Hereditary Cancer Gene Panel

For Proband, test Male

Proband, test
Referring Clinician:

D.O.B.
Lab Ref: test

LAB ID	Specimen type:	Collected:	Received:	Reported:
200002466			Sep 30, 2022	Dec 27, 2022

CLINICAL SUMMARY

Mock Report

RESULT SUMMARY [SEQUENCING AND DELETION/DUPLICATION CNV ANALYSES]

SIGNIFICANCE OF THE FINDINGS	GENE	VARIANT COUNT
High Impact	BRCA2	1 (P)
Possibly High Impact	--	--

INTERPRETATION & RECOMMENDATIONS

A heterozygous c.5351del (p.N1784fs) pathogenic variant in the BRCA2 was detected in this individual. Defects in BRCA2 cause disorders including breast-ovarian cancer, familial, 2 [MIM: 612555], an autosomal dominant condition associated with familial predisposition to cancer of the breast and ovaries.

The identification of a pathogenic variant in the BRCA2 in this individual indicate that this individual is at much higher-than-average risk of developing BRCA2 related cancer over the lifetime. Clinical correlations and genetic counseling are recommended. Cancer surveillance for this individual and targeted testing for the BRCA2 variant in the family members are also recommended.

More information about breast cancer treatment and care can be found at professional websites such as the website for the US National Cancer Institute (https://www.cancer.gov/).

RESULT DETAILS

High Impact

BRCA2

Position	Variant	Zygo-sity	Parental Results	Comments	Population Freq*	In Silico (REVEL)	Variant Sig.
13:32913836 CA>C	NM_000059.4 exon11/27 c.5351del p.Asn1784ThrfsTer7	Het		ACMG: PVS1+PM2+PP5 PMID: 8988179, 34645131, 30093976, 30875412, 29907814, 30787465, 26360800; rs80359507; ClinVarID: 37961	0/0	--	P

*Total frequency/highest population frequency in gnomAD

DISEASE: Fanconi anemia complementation group D1 [MIM: 605724], Autosomal recessive; {Glioblastoma 3} [MIM: 613029], Autosomal recessive; {Medulloblastoma} [MIM: 155255], Somatic mutation, Autosomal recessive, Autosomal dominant; {Prostate cancer} [MIM: 176807], Somatic mutation, Autosomal dominant; {Breast-ovarian cancer familial 2} [MIM: 612555], Autosomal dominant; {Breast cancer male susceptibility to} [MIM: 114480], Somatic mutation, Autosomal dominant; {Pancreatic cancer 2} [MIM: 613347]; Wilms tumor [MIM: 194070], Somatic mutation, Autosomal dominant

INTERPRETATIONS:

Variant:
A heterozygous pathogenic variant, c.5351del(p.Asn1784ThrfsTer7), in the BRCA2 gene was detected. The variant is currently not reported in the gnomAD database (v2.1.1). This variant has been previously reported in multiple patients with ovarian cancer, breast cancer, and/or prostate cancer [PMID: 8988179, 25863477, 22923021, 26360800]. This variant is classified as pathogenic by multiple laboratories and expert review panels in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/variation/37961/). It is interpreted as pathogenic according to ACMG/AMP guidelines.

Gene:
BRCA2 encodes BRCA2, DNA Repair Associated, a nuclear protein that contains several copies of a 70 aa motif called the BRC motif, and these motifs mediate binding to the RAD51 recombinase which functions in DNA repair. BRCA2 is considered a tumor suppressor gene and like BRCA1, is involved in maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair.

Disease:
Defects in the BRCA2 gene cause Breast cancer [MIM:114480]: A common malignancy originating from breast epithelial tissue. Breast neoplasms can be distinguished by their histologic pattern. Invasive ductal carcinoma is by far the most common type. Breast cancer is etiologically and genetically heterogeneous. Important genetic factors have been indicated by familial occurrence and bilateral involvement. Mutations at more than one locus can be involved in different families or even in the same case. The inheritance manner is autosomal dominant.

Defects in the BRCA2 gene cause Medulloblastoma [MIM:155255]: Malignant, invasive embryonal tumor of the cerebellum with a preferential manifestation in children. The inheritance manner is autosomal dominant or autosomal recessive.

Defects in the BRCA2 gene cause Prostate Cancer [MIM:176807]: A malignancy originating in tissues of the prostate. Most prostate cancers are adenocarcinomas that develop in the acini of the prostatic ducts. Other rare histopathologic types of prostate cancer that occur in approximately 5% of patients include small cell carcinoma, mucinous carcinoma, prostatic ductal carcinoma, transitional cell carcinoma, squamous cell carcinoma, basal cell carcinoma, adenoid cystic carcinoma (basaloid), signet-ring cell carcinoma and neuroendocrine carcinoma. The inheritance manner is autosomal dominant.

Defects in the BRCA2 gene cause Pancreatic cancer 2 [MIM:613347]: A malignant neoplasm of the pancreas. Tumors can arise from

both the exocrine and endocrine portions of the pancreas, but 95% of them develop from the exocrine portion, including the ductal epithelium, acinar cells, connective tissue, and lymphatic tissue. The inheritance manner is autosomal dominant.

Defects in the BRCA2 gene cause Glioma 3 [MIM:613029]: Gliomas are benign or malignant central nervous system neoplasms derived from glial cells. They comprise astrocytomas and glioblastoma multiforme that are derived from astrocytes, oligodendrogliomas derived from oligodendrocytes and ependymomas derived from ependymocytes. The inheritance manner is autosomal recessive.

Defects in the BRCA2 gene cause Wilms tumor 1 [MIM:194070]: Embryonal malignancy of the kidney that affects approximately 1 in 10'000 infants and young children. It occurs both in sporadic and hereditary forms. The inheritance manner is autosomal dominant.

Defects in the BRCA2 gene cause Fanconi anemia complementation group D1 [MIM:605724]: A disorder affecting all bone marrow elements and resulting in anemia, leukopenia and thrombopenia. It is associated with cardiac, renal and limb malformations, dermal pigmentary changes, and a predisposition to the development of malignancies. At the cellular level it is associated with hypersensitivity to DNA-damaging agents, chromosomal instability (increased chromosome breakage) and defective DNA repair. The inheritance manner is autosomal recessive.

Defects in the BRCA2 gene cause Breast-ovarian cancer, familial, 2 [MIM:612555]: A condition associated with familial predisposition to cancer of the breast and ovaries. Characteristic features in affected families are an early age of onset of breast cancer (often before age 50), increased chance of bilateral cancers (cancer that develop in both breasts, or both ovaries, independently), frequent occurrence of breast cancer among men, increased incidence of tumors of other specific organs, such as the prostate. The inheritance manner is autosomal dominant.

Defects in the BRCA2 gene cause Breast cancer male susceptibility to [MIM:114480]: A common malignancy originating from breast epithelial tissue. Breast neoplasms can be distinguished by their histologic pattern. Invasive ductal carcinoma is by far the most common type. Breast cancer is etiologically and genetically heterogeneous. Important genetic factors have been indicated by familial occurrence and bilateral involvement. Mutations at more than one locus can be involved in different families or even in the same case. The inheritance manner is autosomal dominant.

METHODOLOGY & LIMITATIONS

Next generation sequencing (NGS): for the paired-end pre-capture library procedure, genomic DNA was fragmented by and ligated to multiplexing PE adapters. The adapter-ligated DNA was then PCR amplified using primers with sequencing barcodes (indexes). For target enrichment procedure, the pre-capture library was enriched by hybridizing to biotin labeled in-solution probes. For massively parallel sequencing, the post-capture library DNA was subjected to sequence analysis on an NGS sequencing platform. The following quality control metrics of the sequencing data are generally achieved: >=90% target base covered at >=20X, mean coverage of target bases >=100X. Usually pathogenic or likely pathogenic Copy Number Variations (CNVs) affecting three or more exons will be included in the report. This test may not provide detections of certain genes or portions of certain genes due to local sequence characteristics or the presence of closely related pseudogenes. Some deletions or duplications, or changes from repetitive sequences may not be accurately identified by this methodology. Genes included in this test are listed in the supplementary table.

Data analysis and interpretation (NGS pipeline version 1.1): The output data were converted from BCL file to FASTQ file, and then mapped by BWA program (reference sequence: GRCh37/Hg19). The variant calls were performed using GATK and annotations were performed using in-house developed pipelines. Synonymous variants, deep intronic variants not affecting splicing site, and common benign variants were excluded from interpretation unless they were previously reported as pathogenic variants. The variants were interpreted according to ACMG guidelines (Richards, et al. Genetics in Medicine (2015) 17, 405) and patient phenotypes and were classified as pathogenic (P), likely pathogenic (LP), unknown significance (VUS), likely benign (LB) or benign (B). It should be noted that the data interpretations were based on our current understanding of genes and variants at the time of reporting. Usually only P and LP variants will be included in the report.

Supplementary Table 1. Gene List (113 Genes)

ABRAXAS1	ACD	AIP	AKT1	APC	ATM	BAP1	BARD1	BLM	BMPR1A
BRCA1	BRCA2	BRIP1	CASR	CDC73	CDH1	CDK4	CDKN1B	CDKN2A	CEBPA
CHEK2	CTRC	DDB2	DICER1	DIS3L2	EPCAM	ERCC1	ERCC2	ERCC3	ERCC4
ERCC5	FANCA	FANCB	FANCC	FANCD2	FANCE	FANCF	FANCG	FANCI	FANCL
FANCM	FH	FLCN	GALNT12	GATA2	GPC3	GREM1	HOXB13	KIF1B	KIT
LZTR1	MAX	MEN1	MET	MITF	MLH1	MRE11	MSH2	MSH3	MSH6
MUTYH	NBN	NF1	NF2	NSD1	NTHL1	PALB2	PDGFRA	PHOX2B	PIK3CA
PMS2	POLD1	POLE	POT1	PRKAR1A	PTCH1	PTEN	RAD50	RAD51	RAD51B
RAD51C	RAD51D	RB1	RECQL4	RET	RHBDF2	RINT1	RUNX1	SDHA	SDHAF2
SDHB	SDHC	SDHD	SLX4	SMAD4	SMARCA4	SMARCB1	SMARCE1	SPINK1	SPRED1
STK11	SUFU	TERF2IP	TERT	TMEM127	TP53	TSC1	TSC2	VHL	WT1
XPA	XPC	XRCC2							