

Supplementary Material

- **Supplemental Table 1.** Gene list and NCBI reference sequence
- **Supplemental Table 2.** Frequency of multiple primary cancers by most frequent double pathogenic variant (DPV) combination matched to single PV controls
(Please see the separate Excel file posted online.)
- **Supplemental Table 3.** Clinical and tumor characteristics of females with DPVs with breast, ovarian and colorectal cancer compared to single PV controls
(Please see the separate Excel file posted online.)
- **Supplemental Table 4.** Female breast cancer (BC) and hormone receptor (HR) for individuals with DPVs by gene combination

Supplemental Table 1: Gene list and NCBI reference sequence

Gene	NCBI Reference Sequence	Gene	NCBI Reference Sequence
<i>AIP</i>	NM_003977.2	<i>NF2</i>	NM_000268.3
<i>ALK</i>	NM_004304.4	<i>PALB2</i>	NM_000268.3
<i>APC</i>	NM_000038.5	<i>PHOX2B</i>	NM_024675.3
<i>ATM</i>	NM_000051.3	<i>PMS2</i>	NM_000535.5
<i>BAP1</i>	NM_004656.2	<i>POLD1</i>	NM_002691.2
<i>BARD1</i>	NM_000465.2	<i>POLE</i>	NM_006231.2
<i>BLM</i>	NM_000057.2	<i>POT1</i>	NM_015450.2
<i>BMPR1A</i>	NM_004329.2	<i>PRKAR1A</i>	NM_002734.3
<i>BRCA1</i>	NM_007294.3	<i>PTCH1</i>	NM_000264.3
<i>BRCA2</i>	NM_000059.3	<i>PTEN</i>	NM_000314.4
<i>BRIP1</i>	NM_032043.2	<i>RAD50</i>	NM_005732.3
<i>CDH1</i>	NM_004360.3	<i>RAD51C</i>	NM_058216.1
<i>CDK4</i>	NM_000075.3	<i>RAD51D</i>	NM_002878.3
<i>CDKN1B</i>	NM_004064.3	<i>RB1</i>	NM_000321.2
<i>CDKN2A</i>	NM_000077.4 and NM_058195.3 (p14ARF)	<i>RET</i>	NM_020975.4
<i>CHEK2</i>	NM_007194.3	<i>SDHA</i>	NM_004168.2
<i>DICER1</i>	NM_007194.3	<i>SDHAF2</i>	NM_017841.2
<i>FANCC</i>	NM_177438.2	<i>SDHB</i>	NM_003000.2
<i>FH</i>	NM_000136.2	<i>SDHC</i>	NM_003001.3
<i>FLCN</i>	NM_000143.3	<i>SDHD</i>	NM_003002.2
<i>GALNT12</i>	NM_024642.4	<i>SMAD4</i>	NM_005359.5
<i>HOXB13</i>	NM_006361.5	<i>SMARCA4</i>	NM_001128849.1
<i>MAX</i>	NM_002382.3	<i>SMARCB1</i>	NM_003073.3
<i>MEN1</i>	NM_130799.2	<i>SMARCE1</i>	NM_002079.4
<i>MET</i>	NM_000245.1	<i>STK11</i>	NM_000455.4
<i>MITF</i>	NM_000248.3	<i>SUFU</i>	NM_016169.3
<i>MUTYH</i>	NM_001128425.1	<i>TMEM127</i>	NM_017849.3
<i>MRE11A</i>	NM_005591.3	<i>TP53</i>	NM_000546.4
<i>MLH1</i>	NM_000249.3	<i>TSC1</i>	NM_000368.4
<i>MSH2</i>	NM_000251.1	<i>TSC2</i>	NM_000548.
<i>MSH6</i>	NM_000179.2	<i>VHL</i>	NM_000551.3
<i>NBN</i>	NM_002485.4	<i>XRCC2</i>	NM_005431.1
<i>NF1</i>	NM_000267.3		

Supplemental Table 4: Female breast cancer (BC) and hormone receptor (HR) for individuals with DPVs by gene combination

Concurrent PVs	Total females	N of female BC (%)^a	ER/PR provided (%)^b	ER/PR-positive tumors (%)^c	HER2 Provided^b	HER2-positive tumors (%)^d
<i>ATM+BRCA2</i>	19	11 (57.9)	6 (54.5)	3 (50.0)	3 (27.3)	1 (33.3)
<i>ATM+CHEK2</i>	23	20 (87.0)	15 (75.0)	14 (93.3)	13 (65.0)	2 (15.4)
<i>BRCA1+CHEK2</i>	17	9 (52.9)	7 (77.7)	6 (85.7)	7 (77.7)	2 (28.6)
<i>CHEK2+CHEK2</i>	18	17 (94.4)	12 (70.6)	12 (100.0)	5 (29.4)	2 (40.0)
<i>CHEK2+PALB2</i>	18	17 (94.4)	15 (88.2)	14 (82.4)	11 (64.7)	0 (0)
<i>BRCA2+CHEK2</i>	15	10 (66.7)	7 (70.0)	6 (85.7)	6 (60.0)	1 (16.7)
<i>ATM+PALB2</i>	12	9 (75.0)	4 (44.4)	3 (75.0)	4 (44.4)	2 (50.0)
<i>ATM+BRCA1</i>	10	4 (40.0)	2 (50.0)	1 (50.0)	2 (50.0)	1 (50.0)
<i>BRCA1+BRCA2</i>	9	5 (55.6)	5 (100.0)	1 (20.0)	5 (100.0)	1 (20.0)

^aThe percentage represents those among females.

^bThe percentage represents those among all females with breast cancer.

^cThe percentage represents those among all females with breast cancer and ER/PR subtype data.

^dThe percentage represents those among all females with breast cancer and HER2 subtype data.

PV = pathogenic or likely pathogenic variant (single noun)

PVs = pathogenic or likely pathogenic variants (plural noun)

DPVs= double PVs in one individual (plural noun)

ER: Estrogen receptor

PR: Progesterone receptor

HER2: Human epidermal growth factor receptor 2