Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 游淑靜
Gender: Female
ID No.: G220768397
History No.: 22270037
Age: 60

Ordering Doctor: DOC3577C 黃楷中
Ordering REQ.: 0CVNVTT
Signing in Date: 2024/1/9

Path No.: M113-00008
MP No.: BR24001
Assay: Oncomine BRCA1/2 Assay
Sample Type: FFPE
Block No.: S112-62601H
Percentage of tumor cells: 60%

Reporting Doctor: DOC5424G 彭昱璟 (Phone: 8#5424)

Note:

Sample Cancer Type: Ovarian Cancer

Table of Contents	Page

Report Highlights
0 Relevant Biomarkers
0 Therapies Available
0 Clinical Trials

Relevant Ovarian Cancer Variants

Gene	Finding
BRCA1	***BRCA1 deletion***
BRCA2	None detected

Relevant Biomarkers

No clinically significant biomarkers found in this sample.

Prevalent cancer biomarkers without relevant evidence based on included data sources
BRCA1 deletion

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Locus	Allele Frequency	Transcript	Variant Effect	ClinVar[1]	Coverage
BRCA2	p.(N372H)	c.1114A>C	chr13:32906729	50.30%	NM_000059.3	missense	Benign	1996
BRCA2	p.(V1269=)	c.3807T>C	chr13:32912299	48.12%	NM_000059.3	synonymous	Benign	1999
BRCA2	p.(L1521=)	c.4563A>G	chr13:32913055	99.70%	NM_000059.3	synonymous	Benign	1992
BRCA2	p.(V2171=)	c.6513G>C	chr13:32915005	99.85%	NM_000059.3	synonymous	Benign	1999
BRCA2	p.(V2466A)	c.7397T>C	chr13:32929387	99.80%	NM_000059.3	missense	Benign	1999
BRCA1	p.(S1613G)	c.4837A>G	chr17:41223094	99.85%	NM_007294.4	missense	Benign	2000
BRCA1	p.(S1436=)	c.4308T>C	chr17:41234470	99.60%	NM_007294.4	synonymous	Benign	2000
BRCA1	p.(K1183R)	c.3548A>G	chr17:41244000	99.55%	NM_007294.4	missense	Benign	2000
BRCA1	p.(E1038G)	c.3113A>G	chr17:41244435	99.70%	NM_007294.4	missense	Benign	2000
BRCA1	p.(P871L)	c.2612C>T	chr17:41244936	99.75%	NM_007294.4	missense	Benign	1999
BRCA1	p.(L771=)	c.2311T>C	chr17:41245237	99.65%	NM_007294.4	synonymous	Benign	1999
BRCA1	p.(S694=)	c.2082C>T	chr17:41245466	99.85%	NM_007294.4	synonymous	Benign	2000

[1] Based on Clinvar version 20200329

Copy Number Variations

Gene	Locus	Copy Number	ClinVar[1]
BRCA1	chr17:41197601	1	

[1] Based on Clinvar version 20200329

Biomarker Descriptions

BRCA1 deletion

BRCA1 DNA repair associated

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[1,2]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[1,2]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer[3,4,5]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%[3,6].

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer[7,8,9,10,11,12,13,14]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[15,16].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[17]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[18,19]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[20] (2014) was the first PARPi to be approved by the FDA for BRCA1/2

Biomarker Descriptions (continued)

aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[20] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[21] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[22] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[22] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[23] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[24] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[25]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[26]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[27], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

References

1. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. Breast Cancer Res. 2002;4(1):9-13. PMID: 11879553
2. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. Oncogene. 2002 Dec 16;21(58):8981-93. PMID: 12483514
3. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017 Jun 20;317(23):2402-2416. PMID: 28632866
4. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J. Natl. Cancer Inst. 2007 Dec 5;99(23):1811-4. PMID: 18042939
5. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br. J. Cancer. 2007 Jan 15;96(1):11-5. PMID: 17213823
6. Chen et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis . JNCI Cancer Spectr. 2020 Aug;4(4):pkaa029. PMID: 32676552
7. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425
8. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. Mayo Clin. Proc. 2010 Dec;85(12):1111-20. PMID: 21123638
9. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc. Natl. Acad. Sci. U.S.A. 2011 Nov 1;108(44):18032-7. PMID: 22006311
10. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J. Clin. Oncol. 2012 Jul 20;30(21):2654-63. PMID: 22711857
11. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiol. Biomarkers Prev. 2004 Dec;13(12):2078-83. PMID: 15598764
12. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003 Oct 24;302(5645):643-6. PMID: 14576434
13. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br. J. Cancer. 2000 Nov;83(10):1301-8. PMID: 11044354
14. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. Environ Mol Mutagen. 2022 Jul;63(6):308-316. PMID: 36054589
15. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
16. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
17. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. Br. J. Cancer. 2018 Nov;119(11):1401-1409. PMID: 30353044
18. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005 Apr 14;434(7035):913-7. PMID: 15829966
19. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14;434(7035):917-21. PMID: 15829967
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211651s010lbl.pdf
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208447s027lbl.pdf
24. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf
25. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. J. Pathol. 2013 Feb;229(3):422-9. PMID: 23165508
26. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437
27. https://www.senhwabio.com//en/news/20220125