Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	10/23/2020
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Infantile Epilepsy Panel, Sequence Analysis and Exon-Level Deletion/Duplication

ARUP test code 2007535

Ordering Physician Name

[redacted]
Performed by: GeneDx
207 Perry Parkway
Gaithersburg, MD 20877

Anne Maddalena, Ph.D.,FACMG,

Ordering Physician Phone Number

[redacted]
Performed by: GeneDx
207 Perry Parkway
Gaithersburg, MD 20877

Anne Maddalena, Ph.D.,FACMG,

Infantile Epilepsy Panel *

POSITIVE - LIKELY PATHOGENIC VARIANT

Date Test(s) Started: 10/28/2021 10:22:21
Sample Source: Blood in EDTA Date Collected: 10/21/2021 Date Received:
10/27/2021 Testing Date Started: 10/28/2021 Date Reported: 11/22/2021
Provider Account #: [redacted] ARUP LABORATORIES Additional Provider:
Test(s) Requested Infantile Epilepsy Panel / Sequencing and Deletion/Duplication Analysis
Clinical Indications Reported history of complex seizures
Result(s): POSITIVE - LIKELY PATHOGENIC VARIANT
Gene Mode of Inheritance Variant Zygosity Classification
PCDH19 X-Linked c.1031 C>A
p.(P344Q) Heterozygous Likely Pathogenic Variant
Additional variant(s) of uncertain significance that do not establish a
molecular diagnosis are listed in the table below.
Interpretation This individual is heterozygous for a likely pathogenic variant
in the PCDH19 gene, which is likely consistent with the diagnosis of a
PCDH19-related disorder in this individual. Pathogenic variants in the PCDH19
gene are inherited in an unusual X-linked manner, whereby heterozygous females
develop epilepsy while hemizygous male carriers of a pathogenic

H=High, L=Low, *=Abnormal, C=Critical

variant are
typically unaffected.
Recommendation(s) Genetic counseling is recommended to discuss the implications
of these results.
Correlation of these findings with the clinical features of this individual is
recommended.
Targeted testing of the parents of this individual will help determine if the
variant in the PCDH19 gene was inherited or arose de novo. Parental testing for
the PCDH19 variant can be performed at GeneDx for no additional charge if
clinical information on the parents is provided.
If desired, molecular prenatal diagnosis is available for the likely pathogenic
variant.
Resources MyGene2 is a portal through which families with rare genetic
conditions who are interested in sharing their health and genetic information
can connect with other families, clinicians, and researchers. If you are
interested in learning more and/or participating, please visit www.mygene2.org.
GenomeConnect is an NIH initiative created to enable individuals and families
with the same genetic variant or medical history to connect and share
de-identified information. If you are interested in participating, please visit
www.genomeconnect.org.
Support and information for individuals with PCDH19 pathogenic variants and
their families is available through the PCDH19 Alliance. They can be contacted
through their website: http: //www.pcdh19info.org/
PCDH19 Gene Summary
The PCDH19 gene encodes protocadherin-19, which is a calcium-dependent
cell-cell adhesion molecule that is primarily expressed in the brain.
Pathogenic variants in PCDH19 cause a type of early infantile epileptic
encephalopathy (EIEE) that is sometimes referred to as epilepsy and mental
retardation limited to females (EFMR). The clinical phenotype is variable, but
the most common clinical features include clusters of focal and/or generalized
seizures beginning in infancy or early childhood that are often precipitated by
fever, sometimes leading to a clinical diagnosis of Dravet syndrome (Higurashi
et al., 2013; Specchio et al., 2011; Marini et al., 2010). Seizures are often
difficult to control in early childhood; however, over time the seizure
frequency typically decreases and antiepileptic medications are more effective
(Specchio et al., 2011; Depienne et al., 2011). Developmental regression
leading to intellectual disability and autism is common, although some females
have normal cognitive development (Higurashi et al., 2013; Marini et al.,
2010). Pathogenic variants in PCDH19 are inherited in an unusual X-linked
manner, as heterozygous females develop epilepsy while hemizygous male carriers
are unaffected, although affected males with somatic mosaicism

have been
identified (Terracciano et al. 2016). Somatic and gonadal mosaicism have also
been reported in females, and rarely unaffected female carriers who are
heterozygous for a PCDH19 pathogenic variant have been described (Marini et
al., 2010; Dibbens et al., 2011; Dimova et al., 2012).p.(Pro344Gln) (CCG>CAG):
c.1031 C>A in exon 1 of the PCDH19 gene (NM_001184880.1)Not observed at
significant frequency in large population cohorts (Lek et al., 2016)A different
missense change at this residue (p.(P344L)) has been reported as likely
pathogenic at GeneDx in association with epilepsy (van Harssel et al., 2013)
Missense variants in this gene are often considered pathogenic (Stenson et al.,
2014)In silico analysis supports that this missense variant has a deleterious
effect on protein structure/functionHas not been previously published as
pathogenic or benign to our knowledgeWe interpret this as a Likely Pathogenic
Variant.
Additional Variants of Uncertain Significance (See Below)
GeneMode of InheritanceVariantZygosityClassification
PIGOAutosomal Recessive
c.1844 G>A
p.(R615Q)HeterozygousVariant of Uncertain Significance
At this time, the above variants are classified as variants of uncertain
significance as they do not meet criteria to be classified otherwise. This
table may include single heterozygous variants of uncertain significance (VUS)
in genes associated with autosomal recessive inheritance, VUS in genes
associated with dual inheritance that are unlikely to be related to the
referring phenotype, and VUS in candidate genes that have been suggested to be
associated with autosomal recessive or dual inheritance human disease.
Information on population data and in-silico analysis can be found in the
supplemental variant information tables at the end of the report.
Genes Evaluated ADSL, ALDH5A1, ALDH7A1, ALG13, ARHGEF9, ARX, ASNS, ATP1A3,
ATP6AP2, ATRX, BRAT1, C12ORF57, CACNA1A, CACNA1E, CACNA1G, CASK, CDKL5, CHD2,
CHRNA7, CLCN4, CLN3, CLN5, CLN6, CLN8, CNTNAP2, CTSD, CUL4B, DCX, DDX3X,
DEPDC5, DNM1, DOCK7, DYRK1A, EEF1A2, EHMT1, FGF12, FOLR1, FOXG1, FRRS1L,
GABBR2, GABRA1, GABRB2, GABRB3, GABRG2, GAMT, GATM, GLDC, GNAO1, GRIN1, GRIN2A,
GRIN2B, HCN1, HNRNPU, IQSEC2, KANSL1, KCNA2, KCNB1, KCNH1, KCNJ10, KCNMA1,
KCNQ2, KCNQ3, KCNT1, KCTD7, KDM6A, MAGI2, MBD5, MECP2, MEF2C, MFSD8, NALCN,
NEXMIF, NGLY1, NPRL3, NR2F1, NRXN1, PACS1, PAFAH1B1, PCDH19, PIGA, PIGG, PIGN,
PIGO, PIGT, PIGV, PLCB1, PNKP, PNPO, POLG, PPP2R5D, PPT1, PRRT2, PURA, QARS,
SCN1A, SCN1B, SCN2A, SCN8A, SHANK3, SLC13A5, SLC19A3, SLC25A22, SLC2A1,
SLC35A2, SLC6A1, SLC6A8, SLC9A6, SMARCA2, SMC1A, SNAP25, SPATA5, SPTAN1, STX1B,
STXBP1, SYNGAP1, SZT2, TBC1D24, TBL1XR1, TCF4, TPP1, TSC1, TSC2, TUBB2A, UBE3A,

WDR45, WWOX
Methods Genomic DNA was extracted from the submitted specimen. For skin punch
biopsies, fibroblasts were cultured and used for DNA extraction. The DNA was
enriched for the complete coding regions and splice junctions of the genes on
this panel using a proprietary targeted capture system developed by GeneDx for
next-generation sequencing with CNV calling (NGS-CNV).). The enriched targets
were simultaneously sequenced with paired-end reads on an Illumina platform.
Bi-directional sequence reads were assembled and aligned to reference sequences
based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After
gene specific filtering, data were analyzed to identify sequence variants and
most deletions and duplications involving coding exons at the exon-level;
however, technical limitations and inherent sequence properties effectively
reduce this resolution for some genes. Gene specific exclusions for exon-level
deletion/duplication testing for this panel are: C12orf57, FGF12, FOXG1, PIGG,
PIGT, SLC35A2, SLC6A8, and SNAP25 genes no copy number testing; ARX, ASNS,
CHRNA7, FOLR1, GAMT, KCNT1, NR2F1, PCDH19, SCN1B, SHANK3, and TUBB2A genes only
whole gene deletions or duplications may be detected; deletions/duplications
involving the 3' end of the TSC2 gene (exons 36-42) may not be identified. For
the CHRNA7 and MAGI2 genes, deletion/duplication analysis, but not sequencing,
was performed. Alternative sequencing or copy number detection methods were
used to analyze or confirm regions with inadequate sequence or copy number data
by NGS. Sequence variants are reported according to the Human Genome Variation
Society (HGVS) guidelines. Copy number variants are reported based on the probe
coordinates, the coordinates of the exons involved, or precise breakpoints when
known. Reportable variants include pathogenic variants, likely pathogenic
variants and variants of uncertain significance. Likely benign and benign
variants, if present, are not routinely reported but are available upon
request. Available evidence for variant classification may change over time and
the reported variant(s) may be re-classified according to the AMP/ACMG
guidelines for variant classification (Richards et al. 2015), which may lead to
re-issuing a revised report.
Disclaimer Genetic testing using the methods applied at GeneDx is expected to
be highly accurate. Normal findings do not rule out the diagnosis of a genetic
disorder since some genetic abnormalities may be undetectable by this test. The
methods used cannot reliably detect deletions of 20bp to 500bp in size, or
insertions of 10bp to 500 bp in size. Sequencing cannot detect low-level
mosaicism. The copy number assessment methods used with this test cannot

reliably detect mosaicism and cannot identify balanced chromosome aberrations.
Rarely, incidental findings of large chromosomal rearrangements outside the
gene of interest may be identified. Regions of certain genes have inherent
sequence properties (for example: repeat, homology, or pseudogene regions, high
GC content, rare polymorphisms) that yield suboptimal data, potentially
impairing accuracy of the results. False negative results may also occur in the
setting of bone marrow transplantation, recent blood transfusion, or suboptimal
DNA quality. As the ability to detect genetic variants and naming conventions
can differ among laboratories, rare false negative results may occur when no
positive control is provided for testing of a specific variant identified at
another laboratory. The chance of a false positive or false negative result due
to laboratory errors incurred during any phase of testing cannot be completely
excluded. Interpretations are made with the assumption that any clinical
information provided, including family relationships, are accurate.
Consultation with a genetics professional is recommended for interpretation of
results.
This test was developed and its performance characteristics determined by
GeneDx. This test has not been cleared or approved by the U.S. Food and Drug
Administration. The FDA has determined that such clearance or approval is not
necessary. The test is used for clinical purposes and should not be regarded as
investigational or for research. The laboratory is certified under the Clinical
Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform
high-complexity clinical testing.
References Lek et al. (2016) Nature 536 (7616): 285-91 (PMID: 27535533);Stenson
et al. (2014) Human genetics 133 (1): 1-9 (PMID: 24077912);Landrum et al.
(2016) Nucleic Acids Res. 44 (D1): D862-8 (PMID: 26582918);Lott et al. (2013)
Curr Protoc Bioinformatics 44 : 1.23.1-26 (PMID: 25489354);Richards et al.
(2015) Genetics In Medicine: 17 (5): 405-24 (PMID: 25741868);Depienne C et al.
(2011) Hum Mutat 32 (1): E1959-75 (PMID: 21053371);Dibbens LM et al. (2011)
Neurology 76 (17): 1514-9 (PMID: 21519002);Marini C et al. (2010) Neurology 75
(7): 646-53 (PMID: 20713952);Specchio N et al. (2011) Epilepsia 52 (7): 1251-7
(PMID: 21480887);Dimova PS et al. (2012) Pediatric neurology 46 (6): 397-400
(PMID: 22633638);Higurashi N et al. (2013) Epilepsy research 106 (1-2): 191-9
(PMID: 23712037);Terracciano A et al. (2016) Epilepsia 57 (3): e51-5 (PMID:
26765483); van Harssel JJ et al. (2013) Neurogenetics 14 (1): 23-34 (PMID:
23334464)
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Variant Table
Gene: Coding DNAPCDH19: c.1031 C>APIGO: c.1844 G>A

H=High, L=Low, *=Abnormal, C=Critical

Variant (Protein)p.(Pro344Gln) ((P344Q))p.(Arg615Gln) ((R615Q))
ClassificationLikely Pathogenic VariantVariant of Uncertain Significance
ZygosityHeterozygousHeterozygous
Chr: PositionX: 996625659: 35092040
dbSNP
rs142897141
gnomAD_Freq
0.0001
gnomAD_AMR
0.00008468
gnomAD_NFE
0.00006199
gnomAD_AFR
0.00004007
gnomAD_EAS
0.00010025
gnomAD_FIN
0.00000000
gnomAD_Other
0.00013847
gnomAD_SAS
0.00000000
gnomAD_ASJ
0.00000000
gnomAD_Hom
1
Provean-6.32 (D)-0.91 (N)
ClinVarUncertain significanceLikely benign
This supplement provides evidence to support the classification of each
reportable variant in the attached result report. This information is provided
as a resource. It is not inclusive of all available information used by GeneDx
for variant classification, and individual data elements may be weighted
differently to derive at the classification. This information is subject to
change and may differ from what is currently available. Results should always
be interpreted in the context of the patient's clinical presentation. Blank
fields indicate that no data were available at time of analysis.
dbSNP - NCBI repository for single base nucleotide substitutions and short
deletion and insertion polymorphisms https: //www.ncbi.nlm.nih.gov/snp/The
Genome Aggregation Database (gnomAD) combines exome and genome sequencing data
from a variety of large-scale sequencing projects, including approximately
15,000 genomes and 123,000 exomes, including individuals recruited for
disease-specific studies such as cancer and cardiovascular diseases. (PMID
32461654).gnomAD_Freq - variant allele frequency (in percent) from
approximately 15,000 genomes and 123,000 exomes in the Genome Aggregation
Database. Select ancestries include: gnomAD_AMR (Admixed American/Latino);
gnomAD_AFR (African); gnomAD_EAS (East Asian); gnomAD_FIN (Finnish of European
ancestry); gnomAD_NFE (non-Finnish of European ancestry); gnomAD_SAS (South
Asian); gnomAD_ASJ (Ashkenazi Jewish). gnomAD_Hom - number of individuals
homozygous for the variant.gnomAD_AMR- variant frequency (in percent) for
individuals of Latino ancestryPROVEAN (Protein Variation Effect Analyzer) -

predicts whether an amino acid substitution or indel affects the biological
function of a protein using a delta alignment score from -14 to +14 (< or =
-2.5, predicted deleterious; >-2.5, predicted neutral).Other published in
silico algorithms, including those that predict splicing impact, may be
considered for variant analysis. In silico scores may change. In silico models
use algorithms that predict the effect a variant may have on the protein. Thus,
predictions should be interpreted with caution and only be used in combination
with other available evidence to support the classification of any variant
(PMID 23056405).ClinVar - Classification of variant in ClinVar database, an
NCBI archive of human variants with supporting evidence of phenotypic
association. https: //www.ncbi.nlm.nih.gov/clinvar/ (PMID 26582918).
S S S
Report electronically signed by: Erin Wakeling PhD, FACMG
Performed by: GeneDx
207 Perry Parkway
Gaithersburg, MD 20877

Anne Maddalena, Ph.D.,FACMG,

EER Infantile Epilepsy Panel

See Note

Access ARUP Enhanced Report using the link below:

-Direct access: [redacted]

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Ordering Physician Name	21-295-400398	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Ordering Physician Phone Number	21-295-400398	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Infantile Epilepsy Panel	21-295-400398	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
EER Infantile Epilepsy Panel	21-295-400398	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical