MAYO CLINIC

1-800-533-1710

Comprehensive Epilepsy Gene Panel

EPPAN

PATIENT NAME				ORDER NUMBER
TESTRNV, IMPLEMENTATION				**L624000481**
PATIENT ID X100383795	DATE OF BIRTH 02/19/1968	AGE 54 Y	SEX Male	REQUESTED BY PROVIDER UNKNOWN
COLLECTED 3/24/2022, 10:30 AM	RECEIVED 3/25/2022, 10:13 AM	REPORTED 4/12/2022, 2:27 PM		

The collected, received, and reported dates and times on the report are in the time zone of the performing location.

7028846
MCL RochesterCampus
Rochester MN 55901

CLIENT ORDER NUMBER
X100383795

CLIENT MRN
321

TEST DESCRIPTION

Evaluation of 319 genes associated with epilepsy

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

The following heterozygous PATHOGENIC variant was detected:
SCN1A (NM_001165963.1), chr2(GRCh37):g.166903480G>A, c.1177C>T, p.Arg393Cys (p.R393C)

No additional reportable variants were detected within all other tested genes. See the Method section for a complete list of genes evaluated by this assay.

INTERPRETATION

SCN1A c.1177C>T (p.Arg393Cys): The heterozygous c.1177C>T (p.Arg393Cys) missense variant in the SCN1A gene (MIM:182389) is classified as pathogenic. Pathogenic variants in the SCN1A gene are associated with autosomal dominant seizure disorders including Dravet syndrome, familial febrile seizures, familial hemiplegic migraine, and developmental and epileptic encephalopathy. This variant occurs in a mutational hotspot and has been reported in patients with Dravet syndrome and epileptic encephalopathy, often as a de novo variant (1-4). However, functional studies have not been performed to either support or refute the pathogenicity of this variant. Multiple additional missense changes have also classified as pathogenic at this position. This variant is absent from large control databases (5-6). Overall, this result is consistent with a diagnosis of a SCN1A-related disorder for this individual. Clinical correlation is recommended.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:
1) Depienne C, Trouillard O, Saint-Martin C, et al. Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. J Med Genet. 2009;46(3):183-191. doi:10.1136/jmg.2008.062323 (PMID 18930999)
2) Claes LR, Deprez L, Suls A, et al. The SCN1A variant database: a novel research and diagnostic tool. Hum Mutat. 2009;30(10):E904-E920. doi:10.1002/humu.21083 (PMID 19585586)
3) Epi4K Consortium; Epilepsy Phenome/Genome Project, Allen AS, et al. De novo mutations in epileptic

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encephalopathies. Nature. 2013;501(7466):217-221. doi:10.1038/nature12439 (PMID 23934111)
4) Zhu X, Padmanabhan R, Copeland B, et al. A case-control collapsing analysis identifies epilepsy genes implicated in trio sequencing studies focused on de novo mutations. PLoS Genet. 2017;13(11):e1007104. Published 2017 Nov 29. doi:10.1371/journal.pgen.1007104 (PMID 29186148)
5) dbSNP: www.ncbi.nlm.nih.gov/snp; Sherry ST, Ward M and Sirotkin K. dbSNP-Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation. Genome Res. 1999;9:677-679 (PMID 10447503)
6) gnomAD Browser: gnomad.broadinstitute.org/; Karczewski K, Francioli LC, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020; 581(7809):434-443 (PMID 32461654)

RESOURCES

Disease specific information, including current therapies may be available at:
1. GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1318/
2. https://www.fda.gov/drugs

Information regarding clinical trials, if available, can be found at the following sites:
1. ClinicalTrials.gov: http://clinicaltrials.gov/ct2/search/advanced

ADDITIONAL INFORMATION

Variant nomenclature is based on the following GenBank Accession numbers (build GRCh37 (hg19)): SCN1A NM_001165963.

METHOD

Next generation sequencing (NGS) and/or Sanger sequencing was 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 pathogenic 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 indels 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 was 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 was utilized to detect expansions of a dodecamer repeat region in the CSTB gene. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com (TEST ID EPPAN) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ABAT, ACO2, ACY1, ADARB1, ADGRG1, ADSL, AFG3L2, AIFM1, AKT2, ALDH3A2, ALDH5A1, ALDH7A1, ALG13, AMT, AP2M1, 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, COG7, COG8, COL18A1, COL4A1, COQ2, COQ4, COQ6, COQ8A, COQ9, COX10, COX15, CPT2, CSF1R, CSTB, CTSD, CTSF, CUL4B, D2HGDH, DCX, DDC, DDX3X,

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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, 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

DISCLAIMER

Clinical Correlations
An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

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(s) in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710.

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, but 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 for sequencing or deletion and duplication analysis

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as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed 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. Please refer to the Targeted Genes and Methodology Details for the Comprehensive Epilepsy with or without Encephalopathy Gene Panel in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID EPPAN) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

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

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 U.S. Food and Drug Administration.

RELEASED BY

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