Test Definition: HHTGG

Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel, Varies

Overview

Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of hereditary hemorrhagic telangiectasia (HHT), cerebral cavernous malformation (CCM), capillary malformation-arteriovenous malformation syndrome (CV-AVM), or other hereditary vascular malformation syndromes of germline origin

Establishing a diagnosis of HHT, CCM, CM-AVM, or other hereditary vascular malformation syndromes of germline origin

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	No	No

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 12 genes associated with hereditary hemorrhagic telangiectasia (HHT), cerebral cavernous malformation (CCM), capillary malformation-arteriovenous malformation syndrome (CM-AVM), and other hereditary vascular malformation syndromes of germline origin: *ACVRL1, BMPR2, CCM2, ENG, EPHB4, GDF2, GLMN, KRIT1, PDCD10, RASA1, SMAD4,* and *TEK*. See Targeted Genes and Methodology Details for Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for HHT, CCM, CM-AVM, and other hereditary vascular malformation syndromes of germline origin.

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture testing will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel Patient Information
- Targeted Genes and Methodology Details for Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel
- Hereditary Hemorrhagic Telangiectasia and Vascular Gene Panel (HHTGG) Prior Authorization Ordering Instructions

Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger

Sequencing

NY State Available
Yes

Specimen

Specimen Type
Varies

Ordering Guidance
Upon request and after initial testing is complete, WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies may be added to this test. To obtain more information about this option or add WESPR testing, call 800-533-1710.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Necessary Information
Prior Authorization is available, **but not required**, for this test. If proceeding with the prior authorization process, submit the required form with the specimen.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a bone marrow transplant, call 800-533-1710.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Green top (Sodium heparin)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens

received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA are met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies:
DNA Saliva Kit High Yield (T1007)
Saliva Swab Collection Kit (T786)
Container/Tube:
Preferred: High-yield DNA saliva kit
Acceptable: Saliva swab
Specimen Volume: 1 Tube if using T1007 or 2 swabs if using T786
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

Specimen Type: Cultured fibroblasts
Source: Skin
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy. Cultured cells from a prenatal specimen will not be accepted.
Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and/or extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Tissue biopsy
Supplies: Hank's Solution (T132)
Container/Tube: Sterile container with sterile Hank's balanced salt solution, Ringer's solution, or normal saline
Specimen Volume: 0.5 to 3 cm(3) or larger
Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Blood spot
Supplies: Card-Blood Spot Collection (Filter Paper) (T493)
Container/Tube:
Preferred: Collection card (Whatman Protein Saver 903 Paper)
Acceptable: PerkinElmer 226 filter paper or blood spot collection card
Specimen Volume: 2 to 5 Blood spots
Collection Instructions:
1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see How to Collect Dried Blood Spot Samples.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.
Specimen Stability Information: Ambient (preferred)/Refrigerated
Additional Information:
1. Blood spot specimens are acceptable but not recommended. Multiple extractions will be required to obtain sufficient yield for supplemental analysis, and there is significant risk for test failure due to insufficient DNA.
2. Due to lower concentration of DNA yielded from blood spot, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.
3. For collection instructions, see Blood Spot Collection Instructions
4. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777)
5. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800)

Specimen Type: Extracted DNA
Container/Tube:
Preferred: Screw Cap Micro Tube, 2mL with skirted conical base
Acceptable: Matrix tube, 1mL
Collection Instructions:
1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated
Additional Information: DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

Forms

1. **New York Clients-Informed consent is required.** Please document on the request form or electronic order that a copy is on file.
The following documents are available:
-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing (Spanish) (T826)
2. Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel Patient Information
3. Hereditary Hemorrhagic Telangiectasia and Vascular Gene Panel (HHTGG) Prior Authorization Ordering Instructions
4. If not ordering electronically, complete, print, and send a Cardiovascular Test Request Form (T724) with the specimen.

Specimen Minimum Volume
See Specimen Required

Reject Due To
All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information
Hereditary vascular malformation syndromes include a group of genetic conditions characterized by abnormal blood vessel development. These syndromes can be of germline or somatic origin. This gene panel is restricted to analysis of genes associated with vascular malformation syndromes of germline origin.

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia characterized by the presence of arteriovenous malformations (AVM) of the skin, mucosa, and viscera. Small AVM, or telangiectasias, develop predominantly on the face, oral cavity, and hands, and spontaneous, recurrent epistaxis (nose bleeding) is a common presenting sign.(1) HHT has an estimated prevalence of 1:5000 and is primarily caused by heterozygous, disease-causing variants in the *ACVRL1* and *ENG* genes. Rarely, HHT can be caused by disease-causing variants in the *GDF2* gene (also known as *BMP9*). Additionally, *SMAD4* disease-causing variants cause autosomal dominant juvenile polyposis/HHT syndrome, which includes features of juvenile polyposis syndrome and HHT.(2) An overlapping pulmonary arterial hypertension and HHT phenotype have also been reported in association with the *BMPR2* gene.(3,4)

Familial cerebral cavernous malformation (CCM) is an autosomal dominant condition characterized by structurally abnormal capillaries in the central nervous system leading to an increased risk of cerebral hemorrhage.(5) The estimated prevalence of familial CCM ranges from 1:3300 to 1:10,000,(5) and the condition displays age-related penetrance with up to 50% of individuals remaining symptom free throughout their life.(5,6) Disease-causing variants in three genes have been associated with familial CCM: *KRIT1*, *CCM2*, and *PDCD10*.

Capillary malformation-arteriovenous malformation syndrome (CM-AVM) is an autosomal dominant condition primarily characterized by capillary malformations localized to the dermis of the face and limbs, AVM or arteriovenous fistulas of the skin, muscle, bone, spine, and brain, and Parkes Weber syndrome.(6) The prevalence of CM-AVM has been estimated in Northern European cohorts at approximately 1:100,000, with penetrance estimated at 90% to 99%.(6)

Approximately 60% of cases of CM-AVM can be attributed to disease-causing variants in the *EPHB4* and *RASA1* genes. The genetic etiology remains unknown in approximately 40% of cases.(6)

Hereditary glomuvenous malformation is a rare autosomal dominant condition characterized by multiple venous malformations within the glomerulus of the kidney. The condition is associated with germline disease-causing variants in the *GLMN* gene. However, it is thought that a second, somatic (acquired) variant on the second allele, or acquired uniparental disomy, is required for the development of venous malformations.(7,8)

Multiple cutaneous and mucosal venous malformations (also known as cutaneomucosal venous malformation: VMCM) is an autosomal dominant condition characterized by small multifocal cutaneous and mucosal vascular malformations that typically present at birth.(9) These lesions are usually asymptomatic but may become painful if they are large enough to impact the underlying muscle tissue. The prevalence of this condition is unknown but thought to be rare. VMCM is associated with disease-causing variants in the *TEK* gene, and penetrance is estimated at 90% in individuals with a known genetic etiology.(9)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on

internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Refer to the Targeted Genes and Methodology Details for Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel for the most up to date list of genes included in this test. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(10) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions

made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Faughnan ME, Mager JJ, Hetts SW, et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. Ann Intern Med. 2020;173(12):989-1001. doi:10.7326/M20-1443
2. McDonald J, Stevenson DA. Hereditary hemorrhagic telangiectasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds: GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated November 24, 2021. Accessed December 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1351/
3. Rigelsky CM, Jennings C, Lehtonen R, Minai OA, Eng C, Aldred MA. BMPR2 mutation in a patient with pulmonary arterial hypertension and suspected hereditary hemorrhagic telangiectasia. Am J Med Genet A. 2008;146A(19):2551-2556. doi:10.1002/ajmg.a.32468
4. Ye F, Jiang W, Lin W, et al. A novel BMPR2 mutation in a patient with heritable pulmonary arterial hypertension and suspected hereditary hemorrhagic telangiectasia: A case report. Medicine (Baltimore). 2020;99(31):e21342. doi:10.1097/MD.0000000000021342
5. Zafar A, Quadri SA, Farooqui M, et al. Familial cerebral cavernous malformations. Stroke. 2019;50(5):1294-1301. doi:10.1161/STROKEAHA.118.022314
6. Bayrak-Toydemir P, Stevenson DA. Capillary malformation-arteriovenous malformation syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2011. Updated September 12, 2019. Accessed December 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK52764/
7. Brouillard P, Boon LM, Mulliken JB, et al. Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations ("glomangiomas"). Am J Hum Genet. 2002;70(4):866-874. doi:10.1086/339492
8. Amyere M, Aerts V, Brouillard P, et al. Somatic uniparental isodisomy explains multifocality of glomuvenous malformations. Am J Hum Genet. 2013;92(2):188-196. doi:10.1016/j.ajhg.2012.12.017
9. Seront E, Boon LM, Vikkula M. TEK-Related venous malformations. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated March 2, 2023. Accessed December 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1967/
10. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30

Performance

Method Description

Next-generation sequencing (NGS) and Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At

least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *ACVRL1, BMPR2, CCM2, ENG, EPHB4, GDF2, GLMN, KRIT1, PDCD10, RASA1, SMAD4,* and *TEK*

PDF Report
No

Day(s) Performed
Varies

Report Available
14 to 21 days

Specimen Retention Time
Whole blood: 30 days (if available); Extracted DNA: 3 months

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81406 x3
81479
81479 (if appropriate for government payers)

Prior Auhtorization

Insurance preauthorization is available for this testing; forms are available.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
HHTGG	HHT and Vascular Gene Panel	51966-0

Result ID	Test Result Name	Result LOINC® Value
617296	Test Description	62364-5
617297	Specimen	31208-2
617298	Source	31208-2
617299	Result Summary	50397-9
617300	Result	82939-0
617301	Interpretation	69047-9
617302	Additional Results	82939-0
617303	Resources	99622-3
617304	Additional Information	48767-8
617305	Method	85069-3
617306	Genes Analyzed	48018-6
617307	Disclaimer	62364-5
617308	Released By	18771-6