OMNIHEALTH DIAGNOSTICS

Hereditary Neurological Disease Risk Panel

Patient		Specimen		Ordering Physician	
First Name:	John	**Specimen Type:**	Buccal Swab	**Physician:**	Test Doctor
Last name:	Doe	**Collection Date:**	04-01-2023	**Institution:**	Test Facility
Date of Birth:	09-31-9999	**Received Date:**	04-11-2023	**Reported Date:**	04-18-2023
Gender:	Male	**Panel Coverage :**	96.48%	**Ref Accession:**	N/A
Accession ID:	NDD04172023	**Average Read Depth:**	211x		

Test Result:

Pathogenic / Likely Pathogenic variant detected on TSC2 gene.

Gene & Transcript	Variant	Inheritance	Disorder or Phenotype	Criteria	Classification
TSC2 NM_000548.5	c.138+5G>C	Autosomal Dominant / Heterozygous	Tuberous sclerosis 2	PM2, PP3_Strong, PP5	Likely Pathogenic

Location	Allele State	Allelic Read Depths
Exon 2	Heterozygous	Ref(G): 112, Alt(C): 26, VAF: 18.84%

Genomic Position	Variant Frequency
Chr16:NC_000016.9:g.2098759G>C	Not identified in large population studies

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OMNIHEALTH DIAGNOSTICS, LLC

CLIA: 45D2088485 | Address: 1840 N Greenville Ave, Suite 174, Richardson, TX 75081

Name : John Doe **Date of Birth: 09-31-9999** **Accession : NDD04172023**

Gene info	TSC2 NM_000548.5
Variant Info	The Variant is found at Chr16:NC_000016.9:g.2098759G>C location with a splice region variant c.138+5G>C change on the patient's TSC2.
Variant interpretation	The splice region variant NM_000548.5(TSC2):c.138+5G>C has been reported to ClinVar as Pathogenic with a status of (1 stars) criteria provided, single submitter (Variation ID 1069935 as of 2022-10-06). The c.138+5G>C variant is novel (not in any individuals) in gnomAD All. The c.138+5G>C variant is novel (not in any individuals) in 1kG All. This variant is predicted to disrupt a donor splice site by 4 of 4 splice site algorithms. This variant disrupts the donor splice site for an exon upstream from the penultimate exon junction and is therefore predicted to cause nonsense mediated decay. The nucleotide c.138+5G>C in TSC2 is predicted conserved by GERP++ and PhyloP across 100 vertebrates. For these reasons, this variant has been classified as Likely Pathogenic. Overview: Tuberous sclerosis mapped to chromosome 16p13.3 (TSC2 gene)
Inheritance	Autosomal Dominant / Heterozygous
ACMG-Classification	Likely Pathogenic (PM2, PP3_Strong, PP5)
Gene & Disorder or Phenotype	Tuberous sclerosis 2
What's next	Correlate the findings with clinical symptoms, biochemical profile and family history whilst closely monitoring the subject with periodical visits.Genetic counseling is recommended.

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Patient

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Test Methodology

Hereditary Neurological Disease Risk Panel screens 164 genes on the Next Generation Sequencing (NGS) technology using the targeted gene enrichment chemistry on the IIlumina® MiniSeq platform. Genomic DNA extracted from Buccal swabs (Dry and Wet) are tagemented and enriched for regions of interest using probes specific for each region specified in the BED (Browser Extensible Data) file. Positive (www.coriell.org) and Negative controls are included with each machine run to ensure the accuracy of amplicon preparation alongside targeted sequencing on coding regions and intronic/exonic boundaries of interest and precise finding of the variant on the positive control and negative control respectively. Exclusions from analysis are listed below Sequences obtained are then aligned against a human reference genome and variants such as SNVs (Small Nucleotide Variants) and Indels (Insertions and Deletions) are noted. For a detailed list of regions covered and comprehensive statistics by Ipseity Diagnostics LLC Hereditary Neurological Disease screen, please contact us on Email: 12345@omnihealthdx.com

Computational analysis and variant calling were performed by ipseity (www.ipseitys.com). Briefly, reads from the sequence output were aligned to the human reference genome (GRCh37) using the Burrows-Wheeler Aligner (BWA). Variants to the reference were called using the Genomic Analysis Tool Kit (GATK). The variants were annotated and filtered using the Ipseity Diagnostics LLC analysis work flow implementing the ACMG guidelines for interpretation of sequence variants. This includes comparison against the gnomAD population catalog of variants in 123,136 exomes, the 1000 Genomes Project Consortium's publication of 2,500 genomes, the NCBI-ClinVar database of clinical assertions on variant's pathogenicity and multiple lines of computational evidence on conservation and functional impact. The following databases and insilico algorithms are used to annotate and evaluate the impact of the variant in the context of human disease: 1000 genomes, gnomAD, ClinVar, OMIM, dbSNP, NCIB Ref Seq Genes, ExAC Gene Constraints, VS-SIFT, VS PolyPhen2, PhyloP, GERP+, GeneSplicer, Max EntScan, NNSplice, PWM Splice Predictor. Analysis was reported using the HGVS nomenclature (www.hgvs.org/mutnomen)as implemented by custom transcript annotation algorithm. Only variants with an end ACMG classification of "Pathogenic" or "Likely Pathogenic" are reported and VUS/Benign/Likely Benign variants are not reported. Classification of pathogenicity is consistently updated by the National Institutes of Health and the information found within this report is consistent with the current knowledge base as the knowledge base changes, so may clinical interpretation of variants. All reports are reviewed prior to release by either Ipseity Diagnostics LLC's Technical Supervisor or the General Supervisor.

Genes Evaluated

ADNP, AFF2, ALDH7A1, ANG, APTX, ARX, ASPA, ASXL1, ATN1, ATP1A2, ATP7B, ATXN1, ATXN10, ATXN2, ATXN3, ATXN7, ATXN8OS, BCL11A, BSCL2, C12orf4, CACNA1A, CACNA1C, CC2D1A, CDKL5, CHD2, CNOT3, CNTN6, COL4A1, COL4A3BP, CSNK2A1, CSTB, CTNND2, DHCR7, DPYD, EGR2, EHMT1, EN2, EZH2, FBXO11, FMR1, FOXG1, FOXP1, FTSJ1, FXN, GABRG2, GAMT, GARS, GATM, GBA, GCH1, GRIN2A, GRN, HEXA, HFE, HSPB1, HTT, IKBKAP, KCNQ2, KDM5C, L1CAM, LRRK2, MAPT, MBOAT7, MECP2, MED12, MTHFR, MTM1, NDP, NDUFA1, NLGN3, NLGN4X, NOTCH3, NSD1, NTRK1, NTRK2, PABPN1, PCDH19, PDGFB, PDHA1, PIK3CA, PINK1, PMP22, PNKD, POLG, PPP2R2B, PRRT2, PSEN1, PTEN, REEP1, SCN1A, SCN1B, SCN2A, SCN8A, SCO2, SGCE, SLC16A2, SLC2A1, SLC6A8, SLC9A6, SMN1, SMN2, SOD1, SPG11, STXBP1, SYNGAP1, TARDBP, TBP, TCF4, TH, THAP1, TOR1A, TPP1, TSC1, TSC2, TTR, UBA1, ZEB2, ZNF41, ACADM, APOE, APP, ARSA, ATM, BCKDHA, BCKDHB, BCS1L, BLM, C10orf2, COQ2, COX10, DGUOK, ERBB4, FANCC, FUS, G6PC, GAA, GALT, GBE1 , GJB1 , HBB , MCOLN1 , MFN2 , MPV17 , MPZ , NPC1 , OPA1 , OPTN , PAH , PDSS2 , PLCG2 , POLG2 , PRNP , PSEN2 , RRM2B , SCO1 , SETX , SLC25A4 , SPAST , SPTLC1 , SUCLA2 , SUCLG1 , TAZ , TK2 , TYMP.

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Test Limitations

Some Genes/variations for the following genomic regions may not be reported such as: large genomic rearrangements greater than 50 bp in length, rare (low frequency) mutations, or structural (non-coding) variations and pseudogenes. Rare diagnostics errors may occur if these mutations occur within the priming sequencing regions Presence of a pathogenic/likely pathogenic variant does not guarantee that an individual will develop Hereditary Neurological Disease, nor is the absence of such variants a guarantee that an individual will not develop a 'Hereditary Neurological Disease'. The results of this genetics screening is strictly meant to guide a physician in the management of their patient's health. Any Likely pathogenic or Pathogenic variants detected in the report should be clinically correlated (As per Physicians Advice) and confirmed via the orthogonal testing platforms (Sanger Sequencing or PCR based tests).

Regulatory Disclosures

Genetic screening for Neurological Disease predisposition is intended as a tool to guide physicians in the management of their patients and should NOT be treated as a diagnostic tool. NGS-based Hereditary Neurological Disease screening is considered a high-complexity laboratory-developed test (LDT) by CMS under the Clinical Laboratory Improvement Amendment (CLIA) and is not FDA-cleared. The test and performance metrics were validated in house by Ipseity Diagnostics LLC technical personnel (or designated scientific advisors) and approved by their Laboratory Director The results are intended for use only by the ordering physician and/or designated healthcare provider. The ordering provider is responsible for 1) ascertaining the medical necessity of the ordered test, 2) resulting diagnoses, 3) management of the disease and/or decisions based on the data provided. Results rely on collection personnel following specified collection and shipment protocols.

REFERENCES

Richards, Sue, 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. Genetics in medicine 17.5 (2015): 405.Exome Aggregation Consortium et al. Analysis of Protein-Coding Genetic Variation in 60,706 Humans. Nature 536.7616 (2016): 285–291. PMC. Web. 13 May 2018. The 1000 Genomes Project Consortium. A Global Reference for Human Genetic Variation. Nature 526.7571 (2015): 68–74. PMC. Web. 13 May 2018.

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