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PATIENT REPORT

Patient Age/Sex: Male

Specimen Collected: 20-Jun-23 12:16

Epilepsy Panel by NGS, DelDup |Received: 20-Jun-23 12:17 Report/Verified: 21-Jun-23 08:27

Procedure	Result	Units	Reference Interval
EPI Specimen	Whole Blood		
EPI Interp	Positive [f1 i1]		

Result Footnote

f1: EPI Interp

RESULT
One pathogenic variant was detected in the SCN1A gene.

PATHOGENIC VARIANT
Gene: SCN1A (NM_001165963.4)
Nucleic Acid Change: c.264+2T>G; Heterozygous
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.264+2T>G, was detected in the SCN1A gene by massively parallel sequencing. Pathogenic SCN1A variants are inherited in an autosomal dominant manner, and are associated with numerous seizure disorders, most notably Dravet syndrome (MIM: 607208). Additional disorders include non-Dravet developmental and epileptic encephalopathy 6B (MIM: 619317), familial febrile seizures, 3A and generalized epilepsy with febrile seizures plus, type 2 (MIM: 604403), and familial hemiplegic migraine 3 (MIM: 609634).This result is consistent with a diagnosis of a SCN1A-related disorder. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The SCN1A c.264+2T>G variant is reported in the literature in at least one individual affected with Dravet syndrome (Ishii 2017). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant disrupts the canonical splice donor site of intron 4, which is likely to negatively impact gene function. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
ASAH1(NM_177924.5) intron 2
CUL4B(NM_003588.3) intron 14

REFERENCES
Ishii A et al. Clinical implications of SCN1A missense and truncation variants in a large Japanese cohort with Dravet syndrome. Epilepsia. 2017 Feb;58(2):282-290. PMID: 28012175.

Test Information

i1: EPI Interp

BACKGROUND INFORMATION: Comprehensive Epilepsy Panel, Sequencing and Deletion/Duplication

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

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CHARACTERISTICS: Epilepsy is a neurological disorder that causes recurrent unprovoked seizures. It can be subclassified by seizure type (focal, generalized, generalized and focal, and unknown). Epilepsy has significant genetic and phenotypic heterogeneity. Many genetic epilepsy syndromes have been described and individuals with epilepsy who have neurodevelopmental comorbidities are more likely to have a genetic etiology. This panel includes genes associated with idiopathic epilepsy and syndromic epilepsy in which seizures are a major or presenting feature.

EPIDEMIOLOGY: Prevalence of epilepsy is approximately 0.64 percent worldwide with lifetime risk of 1 in 26.

CAUSE: Etiology can include infectious, structural, genetic, metabolic, immune, and unknown causes. An estimated 30 percent of epilepsy has a genetic cause. Pathogenic germline variants in numerous genes have been associated with epilepsy.

INHERITANCE: Epilepsy may occur as a familial trait with autosomal dominant, autosomal recessive, or X-linked inheritance, or sporadically. De novo variation is a common cause of sporadic epileptic encephalopathy.

PENETRANCE: Variable; influenced by gene and variant.

CLINICAL SENSITIVITY: Dependent on clinical phenotype.

GENES TESTED: AARS; ABAT*; ADGRG1; ADSL*; ALDH5A1; ALDH7A1; ALG1*; ALG13*; ALG3; ALG6; ALG8; ALG9*; AMACR; AMT; ANKRD11*; AP3B2*; ARFGEF2; ARG1; ARHGEF9*; ARV1*; ARX*; ASAH1*; ASNS; ATN1; ATP1A1; ATP1A3; ATP6AP2; ATP7A; ATRX*; BCKDK; BRAT1*; BTD*; C12orf57; CACNA1A; CACNA1D; CACNA1E; CACNA2D2; CAD; CARS2*; CASK; CDKL5; CHD2; CHRNA4; CHRNB2; CLCN4; CLN3; CLN5*; CLN6*; CLN8; CLTC; CNKSR2*; CNTNAP2; COL4A1; CPT2; CSTB; CTSD; CTSF; CUL4B*; DCX; DDX3X*; DEAF1*; DEPDC5; DHDDS; DIAPH1; DMXL2*; DNAJC5; DNM1*; DNM1L; DOCK7; DPAGT1; DPM1; DPYD; DYNC1H1**; DYRK1A; EEF1A2; EHMT1*; EPM2A***; FARS2**; FGF12; FKTN*; FLNA; FOLR1; FOXG1*; FRRS1L; GABBR2*; GABRA1; GABRB2; GABRB3*; GABRD; GABRG2*; GALC; GAMT; GATM; GFAP; GNAO1; GNB1; GOSR2; GPHN*; GRIA3; GRIN1; GRIN2A; GRIN2B; HACE1; HCN1; HECW2; HNRNPU; HSD17B10; IQSEC2; ITPA; KANSL1*; KCNA1; KCNA2; KCNB1; KCNC1; KCNH1; KCNJ10; KCNJ11; KCNMA1; KCNQ2*; KCNQ3; KCNT1; KCTD7*; KDM5C*; KIF1A*; LGI1; MBD5*; MDH2; MECP2; MED17; MEF2C; MFSD8; MOCS2; MOGS; MPDU1; MTHFR; MTOR; NDE1; NECAP1; NEDD4L; NEU1; NEXMIF; NGLY1; NHLRC1; NPRL2; NPRL3; NR2F1*; NRXN1*; NSD1; NTRK2*; OPHN1; PACS1; PAFAH1B1*; PCDH19; PEX1; PEX12; PEX2; PEX3; PEX6; PHF6; PHGDH; PIGA; PIGG; PIGN; PIGO; PIGQ; PIGT; PIGV; PLCB1; PLPBP*; PMM2; PNKP; PNPO; POLG; PPT1; PRICKLE2; PRRT2; PSAP; PTPN23; PURA; QARS1; QDPR; RELN; RFT1; RNASEH2A; RNASEH2B; RNASEH2C; ROGDI; RORB*; SAMHD1*; SATB2; SCARB2; SCN1A*; SCN1B; SCN2A; SCN3A; SCN8A; SERPINI1; SETBP1; SLC12A5; SLC13A5; SLC19A3***; SLC1A2; SLC25A12*; SLC25A22; SLC2A1; SLC35A2; SLC6A1; SLC9A6*; SMARCA2*;

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SMC1A; SMS; SNAP25; SPATA5; SPTAN1*; ST3GAL3*; ST3GAL5; STRADA; STX1B; STXBP1*; SUOX; SYN1; SYNGAP1*; SYNJ1; SZT2*; TBC1D24; TBL1XR1; TCF4; TPK1*; TPP1; TREX1; TSC1; TSC2; TSEN54*; UBA5; UBE3A*; UNC80*; VPS13A; WDR45; WWOX**; ZEB2*
*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.
**Deletion/duplication detection is not available for this gene.
***One or more exons are not covered by sequencing, and deletion/duplication detection is not available for this gene; see limitations section below.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications were confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a heritable form of epilepsy. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions (including

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common expansions in ANT1 exon 5, ARX, and CSTB 5'UTR). Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

SNVs and indels will not be called in the following regions due to technical limitations of the assay:
ABAT (NM_001386615) 6; ABAT (NM_001386616) partial exon 16(Chr16:8875107-8875145); ADSL (NM_001363840) 14; ALG13 (NM_001099922, NM_001257231) partial exon 24(ChrX:110987954-110988035); ALG9 (NM_001352420, NM_001352421) 15; ALG9 (NM_001352415, NM_001352416, NM_001352419) 16; ALG9 (NM_001352417) 17; ANKRD11 (NM_013275, NM_001256183) partial exon 9(Chr16:89345816-89346020); ANKRD11 (NM_001256182) partial exon 10(Chr16:89345816-89346020); ANKRD11 (NM_013275, NM_001256183) 13; ANKRD11 (NM_001256182) 14; AP3B2 (NM_001348440) 5; ARHGEF9(NM_001353923) 1; ARV1 (NM_001346992) 4; ARX(NM_139058) partial exon 2(ChrX:25031469-25031834); BRAT1(NM_001350626) partial exon 14(Chr7:2578419-2578578); BTD (NM_001370752) 5; BTD (NM_001370753) 4; CARS2 (NM_001352253) 9; CLN5 (NM_001366624) 4; CUL4B(NM_001369145) 1; DMXL2 (NM_001378459) 32; DMXL2(NM_001378463) partial exon 32(Chr15:51755500-51755555); DMXL2 (NM_001378457, NM_001378458) 34; DNM1 (NM_001374269) 22; EHMT1 (NM_024757, NM_001145527, NM_001354263, NM_001354611) 1; EHMT1 (NM_001354259) 16; EHMT1 (NM_001354612) partial exon 9(Chr9:140657293-140657296); EHMT1 (NM_001354611) partial exon 10(Chr9:140657293-140657296); EPM2A (NM_001368129, NM_001368132) 3; EPM2A (NM_001368130) partial exon 3(Chr6:145956295-145956360); FKTN (NM_001351497) 6; FKTN(NM_001351498) partial exon 9(Chr9:108382363-108382373); FOXG1 (NM_005249) partial exon 1(Chr14:29236682-29236856); GABBR2 (NM_005458, NM_001375347) 1; GABRG2 (NM_001375344) 7; GPHN (NM_001377519, NM_001377514) 5; GPHN (NM_001377515, NM_001377516, NM_001377517, NM_001377518) 9; GPHN(NM_001377514, NM_001377515, NM_001377516) 10; GPHN (NM_001377514) 11; KCNQ2 (NM_001382235) 15; KCTD7 (NM_001167961) 5; KDM5C (NM_001353979, NM_001353981, NM_001353982, NM_001353984) 26; KIF1A (NM_001379636) 36; KIF1A (NM_001379639) 37; KIF1A (NM_001379635, NM_001379638, NM_001379646) 38; MBD5 (NM_001378120) partial exon 9(Chr2:149241026-149241704); NR2F1(NM_005654) partial exon 1(Chr5:92920778-92920891); NTRK2 (NM_001369547) 13; PLPBP (NM_001349349) partial exon 1(Chr8:37620073-37620157); PLPBP (NM_001349349) 5; PLPBP (NM_001349346) partial exon 6(Chr8:37632827-37632836); RORB (NM_001365023) 1; SAMHD1 (NM_001363733) 16; SLC19A3 (NM_001371413, NM_001371414) 3; SLC9A6 (NM_001379110) 14; SMARCA2 (NM_003070, NM_001289396, NM_001289397, NM_139045) 5; SPTAN1 (NM_001375318, NM_001375312) 2; SPTAN1 (NM_001375310) 50; SPTAN1 (NM_001363759) 52; SPTAN1(NM_001375318) 53; ST3GAL3 (NM_001350619, NM_001350620) 12; ST3GAL3(NM_001350621) 6,13; STXBP1 (NM_001374313, NM_001374314) 19; SYNGAP1 (NM_006772) partial exon 19(Chr6:33419581-33419683); SZT2 (NM_001365999) 22; TPK1 (NM_001350884) 3; TPK1 (NM_001350883) 4; TPK1 (NM_001350882) 5; TPK1 (NM_001350895)

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7; TPK1 (NM_001350881) 9; TSEN54 (NM_207346) 1; UBE3A (NM_001354523) 5; UNC80 (NM_001371986) 27

The following deletions/duplications will not be called:
ABAT (NM_001386615) 6; ADSL (NM_001363840) 14; ALG1 (NM_019109, NM_001330504) 6-9; ALG9 (NM_001352415, NM_001352416, NM_001352419) 16; ALG9 (NM_001352417) 17; ALG9 (NM_001352420, NM_001352421) 15; ANKRD11 (NM_013275, NM_001256183) 13; ANKRD11 (NM_001256182) 14; AP3B2 (NM_001348440) 5; ARHGEF9 (NM_001353923) 1; ASAH1 (NM_001127505) 3; ATRX (NM_000489) 22,25,28; ATRX (NM_138270) 21,24,27; BTD (NM_001370752) 5; BTD (NM_001370753) 4; CARS2 (NM_001352253) 9; CLN5 (NM_001366624) 4; CLN6 (NM_017882) 1; CNKSR2 (NM_014927, NM_001168647, NM_001168648, NM_001168649, NM_001330770, NM_001330771, NM_001330772, NM_001330773) 5; CUL4B (NM_001369145) 1; DDX3X (NM_001193416, NM_001356) 3; DEAF1 (NM_021008, NM_001293634) 1; DMXL2 (NM_001378457, NM_001378458) 34; DMXL2 (NM_001378459) 32; DNM1 (NM_001374269) 22; EHMT1 (NM_024757, NM_001145527, NM_001354263, NM_001354611) 1; EHMT1 (NM_001354259) 16; FKTN (NM_001351497) 6; GABBR2 (NM_005458) 1; GABRB3 (NM_000814) 1-2; GABRB3 (NM_021912) 2; GABRG2 (NM_001375344) 7; GABRG2 (NM_001375347) 1; GPHN (NM_001377514) 5,10-11; GPHN (NM_001377515) 9-10; GPHN (NM_001377516) 9-10; GPHN (NM_001377517, NM_001377518) 9; GPHN (NM_001377519) 5; KANSL1 (NM_001193466, NM_015443) 3; KANSL1 (NM_001193465, NM_001379198) 4; KCNQ2 (NM_001382235) 15; KCTD7 (NM_001167961) 5; KDM5C (NM_001353979, NM_001353981, NM_001353982, NM_001353984) 26; KIF1A (NM_001379635, NM_001379638, NM_001379646) 38; KIF1A (NM_001379636) 36; KIF1A (NM_001379639) 37; NRXN1: NM_001330079, NM_001330081, NM_001330090) 5; NRXN1 (NM_001330091, NM_001330092, NM_001330097, NM_138735) 1; NTRK2 (NM_001369547) 13; PAFAH1B1 (NM_000430) 4; PLPBP (NM_001349349) 5; RORB (NM_001365023) 1; SAMHD1 (NM_001363733) 16; SCN1A (NM_001165963, NM_006920) 12,27; SCN1A (NM_001165964, NM_001202435, NM_001353950, NM_001353952, NM_001353954, NM_001353958, NM_001353960) 11,26; SCN1A (NM_001353948, NM_001353949, NM_001353951, NM_001353955, NM_001353957) 10,25; SCN1A (NM_001353961) 26; SLC25A12 (NM_003705) 9; SLC9A6 (NM_001379110) 14; SPTAN1 (NM_001363759) 52; SPTAN1 (NM_001375310) 50; SPTAN1 (NM_001375312) 2; SPTAN1 (NM_001375318) 2,53; ST3GAL3 (NM_001350619, NM_001350620) 12; ST3GAL3 (NM_001350621) 6,13; STXBP1 (NM_001374313, NM_001374314) 19; SZT2 (NM_001365999) 22; TPK1 (NM_001350881) 9; TPK1 (NM_001350882) 5; TPK1 (NM_001350883) 4; TPK1 (NM_001350884) 3; TPK1 (NM_001350895) 7; TSEN54 (NM_207346) 1; UBE3A (NM_130838, NM_001354548, NM_001354549) 4; UBE3A (NM_000462, NM_001354508, NM_001354511, NM_001354512, NM_001354513, NM_001354538:7; NM_001354539, NM_001354547, NM_001354523) 7; UBE3A (NM_001354505, NM_001354545, NM_001374461, NM_130839) 6; UBE3A (NM_001354506, NM_001354507, NM_001354509, NM_001354526, NM_001354541, NM_001354544) 8; UBE3A (NM_001354523, NM_001354542) 5; UBE3A (NM_001354540) 9; UBE3A (NM_001354543) 10; UBE3A (NM_001354546) 3; UNC80 (NM_001371986) 27; ZEB2 (NM_014795) 10; ZEB2 (NM_001171653) 9

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This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.