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QIAGEN

Your Lab
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Additional Information

Report Date May 11, 2023
Status FINAL

Actionable Exome Panel

Patient		Client		Specimen	
Patient Name	Jane Doe	Client	General Hospital	Accession ID	Patient 12878
Date of Birth		Physician	Dr. E Smith	Collection	May 10, 2023
Sex	Female			Accession	May 10, 2023
Symptoms	Late-onset ataxia, Pyramidal sign, Distal amyotrophy				
Indication	Hereditary Disorder				

Result: Positive

1
Pathogenic

1
Likely Pathogenic

Report Summary

Optional Report Comment:

- Patient/sample-specific details can be added here.
- Actionable Exome delivers 99% base-level coverage at ≥20x depth, enabling >98% combined sensitivity for SNVs and indels, while minimizing dropouts.

Variant Summary

Gene / Variant	Genotype	Assessment	Mode of Inheritance	Phenotype
TPP1 c.509-1G>A g.6617154C>T	Heterozygous	Pathogenic	recessive	Neuronal ceroid lipofuscinosis 2
IRF2BPL c.345_346delGC p.Q116fs*16 g.77027447_77027448delGC	Homozygous	Likely Pathogenic	dominant	Neurodevelopmental disorder with regression, abnormal movements, loss of speech and seizures

Individual Variant Interpretations

Gene ***TPP1***
Exon 6
Amino Acid
Nucleotide NM_000391.4:
g.6617154C>T
c.509-1G>A
Assessment Pathogenic
Genotype Heterozygous

Interpretation

Report comments can be added and re-used at the gene, or variant level. Additionally, the ACMG criteria used to classify this variant can be added to this comment:

Evidence for Pathogenicity

- PA2 - Established common pathogenic founder mutation (Standalone)

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS3 - Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product (Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 942.06; 95% confidence interval = (124.34, 7137.72); FET 2-tail p-value < 0.0001; affected individual count = 15] (Strong)
- PM2 - Absent from controls (or at extremely low frequency if recessive) in gnomAD [In these sources of population frequency data, this variant's frequency falls below the max recessive frequency (0.95%) expected for this phenotype] (Moderate)
- PM3 - For recessive disorders, detected in trans with a pathogenic variant (Moderate)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene ***IRF2BPL***
Exon 1
Amino Acid p.Q116fs*16
Nucleotide NM_024496.4:
g.77027447_77027448
delGC
c.345_346delGC
Assessment **Likely Pathogenic**
Genotype Homozygous

Interpretation

Report comments can be added and re-used at the gene, or variant level. Additionally, the ACMG criteria used to classify this variant can be added to this comment:

Evidence for Pathogenicity

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PM2 - Absent from controls (or at extremely low frequency if recessive) in gnomAD [In these sources of population frequency data, this variant's frequency is 0% or <= 0.001%] (Moderate)

Methods and Limitations

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools: QIAGEN Clinical Insight Interpret (9.1.1.20230406), Ingenuity Knowledge Base (H-release), CADD (v1.6), NCBI Gene (2022-02-22), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2022-02-22), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2023-04-16 07:41:41.298), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (H-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2 (HumVar)), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Dec 16 09:34), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 37), CentoMD (5.3), dbVar (2021_04), OMIM (April 13, 2022), gnomAD (GRCh37 (hg19) 2.1.1, GRCh38 (hg38) 3.1.2), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2023-04-25), DGV (2016-05-15), COSMIC (v95), HGMD (2023.1), OncoTree (oncotree_2019_03_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 154, GRCh38 154), SIFT4G (2016-02-23)

Reviewed and approved by:

Keegan Dean, PhD

Approved on: May 11, 2023

Selected Citations

1. Dozières-Puyravel B, Nasser H, Elmaleh-Bergès M, Lopez Hernandez E, Gelot A, Ilea A, Delanoë C, Puech JP, Caillaud C, Pichard S, Auvin S (2019) Paediatric-onset neuronal ceroid lipofuscinosis: first symptoms and presentation at diagnosis. Dev Med Child Neurol. 2020 Apr;62(4):528-530. Epub 2019 Sep 5 (PMID: 31489614)

2. Hartikainen JM, Ju W, Wisniewski KE, Moroziewicz DN, Kaczmarski AL, McLendon L, Zhong D, Suarez CT, Brown WT, Zhong N (1999) Late infantile neuronal ceroid lipofuscinosis is due to splicing mutations in the CLN2 gene. Mol Genet Metab. 1999 Jun;67(2):162-8 (PMID: 10356316)

3. Le NM, Parikh S (2011) Late infantile neuronal ceroid lipofuscinosis and dopamine deficiency. J Child Neurol. 2012 Feb;27(2):234-7. Epub 2011 Sep 22 (PMID: 21940688)

4. Li J, Gao K, Yan H, Xiangwei W, Liu N, Wang T, Xu H, Lin Z, Xie H, Wang J, Wu Y, Jiang Y (2019) Reanalysis of whole exome sequencing data in patients with epilepsy and intellectual disability/mental retardation. Gene 2019 Jun 5; 700:168-175 (PMID: 30904718)

5. Muller VJ, Paton BC, Fietz MJ (2001) An Australasian diagnostic service for the neuronal ceroid lipofuscinoses. Eur J Paediatr Neurol. 2001;5 Suppl A:197-201 (PMID: 11588997)

6. Pérez-Poyato MS, Marfa MP, Abizanda IF, Rodriguez-Revenga L, Sánchez VC, González MJ, Puñal JE, Pérez AV, González MM, Bermejo AM, Hernández EM, Rosell MJ, Gort L, Milá M (2012) Late infantile neuronal ceroid lipofuscinosis: mutations in the CLN2 gene and clinical course in Spanish patients. J Child Neurol. 2013 Apr;28(4): 470-8. Epub 2012 Jul 25 (PMID: 22832778)

7. Sleat DE, Gin RM, Sohar I, Wisniewski K, Sklower-Brooks S, Pullarkat RK, Palmer DN, Lerner TJ, Boustany RM, Uldall P, Siakotos AN, Donnelly RJ, Lobel P (1999) Mutational analysis of the defective protease in classic late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. Am J Hum Genet. 1999 Jun;64(6): 1511-23 (PMID: 10330339)