Test Definition: CVHBG

Comprehensive Cerebrovascular Gene Panel, Varies

Overview

Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of a monogenic condition in which there is an increased risk for a cerebrovascular accident

Establishing a diagnosis of a monogenic condition in which there is an increased risk for a cerebrovascular accident

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 30 genes associated with monogenic conditions in which there is an increased risk for cerebrovascular accident (stroke): *ACTA2, ACVRL1, ADA2, CBS, CCM2, COL3A1, COL4A1, COL4A2, CST3, ENG, EPHB4, GDF2, GLA, GUCY1A1, HTRA1, KRIT1, NOTCH3, PDCD10, RASA1, RNF213, SLC2A10, SMAD2, SMAD3, SMAD4, TEK, TGFB2, TGFB3, TGFBR1, TGFBR2,* and *TREX1.* See Targeted Genes and Methodology Details for Comprehensive Cerebrovascular Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for monogenic conditions in which there is an increased risk for a cerebrovascular accident (stroke).

Prior Authorization is available for this assay.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information
- Targeted Genes and Methodology Details for Comprehensive Cerebrovascular Gene Panel
- Comprehensive Cerebrovascular Gene Panel (CVHBG) 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. To modify this panel via CGPH, please use the Cardiovascular/Connective Tissue/Dyslipidemia/Cerebrovascular/Primary Ciliary Dyskinesia disease state for step 1 on the Custom Gene Ordering Tool.

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.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

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 instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
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)/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:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information
3. Cerebrovascular Gene Panel (CVHBG) Prior Authorization Ordering Instructions
4.If not ordering electronically, complete, print, and send a Cardiovascular Test Request (T724) with the specimen.

Specimen Minimum Volume

1 mL

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

There are many known monogenic conditions that increase an individual's risk for cerebrovascular accident or stroke. Most of these conditions are characterized by abnormal vascular development, abnormal intracranial blood flow, and weakening of the cerebral vessels. Depending on the pathophysiology of the associated condition, risk may be increased for ischemic stroke, hemorrhagic stroke, or both.(1)

Several vascular malformation syndromes are associated with an increased risk for stroke due to abnormalities in vascular development throughout the body.(1) Pulmonary arteriovenous malformations (AVM) are common features of autosomal dominant hereditary hemorrhagic telangiectasia and autosomal dominant capillary malformation-AVM. Pulmonary AVM increase the risk for ischemic stroke by allowing emboli to bypass the lungs and enter the cerebral vasculature.(1) Autosomal dominant familial cerebral cavernous malformation causes abnormal development of capillary channels within the brain and is associated with an increased risk for hemorrhagic stroke.(1,2)

Several monogenic connective tissue conditions leading to vascular fragility are associated with an increased risk for arterial dissection and ischemic stroke.(1) These conditions lead to defects impacting the structural integrity of blood vessels throughout the body resulting in a high risk for vessel rupture. This panel assesses several vascular fragility syndromes, including autosomal dominant vascular Ehlers-Danlos syndrome, autosomal dominant Loeys-Dietz syndrome, autosomal dominant familial aortic aneurysm and dissection, and autosomal recessive arterial tortuosity syndrome.(3-6)

Hereditary cerebral small vessel disease (SVD) is a group of conditions generally characterized by lacunar infarcts and white matter hyperintensities on magnetic resonance imaging and an increased risk for ischemic and/or hemorrhagic stroke.(1,7) The monogenic SVDs assessed on this panel include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), autosomal dominant retinal vasculopathy with leukodystrophy, autosomal dominant *COL4A1*-associated SVD, and autosomal dominant *COL4A2*-associated SVD.(1, 7)

Moyamoya disease, a condition characterized by progressive narrowing of the blood vessels and an increased risk for ischemic stroke, can be inherited in an autosomal dominant manner. However, in most individuals, the genetic etiology (if any) remains unknown.(1,8)

Other conditions associated with increased risk for ischemic and hemorrhagic stroke assessed on this panel include

X-linked Fabry disease, autosomal recessive homocystinuria due to variants in the *CBS* gene, and autosomal recessive adenosine deaminase 2 deficiency.(1,9)

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 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 Comprehensive Cerebrovascular 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 heterologous 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. Tan RY, Markus HS. Monogenic causes of stroke: now and the future. J Neurol. 2015;262(12):2601-2616. doi:10.1007/s00415-015-7794-4
2. Zafar A, Quadri SA, Farooqui M, et al. Familial cerebral cavernous malformations. Stroke. 2019;50(5):1294-1301.

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3. Byers PH. Vascular Ehlers-Danlos syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated February 21, 2019. Accessed September 6, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1494/
4. Loeys BL, Dietz HC. Loeys-Dietz syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated March 1, 2018. Accessed September 6, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1133/
5. Milewicz DM, Regalado E: Heritable thoracic aortic disease overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated May 4, 2023. Accessed September 6, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1120/
6. Callewaert B, De Paepe A, Coucke P: Arterial Tortuosity Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2014. Updated February 23, 2023. Accessed September 6, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK253404/
7. Litak J, Mazurek M, Kulesza B, et al. Cerebral small vessel disease. Int J Mol Sci. 2020;21(24):9729. doi:10.3390/ijms21249729
8. Shang S, Zhou D, Ya J, et al. Progress in moyamoya disease. Neurosurg Rev. 2020;43(2):371-382. doi:10.1007/s10143-018-0994-5
9. Aksentijevich I, Sampaio Moura N, Barron K. Adenosine deaminase 2 deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2019. Accessed September 6, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK544951
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

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 deletion/insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp, and insertions up to 47 bp. NGS and/or 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 Comprehensive Cerebrovascular 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: *ACTA2, ACVRL1, ADA2, CBS, CCM2, COL3A1, COL4A1, COL4A2, CST3, ENG, EPHB4, GDF2, GLA, GUCY1A1, HTRA1, KRIT1, NOTCH3, PDCD10, RASA1, RNF213, SLC2A10, SMAD2, SMAD3, SMAD4, TEK, TGFB2, TGFB3, TGFBR1, TGFBR2,* and *TREX1*

PDF Report
No

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (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
81405 x5
81406 x3
81408
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
CVHBG	Cerebrovascular Gene Panel	55232-3

Result ID	Test Result Name	Result LOINC® Value
617226	Test Description	62364-5
617227	Specimen	31208-2
617228	Source	31208-2
617229	Result Summary	50397-9
617230	Result	82939-0
617231	Interpretation	69047-9
617232	Additional Results	82939-0
617233	Resources	99622-3
617234	Additional Information	48767-8
617235	Method	85069-3
617236	Genes Analyzed	48018-6
617237	Disclaimer	62364-5
617238	Released By	18771-6