

## **SUPPLEMENTARY MATERIALS**

**Homologous recombination DNA repair defects in *PALB2*-associated breast cancers**

**Li et al.**

**Supplementary Methods**

**Supplementary Figures 1-6**

**Supplementary Tables 1-5**

## **SUPPLEMENTARY METHODS**

### **Massively parallel sequencing and bioinformatics analysis**

DNA samples derived from microdissected tumor and normal tissue were subjected to WES (n=14) or MSK-IMPACT<sup>1</sup> (n=8), which targets all exons and selected introns of 410 cancer genes. Reads were aligned to the reference human genome GRCh37 using the Burrows-Wheeler Aligner (BWA, v0.7.10).<sup>2</sup> Local realignment, duplicate removal and base quality recalibration were performed using the Genome Analysis Toolkit (GATK, v3.1.1).<sup>3</sup> *PALB2* and *BRCA1/2* germline variants were detected by HaplotypeCaller from GATK in the gvcf mode with default settings, and were retained if the germline variants were present in both normal and tumor samples.<sup>4</sup> Somatic single nucleotide variants (SNVs) were detected by MuTect (v1.0),<sup>5</sup> small insertions and deletions (indels) by Strelka (v2.0.15)<sup>6</sup>, VarScan 2 (v2.3.7)<sup>7</sup>, Lancet (v1.0.0)<sup>8</sup> and Scalpel (v0.5.3)<sup>9</sup>, and further curated by manual inspection. SNVs and indels located outside of the target regions were disregarded.<sup>10</sup> We excluded SNVs and indels for which the tumor mutant allele fraction (MAF) was <5 times that of the paired normal MAF, as well as SNVs and indels found at >5% global minor allele frequency of dbSNP (build 137) as previously described.<sup>10, 11</sup>

The cancer cell fraction (CCF) of each mutation was inferred using ABSOLUTE (v1.0.6)<sup>12</sup> and manually reviewed<sup>11-13</sup> A mutation was classified as clonal if its probability of being clonal was >50%<sup>13</sup> or if the lower bound of the 95% confidence interval of its CCF was >90%;<sup>11, 14</sup>. Somatic LOH of the *PALB2* germline mutations was classified as subclonal if the CCF was lower than the tumor purity (delta  $\geq 0.2$ ) as determined by FACETS,<sup>15</sup> as previously described.<sup>14</sup> We employed a combination of mutation function predictors<sup>16</sup> to infer whether a mutation was potentially pathogenic, as previously described.<sup>11</sup> Mutation hotspots were defined according to Chang et al.<sup>15</sup>

### **Comparisons with breast cancers from TCGA**

Comparisons of mutation burden, mutation frequencies, CNAs and genomic features indicative of HRD were conducted between the *PALB2*-associated breast cancers, non-*BRCA1/2/PALB2*-

associated breast cancers with matched ER and HER2 status (n=683), and *BRCA1*- (n=17) and *BRCA2*-associated (n=16) breast cancers with bi-allelic inactivation from TCGA<sup>17</sup>. The bi-allelic inactivation status of *BRCA1* and *BRCA2* was retrieved from Riaz et al.<sup>4</sup> TCGA breast cancers with available data to assess LST scores and numbers of somatic mutations adequate for mutational signature assessment were employed for comparative analyses of genomic features indicative of HRD. The recently updated publicly available MC3 dataset from the TCGA was obtained at <https://gdc.cancer.gov/about-data/publications/mc3-2017> and <https://gdac.broadinstitute.org> (01/28/2016).

### **Statistical analysis**

Comparisons of the tumor mutation burden, LST scores, gene-level copy number states and mutational signatures between *PALB2*-associated breast cancers and non-*BRCA1/2/PALB2*-, *BRCA1*- and *BRCA2*-associated breast cancers were performed using the Mann-Whitney *U* test and Fisher's exact test, respectively. To account for differences in sample sizes, a bootstrap resampling analysis was performed for the comparisons of mutation burden, mutation frequencies, gene-level copy number states, LSTs and mutational signatures between the *PALB2*-associated and TCGA non-*BRCA1/2/PALB2*-associated breast cancers at a 1:3 ratio. In brief, 3 non-*BRCA1/2/PALB2*-associated breast cancers were randomly selected for each *PALB2*-associated breast cancer, allowing for a given non-*BRCA1/2/PALB2*-associated sample to be included in the distinct random subsets. We iterated this process 100 times and two-tailed *P*-values were calculated using either Mann-Whitney *U* test or Fisher's exact test for each iteration, as appropriate. A bootstrapping-corrected *P*-value was determined as the mean *P*-value of all iterations for a given comparison. Two-tailed *P*-values < 0.05 were considered statistically significant. Statistical analyses were performed with R v3.1.2.

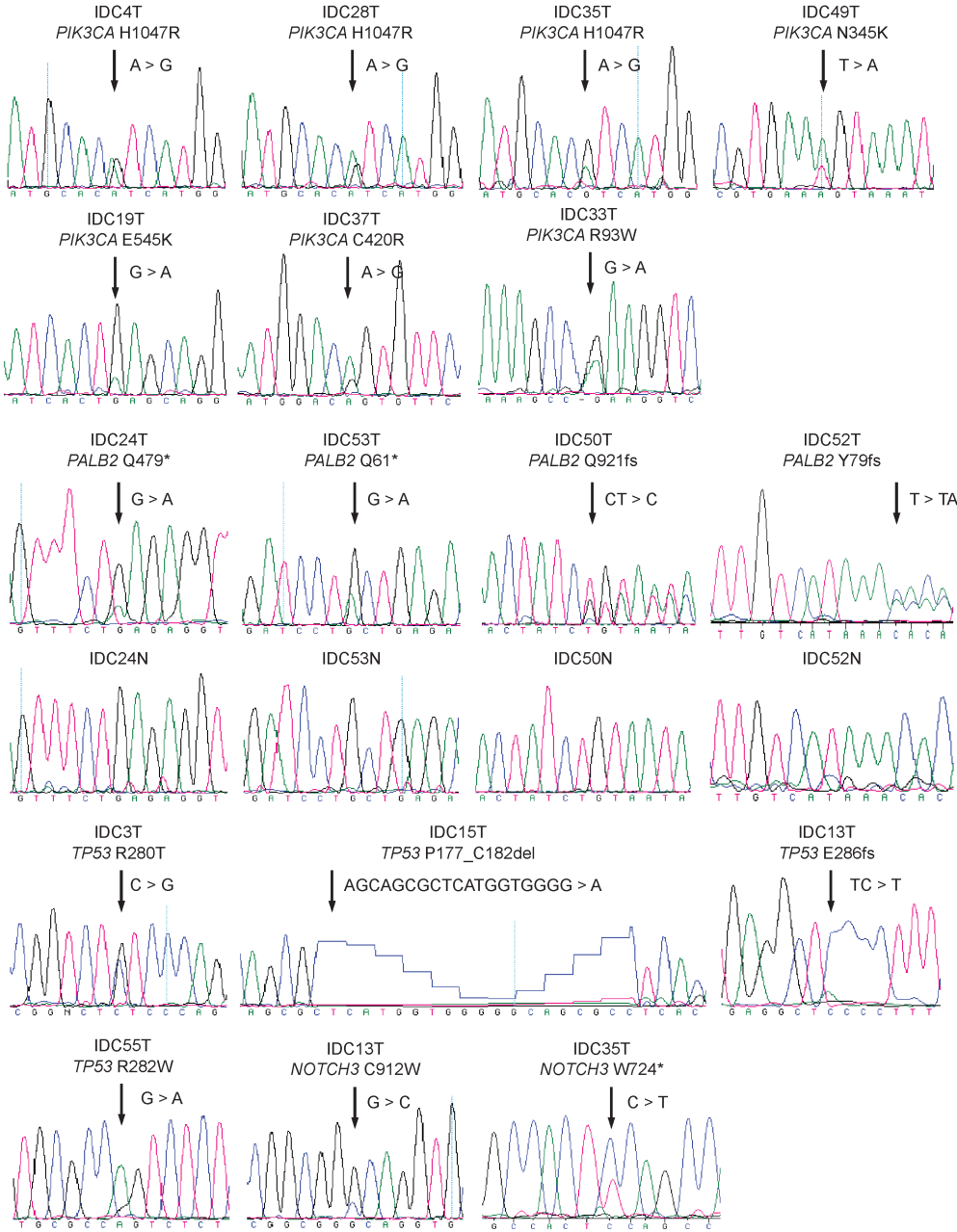
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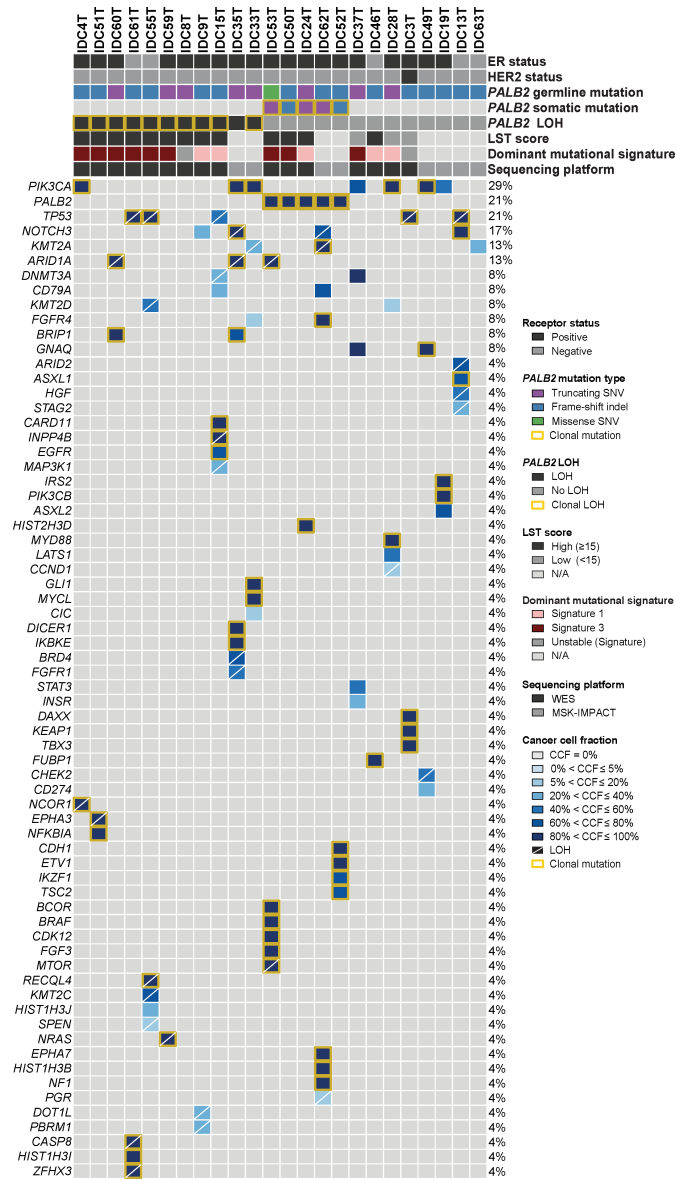
**Supplementary Figure 1**



**Supplementary Figure 1. Validation of *PIK3CA*, *TP53*, *PALB2* and *NOTCH3* somatic mutations using Sanger sequencing.**

Representative Sanger sequence electropherograms of *PIK3CA* (n=7), *TP53* (n=4) and *NOTCH3* (n=2) somatic mutations in index tumor samples, and somatic *PALB2* (n=4) mutations in both index tumor and matched normal samples. The presence of the mutation is indicated by a black arrow.

## Supplementary Figure 2

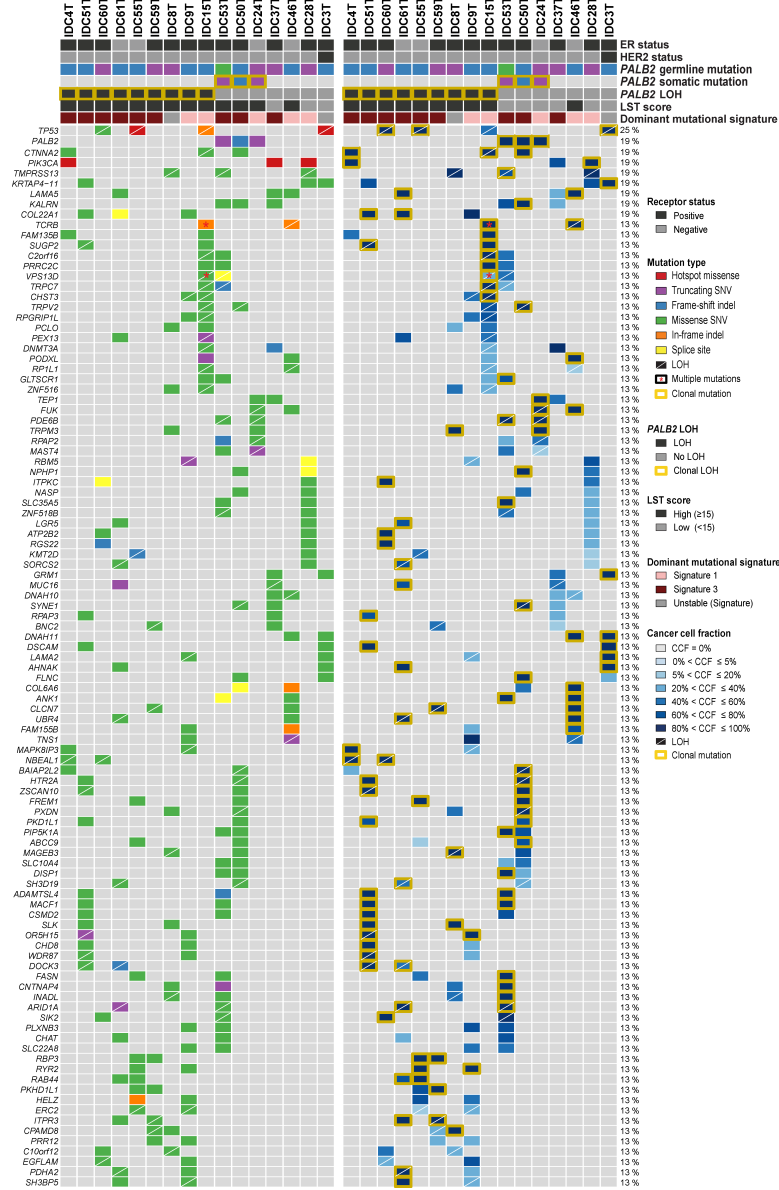


### Supplementary Figure 2. Cancer cell fractions of somatic mutations affecting 410 cancer genes in *PALB2*-associated breast cancers.

Cancer cell fractions (i.e. bioinformatically inferred percentage of cancer cells harboring a given somatic mutation) of non-synonymous somatic mutations affecting 410 cancer genes as defined by ABSOLUTE in the 24 *PALB2*-associated breast cancers sequenced by whole-exome (n=16) or MSK-IMPACT (n=8) sequencing. Immunohistochemical features, *PALB2* germline mutation type, presence of a second somatic *PALB2* mutation or loss of heterozygosity (LOH) of the *PALB2* wild-type allele, LST score, dominant mutational signature and sequencing platform are shown in the phenobar (top), color-coded according to the legend. Clonal somatic mutations or clonal LOH of the *PALB2* wild-type allele are indicated by a yellow box. Cancer cell fractions are color-coded according to the legend; the presence of LOH of the wild-type allele of mutated genes other than *PALB2* is represented by a diagonal bar. CCF, cancer cell fraction; indel, small insertion/deletion; LOH, loss of heterozygosity; LST, large-scale transition; N/A, not assessed; SNV, single nucleotide variant; WES, whole-exome sequencing.



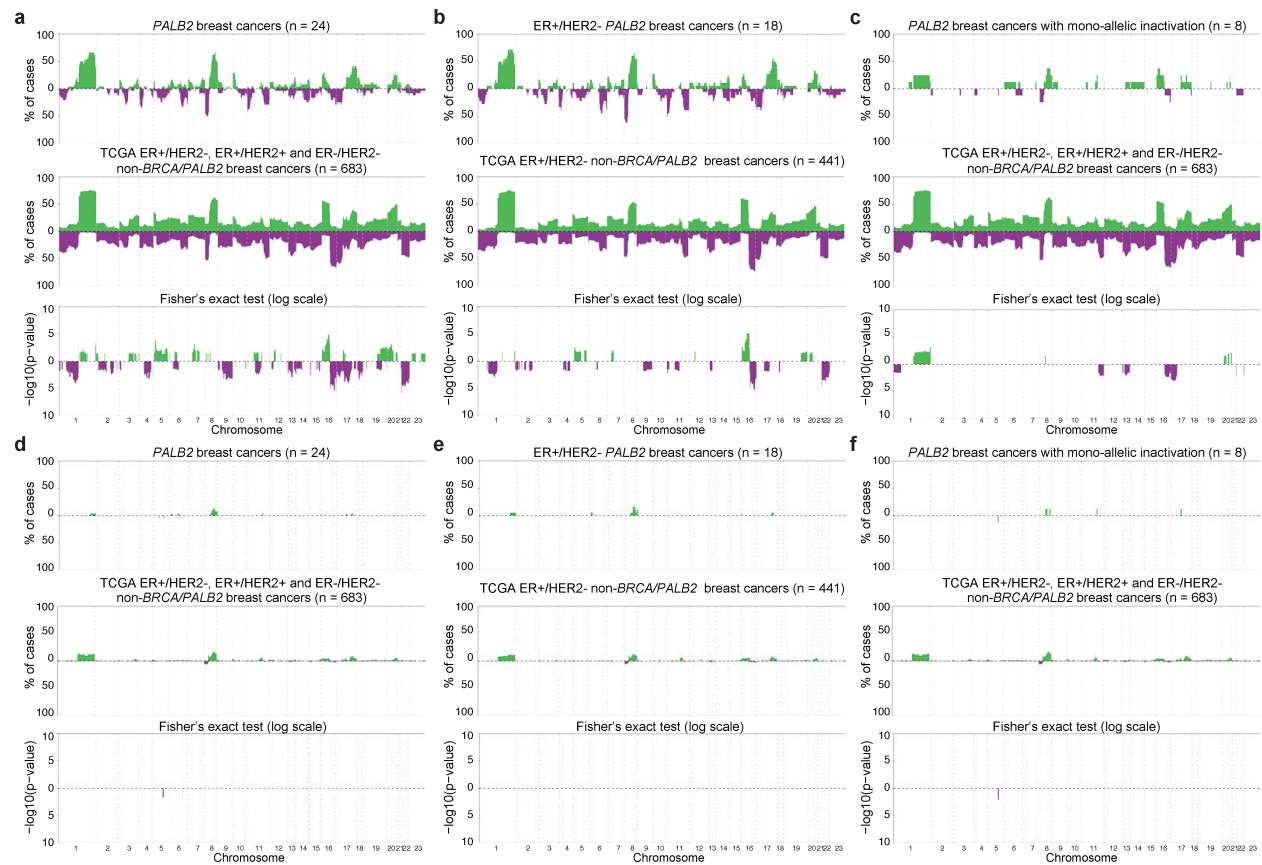
### Supplementary Figure 3



### Supplementary Figure 3. Repertoire of recurrent somatic mutations and corresponding cancer cell fractions in *PALB2*-associated breast cancer subjected to whole-exome sequencing.

Repertoire of recurrent ( $n \geq 2$ ) non-synonymous somatic mutations (left), and their corresponding cancer cell fraction (i.e. bioinformatically inferred percentage of cancer cells harboring a given somatic mutation; right) identified in the 16 *PALB2*-associated breast cancer profiled by whole-exome sequencing. Immunohistochemical features, *PALB2* germline mutation type, presence of a second somatic *PALB2* mutation or loss of heterozygosity (LOH) of the *PALB2* wild-type allele, LST score and dominant mutational signature are shown in the phenobar (top), color-coded according to the legend. Clonal somatic mutations or clonal LOH of the *PALB2* wild-type allele are indicated by a yellow box. The presence of multiple somatic mutations affecting the same gene is indicated by a red asterisk. CCF, cancer cell fraction; indel, small insertion/deletion; LOH, loss of heterozygosity; LST, large-scale state transition; SNV, single nucleotide variant.

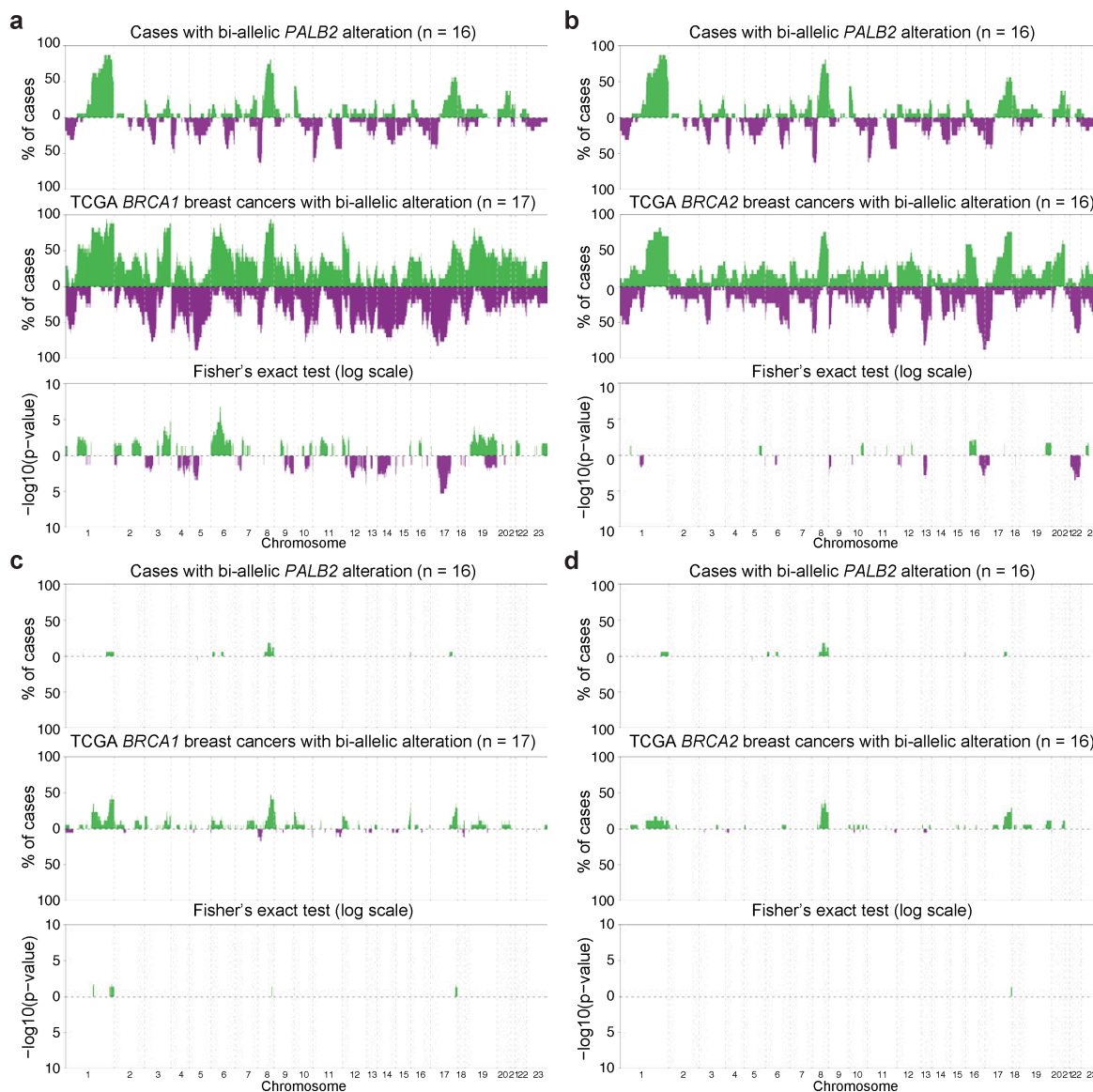
## Supplementary Figure 4



**Supplementary Figure 4. Comparisons of the frequencies of copy number alterations in *PALB2*-associated breast cancers and non-*BRCA1/2/PALB2* breast cancers from TCGA.**

Frequency plots and multi-Fisher's exact test comparisons of gains and losses (**a-c**), amplifications and homozygous deletions (**d-f**) were performed between (**a, d**) the 24 *PALB2*-associated breast cancers and 683 non-*BRCA1/2/PALB2*-associated breast cancers (ER+/HER2-, ER+/HER2+ and ER-/HER2-), (**b, e**) between the 18 ER+/HER2- *PALB2*-associated breast cancers and 441 ER+/HER2- non-*BRCA1/2/PALB2*-associated breast cancers, (**c, f**) between the eight *PALB2*-associated breast cancers with mono-allelic *PALB2* alterations and 683 non-*BRCA1/2/PALB2*-associated breast cancers (ER+/HER2-, ER+/HER2+ and ER-/HER2-) from TCGA. The frequency of gains/amplifications (green bars) or losses/homozygous deletions (purple bars) for each gene is plotted on the y-axis, according to their genomic position on the x-axis. Inverse Log<sub>10</sub> values of the Fisher's exact test *P*-values are plotted according to genomic location (x-axis).

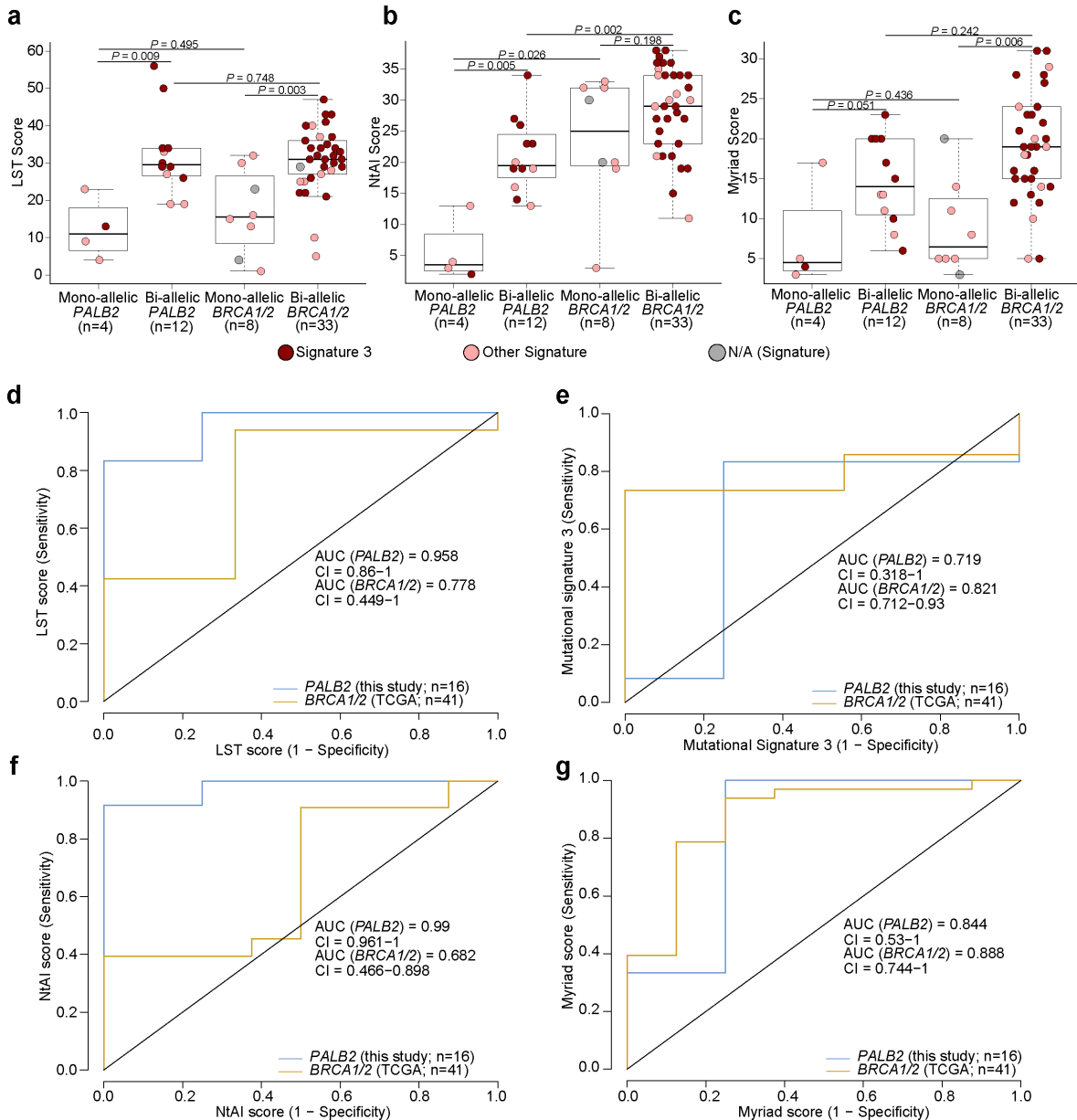
## Supplementary Figure 5



### Supplementary Figure 5. Comparisons of the frequencies of copy number gains and losses in *PALB2*-associated breast cancers with bi-allelic *PALB2* alterations and *BRCA1*- and *BRCA2*-associated breast cancers with bi-allelic alterations from TCGA.

(a-d) Frequency plots and multi-Fisher's exact test comparisons of copy number gains and losses between (a) the 16 *PALB2*-associated breast cancers with bi-allelic *PALB2* alterations and the 17 *BRCA1*-associated breast cancers with bi-allelic *BRCA1* alterations, and (b) the 16 *BRCA2*-associated breast cancers with bi-allelic *BRCA2* alterations from TCGA. (c-d) Frequency plots and multi-Fisher's exact test comparisons of high-level gains/amplifications and homozygous deletions between (c) the 16 *PALB2*-associated breast cancers with bi-allelic *PALB2* alterations and the 17 *BRCA1*-associated breast cancers with bi-allelic *BRCA1* alterations, and (d) the 16 *BRCA2*-associated breast cancers with bi-allelic *BRCA2* alterations. The frequency of gains/amplifications (green bars) or losses/homozygous deletions (purple bars) for each gene is plotted on the y-axis, according to their genomic position on the x-axis. Inverse  $\text{Log}_{10}$  values of the Fisher's exact test *P*-values are plotted according to genomic location (x-axis).

## Supplementary Figure 6



### Supplementary Figure 6. Comparisons of measurements of homologous recombination deficiency in *PALB2*-associated breast cancers and *BRCA1/2*-associated breast cancers with mono-allelic and bi-allelic *PALB2* or *BRCA1/2* inactivation.

(a-c) Comparisons of (a) Large-scale transition (LST) score, (b) NtAI scores and (c) Myriad scores of the four *PALB2*-associated breast cancers with mono-allelic *PALB2* alterations, the 12 *PALB2*-associated breast cancers with bi-allelic *PALB2* alterations, the eight *BRCA1/2*-associated breast cancers with mono-allelic *BRCA1* or *BRCA2* alterations and the 33 *BRCA1/2*-associated breast cancers with bi-allelic *BRCA1* or *BRCA2* alterations. (d-g) Receiver operating characteristic (ROC) curves comparing performance of (d) LST scores, (e) mutational signature 3 (%), (f) NtAI scores and (g) Myriad scores in *PALB2*-associated breast cancers and *BRCA1/2*-associated breast cancers for the identification of *PALB2* and *BRCA1/2* bi-allelic inactivation. AUC, area under the ROC curve; CI, confidence interval.

**Supplementary Table 1. Sequencing statistics of tumor and paired normal samples of *PALB2*-associated breast cancers sequenced by whole-exome or MSK-IMPACT targeted massively parallel sequencing.**

Case ID	Sequencing type	Target Territory	Total Reads	Percent Selected Bases	Mean Target Coverage	Percent Target Bases 2X	Percent Target Bases 10X	Percent Target Bases 20X	Percent Target Bases 30X	Percent Target Bases 40X	Percent Target Bases 50X	Percent Target Bases 100X
IDC13N	MSK-IMPACT	1362579	17,587,599	67.86%	316	99.50%	99.25%	99.04%	98.79%	98.49%	98.04%	92.95%
IDC13T	MSK-IMPACT	1362579	21,890,639	54.60%	128	98.95%	98.25%	97.65%	96.58%	94.91%	92.47%	65.62%
IDC19N	MSK-IMPACT	1362579	104,539,241	75.41%	789	99.53%	99.43%	99.35%	99.28%	99.19%	99.12%	98.77%
IDC19T	MSK-IMPACT	1362579	38,378,568	51.96%	227	99.25%	98.77%	98.34%	97.75%	96.73%	95.05%	78.22%
IDC33N	MSK-IMPACT	1522367	22,171,814	84.58%	585	99.46%	99.34%	99.23%	99.12%	98.98%	98.83%	97.67%
IDC33T	MSK-IMPACT	1522367	15,369,766	82.02%	324	99.16%	98.76%	98.50%	98.29%	98.04%	97.66%	93.05%
IDC35N	MSK-IMPACT	1362579	14,260,504	67.93%	172	99.19%	98.58%	96.96%	93.67%	89.14%	83.72%	53.91%
IDC35T	MSK-IMPACT	1362579	6,712,966	55.84%	124	99.02%	97.84%	94.32%	88.10%	80.93%	73.46%	42.67%
IDC49N	MSK-IMPACT	1362579	54,791,577	77.98%	1452	99.51%	99.45%	99.40%	99.35%	99.31%	99.25%	99.02%
IDC49T	MSK-IMPACT	1362579	36,941,697	62.09%	236	98.87%	98.26%	97.89%	97.39%	96.65%	95.65%	87.28%
IDC52N	MSK-IMPACT	1362579	30,113,913	68.94%	572	99.53%	99.44%	99.33%	99.21%	99.11%	99.00%	97.77%
IDC52T	MSK-IMPACT	1362579	9,519,069	62.84%	73	98.35%	93.74%	83.48%	71.71%	60.98%	51.78%	24.03%
IDC62N	MSK-IMPACT	1522367	15,173,050	84.93%	502	99.42%	99.15%	98.95%	98.75%	98.55%	98.35%	97.58%
IDC62T	MSK-IMPACT	1522367	32,271,761	84.50%	904	99.46%	99.30%	99.16%	99.06%	98.96%	98.86%	98.41%
IDC63N	MSK-IMPACT	1522367	15,767,985	89.13%	518	99.46%	99.26%	99.09%	98.96%	98.82%	98.65%	97.89%
IDC63T	MSK-IMPACT	1522367	21,077,959	89.66%	678	99.28%	99.05%	98.85%	98.67%	98.53%	98.40%	97.72%
IDC15N	Whole exome	51542852	133,574,121	85.80%	146	93.49%	91.44%	89.75%	87.45%	84.53%	81.20%	60.98%
IDC15T	Whole exome	51542852	67,920,645	81.58%	40	87.47%	74.55%	61.01%	47.91%	36.45%	27.26%	6.62%
IDC24N	Whole exome	51542852	75,039,053	85.83%	88	91.64%	85.64%	79.57%	73.71%	67.56%	60.98%	30.49%
IDC24T	Whole exome	51542852	109,782,207	87.43%	130	92.15%	87.81%	83.63%	79.78%	76.02%	72.20%	50.30%
IDC28N	Whole exome	51542852	88,885,131	89.73%	106	92.14%	88.21%	83.49%	78.94%	74.43%	69.75%	43.19%
IDC28T	Whole exome	51542852	100,553,535	87.98%	105	91.69%	86.60%	81.46%	76.63%	71.71%	66.44%	38.35%
IDC37N	Whole exome	51189318	233,784,412	82.85%	247	99.67%	99.28%	98.92%	98.52%	97.98%	97.22%	88.66%
IDC37T	Whole exome	51189318	250,533,924	78.34%	268	99.79%	99.57%	99.24%	98.70%	97.80%	96.52%	85.10%
IDC3N	Whole exome	51542852	86,590,460	82.29%	85	92.30%	86.29%	77.82%	68.33%	58.12%	48.31%	21.15%
IDC3T	Whole exome	51542852	110,163,811	90.09%	136	92.18%	88.46%	84.66%	81.29%	78.07%	74.87%	57.27%
IDC46N	Whole exome	51542852	139,890,230	83.78%	155	93.59%	91.31%	89.46%	86.99%	84.05%	80.79%	61.75%
IDC46T	Whole exome	51542852	44,683,165	88.43%	33	85.88%	70.18%	52.42%	37.15%	26.07%	18.72%	5.14%
IDC4N	Whole exome	51542852	107,232,015	85.31%	122	93.31%	91.13%	88.67%	85.40%	81.61%	77.58%	54.44%
IDC4T	Whole exome	51542852	114,347,035	89.63%	139	92.32%	88.89%	85.18%	81.81%	78.57%	75.34%	57.72%
IDC50N	Whole exome	51542852	123,171,969	85.09%	136	93.25%	90.97%	88.94%	86.21%	82.96%	79.38%	58.75%
IDC50T	Whole exome	51542852	72,671,924	84.91%	77	91.18%	83.69%	75.58%	67.74%	60.03%	52.73%	26.06%
IDC51N	Whole exome	51542852	112,888,954	81.16%	118	93.54%	90.84%	88.22%	84.66%	80.34%	75.45%	48.79%
IDC51T	Whole exome	51542852	66,148,714	87.59%	70	90.09%	81.77%	73.48%	64.98%	56.15%	47.52%	19.19%
IDC53N	Whole exome	51542852	186,199,465	84.58%	193	93.87%	91.33%	89.56%	87.52%	85.14%	82.40%	66.03%
IDC53T	Whole exome	51542852	68,290,444	80.92%	69	91.90%	85.02%	75.96%	66.47%	57.10%	48.43%	20.94%
IDC55N	Whole exome	51189318	165,293,498	62.27%	139	99.69%	99.17%	98.38%	96.97%	94.63%	91.24%	64.21%
IDC55T	Whole exome	51189318	267,310,420	81.28%	289	99.77%	99.53%	99.18%	98.69%	97.94%	96.88%	87.42%
IDC59N	Whole exome	51189318	185,081,923	84.63%	173	99.80%	99.49%	98.86%	97.81%	96.22%	94.06%	75.86%
IDC59T	Whole exome	51189318	175,236,053	91.76%	213	99.80%	99.51%	99.00%	98.20%	97.04%	95.45%	81.82%
IDC60N	Whole exome	51189318	73,994,558	65.70%	46	96.57%	91.44%	81.89%	68.30%	52.88%	38.47%	4.96%
IDC60T	Whole exome	51189318	89,242,346	57.28%	46	96.68%	92.05%	83.10%	69.18%	52.84%	37.56%	4.33%
IDC61N	Whole exome	51189318	152,388,926	57.82%	86	94.27%	86.65%	81.91%	76.44%	70.40%	64.04%	33.92%
IDC61T	Whole exome	51189318	143,124,548	50.78%	77	94.81%	85.35%	78.76%	71.65%	64.33%	57.05%	27.50%
IDC8N	Whole exome	51542852	101,656,174	86.68%	121	93.09%	90.79%	87.94%	84.45%	80.75%	76.96%	55.65%
IDC8T	Whole exome	51542852	124,287,664	89.61%	151	92.46%	89.37%	86.03%	83.02%	80.17%	77.37%	62.44%
IDC9N	Whole exome	51542852	122,188,395	85.89%	142	93.35%	91.31%	89.22%	86.56%	83.52%	80.31%	62.76%
IDC9T	Whole exome	51542852	107,445,459	86.92%	119	91.72%	86.91%	82.76%	79.16%	75.63%	72.00%	51.24%

**Supplementary Table 2. Clonal and subclonal variants, variant allele fraction range and tumor purity of the *PALB2*-associated breast cancers in this study**

Sample ID	# Clonal Variants	# Subclonal Variants	# Total Variants	VAF Min	VAF Max	Purity	<i>PALB2</i> Status
IDC13T	3	3	6	6.38%	29.63%	0.47	Monoallelic
IDC15T	73	82	155	4.17%	75%	0.76	Biallelic
IDC19T	2	2	4	10.48%	26.09%	0.47	Monoallelic
IDC24T	32	22	54	4.94%	38.46%	0.43	Biallelic
IDC28T	9	58	67	4.11%	23.33%	0.52	Monoallelic
IDC33T	3	3	6	4.64%	40.93%	0.71	Biallelic
IDC35T	6	2	8	17.02%	64.52%	0.25	Biallelic
IDC37T	9	70	79	2.92%	23.08%	0.41	Monoallelic
IDC3T	27	10	37	3.45%	43.71%	0.45	Monoallelic
IDC46T	55	18	73	5.75%	77.65%	0.69	Monoallelic
IDC49T	2	2	4	5.71%	35%	0.51	Monoallelic
IDC4T	41	35	76	3.55%	76.09%	0.68	Biallelic
IDC50T	110	37	147	3.07%	81.82%	0.7	Biallelic
IDC51T	109	22	131	5.68%	64.71%	0.55	Biallelic
IDC52T	5	0	5	14.29%	41.94%	0.56	Biallelic
IDC53T	124	71	195	3.28%	67.57%	0.55	Biallelic
IDC55T	65	40	105	2.84%	73.51%	0.79	Biallelic
IDC59T	33	39	72	3.72%	77.78%	0.68	Biallelic
IDC60T	64	39	103	4.96%	47.69%	0.44	Biallelic
IDC61T	47	39	86	2.84%	86.67%	0.68	Biallelic
IDC62T	7	3	10	3.41%	53.45%	0.67	Biallelic
IDC63T	0	1	1	6.99%	6.99%	0.3	Monoallelic
IDC8T	15	26	41	5.14%	40%	0.4	Biallelic
IDC9T	25	136	161	3.55%	83.33%	0.6	Biallelic

VAF, variant allele fraction



















**Supplementary Table 4. Clinicopathologic characteristics of the *PALB2*-associated breast cancers according to bi-allelic inactivation of the *PALB2* wild-type allele.**

	All cases		Bi-allelic <i>PALB2</i> alterations		Mono-allelic <i>PALB2</i> alterations		P value
	No.	Percentage	No.	Percentage	No.	Percentage	
<b>Study</b>							
Li et al.	24	62%	16	62%	8	62%	
Lee et al.	15	38%	10	38%	5	38%	
<b>Age (years)</b>							
<50	21	54%	11	42%	10	77%	0.051
≥50	18	46%	15	58%	3	23%	
<b>Receptor status</b>							
ER+/HER2-	21	54%	16	62%	5	38%	0.383
ER+/HER2+	5	13%	3	12%	2	15%	
ER-/HER2-	13	33%	7	27%	6	46%	
<b>Histologic grade</b>							
I/II	13	33%	8	31%	5	38%	0.725
III	26	67%	18	69%	8	62%	
<b>Germline mutation type</b>							
Frameshift	22	56%	12	46%	10	77%	0.175
Truncating	16	41%	13	50%	3	23%	
Missense	1	3%	1	4%	0	0%	
<b><i>TP53</i> gene</b>							
Mutant	10	26%	5	19%	5	38%	0.254
Wild-type	29	74%	21	81%	8	62%	
<b>LSTs*<sup>1</sup></b>							
High	27	87%	22	100	5	62.5	0.004
Low	4	13%	0	0	4	37.5	

Abbreviations: Age, age at diagnosis; ER, estrogen receptor; LST, large-scale state transition; \*, LST high, ≥15; LST low, <15; No., number of cases.

<sup>1</sup>LSTs were investigated in 16 *PALB2*-associated breast cancers from this study and 15 *PALB2* breast cancers from Lee et al, J Pathol 2018.





Supplementary Table 5  
Page 2

FBXW7	0	0%	14	2.0%	1	0.90	0	0%	6	1.4%	1	0.99	0	0%	2	11.8%	0.48	0	0%	0	0%	1	
FGF19	0	0%	0	0%	1	0	0	0%	0	0%	1	1	1	0	0%	0	0%	1	0	0%	0	0%	1
FGF3	1	4.2%	0	0%	0.07	0.27	1	5.6%	0	0%	0.27	1	1	6.2%	0	0%	0.48	0	0%	1	6.2%	0	
FGF4	0	0%	0	0%	0	0	0	0%	0	0%	0	0	0	0	0%	0	0	0	0	0	0	0	
FGFR1	1	4.2%	5	0.7%	0.19	0.38	1	5.6%	5	1.1%	0.21	0.39	1	6.2%	1	5.9%	1	1	6.2%	0	0%	1	
FGFR2	0	0%	12	1.8%	1	0.96	0	0%	8	1.8%	1	0.97	0	0%	1	5.9%	1	0	0%	0	0%	1	
FGFR3	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	0	0	0%	0	0%	1	
FGFR4	2	8.3%	4	0.6%	0.02	0.11	2	11.1%	2	0.5%	0.008	0.08	2	12.5%	0	0%	0.23	2	12.5%	0	0%	0.48	
FH	0	0%	3	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	0	0	0%	0	0%	1	
FLCN	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
FLT1	0	0%	6	0.9%	1	1	0	0%	0	0%	1	1	0	0%	1	5.9%	1	0	0%	0	0%	1	
FLT3	0	0%	5	0.7%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
FLT4	0	0%	1	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
FOXA1	0	0%	22	3.2%	1	0.86	1	0%	18	4.1%	1	0.83	0	0%	0	0%	0	1	0	0%	0%	1	
FOXO2	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
FOXO1	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
FOXP1	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
FUBP1	1	4.2%	4	0.6%	0.16	0.35	0	0%	2	0.5%	1	0.31	0	0%	0	0%	0	1	0	0%	0%	1	
FYW	0	0%	2	0%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
GATA1	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
GATA2	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
GATA3	0	0%	89	13.0%	0.06	0.15	0	0%	70	15.9%	0.09	0.22	0	0%	0	0%	0	1	0	0%	2	12.5%	0.48
GLI1	1	4.2%	4	0.6%	0.16	0.35	1	5.6%	3	0.7%	0.15	0.34	1	6.2%	0	0%	0.48	1	6.2%	0	0%	0	
GNA11	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
GNAQ	2	8.3%	2	0%	0.006	0.08	2	11.1%	1	0.2%	0.004	0.07	0	0%	0	0%	1	0	0%	0	0%	1	
GNAS	0	0%	11	1.6%	1	0.97	0	0%	10	2.3%	1	0.96	0	0%	0	0%	1	0	0%	0	0%	1	
GPS2	0	0%	8	1.2%	1	0.99	0	0%	6	1.4%	1	0.99	0	0%	0	0%	1	0	0%	0	0%	1	
GREM1	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
GRIN2A	0	0%	17	2.5%	1	0.91	0	0%	12	2.7%	1	0.95	0	0%	0	0%	0	1	0	0%	0%	1	
GSK3B	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
H3F3A	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
H3F3B	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
H3F3C	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
HGF	1	4.2%	4	0.6%	0.16	0.35	0	0%	1	0.2%	1	0.33	0	0%	0	0%	0	1	0	0%	0%	1	
HIST1H1C	0	0%	5	0.7%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
HIST1H2B	0	0%	2	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
HIST1H3A	0	0%	1	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
HIST1H3B	1	4.2%	11	1.6%	0.34	0.56	1	5.6%	5	1.1%	0.21	0.40	1	6.2%	0	0%	0.48	1	6.2%	0	0%	1	
HIST1H3C	0	0%	2	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
HIST1H3D	0	0%	2	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
HIST1H3E	0	0%	1	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
HIST1H3F	0	0%	4	0.6%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
HIST1H3G	0	0%	4	0.6%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
HIST1H3H	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
HIST1H3I	1	4.2%	1	0%	0.07	0.27	0	0%	0	0%	1	0.25	1	6.2%	0	0%	0.48	1	6.2%	0	0%	1	
HIST1H3J	1	4.2%	1	0%	0.07	0.27	0	0%	1	0.2%	1	0.27	1	6.2%	0	0%	0.48	1	6.2%	0	0%	1	
HIST2H3C	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
HIST2H3D	1	4.2%	3	0%	0.13	0.33	1	5.6%	2	0.5%	0.11	0.30	1	6.2%	1	5.9%	1	1	6.2%	0	0%	1	
HIST2H3E	0	0%	3	0%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
HNF1A	0	0%	3	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
HOXB13	0	0%	2	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
HRAS	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
ICOSLG	0	0%	2	0%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
ID3	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	0	1	0	0%	0%	1	
IDH1	0	0%	2	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	6.2%	1	
IDH2	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
IFNGR1	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
IGF1	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
IGF1R	0	0%	8	1.2%	1	0.99	0	0%	5	1.1%	1	0.98	0	0%	0	0%	0	1	0	0%	0%	1	
IGF2	0	0%	1	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
IKBKE	1	4.2%	3	0%	0.13	0.30	1	5.6%	1	0.2%	0.08	0.28	1	6.2%	0	0%	0.48	1	6.2%	1	6.2%	1	
IKZF1	1	4.2%	3	0%	0.13	0.34	1	5.6%	1	0.2%	0.08	0.27	1	6.2%	1	5.9%	1	1	6.2%	0	0%	1	
IL10	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
IL7R	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
INH1A	0	0%	3	0%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
INH1B	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
INPP4A	0	0%	6	0.9%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
INPP4B	1	4.2%	6	0.9%	0.22	0.43	1	5.6%	6	1.4%	0.25	0.41	1	6.2%	1	5.9%	1	1	6.2%	0	0%	1	
INSR	1	4.2%	10	1.5%	0.32	0.57	1	5.6%	5	1.1%	0.21	0.40	0	0%	0	0%	0.48	5	11.1%	0	0%	1	
IRF4	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
IRS1	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
IRS2	1	4.2%	0	0%	0.03	0.25	1	5.6%	0	0%	0.04	0.25	0	0%	0	0%	0	1	0	0%	0%	1	
JAK1	0	0%	10	1.5%	1	0.96	0	0%	8	1.8%	1	0.98	0	0%	0	0%	1	0	0%	0	0%	1	
JAK2	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
JAK3	0	0%	10	1.5%	1	0.96	0	0%	6	1.4%	1	0.99	0	0%	0	0%	1	0	0%	0	0%	1	
JUN	0	0%	3	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
KDMSA	0	0%	8	1.2%	1	0.97	0	0%	4	0.9%	1	1	0	0%	1	5.9%	1	0	0%	0	0%	1	
KDMSC	0	0%	7	1.0%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
KDMSA	0	0%	15	2.2%	1	0.99	0	0%	10	2.3%	0.99	0.95	0	0%	0	0%	1	5.9%	1	0	0%	1	
KDR	0	0%	7	1.0%	1	0.98	0	0%	5	1.1%	1	1	0	0%	0	0%	1	0	0%	0	0%	1	
KEAP1	1	4.2%	2	0%	0.10	0.30	0																

NTRK2	0	0%	5	0.7%	1	0.99	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	1	6.2%	1
NTRK3	0	0%	8	1.2%	1	0.98	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
NUPB3	0	0%	3	0.4%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PAK1	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PAK7	0	0%	5	0.7%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PALB2	5	20.8%	4	0.6%	0.000003	0.002	5	27.8%	1	0.2%	0.000003	0.001	5	31.2%	0	0%	0.02	5	31.2%	0	0%	0.04
PARK2	0	0%	5	0.7%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PARRP1	0	0%	5	0.7%	1	1	0	0%	2	0.5%	1	1	0	0%	1	5.9%	1	0	0%	1	0%	1
PAX5	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PBRM1	1	4.2%	8	1.2%	0.27	0.48	1	5.6%	4	0.9%	0.18	0.36	1	6.2%	1	5.9%	1	1	6.2%	0	0%	1
PCCD1	0	0%	3	0%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PDGFRA	0	0%	5	0.7%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	1	6.2%	1
PDGFRA	0	0%	7	1.0%	1	0.99	0	0%	7	1.6%	1	0.98	0	0%	0	0%	1	0	0%	1	0%	1
PGR1	0	0%	2	0%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PGR	1	4.2%	4	0.6%	0.16	0.35	1	5.6%	3	0.7%	0.15	0.32	1	6.2%	0	0%	0.48	1	6.2%	0	0%	1
PHOX2B	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PIK3C2G	0	0%	8	1.2%	1	0.97	0	0%	4	0.9%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PIK3G3	0	0%	5	0.7%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PIK3G4	7	29.2%	246	36.0%	0.67	0.77	7	39.9%	187	42.4%	0.81	0.81	3	18.8%	0	0%	0.10	3	18.8%	0	0%	0.60
PIK3CB	1	4.2%	7	1.0%	0.24	0.43	1	5.6%	5	1.1%	0.21	0.44	0	0%	1	5.9%	1	0	0%	1	0%	1
PIK3CD	0	0%	3	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PIK3CG	0	0%	5	0.7%	1	0.99	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PIK3R1	0	0%	21	3.1%	1	0.82	0	0%	14	3.2%	1	0.89	0	0%	2	11.8%	0.48	0	0%	0%	0%	1
PIK3R2	0	0%	3	0%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PIK3R3	0	0%	4	0.6%	1	1	0	0%	4	0.9%	1	1	0	0%	1	5.9%	1	0	0%	1	0%	1
PIM1	0	0%	1	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PLCG2	0	0%	5	0.7%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	6.2%	1
PLK2	0	0%	8	1.2%	1	0.98	0	0%	5	1.1%	1	1	0	0%	0	0%	1	0	0%	1	6.2%	1
PMAIP1	0	0%	8	1.2%	1	0.98	0	0%	4	0.9%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PMS1	0	0%	8	1.2%	1	0.98	0	0%	4	0.9%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PMS2	0	0%	5	0.7%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PNRC1	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
POLD1	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
POLK	0	0%	10	1.5%	1	0.99	0	0%	6	0.9%	1	0.97	0	0%	0	0%	1	0	0%	1	6.2%	1
PPM1D	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PPP2R1A	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PPP6C	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PRDM11	0	0%	10	1.5%	1	0.95	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PRKAR1A	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PTCH1	0	0%	7	1.0%	1	0.98	0	0%	4	0.9%	1	1	0	0%	2	11.8%	0.48	0	0%	0%	0%	1
PTEN	0	0%	42	6.1%	0.39	0.49	0	0%	26	5.9%	0.61	0.68	0	0%	3	17.6%	0.23	0	0%	1	6.2%	1
PTPN11	0	0%	2	0%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PTPRD	0	0%	19	2.8%	1	0.82	0	0%	12	2.7%	1	0.96	0	0%	1	5.9%	1	0	0%	1	0%	1
PTPRG5	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
PTPR	0	0%	7	1.0%	1	0.99	0	0%	5	1.1%	1	0.99	0	0%	0	0%	1	0	0%	1	0%	1
RAB35	0	0%	2	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RAC1	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RAD21	0	0%	7	1.0%	1	0.98	0	0%	4	0.9%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RAD50	0	0%	7	1.0%	1	0.99	0	0%	5	1.1%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RAD51	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RAD51B	0	0%	3	0%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RAD51C	0	0%	3	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	2	12.5%	0.48
RAD51D	0	0%	1	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RAD52	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RAD54L	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RAF1	0	0%	5	0.7%	1	1	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RARA	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RASA1	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RBBP1	0	0%	16	2.3%	1	0.99	0	0%	6	0.9%	1	0.99	0	0%	0	0%	1	0	0%	3	18.8%	0.23
RBM10	0	0%	6	0.9%	1	0.98	0	0%	4	0.9%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RECQL4	1	4.2%	3	0%	0.13	0.32	0	0%	2	0.5%	1	0.30	1	6.2%	1	5.9%	1	1	6.2%	0	0%	1
REL	0	0%	1	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RET	0	0%	6	0.9%	1	1	0	0%	5	1.1%	1	1	0	0%	1	5.9%	1	0	0%	1	0%	1
RHBD2	0	0%	3	0%	1	1	0	0%	1	0.2%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RHEB	0	0%	1	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RHOA	0	0%	6	0.9%	1	0.99	0	0%	5	1.1%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RICTOR	0	0%	6	0.9%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RIT1	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	1	5.9%	1	0	0%	1	0%	1
RNF43	0	0%	9	1.3%	1	0.98	0	0%	3	0.7%	1	1	0	0%	0	0%	1	0	0%	1	6.2%	1
RGS1	0	0%	14	2.0%	1	0.92	0	0%	11	2.5%	1	0.94	0	0%	2	11.8%	0.48	0	0%	0%	0%	1
RPS6K4	0	0%	4	0.6%	1	1	0	0%	4	0.9%	1	0.99	0	0%	0	0%	1	0	0%	1	0%	1
RPS6KB2	0	0%	4	0.6%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
RPTOR	0	0%	13	1.9%	1	0.94	0	0%	5	1.1%	1	0.61	0	0%	1	5.9%	1	0	0%	1	0%	1
RUNX1	0	0%	33	4.8%	0.82	0.83	0	0%	25	5.7%	0.61	0.69	0	0%	0	0%	1	0	0%	3	18.8%	0.23
RYPB	0	0%	3	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
SDHA	0	0%	3	0%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
SDHAF2	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
SDHB	0	0%	2	0%	1	1	0	0%	2	0.5%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
SDHC	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
SDHD	0	0%	0	0%	1	1	0	0%	0	0%	1	1	0	0%	0	0%	1	0	0%	1	0%	1
SETD2	0	0%	17	2.5%	1	0.89	0	0%	11	2.5%	1	0.96	0	0%</								