SAMPLE REPORT

GC Genome

GCG Hereditary Cancer Panel

Test Report

Name	Jane Doe		
DOB / Gender	1970-01-01 / Female	**Sample ID**	20220101-971-2101
MRN	M0000000	**Collection Date**	2022-01-01
Institution	Hospital A	**Received Date**	2022-01-05
Ordering Physician	Dr. Smith	**Reporting Date**	2022-01-19

Tested by : Myeong-Keun Lee M.T(20058) Confirmed by : Sae-Mi, Lee M.D(1067) Cho,EunHae M.D(690)

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COLLEGE of AMERICAN PATHOLOGISTS

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Summary

Positive

Variant of uncertain significance in the PALB2 gene was found.
Additionally, likely pathogenic variant in the SDHB gene was found.

Results

Gene	DNA Change	AA Change	Zygosity	OMIM Disease	Inherit	Class
PALB2	DNA c.1054G>C	p.Glu352Gln	Het	BCs	AD	VUS
SDHB	c.406del	p.Ile136Ter	Het	GIST	AD	LPV

· Reference sequence : NM_024675.3(PALB2);NM_003000.2(SDHB)
· Abbreviations: Het=Heterozygote; BCs=Susceptibility to breast cancer; AD=Autosomal dominant; VUS=Variant of uncertain
· significance; GIST= Gastrointestinal stromal tumor; LPV= Likely pathogenic variant;

Interpretation

A Heterozygous variant (c.1054G>C;p.Glu352Gln) in the PALB2 gene was detected. This variant has been classified as a Likely benign(2);Uncertain significance(3) in Clinvar and as a possible pathological mutation in HGMD. This variant has not been reported in the South Asian population database, while minor allele frequency (MAF) of the variant was estimated to be 0.000061 (gnomAD_all). Taken together, this PALB2 variant can be classified as VUS. Pathogenic variants in PALB2 are known to cause Breast cancer, Fanconi anemia, Pancreatic cancer, etc.

As further analysis, a Heterozygous variant (c.406del;p.Ile136Ter) in the SDHB gene was detected. This variant has been classified as a deleterious mutation in HGMD and this variant has not been reported in the population database (gnomAD). Taken together, this SDHB variant can be classified as Likely pathogenic. Pathogenic variants in SDHB are known to cause Gastrointestinal stromal tumor, Paraganglioma and gastric stromal sarcoma, Paragangliomas 4, Pheochromocytoma, etc.

This test analyzes the coding exons and adjacent intron areas of the genes included in the panel and cannot detect exon deletions/duplications, and copy number variants including genomic rearrangements etc. For more information on the technical limitations of a test, see the limits of the test below.

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The result details and related diseases

Cancer	Gene	RESULTS
Breast	ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, NBN, NF1, **PALB2**, PPM1D, PTEN, RAD51C, STK11, TP53	**Detected**
Ovarian	BRCA1, BRCA2, BRIP1, DICER1, EPCAM, MLH1, MSH2, MSH6, **PALB2**, PMS2, PPM1D, RAD51C, RAD51D, STK11, TP53	**Detected**
Uterine	EPCAM, FH, MLH1, MSH2, MSH6, PMS2, PTEN, STK11, TP53	Not Detected
Prostate	ATM, BRCA1, BRCA2, CHEK2, HOXB13, MLH1, MSH2, MSH6, NBN, **PALB2**, PMS2, TP53	**Detected**
Stomach	APC, BMPR1A, CDH1, EPCAM, KIT, MLH1, MSH2, MSH6, PMS2, SMAD4, STK11	Not Detected
Colorectal	APC, BLM, BMPR1A, CDH1, CHEK2, EPCAM, KIT, MLH1, MSH2, MSH6, MUTYH, PMS1, PMS2, PTEN, SMAD4, STK11, TP53	Not Detected
Lung and Pleura	BAP1, DICER1, EGFR	Not Detected
Small Intestines	KIT, MLH1, MSH2, MSH6, SDHB, SDHC, SDHD, STK11	Not Detected
Esophagus	FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, RHBDF2	Not Detected
Urinary Tract and Bladder	HRAS, MLH1, MSH2, MSH6	Not Detected
Pancreatic	APC, ATM, BMPR1A, BRCA1, BRCA2, CDK4, CDKN2A, EPCAM, MEN1, MLH1, MSH2, MSH6, NF1, PALB2, PMS2, SMAD4, STK11, TP53, VHL	Not Detected
Kidneys	BAP1, BUB1B, CEP57, DICER1, DIS3L2, FH, FLCN, MET, PTEN, **SDHB**, SDHC, SDHD, SMARCB1, TSC1, TSC2, VHL, WT1	**Detected**
Cervix	STK11	Not Detected

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Cancer	Gene	RESULTS
Skin	BAP1, CDK4, CDKN2A, DDB2, ERCC2, ERCC3, ERCC4, ERCC5, NF2, PTEN, TP53, XPA, XPC	Not Detected
Bone	EXT1, EXT2, RECQL4, TP53	Not Detected
Thyroid Gland	APC, CHEK2, DICER1, MEN1, PRKAR1A, PTEN, RET, TP53	Not Detected
Liver	APC, HNF1A	Not Detected
Soft Tissue	RB1, WRN	Not Detected
Miscellaneous Endocrine Glands	CDC73, FH, MAX, MEN1, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL	Not Detected
Blood	CEBPA, GATA2, PRF1, RUNX1, SBDS	Not Detected
Head and Neck	CDK4, CYLD, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, SLX4	Not Detected
Central Nervous System	AIP, APC, CDKN1C, CDKN2A, DICER1, GPC3, MLH1, MSH2, MSH6, NBN, NF2, PMS2, PRKAR1A, PTCH1, PTEN, SMARCA4, SMARCB1, SUFU, TP53, TSC2	Not Detected
Peripheral Nervous System	ALK, EZH2, FH, NF1, NF2, NSD1, PHOX2B, SDHAF2, SDHB	Not Detected

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Relevant Disease Information

Breast Cancer

Disease Information

Breast cancer is a malignant tumor that may spread beyond the breast and threaten a patient's life. Any cells of the breast may become cancer. In general, breast cancer may initially cause no symptoms. The most common symptom is a painless fixed lump in a breast or breast enlargement. 50% of breast cancer cases are located in the exterior part of the upper breast. Females can check their breasts through breast self-examination. Over 70% of patients with breast cancer discover their condition through a self-examination. The best time to examine your breasts is 1 week after the end of your menstrual period when your breasts are tender. If you had hysterectomy or are in menopause, breast self-examination is recommended every month.

Genetic features

Hereditary breast cancers are usually autosomal dominant and associated with pathogenic variants of the BRCA1 and BRCA2 genes. BRCA1 and BRCA2, identified in 1994 and 1995, respectively, are considered to be one of the most important factors for the pathogenesis of breast cancers because the incidence of breast cancer is significantly increased with pathogenic variants of BRCA1 and BRCA2. BRCA1 and BRCA2 are located on the long arm of chromosome 17 and chromosome 13, respectively. In case of DNA damage, these genes, reacting with other proteins, play a role in repairing the damaged double strand DNA. If BRCA1 or BRCA2 is damaged, the DNA repair process is not properly performed, and therefore, the risk of cancer increases. Pathogenic variants of the BRCA genes are autosomal dominantly inherited and the same genetic disorders have a 50% probability of occurring in the patient's offsprings and other family members. However, not all hereditary breast cancer have BRCA1 or BRCA2 pathogenic variants. Some tumor suppressor genes and DNA repair genes are also associated with increased risk of breast cancer. Pathogenic variants in the ATM, CDH1, CHEK2, NBN, NF1 and PALB2 genes increase breast cancer risk. Depending on the positive genetic results, breast cancer screening through MRI mammography is recommended for those in 30 to 40 years of age. Therefore, when a pathogenic variant is found in a patient, the patient's offsprings and family members in close relatioships are recommended to have genetic testing.

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Relevant Disease Information

Ovarian Cancer

Disease Information

Ovarian cancer is a cancer that forms in an ovary. Ovarian cancer is largely divided into epithelial ovarian cancer, germ cell tumor, and sex cord stromal tumor, depending on the tissue where the tumor develops. Epithelial ovarian cancer means cancer started in epithelial cells on the surface of the ovary. Over 90% of malignant tumors of the ovary are epithelial. Common signs and symptoms of epithelial ovarian cancer include stomachache, abdominal distention, abdominal swelling, intra-abdominal lump, abnormal vaginal bleeding, frequent urination, dysuria, abnormal vaginal discharge, nausea, vomiting, constipation, and backache.

Genetic features

Hereditary ovarian cancers are usually autosomal dominant and associated with pathogenic variants of the BRCA1 and BRCA2 genes. BRCA1 and BRCA2, identified in 1994 and 1995, respectively, are considered to be one of the most important factors for the pathogenesis of ovarian cancers because the incidence risk of breast cancer is significantly increased with pathogenic variants of BRCA1 and BRCA2. BRCA1 and BRCA2 are located on the long arm of chromosome 17 and chromosome 13, respectively. In case of DNA damage, these genes, reacting with other proteins, play a role in repairing the damaged double strand DNA. If BRCA1 or BRCA2 is damaged, the DNA repair process is not properly performed, and therefore, the risk of cancer increases. Pathogenic variants of the BRCA genes are autosomal dominantly inherited and the same genetic disorders have a 50% probability of occurring in the patient's offsprings. However, not all hereditary ovarian cancer have BRCA1 or BRCA2 pathogenic variants. Pathogenic variants in the BRIP1 and RAD51C genes also increase the risk of ovarian cancer. If pathogenic variants are detected in these genes, counseling for prophylactic ovarian resection is required between 45 and 50 years of age based on the family history of ovarian cancer. Therefore, when a pathogenic variant is found in a patient, the patient's offsprings and family members in close relationships are recommended to have genetic testing.

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Relevant Disease Information

Prostate Cancer

Disease Information

Prostate cancer is a medical condition in which the cells of the prostate divide and grow abnormally and consequently become a malignant tumor. The tumor may invade nearby tissues without being confined to the prostate or may spread to other organs through blood vessels or lymphatic vessels. Prostate cancer may initially cause no symptoms. In later stages, patients experience a variety of urinary problems (nocturia, frequent urination, urinary hesitancy, etc.). Symptoms of more advanced prostate cancer include hydronephrosis (the swelling of a kidney due to the blockage of the ureter), renal failure, bone pain due to metastasis (including backache and sciatic neuralgia), and distal femur or spinal fractures.

Genetic features

Hereditary prostate cancer is associated with the pathogenic variants of MLH1, MSH2, MSH6, PMS2, and homologous recombination genes. MLH1, MSH2, MSH6, and PMS2 are associated with Lynch syndrome, the inherited cancer syndrome. The risk of prostate cancer in patients with the pathogenic variants of these genes is about 5-16%. The homologous recombination genes, BRCA1, BRCA2, ATM, PALB2, and CHEK2 are involved in the double-stranded DNA repair process. If there is an abnormality in these gene functions, there is a problem in the DNA repair process, and the risk of cancer increases. If pathogenic variants are detected in these genes, prostate cancer can develop at a relatively early age, under the age of 55, so early screening for prostate cancer is required from the age of 45.

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Test Information

Method

- Target Region:
- Target enrichment method: Hybridization with oligonucleotide probes
- Massively parallel sequencing: MiseqDX (150 bp x 2 paired-ends)
- Reference genome: GRCh37/hg19
- Bioinformatic pipeline:

Coverage

- Mean depth of coverage: 300x
- % of Target Bases ≥ 10X: 99X

Gene List

AIP , ALK, APC, ATM, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, BUB1B, CDC73, CDH1, CDK4, CDKN1C, CDKN2A, CEBPA, CEP57, CHEK2, CYLD, DDB2, DICER1, DIS3L2, EGFR, EPCAM, ERCC2, ERCC3, ERCC4, ERCC5, EXT1, EXT2, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FH, FLCN, GATA2, GPC3, HNF1A, HOXB13, HRAS, KIT, MAX, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, NSD1, PALB2, PHOX2B, PMS1, PMS2, PPM1D, PRF1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL4, RET, RHBDF2, RUNX1, SBDS, SDHAF2, SDHB, SDHC, SDHD, SLX4, SMAD4, SMARCA4, SMARCB1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, WRN, WT1, XPA, XPC

Cancer /Tumor List

- Breast
- Ovaries
- Endometrium, Uterine
- Myometrium, Uterine
- Prostate Gland
- Stomach
- Large Bowel and Rectum
- Lung and Pleura
- Small Intestines
- Esophagus
- Urinary Tract and Bladder
- Exocrine Pancreas
- Endocrine Pancreas
- Kidneys
- Cervix
- Skin
- Bone
- Thyroid Gland
- Liver
- Soft Tissue
- Miscellaneous Endocrine Glands
- Blood
- Head and Neck
- Central Nervous System
- Peripheral Nervous System

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Test Information

Limitation

This test is performed by NGS technique. The genes included in the test include the entire exon, but in some areas sequencing may not be sufficiently covered. In addition, if a highly homologous sequence exists, the sequencing of the base may not be accurate, and exonic deletion/duplication, regulatory or deep intronic region, repeat expansion, imprinting defect etc. may be difficult to detect. Genetic variation is divided into five categories, pathogenic variant (PV), likely pathogenic variant (LPV), variant of unknown significance (VUS), likely benign variant (LBV), and benign variant (BV), according to 2015 ACMG/AMP (Genet Med 2015;17:405-24). Likely benign variant (LBV) and Benign variant (BV) are not reported. However, the interpretation of the variation could be changed as additional evidence builds up after the results are reported.

Reference

1. Breast Cancer Information Core (http://research.nhgri.nih.gov/bic)
2. The Human Gene Mutation Database (http://www.hgmd.cf.ac.uk)
3. Gene Reviews (http://geneclinics.org)

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