MAYO CLINIC LABORATORIES

Test Definition: EPPAN

Comprehensive Epilepsy With or Without Encephalopathy Gene Panel, Varies

Overview

Useful For

Establishing a diagnosis of an epilepsy or seizure disorder associated with known causal genes

Identifying disease-causing variants within genes known to be associated with inherited epilepsy or seizure disorders, allowing for predictive testing of at-risk family members

Impacting patient treatment and management through the identification of a specific underlying etiology for epilepsy (eg, directing appropriate use of antiepileptic drugs and other treatment modalities)

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 319 genes associated with epilepsy and a polymerase chain reaction-based assay to detect *CSTB* dodecamer repeat expansions: *ABAT, ACO2, ACY1, ADARB1, ADGRG1, ADSL, AFG3L2, AIFM1, AKT2, ALDH3A2, ALDH5A1, ALDH7A1, ALG13, AMT, AP2M1, APOPT1 (COA8), ARFGEF2, ARHGEF9, ARX, ASAH1, ASNS, ATN1, ATP1A2, ATP1A3, ATRX, BCKDK, BCS1L, BOLA3, BRAT1, C12orf57, CACNA1A, CACNA1E, CACNA2D2, CAD, CARS2, CASK, CCM2, CDKL5, CHD2, CHRNA2, CHRNA4, CHRNB2, CLCN4, CLN3, CLN5, CLN6, CLN8, CNTNAP2, COA8 (APOPT1), COG7, COG8, COL18A1, COL4A1, COQ2, COQ4, COQ6, COQ8A, COQ9, COX10, COX15, CPT2, CSF1R, CSTB, CTSD, CTSF, CUL4B, D2HGDH, DCX, DDC, DDX3X, DEPDC5, DHFR, DIAPH1, DLD, DMXL2, DNAJC5, DNM1, DNM1L, DOCK7, DYRK1A, EARS2, EEF1A2, EHMT1, EIF2AK2, EPM2A, ETHE1, FARS2, FASTKD2, FBP1, FBXL4, FH, FKRP, FKTN, FLNA, FOLR1, FOXG1, FOXRED1, FRRS1L, GABBR2, GABRA1, GABRB2, GABRB3, GABRG2, GAMT, GATM, GCK, GFM1, GLDC, GLRA1, GLUL, GNAO1, GOSR2, GPAA1, GPC3, GPHN, GRIA3, GRIN1, GRIN2A, GRIN2B, GYS2, HCFC1, HCN1, HIBCH, HNRNPU, HSD17B10, IARS2, IBA57, IDH2, IER3IP1, IQSEC2, ITPA, KANSL1, KCNA1, KCNA2, KCNB1, KCNC1, KCNH1, KCNJ10, KCNMA1, KCNQ2, KCNQ3, KCNT1, KCTD7, KDM5C, KDM6A, KRIT1, L2HGDH, LAMA2, LARGE1, LGI1, LIAS, LRPPRC, MBD5, MECP2, MEF2C, MFSD8, MICU1, MOCS1, MOCS2, MTFMT, MTO1, MTOR, NALCN, NDUFA1, NDUFA2, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFS1, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NECAP1, NEDD4L, NEU1, NEXMIF, NGLY1, NHLRC1, NOTCH3, NPRL2, NPRL3, NR2F1, NR4A2, NRROS, NRXN1, OCLN, OFD1, OPHN1, OTUD6B, P4HTM, PACS1, PACS2, PAFAH1B1, PAK3, PCDH12, PCDH19, PDCD10, PDHA1, PDHB, PDHX, PDP1, PDSS2, PEX7, PHF6, PHGDH, PIGA, PIGG, PIGK, PIGL, PIGM, PIGN, PIGO, PIGQ, PIGS, PIGT, PIGU, PIGV, PIGW, PLCB1, PLP1, PLPBP, PNKP, PNPLA8, PNPO, POLG, POMGNT1, POMT1, POMT2, PPP2R5D, PPT1, PRRT2, PURA, QARS1, RAB39B, RAB3GAP1, RALA, RALGAPA1, RANBP2, RARS2, RELN, RMND1, ROGDI, RRM2B, SATB2, SCARB2, SCN1A, SCN1B, SCN2A, SCN3A, SCN8A, SCO2, SDHAF1, SERAC1, SERPINI1, SETBP1, SETD2, SIK1, SLC12A5, SLC13A5, SLC16A1, SLC19A3, SLC25A1, SLC25A12, SLC25A22, SLC2A1, SLC35A2, SLC35A3, SLC6A1, SLC6A8, SLC9A6, SMARCA2, SMC1A, SMS, SNAP25, SNAP29, SNX27, SPATA5, SPR, SPTAN1, ST3GAL3, ST3GAL5, STRADA, STX1B, STXBP1, SUCLA2, SUOX, SYN1, SYNGAP1, SYNJ1, SYP, SZT2, TBC1D24, TBL1XR1, TCF4, TPK1, TPP1, TSC1, TSC2, TSFM, TUBA1A, TUBA8, TUBB2B, TWNK, UBE3A, UGP2, USP7, VARS2, VLDLR, WDR26, WDR37, WDR45, WDR62, WWOX, YWHAG, ZDHHC9,* and *ZEB2*. See Targeted Genes and Methodology Details for Comprehensive Epilepsy With or Without Encephalopathy Gene Panel and Method Description for additional details.

Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, recurrence risk assessment, and genetic counseling for hereditary forms of epilepsy.

Additional first-tier testing may be considered/recommended. For more information see Ordering Guidance and Testing

Algorithm sections.

Testing Algorithm
For more information see Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm

Special Instructions
- Informed Consent for Genetic Testing
- Molecular Genetics: Neurology Patient Information
- Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Comprehensive Epilepsy With or Without Encephalopathy Gene Panel

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 variant testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies.

Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
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. Molecular Genetics: Neurology Patient Information
3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

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

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Epilepsy is a chronic neurological disorder characterized by recurrent and unprovoked seizures. Epilepsy is common, impacting just over 1% of the population. The underlying cause of epilepsy is multifactorial, with both genetic and nongenetic etiologies.

Inherited forms of epilepsy may present with varying seizure types, age of onset, comorbidities and underlying molecular causes, including channelopathies, metabolic conditions, and disorders associated with structural brain anomalies. Different hereditary epilepsies may follow autosomal dominant, autosomal recessive, or X-linked patterns of inheritance, or may occur as a result of a *de novo* pathogenic variant; therefore, identification of a specific molecular cause is essential to assess recurrence risk and impact to at risk family members.

Clinical diagnoses can be challenging as pathogenic variants in different genes may be associated with strikingly similar clinical presentations. Comprehensive diagnostic genetic testing is useful to determine the molecular etiology which in turn can assist in establishing long-term prognosis and identifying appropriate therapeutic and management strategies.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference values for *CSTB* repeat expansion assay
Normal: <5 dodecamer repeats
Repeat Size of Uncertain Significance: 5-29 dodecamer repeats
Full Penetrance Expansion: >29 dodecamer repeats

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 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 the Comprehensive Epilepsy with or without Encephalopathy Gene Panel in Special Instructions 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. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

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.(1) 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 judgement.

Rarely, incidental findings or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. 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 May;17(5):405-42.
2. Martinez L, Lai Y, Holder J, et al: Genetics in epilepsy. Neurol Clin. 2021 Aug; 39(3):743-777
3. Helbig I, Ellis C: Personalized medicine in genetic epilepsies-possibilities, challenges, and new frontiers. Neuropharmacology. 2020 Aug 1;172:107970

Performance

Method Description

Next-generation sequencing (NGS) and/or 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/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed. Additionally, a combined amplicon-length and repeat-primed PCR-based assay is utilized to detect expansions of a dodecamer repeat region in the *CSTB* gene.

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 the Comprehensive Epilepsy with or without Encephalopathy Gene Panel for details regarding the specific gene regions not routinely covered.(Unpublished Mayo method)

Genes analyzed: *ABAT, ACO2, ACY1, ADARB1, ADGRG1, ADSL, AFG3L2, AIFM1, AKT2, ALDH3A2, ALDH5A1, ALDH7A1, ALG13, AMT, AP2M1, APOPT1 (COA8), ARFGEF2, ARHGEF9, ARX, ASAH1, ASNS, ATN1, ATP1A2, ATP1A3, ATRX, BCKDK, BCS1L, BOLA3, BRAT1, C12orf57, CACNA1A, CACNA1E, CACNA2D2, CAD, CARS2, CASK, CCM2, CDKL5, CHD2, CHRNA2, CHRNA4, CHRNB2, CLCN4, CLN3, CLN5, CLN6, CLN8, CNTNAP2, COA8 (APOPT1), COG7, COG8, COL18A1, COL4A1, COQ2, COQ4, COQ6, COQ8A, COQ9, COX10, COX15, CPT2, CSF1R, CSTB, CTSD, CTSF, CUL4B, D2HGDH, DCX, DDC, DDX3X, DEPDC5, DHFR, DIAPH1, DLD, DMXL2, DNAJC5, DNM1, DNM1L, DOCK7, DYRK1A, EARS2, EEF1A2, EHMT1, EIF2AK2, EPM2A, ETHE1, FARS2, FASTKD2, FBP1, FBXL4, FH, FKRP, FKTN, FLNA, FOLR1, FOXG1, FOXRED1, FRRS1L, GABBR2, GABRA1, GABRB2, GABRB3, GABRG2, GAMT, GATM, GCK, GFM1, GLDC, GLRA1, GLUL, GNAO1, GOSR2, GPAA1, GPC3, GPHN, GRIA3, GRIN1, GRIN2A, GRIN2B, GYS2, HCFC1, HCN1, HIBCH, HNRNPU, HSD17B10, IARS2, IBA57, IDH2, IER3IP1, IQSEC2, ITPA, KANSL1, KCNA1, KCNA2, KCNB1, KCNC1, KCNH1, KCNJ10, KCNMA1, KCNQ2, KCNQ3, KCNT1, KCTD7, KDM5C, KDM6A, KRIT1, L2HGDH, LAMA2, LARGE1, LGI1, LIAS, LRPPRC, MBD5, MECP2, MEF2C, MFSD8, MICU1, MOCS1, MOCS2, MTFMT, MTO1, MTOR, NALCN, NDUFA1, NDUFA2, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFS1, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NECAP1, NEDD4L, NEU1, NEXMIF, NGLY1, NHLRC1, NOTCH3, NPRL2, NPRL3, NR2F1, NR4A2, NRROS, NRXN1, OCLN, OFD1, OPHN1, OTUD6B, P4HTM, PACS1, PACS2, PAFAH1B1, PAK3, PCDH12, PCDH19, PDCD10, PDHA1, PDHB, PDHX, PDP1, PDSS2, PEX7, PHF6, PHGDH, PIGA, PIGG, PIGK, PIGL, PIGM, PIGN, PIGO, PIGQ, PIGS, PIGT, PIGU, PIGV, PIGW, PLCB1, PLP1, PLPBP, PNKP, PNPLA8, PNPO, POLG, POMGNT1, POMT1,*

POMT2, PPP2R5D, PPT1, PRRT2, PURA, QARS1, RAB39B, RAB3GAP1, RALA, RALGAPA1, RANBP2, RARS2, RELN, RMND1, ROGDI, RRM2B, SATB2, SCARB2, SCN1A, SCN1B, SCN2A, SCN3A, SCN8A, SCO2, SDHAF1, SERAC1, SERPINI1, SETBP1, SETD2, SIK1, SLC12A5, SLC13A5, SLC16A1, SLC19A3, SLC25A1, SLC25A12, SLC25A22, SLC2A1, SLC35A2, SLC35A3, SLC6A1, SLC6A8, SLC9A6, SMARCA2, SMC1A, SMS, SNAP25, SNAP29, SNX27, SPATA5, SPR, SPTAN1, ST3GAL3, ST3GAL5, STRADA, STX1B, STXBP1, SUCLA2, SUOX, SYN1, SYNGAP1, SYNJ1, SYP, SZT2, TBC1D24, TBL1XR1, TCF4, TPK1, TPP1, TSC1, TSC2, TSFM, TUBA1A, TUBA8, TUBB2B, TWNK, UBE3A, UGP2, USP7, VARS2, VLDLR, WDR26, WDR37, WDR45, WDR62, WWOX, YWHAG, ZDHHC9, and *ZEB2*

PDF Report
Supplemental

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
81419

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
EPPAN	Comprehensive Epilepsy Gene Panel	112706-7

Result ID	Test Result Name	Result LOINC® Value

616551	Test Description	62364-5
616552	Specimen	31208-2
616553	Source	31208-2
616554	Result Summary	50397-9
616555	Result	82939-0
616556	Interpretation	69047-9
616557	Resources	99622-3
616558	Additional Information	48767-8
616559	Method	85069-3
616560	Genes Analyzed	82939-0
616561	Disclaimer	62364-5
616562	Released By	18771-6