.0%), and has an allele count higher than expected for a pathogenic variant.
- This variant, also known as the Factor V Leiden mutation, is a well documented and common cause of activated protein C resistance (PMID: 8164741, 7910348).
- ClinVar contains an entry for this variant (Variation ID: 642).
- Algorithms developed to predict the effect of variants on protein structure and function are not available or were not evaluated for this variant.
- Experimental studies have shown that this missense change affects F5 function (PMID: 7910348, 7911872).
- For these reasons, this variant has been classified as Pathogenic.

Genes analyzed

This table represents a complete list of genes analyzed for this individual. Genes listed in this table may also have additional reported clinical associations outside of the conditions listed. Additional information about gene-condition associations can be found at http://www.omim.org. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details.

Cancer-related genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
AIP	NM_003977.3	Familial isolated pituitary adenoma (FIPA)
APC*	NM_000038.5	Colorectal, Endocrine, Gastric, Nervous System/ Brain and Pancreatic Cancer, Sarcoma
ATM*	NM_000051.3	Breast, Ovarian, Pancreatic, Prostate cancer
AXIN2	NM_004655.3	Colorectal Cancer
BAP1	NM_004656.3	BAP1 tumor predisposition syndrome
BARD1	NM_000465.3	Breast Cancer
BMPR1A	NM_004329.2	Colorectal, Gastric and Pancreatic Cancer
BRCA1	NM_007294.3	Breast, Gynecologic, Pancreatic and Prostate Cancer
BRCA2	NM_000059.3	Breast, Gynecologic, Pancreatic and Prostate Cancer, Melanoma
BRIP1	NM_032043.2	Ovarian Cancer
CDC73	NM_024529.4	Endocrine and Renal Cancer
CDH1	NM_004360.3	Breast, Colorectal and Gastric Cancer
CDK4	NM_000075.3	Melanoma
CDKN1B	NM_004064.4	Multiple endocrine neoplasia type 4 (MEN4)
CDKN2A (p14ARF)	NM_058195.3	Nervous System/Brain Cancer, Melanoma
CDKN2A (p16INK4a)	NM_000077.4	Pancreatic Cancer, Melanoma
CHEK2	NM_007194.3	Breast, Colorectal, Endocrine, and Prostate Cancer
DICER1*	NM_177438.2	Endocrine, Gynecologic, Nervous System/Brain and Renal/Urinary Tract, Lung Cancer, Sarcoma
EGFR	NM_005228.3	EGFR-related predisposition to lung cancer, Neonatal inflammatory skin and bowel disease
EPCAM*	NM_002354.2	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
FH*	NM_000143.3	Renal/Urinary Tract, Endocrine Cancer
FLCN	NM_144997.5	Renal/Urinary Tract Cancer
GREM1*	NM_013372.6	Colorectal Cancer
HOXB13	NM_006361.5	Prostate Cancer
KIT	NM_000222.2	Gastrointestinal Tumor or Cancer, Blood Cancer
LZTR1	NM_006767.3	Noonan spectrum disorders (NSDs) / RASopathies, Schwannomatosis
MAX*	NM_002382.4	Endocrine Cancer
MEN1*	NM_130799.2	Endocrine, Nervous System/Brain and Pancreatic Cancer
MET*	NM_001127500.1	Renal/Urinary Tract Cancer
MITF	NM_000248.3	Melanoma
MLH1*	NM_000249.3	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
MSH2*	NM_000251.2	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
MSH3*	NM_002439.4	Colorectal Cancer
MSH6*	NM_000179.2	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
MUTYH	NM_001128425.1	Colorectal Cancer
NF1*	NM_000267.3	Breast, Endocrine, Gastric and Nervous System/ Brain Cancer
NF2	NM_000268.3	Nervous System/Brain Cancer
NTHL1	NM_002528.6	Colorectal Cancer
PALB2	NM_024675.3	Breast, Pancreatic, Gynecologic Cancer
PDGFRA	NM_006206.4	Gastrointestinal Tumor or Cancer
PMS2*	NM_000535.5	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
POLD1*	NM_002691.3	Colorectal Cancer
POLE	NM_006231.3	Colorectal Cancer
POT1	NM_015450.2	POT1 tumor predisposition syndrome
PRKAR1A	NM_002734.4	Endocrine and Nervous System/Brain Cancer
PTCH1	NM_000264.3	Nervous System/Brain and Skin Cancer
PTEN*	NM_000314.4	Breast, Colorectal, Endocrine, Gynecologic, Nervous System/Brain and Renal/Urinary Tract Cancer, Melanoma
RAD51C	NM_058216.2	Breast, and Gynecologic Cancer
RAD51D	NM_002878.3	Breast, and Gynecologic Cancer
RB1*	NM_000321.2	Melanoma, Retinoblastoma, Sarcoma
RET	NM_020975.4	Endocrine Cancer
SDHA*	NM_004168.3	Endocrine, Gastrointestinal Tumor or Cancer

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
SDHAF2	NM_017841.2	Endocrine Cancer
SDHB	NM_003000.2	Endocrine, Gastrointestinal Tumor or Cancer, Renal/ Urinary Tract Cancer
SDHC*	NM_003001.3	Endocrine, Gastrointestinal Tumor or Cancer, Renal/ Urinary Tract Cancer
SDHD	NM_003002.3	Endocrine, Gastrointestinal Tumor or Cancer, Renal/ Urinary Tract Cancer
SMAD4	NM_005359.5	Colorectal, Gastric and Pancreatic Cancer
SMARCA4	NM_001128849.1	Gynecologic Cancer
SMARCB1	NM_003073.3	Nervous System/Brain and Renal/Urinary Tract Cancer
STK11	NM_000455.4	Breast, Gastrointestinal, Gynecologic, Testicular, Lung, and Pancreatic Cancer
TMEM127	NM_017849.3	Endocrine Cancer
TP53	NM_000546.5	Breast, Endocrine, Gastrointestinal, Genitourinary, Gynecologic, Hematologic, Nervous System/Brain and Skin Cancer, Sarcoma
TSC1*	NM_000368.4	Nervous System/Brain, Pancreatic and Renal/Urinary Tract Cancer
TSC2	NM_000548.3	Nervous System/Brain, Pancreatic and Renal/Urinary Tract Cancer
VHL	NM_000551.3	Endocrine, Nervous System/Brain, Pancreatic and Renal/Urinary Tract Cancer
WT1	NM_024426.4	Renal/Urinary Tract Cancer

Cardiovascular-related genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
ACTA2	NM_001613.2	Aortopathy
ACTC1*	NM_005159.4	Cardiomyopathy, Congenital Heart Disease
ACTN2*	NM_001103.3	Arrhythmia, Cardiomyopathy
ACVRL1	NM_000020.2	Hereditary Hemorrhagic Telangiectasia, Pulmonary Arterial Hypertension
APOB	NM_000384.2	Familial Hypercholesterolemia, Familial Hypobetalipoproteinemia
BAG3	NM_004281.3	Cardiomyopathy, Neuromuscular Condition
BMPR2	NM_001204.6	Pulmonary Arterial Hypertension
CACNA1C*	NM_000719.6;NM_001129840.1	Arrhythmia, Cardiomyopathy, Congenital Heart Disease
CACNB2	NM_201590.2	Arrhythmia
CALM1	NM_006888.4	Arrhythmia
CALM2	NM_001743.4	Arrhythmia
CALM3	NM_005184.2	Arrhythmia
CASQ2	NM_001232.3	Arrhythmia
CAV1	NM_001753.4	Pulmonary Arterial Hypertension
CAV3	NM_033337.2	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
COL3A1*	NM_000090.3	Connective tissue disorder
COL5A1	NM_000093.4	Connective tissue disorder
COL5A2	NM_000393.3	Connective tissue disorder
CRYAB	NM_001885.2	Cardiomyopathy, Neuromuscular Condition
CSRP3	NM_003476.4	Cardiomyopathy
DES	NM_001927.3	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
DMD	NM_004006.2	Cardiomyopathy, Neuromuscular Condition
DSC2	NM_024422.4	Arrhythmia, Cardiomyopathy
DSG2	NM_001943.3	Arrhythmia, Cardiomyopathy
DSP	NM_004415.2	Arrhythmia, Cardiomyopathy
EMD	NM_000117.2	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
ENG*	NM_000118.3	Hereditary Hemorrhagic Telangiectasia, Pulmonary Arterial Hypertension
F2	NM_000506.3	Hemophilia, Hereditary Thrombophilia
F5	NM_000130.4	Hemophilia, Hereditary Thrombophilia
F9	NM_000133.3	Hemophilia, Hereditary Thrombophilia
FBN1	NM_000138.4	Connective tissue disorder
FHL1	NM_001449.4	Cardiomyopathy, Neuromuscular Condition
FLNC*	NM_001458.4	Cardiomyopathy, Neuromuscular Condition
GDF2	NM_016204.2	Hereditary Hemorrhagic Telangiectasia, Pulmonary Arterial Hypertension
GLA	NM_000169.2	Cardiomyopathy, Lysosomal Storage Disease
GPD1L	NM_015141.3	Arrhythmia
HCN4	NM_005477.2	Arrhythmia, Cardiomyopathy
JUP	NM_002230.2	Arrhythmia, Cardiomyopathy
KCNE1	NM_000219.5	Arrhythmia
KCNE2	NM_172201.1	Arrhythmia
KCNH2	NM_000238.3	Arrhythmia
KCNJ2	NM_000891.2	Arrhythmia
KCNQ1	NM_000218.2	Arrhythmia
LAMP2	NM_002294.2	Cardiomyopathy, Arrhythmia, Glycogen Storage Disease
LDLR	NM_000527.4	Familial Hypercholesterolemia
LDLRAP1	NM_015627.2	Familial Hypercholesterolemia
LMNA	NM_170707.3	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
MYBPC3	NM_000256.3	Cardiomyopathy
MYH11	NM_001040113.1	Aortopathy
MYH7	NM_000257.3	Cardiomyopathy, Neuromuscular Condition
MYL2	NM_000432.3	Cardiomyopathy
MYL3	NM_000258.2	Cardiomyopathy
MYLK	NM_053025.3	Aortopathy
NKX2-5	NM_004387.3	Arrhythmia, Congenital Heart Disease
PCSK9*	NM_174936.3	Familial Hypercholesterolemia
PKP2	NM_004572.3	Arrhythmia, Cardiomyopathy
PLN	NM_002667.3	Arrhythmia, Cardiomyopathy
PRKAG2	NM_016203.3	Arrhythmia, Cardiomyopathy
PRKG1	NM_006258.3	Aortopathy
PROC	NM_000312.3	Hereditary Thrombophilia
PROS1	NM_000313.3	Hereditary Thrombophilia
RBM20	NM_001134363.2	Arrhythmia, Cardiomyopathy
RYR2	NM_001035.2	Arrhythmia, Cardiomyopathy
SCN5A	NM_198056.2	Arrhythmia, Cardiomyopathy
SERPINC1	NM_000488.3	Hereditary Thrombophilia
SGCD	NM_000337.5	Cardiomyopathy, Neuromuscular Condition

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
SMAD3	NM_005902.3	Aortopathy
SMAD4	NM_005359.5	Hereditary Hemorrhagic Telangiectasia
SMAD9	NM_001127217.2	Pulmonary arterial hypertension (PAH)
TCAP	NM_003673.3	Cardiomyopathy, Neuromuscular Condition
TGFB2	NM_003238.3	Aortopathy
TGFB3	NM_003239.3	Aortopathy, Arrhythmia, Cardiomyopathy
TGFBR1	NM_004612.2	Aortopathy
TGFBR2	NM_003242.5	Aortopathy
TMEM43	NM_024334.2	Arrhythmia, Cardiomyopathy
TNNC1	NM_003280.2	Cardiomyopathy
TNNI3	NM_000363.4	Arrhythmia, Cardiomyopathy
TNNT2	NM_001001430.2	Arrhythmia, Cardiomyopathy
TPM1	NM_001018005.1	Cardiomyopathy
TRDN	NM_006073.3	Arrhythmia
TTN*	NM_001267550.2	Arrhythmia, Cardiomyopathy, Neuromuscular condition
TTR	NM_000371.3	Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)
VCL	NM_014000.2	Cardiomyopathy

Other genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
ABCD1	NM_000033.3	X-linked adrenoleukodystrophy
ATP7B	NM_000053.3	Wilson Disease
BTD	NM_000060.3	Biotinidase deficiency
CACNA1S	NM_000069.2	Hypokalemic Periodic Paralysis, Malignant Hyperthermia Susceptibility
G6PD	NM_001042351.2	Glucose-6-phosphate dehydrogenase deficiency
GAA	NM_000152.3	Glycogen storage disease
GCH1	NM_000161.2	Movement Disorder, Hyperphenylalaninemia
HAMP	NM_021175.2	Hereditary Hemochromatosis
HFE	NM_000410.3	Hereditary Hemochromatosis
HJV	NM_213653.3	Hereditary Hemochromatosis
HMBS	NM_000190.3	Acute intermittent porphyria
HNF1A	NM_000545.5	Maturity-onset diabetes of the young (MODY)
HNF1B	NM_000458.3	Renal cysts and diabetes syndrome
MEFV	NM_000243.2	Familial Mediterranean fever
OTC	NM_000531.5	Ornithine Transcarbamylase Deficiency
RPE65	NM_000329.2	Retinal dystrophy
RYR1	NM_000540.2	Malignant Hyperthermia Susceptibility, Neuromuscular Condition
SERPINA1	NM_000295.4	Alpha-1-Antitrypsin Deficiency
SLC40A1	NM_014585.5	Hereditary Hemochromatosis
TFR2	NM_003227.3	Hereditary Hemochromatosis

Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated in the Genes Analyzed table. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes only targeted loci are analyzed. Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Confirmation of the presence and location of reportable variants is performed as needed based on stringent criteria using one of several validated orthogonal approaches (PubMed ID 30610921). Sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). Confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). RNA sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778).

  The following additional analyses are performed if relevant to the requisition. For PMS2 exons 12-15, the reference genome has been modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms are modified to support an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PMS2 and the PMS2CL pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. For C9orf72 repeat expansion testing, hexanucleotide repeat units are detected by repeat-primed PCR (RP-PCR) with fluorescently labeled primers followed by capillary electrophoresis. Interpretation Reference Ranges: Benign (Normal Range): <25 repeat units, Uncertain: 25-30 repeat units, Pathogenic (Full Mutation): >=31 repeat units (PMID: 21944779, 22406228, 23111906, 28689190, 31315673, 33168078, 33575483). A second round of RP-PCR utilizing a non-overlapping set of primers is used to confirm the initial call in the case of suspected allele sizes of 22 or more repeats. For RNA analysis of the genes indicated in the Genes Analyzed table, complementary DNA is synthesized by reverse transcription from RNA derived from a blood specimen and enriched for specific gene sequences using capture hybridization. After high-throughput sequencing using Illumina technology, the output reads are aligned to a reference sequence (genome build GRCh37; custom derivative of the RefSeq transcriptome) to identify the locations of exon junctions through the detection of split reads. The relative usage of exon junctions in a test specimen is assessed quantitatively and compared to the usage seen in control specimens. Abnormal exon junction usage is evaluated as evidence in the Sherloc variant interpretation framework. If an abnormal splicing pattern is predicted based on a DNA variant outside the typical reportable range, as described above, the presence of the variant is confirmed by targeted DNA sequencing.

- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at **http://www.ncbi.nlm.nih.gov/pubmed**.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (**http://exac.broadinstitute.org**), gnomAD (**http://gnomad.broadinstitute.org**), and dbSNP (**http://ncbi.nlm.nih.gov/SNP**).
- A MedGen ID is a unique identifier referring to an article in MedGen, NCBI's centralized database of information about genetic disorders and phenotypes. Search by MedGen ID at **http://www.ncbi.nlm.nih.gov/medgen**. An OMIM number is a unique identifier referring to a comprehensive entry in Online Mendelian Inheritance in Man (OMIM). Search by OMIM number at **http://omim.org/**.
- Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observations.

Limitations

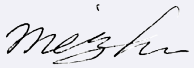
Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. While this test is intended to reflect the analysis of extracted genomic DNA from a referred patient, in very rare cases the analyzed DNA may not represent that individual's constitutional genome, such as in the case of a circulating hematolymphoid neoplasm, bone marrow transplant, blood transfusion, chimerism, culture artifact or maternal cell contamination. Interpretations are made on the assumption that any clinical information provided, including specimen identity, is accurate. Invitae's RNA analysis is not designed for use as a stand-alone diagnostic method and cannot determine absolute RNA levels. Results from the RNA analysis may not be informative for interpreting copy number gains.

ACTC1: Sequencing analysis for exons 6 includes only cds +/- 10 bp. ACTN2: Deletion/duplication analysis is not offered for exon 9. APC: Sequencing analysis for exons 5 includes only cds +/- 10 bp. ATM: Sequencing analysis for exons 6, 24, 43 includes only cds +/- 10 bp. CACNA1C: Deletion/duplication and sequencing analysis is not offered for exons 44-45. COL3A1: Deletion/duplication analysis is not offered for exons 23-24. DICER1: Sequencing analysis for exons 22 includes only cds +/- 10 bp. ENG: Sequencing analysis for exons 7 includes only cds +/- 10 bp. EPCAM: Sequencing analysis is not offered for this gene. FH: Sequencing analysis for exons 9 includes only cds +/- 10 bp. MAX: Sequencing analysis for exons 2 includes only cds +/- 10 bp. MEN1: Sequencing analysis for exons 2 includes only cds +/- 10 bp. MET: Sequencing analysis for exons 12 includes only cds +/- 10 bp. MLH1: Sequencing analysis for exons 12 includes only cds +/- 10 bp. MSH2: Analysis includes the exon 1-7 inversion (Boland mutation). Sequencing analysis for exons 2, 5 includes only cds +/- 10 bp. MSH6: Sequencing analysis for exons 7, 10 includes only cds +/- 10 bp. PCSK9: Sequencing analysis for exons 9 includes only cds +/- 10 bp. PMS2: Sequencing analysis for exons 7 includes only cds +/- 10 bp. PTEN: Sequencing analysis for exons 8 includes only cds +/- 10 bp. RB1: Sequencing analysis for exons 15-16 includes only cds +/- 10 bp. SDHA: Deletion/duplication analysis is not offered for this gene and sequencing analysis is not offered for exon 14. Sequencing analysis for exons 6-8 includes only cds +/- 10 bp. SDHC: Sequencing analysis for exons 2, 6 includes only cds +/- 10 bp. TSC1: Sequencing analysis for exons 21 includes only cds +/- 10 bp. GREM1: Promoter region duplication testing only. POLD1: Sequencing analysis for exons 22 includes only cds +/- 10 bp. FLNC: Deletion/duplication analysis is not offered for exon 47. Sensitivity and specificity for single nucleotide variants, insertions and deletions in exons 47-48 may be reduced due to the presence of segmental duplications overlapping the region. MSH3: Sequencing analysis of the repeat region of exon 1 (5:79950697-79950765) is not offered. NF1: Sequencing analysis for exons 2, 7, 25, 41, 48 includes only cds +/- 10 bp. TTN: Exons 45-46, 147, 149, 164, 172-201 (NM_001267550.2) are excluded from analysis. TTN variants are included in the primary report based on functional effect and/or location. A complete list of variants of uncertain significance, likely benign and benign variants in TTN is available upon request. Variants are named relative to the NM_001267550.2 (meta) transcript. Variants in the coding sequence and intronic boundaries of the clinically relevant NM_133378.4 (N2A) and fetal isoforms are reported (PMID: 25589632, 29598826, 29691892, 31660661), with the exception of the PEVK tandem repeat region (172-198) (PMID: 28040389).

Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

This report has been reviewed and approved by:



Mei Zhu, Ph.D., FACMG
Clinical Molecular Geneticist

mz_49e6_pr

This document is not part of the Invitae® clinical report and does not represent medical advice. These are general guidelines that are not specific to your result and may not represent all relevant international recommendations. You can use this guide to talk to your healthcare provider about your test results, clinical history, and the most current guidelines. This guide may not be appropriate for results that are suspected to be blood-limited, possibly mosaic, or suggestive of a larger imbalance of genetic material. Invitae recognizes that individuals have diverse gender and sexual identities. In this guide, the terms female, male, women, and men refer to sex assigned at birth.

What is a positive F5 result?

A positive test result means that a genetic change (variant) called c.1601G>A (p.Arg534Gln) was found in the F5 gene. This F5 variant is more commonly known as Factor V Leiden and is considered "pathogenic" or "likely pathogenic" because it increases the chance for Factor V Leiden thrombophilia, also called activated protein C resistance.

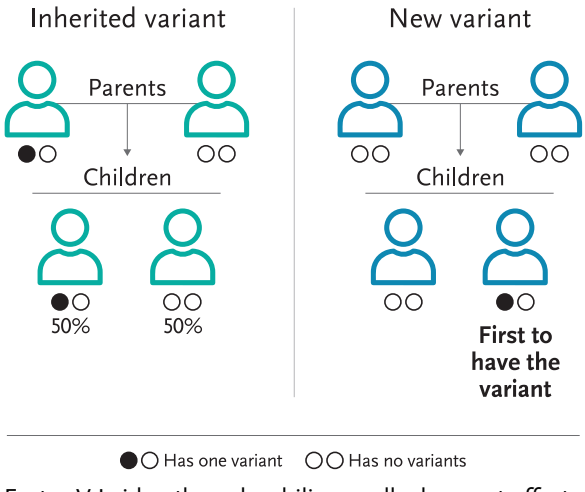
What does this mean?

Factor V Leiden thrombophilia is a blood clotting disorder that increases the chance of developing blood clots in the veins (venous thrombosis, or VTE). VTE most commonly presents as a blood clot in the legs (deep vein thrombosis, or DVT) or in the lungs (pulmonary embolism). Symptoms of DVT may include pain and swelling in the body part where the blood clot is located. Sometimes, blood clots can cause a life-threatening blockage of blood flow, with symptoms that include chest pain, shortness of breath, abdominal pain, severe headache, and nausea. Individuals with a single Factor V Leiden variant have an increased risk of VTE over the general population. Symptoms, severity, and age of onset can vary. Most people who are positive for this F5 variant will not develop a blood clot. Risk for clotting is influenced by several factors including the number of F5 variants and the presence of other inherited, acquired, or circumstantial risk factors. Individuals may have different conditions or symptoms depending on whether they inherit one or two variants in F5. Some people inherit two F5 variants, which may further increase the risk for VTE. See the table later in this guide for more information and possible next steps.

What does this mean for family members?

Relatives should be informed about these results. It is recommended that family members talk with their own healthcare provider about a plan for genetic testing and/or health screening. Genetic testing is a personal choice and some individuals may choose not to have genetic testing. Laws protecting employment and health insurance may apply to individuals undergoing genetic testing (for example, the Genetic Information Nondiscrimination Act in the United States).

Will family members have the same variant(s)?
The image shows where a F5 variant may have come from. Any individual can inherit and pass on a F5 variant, regardless of sex.



F5 variants are usually inherited from a parent. Siblings, children, and other relatives may also have this F5 variant. Being the first person in the family to have a new F5 variant is rare. Factor V Leiden thrombophilia usually does not affect children. Genetic testing for this F5 variant is not typically indicated until age 18 or older.

For individuals who are planning a family, reproductive options may be available to help lower the chance of passing on a variant to children.

Create a plan with a healthcare provider

These options are a guide for an individual and their healthcare provider. They are meant to be used along with an individual's genetic test results and other health information as part of a discussion to make a personalized care plan. Each option may or may not be right for an individual. A positive test result on its own cannot predict how a condition may affect an individual. This guide may not be appropriate for results that are suspected to be blood-limited, possibly mosaic, or suggestive of a larger imbalance of genetic material.

Options to consider

TOPIC	OPTION	MORE INFORMATION
Factor V Leiden thrombophilia	• Referral to a healthcare provider or genetic counselor with knowledge in thrombophilias should be considered. (1)	• Healthcare providers who specialize in thrombophilias can be found at: www.stoptheclot.org/find-provider/
	• For individuals with no personal history of VTE, education to help recognize symptoms of a VTE event can be important.	• Signs of a VTE event may include lightheadedness, fainting, chest pain, discomfort or difficulty breathing, coughing up blood, fast or irregular heartbeat, or pain, swelling, tenderness and redness or warmth of the skin • Preventative anticoagulation may be warranted in situations where risk factors for a VTE event cannot be avoided. (2)
	• For individuals with a history of VTE, this genetic finding may contribute to predisposition to past clotting event(s). • The finding of this positive F5 result slightly elevates the risk for recurrence of VTE; however, treatment decisions are typically not made based on this genetic finding alone. (1)	• Currently, VTE related to the F5 gene is managed in the same way as VTE from other causes. • A Factor V Leiden variant is generally not an indication for long-term anticoagulation in the absence of other risk factors. (1,3)
	• Discuss avoidable risk factors and the impact of lifestyle on risk for VTE. (2)	• Some risk factors for VTE include, but are not limited to, age, antiphospholipid antibodies, family history of VTE, obesity, cancer, smoking, surgery, air travel, central venous catheters, pregnancy, hormone replacement therapy, and estrogen-containing contraception. (1,2,4) • For some individuals, the presence of an inherited thrombophilia may weigh into decisions regarding oral contraceptives or hormone replacement therapy. (2,5)
F5-related research	• Consider options for clinical trials and/or other research. • To find up-to-date information about available clinical trials, visit ClinicalTrials.gov	• There are many factors when considering participation in research studies, including time, location, and whether or not an individual meets the specific requirements to be in a study.
Family planning	• Discuss reproductive risks. (6) • Individuals with a F5 variant have a 50% chance to pass on the variant to a child.	• Preconception and prenatal reproductive options are available and could be discussed in more detail with a reproductive specialist. • Individuals with this specific F5 variant may have an increased chance to have a child with even higher risks for thrombophilia if their reproductive partner also carries this same variant or a different variant predisposing to thrombophilia (F5 or another gene). Specific risk depends on the two variants identified. (2)

These options include recommendations from PMID: 19289024 (1), PMID: 21707594 (2), PMID: 21150787 (3), PMID: 26780744 (4), PMID: 29939939 (5), and PMID: 28225426 (6). We are always learning more about genetics and disease, so please always refer to the current guidelines and recommendations when considering surveillance and treatment options. Information in this document may not include all relevant international recommendations and acts as a

supplement to the Invitae result report. This information is not meant to replace a discussion with your healthcare provider and should not be considered or interpreted as medical advice. Additional resources provided within this document does not indicate or imply any endorsement by Invitae with respect to any third party or any website or the products or services offered by any third party.

Resources

Genetic counseling can help individuals understand their genetic test results and options for next steps. Reviewing test results with a genetic counselor or other healthcare provider is recommended. Local or telehealth genetic counselors can be identified using the Find a Genetic Counselor search tool at nsgc.org (US and Canada). Individuals who had genetic testing through Invitae can also log in to their patient portal (invitae.com) to view their results, contact a genetic counselor, or join Invitae's Patient Insights Network (PIN), an online platform where individuals can share information about their health and experiences to help advance research and drug development.

Notes for personalized assessment