Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hemorrhagic telangiectasia (HHT) or a related disorder

Second-tier testing for patients in whom previous targeted gene variant analyses for specific HHT genes were negative

Establishing a diagnosis of HHT and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved

Identifying variants within genes known to be associated with HHT and allowing for predictive testing of at-risk family members

Genetics Test Information

This test includes next-generation sequencing as well as supplemental Sanger sequencing to evaluate the genes listed on this panel.

Additionally, NGS is used to test for the presence of large deletions and duplications in a subset of genes.

Highlights

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate for variants in the ACVRL1, ENG, GDF2, RASA1, and SMAD4 genes.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

Special Instructions

- Informed Consent for Genetic Testing
- Hereditary Hemorrhagic Telangiectasia (HHT) Gene Testing Patient Information
- Informed Consent for Genetic Testing (Spanish)

Method Name

Custom Sequence Capture and Targeted Next Generation Sequencing followed by qPCR or Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.
Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Necessary Information
1. Hereditary Hemorrhagic Telangiectasia (HHT) Gene Testing Patient Information is required, see Special Instructions. Testing may proceed without the patient information however it aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to complete the form and send it with the specimen.

2. Include physician name and phone number with specimen.

Specimen Required
Submit only 1 of the following specimens:

**Specimen Type:** Whole blood

**Container/Tube:** Lavender top (EDTA)

**Specimen Volume:** 3 mL

**Collection Instructions:**
1. Invert several times to mix blood.
2. Send specimen in original tube.

**Specimen Stability Information:** Ambient (Preferred)/Refrigerated

**Specimen Type:** DNA

**Container/Tube:** 2 mL screw top tube

**Specimen Volume:** 100 mcL (microliters)

**Collection Instructions:**
1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL.
2. Include concentration and volume on tube.

**Specimen Stability Information:** Frozen (preferred)/Ambient/Refrigerated

Forms
1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
   - Informed Consent for Genetic Testing (T576)
   - Informed Consent for Genetic Testing-Spanish (T826)

2. If not ordering electronically, complete, print, and send a Cardiovascular Test Request Form (T724) with the
Specimen Minimum Volume

Whole blood: 1 mL

Reject Due To

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

Specimen Stability Information

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Clinical and Interpretive

Clinical Information

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.

Symptomatic telangiectasias occur in the gastrointestinal tract of about 30% of HHT patients. Additional serious complications associated with HHT include transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemotherax, seizure, and cerebral hemorrhage. These complications are a result of larger AVM, which are most commonly pulmonary, hepatic, or cerebral in origin, and occur in approximately 30%, 40%, and 10% of individuals with HHT, respectively.

HHT is inherited in an autosomal dominant manner and occurs with wide ethnic and geographic distribution. The overall incidence of HHT in North America is estimated to be between 1 in 5,000 and 1 in 10,000. Penetrance seems to be age related, with increased manifestations occurring over one's lifetime. For example, approximately 50% of diagnosed individuals report having nosebleeds by age 10 years, increasing to 80% to 90% by age 21 years, and as many as 90% to 95% of affected individuals eventually developing recurrent epistaxis.

HHT is phenotypically heterogeneous both between families and amongst affected members of the same family. Furthermore, complications associated with HHT have variable ranges of age of onset. Thus, HHT can be diagnostically challenging. Genetic testing allows for the confirmation of a suspected genetic disease. Confirmation of a diagnosis allows for proper treatment and management of the disease, preconception or prenatal counseling, and family counseling. In addition, it has been estimated that genetic screening of suspected HHT individuals and their families is more economically effective than conventional clinical screening.

Two genes are most commonly associated with HHT: the endoglin gene (ENG), and the activin A receptor, type II-like 1 gene (ACVRL1 or ALK1). ENG and ACVRL1 encode membrane glycoproteins involved in transforming growth factor-beta signaling related to vascular integrity. Variants in ENG are associated with HHT type 1 (HHT1), which has been reported to have a higher incidence of pulmonary AVM, whereas ACVRL1 variants occur in HHT type 2 (HHT2), which has been reported to have a higher incidence of hepatic AVM.
The majority of variants in \textit{ENG} and \textit{ACVRL1} are missense, nonsense, splice site, or small intragenic deletions and insertions. Approximately 10\% of \textit{ENG} and \textit{ACVRL1} variants are large genomic deletions and duplications (also known as dosage alterations). Approximately 60\% to 80\% of patients with HHT will have a variant detected in \textit{ENG} or \textit{ACVRL1}.

Pathogenic variants in the \textit{SMAD4} gene are the third most common identifiable cause of HHT, accounting for approximately 10\% of HHT patients who test negative for \textit{ENG} and \textit{ACVRL1}, and approximately 1\% to 2\% of total HHT cases. Pathogenic \textit{SMAD4} variants cause autosomal dominant juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT), which includes features of juvenile polyposis syndrome (JPS) and HHT. JPS is characterized by hamartomatous polyps of the gastrointestinal tract and increased risk of gastrointestinal cancer. \textit{SMAD4} variants have also been detected in families presenting with JPS or HHT only.

Pathogenic variants in the \textit{GDF2} gene (also known as \textit{BMP9}) are a rare cause of HHT. In a study of 191 individuals with clinically suspected HHT and no variants in \textit{ENG}, \textit{ACVRL1}, or \textit{SMAD4}, 3 unrelated individuals were found to carry a rare missense variant in \textit{GDF2}.

Pathogenic variants in the \textit{RASA1} gene cause capillary malformation-arteriovenous malformation syndrome (CMAVM). CMAVM is characterized by the presence of multiple small (1-2 cm in diameter) capillary malformations mostly localized to the face and limbs. Patients may also have arteriovenous malformations (AVM) and arteriovenous fistulas (AVF). In some cases, pathogenic \textit{RASA1} variants may be found in individuals clinically suspected to have HHT. Individuals with apathogenic \textit{RASA1} variant may have a clinical diagnosis of Parkes Weber syndrome (PWS), with multiple micro-AVF associated with a cutaneous capillary stain and excessive soft tissue and skeletal growth of an affected limb.

\begin{table}[h]
  \centering
  \begin{tabular}{|l|l|l|l|l|}
    \hline
    \textbf{Gene Symbol (alias)} & \textbf{Protein} & \textbf{OMIM} & \textbf{Inheritance} & \textbf{Phenotype/Disorder} \\
    \hline
    \textit{ACVRL1} & Activin A receptor like type 1 & 601284 & AD & Telangiectasia, hereditary hemorrhagic, type 2 \\
    \hline
    \textit{ENG} & Endoglin & 131195 & AD & Telangiectasia, hereditary hemorrhagic, type 1 \\
    \hline
    \textit{GDF2} & Growth differentiation factor 2 & 605120 & AD & Telangiectasia, hereditary hemorrhagic, type 5 \\
    \hline
    \textit{RASA1} & RAS p21 protein activator 1 & 139150 & AD & Capillary malformation-arteriovenous malformation, Parkes Weber syndrome \\
    \hline
    \textit{SMAD4} & SMAD family member 4 & 600993 & AD & Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, Myhre syndrome \\
    \hline
  \end{tabular}
  \caption{Genes included in the HHT Gene Panel}
\end{table}

AD: autosomal dominant
AR: autosomal recessive

Reference Values
An interpretive report will be provided.

Interpretation
Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

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 predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions
Clinical Correlations:
Some individuals who have involvement of 1 or more of the genes on the panel may have a variation that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of hereditary hemorrhagic telangiectasia (HHT) or a related disorder.

Test results should be interpreted in 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 family history of HHT or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual would allow for more informative testing of at risk individuals.

Technical Limitations:
Next-generation sequencing may not detect all types of genetic variants. Additionally, rare polymorphisms may be present that could lead to false-negative or false-positive results. If the patient has had an allogeneic blood or marrow transplant or a recent (ie, less than 6 weeks from time of sample collection) heterologous blood transfusion, these results may be inaccurate due to the presence of donor DNA.

Reclassification of Variants Policy:
At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of this patient’s results.

Clinical Reference
Performance

Method Description
Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline for sequence variants and the presence of large intragenic deletions and duplications. Supplemental Sanger sequencing or qPCR may be performed occasionally in regions where NGS is insufficient for data capture or not specific enough to correctly identify a variant. Sanger sequencing or qPCR may also be used for confirmatory testing. (Unpublished Mayo method)

The following genes are evaluated in this multi-gene panel, ACVRL1, ENG, GDF2, RASA1, and SMAD4.

PDF Report
No

Day(s) Performed
Monday

Report Available
2 to 4 weeks

Specimen Retention Time
2 months

Performing Laboratory Location
Rochester
Test Definition: HHTGP
Hereditary Hemorrhagic Telan Panel

Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81479

81406 x 2

LOINC® Information

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