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PATIENT REPORT

Patient Age/Sex: Male

Specimen Collected: 13-Sep-22 10:13

Hereditary Breast Cancer by NGS, DelDup | **Received: 13-Sep-22 10:14** | **Report/Verified: 13-Sep-22 10:17**

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

Result Footnote

f1: BCGUIDE Interp

RESULT
One pathogenic variant was detected in the BRCA1 gene.

PATHOGENIC VARIANT
Gene: BRCA1 (NM_007294.4)
Nucleic Acid Change: c.4485-2A>G; Heterozygous
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.4485-2A>G, was detected in the BRCA1 gene by massively parallel sequencing. This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome. Pathogenic germline variants in BRCA1 are associated with an increased risk for several types of hereditary cancers including female/male breast, ovarian, prostate, and pancreatic; lifetime risks for different cancers vary. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management in heterozygous individuals. Other genetic/environmental factors may influence an individual's risk of developing cancer. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

In addition, autosomal recessive inheritance of two BRCA1 pathogenic variants may be associated with Fanconi anemia, a condition characterized by congenital anomalies, bone marrow failure, and a predisposition to malignancies (Sawyer, 2015; MIM: 617883); thus, this individual is at least a carrier of this disorder.

No additional pathogenic variants were identified in the targeted genes. 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 BRCA1 c.4485-2A>G variant (rs80358054), also known as IVS14-2A>G and 4604-2A>G in traditional nomenclature, is reported in multiple individuals with hereditary breast and ovarian cancer syndrome (Evans, 2003; Park, 2017; Rebbeck, 2018; Shattuck-Eidens, 1997). This variant is also reported in ClinVar (Variation ID: 55214). It is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant disrupts the canonical splice acceptor site of intron 14, 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 Mutation, Targeted Sequencing, ARUP test code 2001961).

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; reportable variants are confirmed by Sanger sequencing:

Result Footnote

f1: BCGUIDE Interp
NONE

REFERENCES
Evans DG, et al. Sensitivity of BRCA1/2 mutation testing in 466 breast/ovarian cancer families. J Med Genet. 2003;40(9):e107. PMID: 12960223.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (2.2022): https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

Park JS, et al. Identification of a novel BRCA1 pathogenic mutation in Korean patients following reclassification of BRCA1 and BRCA2 variants according to the ACMG standards and guidelines using relevant ethnic controls. Cancer Res Treat. 2017;49(4):1012-1021. PMID: 28111427.

Rebbeck TR, et al. Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations. Hum Mutat. 2018;39(5):593-620. PMID: 29446198.

Sawyer S, et al. Biallelic mutations in BRCA1 cause a new Fanconi anemia subtype. Cancer Discov. 2015;5(2): 135-142. PMID: 25472942

Shattuck-Eidens, D et al. BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. JAMA. 1997;278(15):1242-1250. PMID: 9333265.

Test Information

i1: BCGUIDE Interp
BACKGROUND INFORMATION: Hereditary Breast Cancer Guidelines-Based Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary breast cancer. Additional screening, and in some cases, risk-reducing options have been recommended for moderate to high-risk hereditary breast cancer genes. These genes include ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, STK11, and TP53.

EPIDEMIOLOGY: Approximately 5-10 percent of breast cancer is associated with a hereditary cause.

CAUSE: Pathogenic germline variants in genes associated with a moderate to high lifetime risk of hereditary breast cancer.

INHERITANCE: Autosomal dominant. Additionally, some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.

GENES TESTED: ATM; BARD1; BRCA1*; BRCA2; CDH1*; CHEK2*; NF1; PALB2; PTEN*; STK11; TP53

*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

Test Information

i1: BCGUIDE Interp

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 PTEN was performed by bidirectional Sanger sequencing.

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 breast 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. Non-coding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
BRCA1 (NM_007300) exon 13
CHEK2 (NM_001005735) exon 3

Test Information

i1: BCGUIDE Interp

CHEK2 (NM_001349956) exon 4

Deletions/duplications will not be called for the following exons: BRCA1 (NM_007294, NM_007299, NM_007300) 2; BRCA1 (NM_007298) 1; CDH1 (NM_001317185) 10; CHEK2 (NM_007194) 11-15; CHEK2 (NM_001005735) 3,12-16; CHEK2 (NM_001257387) 12-16; CHEK2 (NM_001349956) 4,10-14; CHEK2 (NM_145862) 10-14; PTEN (NM_000314, NM_001304718) 9; PTEN (NM_001304717) 1,10

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.