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PATIENT REPORT

Patient Age/Sex: Male

Specimen Collected: 18-Nov-22 09:28

Hereditary CNS Cancer by NGS, DelDup | **Received: 18-Nov-22 09:31** | **Report/Verified: 18-Nov-22 09:37**

Procedure	Result	Units	Reference Interval
CNSCAN Specimen	Whole Blood		
CNSCAN Interp	Positive f1 i1		

Result Footnote

f1: CNSCAN Interp

RESULT
One pathogenic variant was detected in the DICER1 gene.

PATHOGENIC VARIANT
Gene: DICER1 (NM_177438.3)
Nucleic Acid Change: c.1174C>T; Heterozygous
Amino Acid Alteration: p.Arg392Ter
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1174C>T; p.Arg392Ter, was detected in the DICER1 gene by massively parallel sequencing. Pathogenic germline variants in DICER1 are associated with autosomal dominant increased risk for several types of hereditary cancers/tumors including pleuropulmonary blastoma (MIM: 601200), cystic nephroma, multinodular goiter with/without Sertoli-Leydig cell tumors (MIM: 138800), and embryonal rhabdomyosarcoma (MIM: 180295); lifetime risks for different cancers/tumors vary (Doros, 2019). 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 a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The DICER1 c.1174C>T; p.Arg392Ter variant (rs1131691211) is reported in the literature in individuals affected with pleuropulmonary blastoma and rhabdomyosarcoma (Cai, 2017; Li, 2021). This variant is reported in ClinVar (Variation ID: 429141) and is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. 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 DICER1 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:
NONE

REFERENCES
Cai, et al. DICER1 mutations in twelve Chinese patients with pleuropulmonary blastoma. Sci China Life Sci. 2017;60(7):714-720. PMID: 28624956.

Doros L, et al. DICER1-related disorders. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2019. Accessed online at: https://www.ncbi.nlm.nih.gov/books/NBK196157/

Result Footnote

f1: CNSCAN Interp
Li, et al. Germline cancer predisposition variants in pediatric rhabdomyosarcoma: a report from the Children's Oncology Group. J Natl Cancer Inst. 2021;113(7):875-883. PMID: 33372952.

Test Information

i1: CNSCAN Interp
BACKGROUND INFORMATION: Hereditary Central Nervous System Cancer Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary central nervous system (CNS) tumors and cancer. Hereditary cancer predisposition is often characterized by early age of onset (typically before age 50), the presence of any number of CNS tumors in a single individual or closely related family member(s), and variable systemic manifestations.
EPIDEMIOLOGY: Approximately 5% of central nervous system tumors are associated with a hereditary cause.
CAUSE: Pathogenic germline variants in genes associated with a high lifetime risk of central nervous system tumors or cancer
INHERITANCE: Autosomal dominant. Additionally, some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.
GENES TESTED: ALK; APC*; DICER1; EPCAM**; HRAS; LZTR1; MEN1*; MLH1; MSH2; MSH6; NF1; NF2; PMS2; POT1; PRKAR1A; PTCH1; PTEN*; RB1*; SMARCA4; SMARCB1; SMARCE1*; SUFU; TP53; TSC1; TSC2; VHL*
*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.
**Deletion/duplication analysis of EPCAM (NM_002354) exon 9 only, sequencing is not available for this gene.
METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes (including selected PTEN promoter variants), 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 confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis. Testing of selected exons (and exon/intron boundaries) of PMS2, PTEN, and MSH2 was performed by bidirectional Sanger sequencing. Deletion/duplication testing of PMS2 was performed by multiplex ligation-dependent probe amplification (MLPA).
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

Test Information

i1: CNSCAN Interp

sensitivity. Specificity is greater than 99.9 percent for all variant classes. The analytical sensitivity for MLPA is greater than 99 percent.
LIMITATIONS: A negative result does not exclude a heritable form of central nervous system cancer or other cancer. 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. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.
The following regions may have reduced sequencing sensitivity due to technical limitations of the assay:
RB1 (NM_000321) exon 22
SUFU (NM_016169, NM_001178133) exon 1
The following regions are not sequenced due to technical limitations of the assay:
APC (NM_001354896) exon 12
APC (NM_001354898, NM_001354904) exon 2
APC (NM_001354900) exon 11
MEN1 (NM_001370251) exon 8
VHL (NM_001354723) exon 2
Deletions/duplications will not be called for the following exons:
APC (NM_001354896) 12; APC (NM_001354898, NM_001354904) 2; APC (NM_001354900) 11; MEN1 (NM_001370251) 8; PTEN (NM_000314, NM_001304718) 9; PTEN (NM_001304717) 1,10; RB1 (NM_000321) 22; SMARCE1 (NM_003079) 7,10-11; VHL (NM_001354723) 2

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.