Comprehensive BRCA 1/2 Sequencing Analysis Report

Date: 02/16/2016
Order ID: GM16-4086
Order Date: 02/05/2016

Patient Name: **JANE DOE**

Patient Information	Specimen Information	Physician Information
Name: JANE DOE	**Sample Type:** Peripheral blood	**Referring Physician:** DR. JIM LU
DOB: 09/17/1960	**Collected:** 02/04/2016	**Address**: 1351 BARCLAY BOULEVARD,
Gender: Female	**Received:** 02/05/2016	BUFFALO GROVE, IL 60089
Diagnosis: Breast Cancer	**Specimen ID:**	**Phone**: 224-588-9940 **Fax**: 224-588-9941

Report

TEST PERFORMED	RESULT	ZYGOSITY	SIGNIFICANCE
BRAC1 Sequencing	Variant detected c.1067 A>G (p.Q356R)	Heterozygous	Benign
BRCA1 Del/Dup	Negative	N/A	N/A
BRCA2 Sequencing	Negative	N/A	N/A
BRCA2 Del/Dup	Negative	N/A	N/A

Comments

A missense variant was detected at nucleotide 1067 of coding cDNA sequence (c. 1067 T>C). This rare variant causes amino acid change from glutamine to arginine at codon 356 (p. Q356R) at BRCA1 protein. The detected variant has been classified as benign which is not associated with an increased risk for the Hereditary Breast and Ovarian Cancer Syndrome. Interpretation and classification of clinical significance of this variant as benign variant are based on catalogued information from LOVD database (http://databases.lovd.nl/shared/genes/) and NCBI ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/variation/), as well as the results from a large population follow-up study (see Reference 1 on page 3). No variant was detected in BRCA2 gene.

Comprehensive sequencing analysis was also performed for other genes associated with increased risk of breast and ovarian cancers, including CHEK2, PALB2, PTEN, TP53, BARD1, ATM, CDH1, STK11, BRIP1 and NBN genes. No pathogenic or likely pathogenic variant was detected in any of these genes.

Recommendation

Based on accumulated information from clinical and research sources, the detected BRCA1 variant is classified as benign variant which is not associated with an increased risk for the Hereditary Breast and Ovarian Cancer Syndrome. Genetic counseling with a health care professional who has training and experience in cancer genetics is recommended to discuss cancer risks and other disease risks associated with this genetic test result.
If you have any question about this report and wish to speak with the genetic experts in GoPath Laboratory, please call 855-467-2849 (Toll Free).

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Interpretation Of Results

Interpretation and classification of clinical significance of the identified variants are based on catalogued information from BRCA1/2 mutation databases at the LOVD database (http://databases.lovd.nl/shared/genes/) and NCBI ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/variation/) as well as information from published literatures. Clinical significance of the detected variants are classified into following 5 categories: Pathogenic, the change is proven to cause significant risks; Likely pathogenic, while nothing is proven, the variation is currently believed to be harmful; Variant of unknown significance (VUS): Whether the change has any effect is unknown; Likely benign, while nothing is proven, the variation is currently believed to be harmless; Benign, the change is classified as harmless.

BRCA1 and BRCA2 proteins have a critical role in maintaining genomic stability and is involved in many cellular processes including DNA repair, cell cycle progression, and transcriptional regulation. Inheritance of a pathogenic mutation in the BRCA1 or BRCA2 gene results in hereditary breast and ovarian cancer (HBOC) syndrome, an autosomal dominant disorder associated with increased risk of early-onset, breast and ovarian cancer in females. HBOC syndrome accounts for 5-7% of all breast cancer cases. The average cumulative risks in BRCA1 mutation carriers by age 70 are approximately 65% for breast cancer and 39% for ovarian cancer. The estimates for BRCA2 mutation carriers are 45% for breast cancer and 11% for ovarian cancer.

In addition, it has been reported that mutations in BRCA1 and BRCA2 also increase risk of other cancer types, including but not limited to fallopian tube, peritoneal, pancreatic, prostate and male breast cancers.

Methods And Limitations

Methods and Performance: Germline mutations of BRCA1 and 2 genes were detected by a next generation sequencing method using GoPath Genetic Gene Panel (gpNGS-15). The assay was developed and validated using Kappa library preparation technology and Illunima Miseq instrument combined with NextGene data analysis platform (SoftGeneticsTM). The assay is designed to detect single and multi-nucleotide substitutions, insertions, duplications and small deletions in coding and exon-intron junction of BRCA1/2 genes. The assay provides >1500X average coverage at the targeted genomic regions of BRCA1/2 genes. Sensitivity and specificity of the assay for detection of BRCA1/2 mutations in targeted genomic regions is 96.5% and 100%with a negative predictive value (NPV) and positive predictive value of 96.5% and 100%. Targeted regions with inadequate sequencing read coverage (read depth < 200X) from NGS are sequenced by a Sanger DNA Sequencing method. Variant frequency of ≥10% was defined as the value of limit-of-detection (LOD) of the assay. Variants detected in other genes beside BRCA1/2 in this NGS gene panel are not reported. Large genomic rearrangements (Del/Dup) are detected by a standard multiplex ligation-dependent probe amplification assay (MLPA Assay).

Nucleotide and codon number in data analysis are based on the mRNA isoform NM_007300 for BRCA1 gene and NM_000059 for BRCA2 gene.

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Methods And Limitations (continued)

Limitations:
The BRCA1/2 mutation detection assays developed by GoPath Laboratory are designed to detect single and multi-nucleotide substitutions, small insertions, duplications and insertions as well as large genomic rearrangements present in coding genomic sequences and exon-intron junction of BRCA1/2 genes. The assay detects all genetic alterations which have a proven cancer risk for patients with hereditary breast and ovarian cancer (HBOC) syndrome. Variants in noncoding genomic regions and alterations involving DNA copy number and genomic instability which have no reported association with HBOC cannot be detected.

References

1. Dombernowsky SL et al: Missense polymorphisms in BRCA1 and BRCA2 and risk of breast and ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2009 Aug;18(8):2339-42.

2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology, genetic/familial high-risk assessment: breast and ovarian. Available at: www.nccn.org. 2010. Accessed 5.29.13.

3. American Society of Clinical Oncology Policy Statement Update:Genetic Testing for Cancer Susceptibility. J Clin Oncol. 2003 Jun 15;21(12):2397-406.

4. Engert S. et al. MLPA screening in the BRCA1 gene from 1,506 German hereditary breast cancer cases: novel deletions, frequent involvement of exon 17, and occurrence in single early-onset cases. Hum Mutat. 2008 Jul;29(7):948-58.

5. Judkins T. et al. Clinical significance of large rearrangements in BRCA1 and BRCA2. Cancer. 2012 Nov 1;118(21):5210-6.

6. Jara L, et al. BRCA1 and BRCA2 mutations in a South American population. Cancer Genet Cytogenet. 2006 Apr 1;166(1):36-45.

7. Ford D, et al. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet. 1994 Mar 19;343(8899):692-5.

8. Tai YC, et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 2007 Dec 5;99(23):1811-4.

Disclaimer

The performance characteristics of this test were validated by GoPath Laboratories. The U.S. Food and Drug Administration (FDA) has not approved or cleared this test; however, FDA approval or clearance is currently not required for clinical use of this test. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions. GoPath Laboratory is authorized under Clinical Laboratory Improvement Amendments (CLIA) and by all states to perform high-complexity testing. GoPath is a College of American Pathologists (CAP) accredited laboratory.

Electronically Signed By: Jim Lu M.D. PhD **01/26/2016**