

## Supplementary Information

### Phosphoglycerate dehydrogenase diverts glycolytic flux and contributes to oncogenesis

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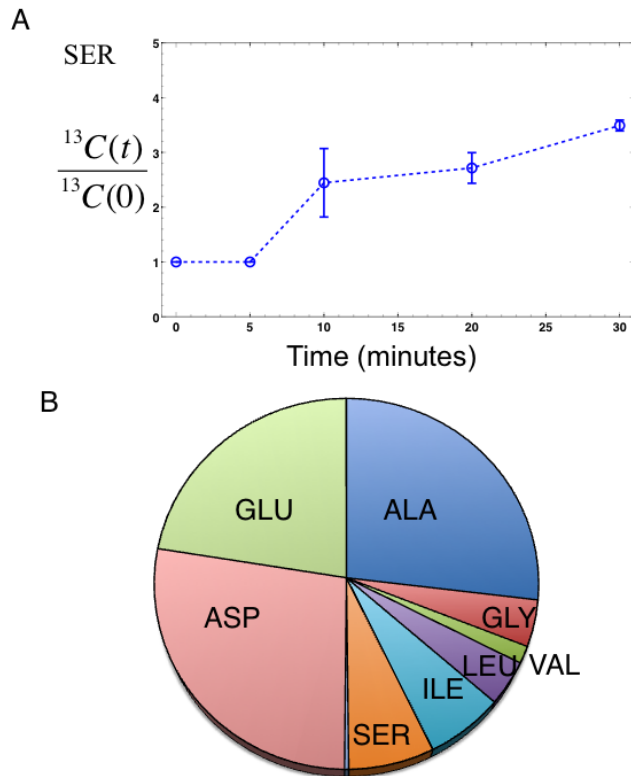
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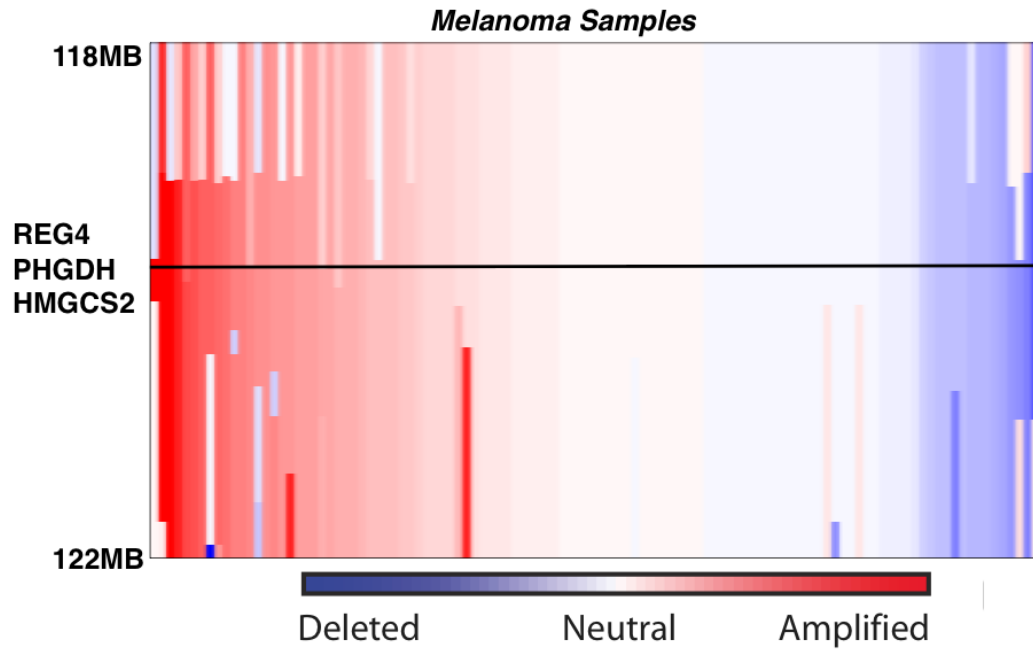
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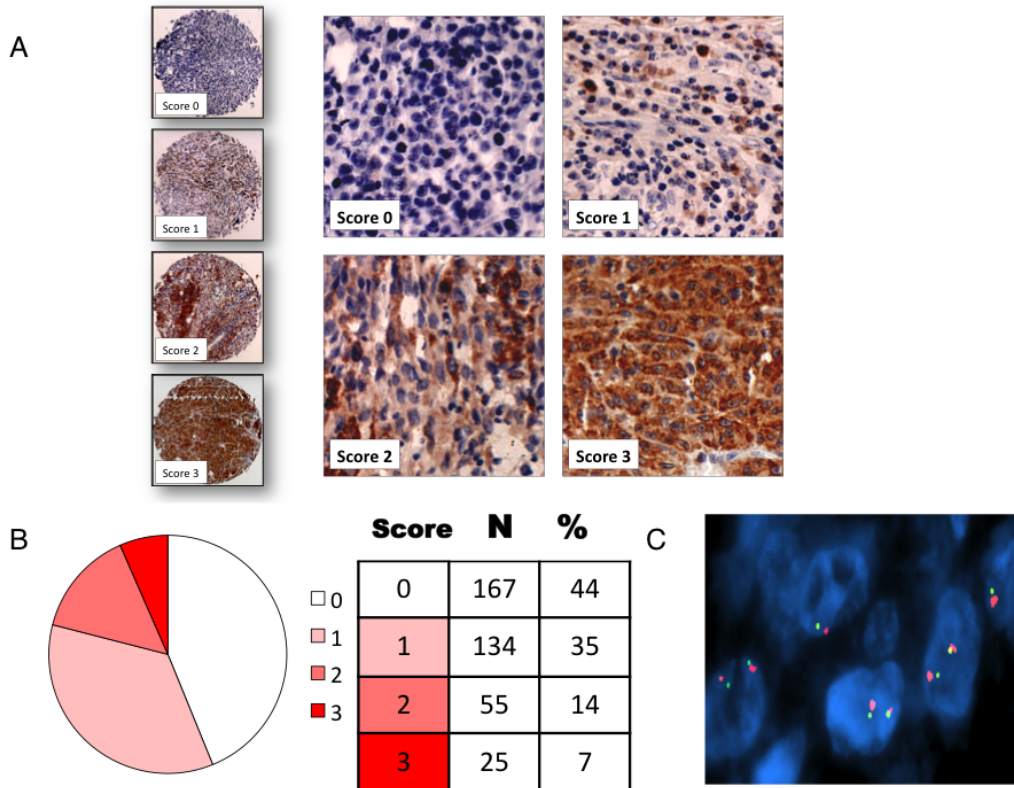
**Supplementary Figure 1 - Time course of glucose flux into de novo serine biosynthesis**

- a.) Labeling of [U-<sup>13</sup>C] L-serine in HEK293T cells after 0,5,10,15 and 30 minutes of [U-<sup>13</sup>C] glucose media replacement quantified by LC/MS. Ratio of <sup>13</sup>C L-serine to <sup>13</sup>C L-serine at time zero is plotted. Serine signal appears between 5 and 10 minutes.
- b.) GC/MS measurement of relative incorporation of [α-<sup>15</sup>N] Glutamine into amino acids in HEK293T cells. Pool sizes of relative incorporation of amino acids are shown in a pie chart.



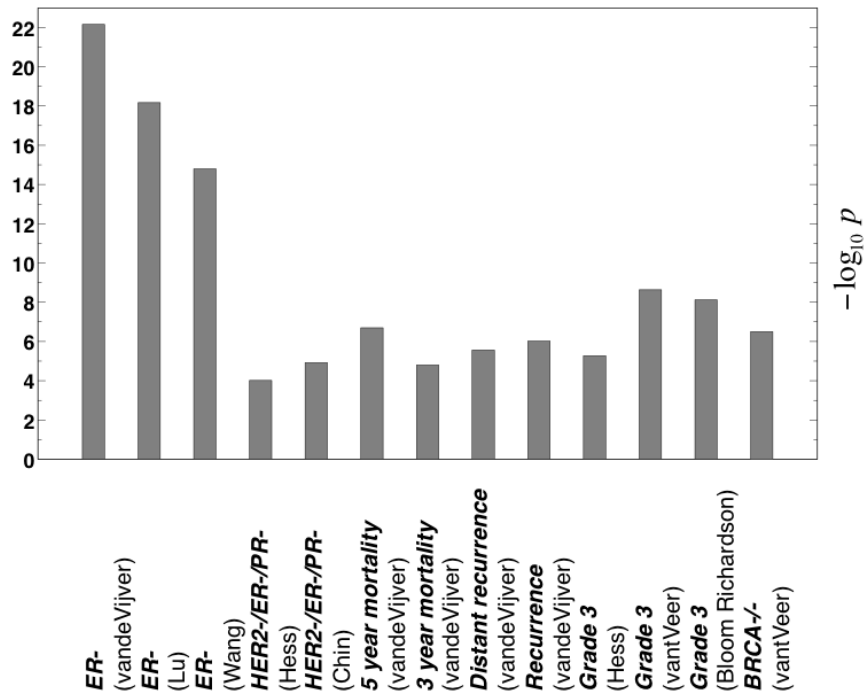
**Supplementary Figure 2 - *PHGDH* copy number gain in Melanoma**

150 Melanoma samples sorted by intensity at the *PHGDH* genomic locus at 1p12. 39% contain copy number gain exhibiting the highest frequency of occurrence in cancer subtypes.



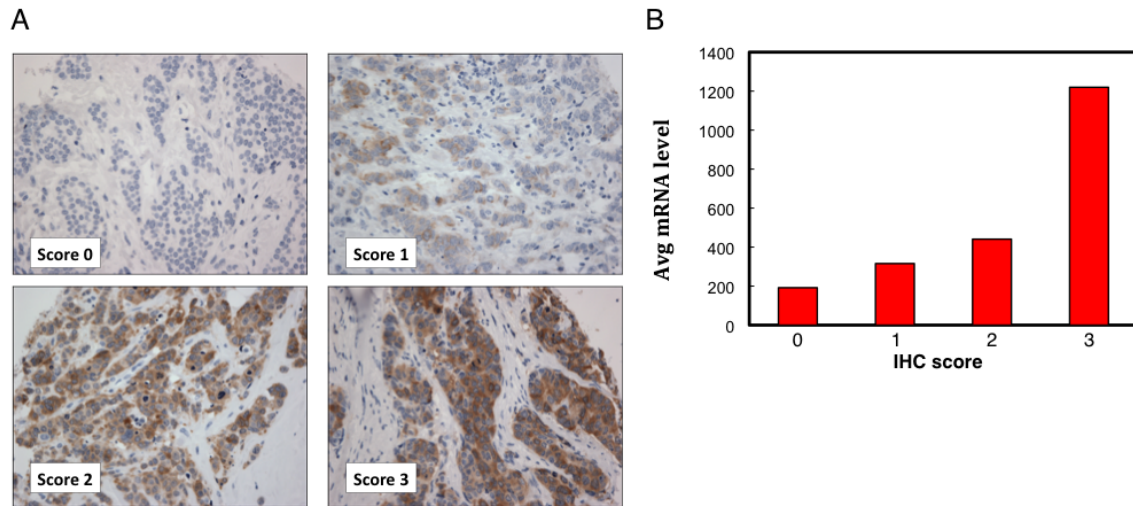
**Supplementary Figure 3 - PHGDH protein expression in human melanoma**

a.) Immunohistochemistry (IHC) of n = 381 samples human tissue samples in a melanoma collection. Samples were scored from 0 (no expression) to 3 (high expression) and representative images are shown. Nuclei are shown in blue (hematoxylin) and PHGDH antibody is shown in brown (3-3'-Diaminobenzidine [DAB]). b.) Statistics of PHGDH expression according to scoring scheme in a.). Number of samples N that stain for each score and percentage values % are shown. c.) Representative image of interphase FISH analysis showing disomy of PHGDH (green) and pericentromeric probe (red) in a representative sample from the tissue microarray.



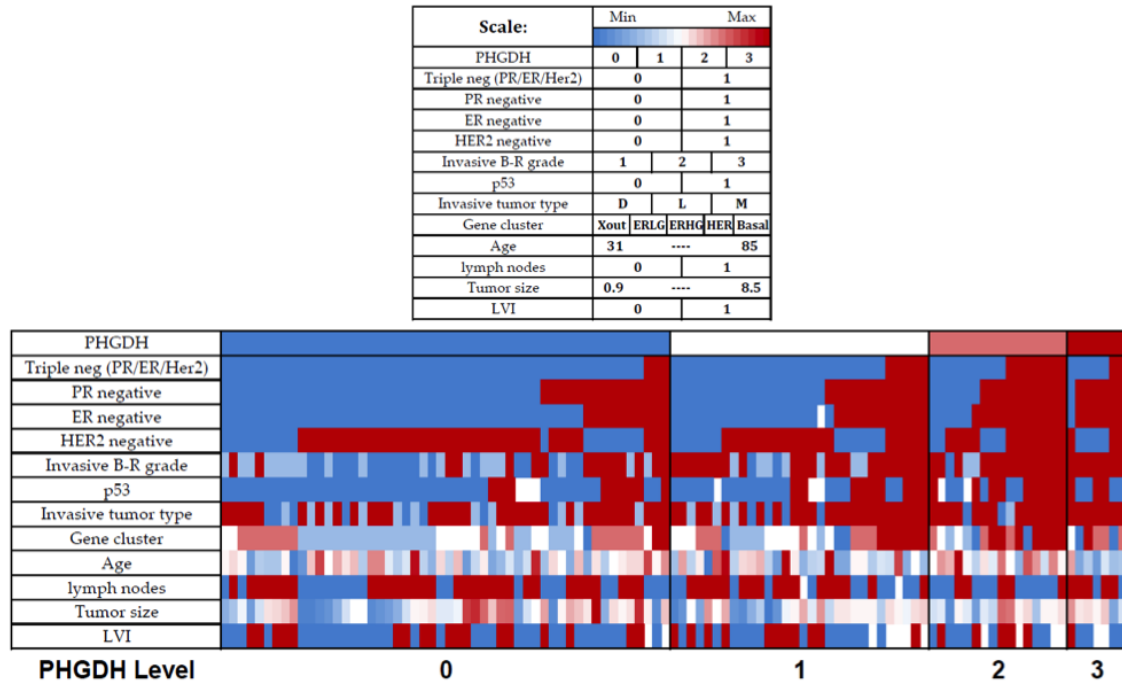
**Supplementary Figure 4 - Analysis of PHGDH expression in human breast cancer microarrays**

Associations of PHGDH expression with clinical parameters and prognosis in human breast cancer tumor microarray data sets. Test statistics are based on centroids and references are described in supplementary table 4.



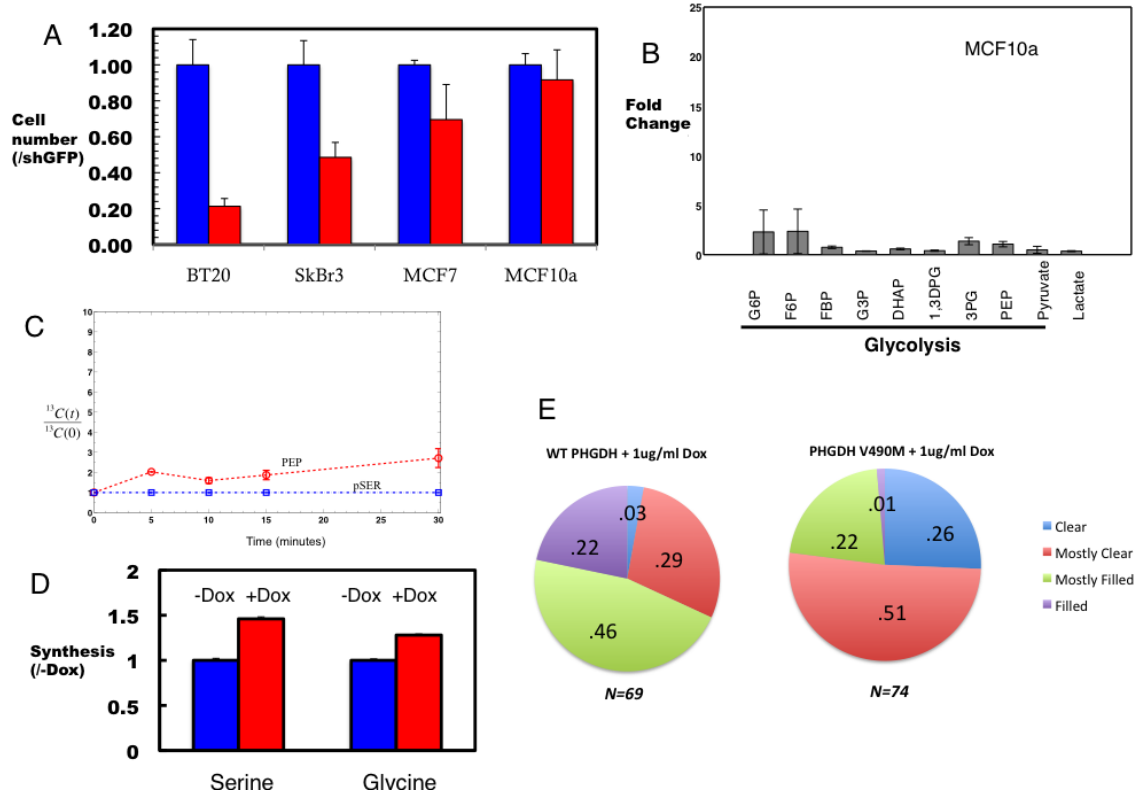
**Supplementary Figure 5 - Analysis of PHGDH protein expression in human breast cancer**

a.) IHC staining of a set of  $n = 106$  human breast tumors. PHGDH is shown in brown (DAB) and nuclei are blue (Hematoxylin). Representative images from expression scores ranging from 0 (no expression) to 3 (high expression) are shown. b.) Average mRNA expression for each IHC expression score.



**Supplementary Figure 6 - Association of PHGDH protein expression in human breast cancer with clinical parameters and breast cancer subtypes**

Overlay of PHGDH expression score (0 - green, 1 - yellow, 2 - orange, and 3 - red) with previously defined clinical parameters. Color correspondence of each clinical parameter is shown in the legend. Abbreviations in legend: PR - Progesterone Receptor, ER – Estrogen Receptor, LVI – lymphovascular invasion.



### Supplementary Figure 7 - Characterization of metabolism and acinar morphogenesis in MCF-10a cells

a.) Growth assay of stable human breast cancer cell lines containing shGFP or shPHGDH. Relative cell numbers for shGFP and shPHGDH normalized to shGFP are plotted for each cell line (BT-20, Sk-BR-3, MCF-7, and MCF-10A). BT-20 cells contain 1p12 copy number gain. Sk-BR-3 and MCF-7 cells do not have 1p12 copy number gain. MCF10a cells are also shown for comparison. Error bars were obtained from the standard deviation of  $n = 3$  independent measurements. b.) Ratio of integrated intensities (fold change), of PHGDH knockdown (shPHGDH) over control (shGFP) plotted for glycolytic intermediates. c.) Labeling of [U-13C] PEP after 0,5,10,15 and 30 minutes of [U-13C] glucose media replacement. No labeling of pSER was observed. Ratios of  $^{13}C$  pSER at time zero to  $^{13}C$  PEP (red, circles) and pSER (blue, squares) are plotted. A baseline noise level of  $1e4$  was chosen. d.) Fold change in serine and glycine synthesis relative to no doxycycline treatment in MCF-10a cells (synthesis(-Dox)) in the absence (-Dox ( $0\mu\text{g/ml}$ ), red) and presence (+Dox ( $1\mu\text{g/ml}$ ), blue) measured by GC/MS with relative incorporation of [ $\alpha$ - $^{15}N$ ] Glutamine into Serine (left) and Glycine (right). e.) Quantitation of acinar filling for  $1\mu\text{g/ml}$  doxycycline with PHGDH construct (+DOX, PHGDH) ( $N=69$ ), and  $1\mu\text{g/ml}$  doxycycline with PHGDH mutant (V490M) construct (+DOX, V490M) ( $N=74$ ) Dox. Each acini was scored as filled, mostly filled, mostly clear, and clear and the

frequencies of each score are shown. Quantitation was obtained from multiple (n=3) independent measurements.

**Supplementary Table 1 – Measured peaks in [<sup>1</sup>H,<sup>13</sup>C] HSQC spectra**

Table S1 – Summary of HSQC peaks

H ppm	C ppm	z score	
			-
4.141	60	0.370017396	-
			-
3.835	56	0.370017396	-
			-
3.812	54.67	0.370017396	-
			-
3.788	58.67	0.370017396	-
			-
3.788	29.33	0.370017396	-
			-
3.788	28	0.370017396	-
			-
3.718	74.67	0.370017396	-
			-
3.718	56	0.370017396	-
			-
3.529	77.33	0.370017396	-
			-
3.2	56	0.370017396	-
			-
2.729	38.67	0.370017396	-
			-
2.518	32	0.370017396	-
			-
2.494	32	0.370017396	-
			-
2.494	28	0.370017396	-
			-
2.471	34.67	0.370017396	-
			-
2.471	30.67	0.370017396	-
			-
2.471	29.33	0.370017396	-
			-
2.471	28	0.370017396	-
			-
2.447	30.67	0.370017396	-
			-
2.424	30.67	0.370017396	-
			-
2.424	28	0.370017396	-
			-
2.376	33.33	0.370017396	-
			-
2.376	30.67	0.370017396	-

2.329	33.33	0.370017396	-
2.329	28	0.370017396	-
2.259	28	0.370017396	-
2.235	28	0.370017396	-
2.212	28	0.370017396	-
2.165	33.33	0.370017396	-
2.165	26.67	0.370017396	-
2.141	32	0.370017396	-
2.141	30.67	0.370017396	-
2.141	26.67	0.370017396	-
2.141	25.33	0.370017396	-
2.118	33.33	0.370017396	-
2.118	32	0.370017396	-
2.118	26.67	0.370017396	-
2.118	25.33	0.370017396	-
2.118	24	0.370017396	-
2.094	33.33	0.370017396	-
2.094	26.67	0.370017396	-
2	28	0.370017396	-
2.447	28	0.369884404	-
2.212	29.33	0.369884404	-
2.471	32	0.369751412	-
2.424	29.33	0.369219444	-
3.224	56	0.369086452	-
3.906	54.67	0.368953461	-
2.376	32	0.368687477	-
2.4	32		-

		0.368554485	-
2.447	29.33	0.368421493	-
3.576	73.33	0.368155509	-
3.506	78.67	0.367889525	-
3.812	57.33	0.367224566	-
3.506	77.33	0.367224566	-
2.776	38.67	0.365761655	-
2.141	33.33	0.365628663	-
4.141	62.67	0.365229687	-
2.424	34.67	0.365096695	-
2.353	29.33	-0.36403276	-
2.753	38.67	0.363633784	-
2.447	34.67	0.363500792	-
2.588	33.33	0.362170873	-
2.118	30.67	0.362170873	-
3.812	56	0.361638905	-
2.024	28	-0.35991001	-
3.271	76	0.356319228	-
2	30.67	0.354457341	-
2.353	30.67	0.353393406	-
3.835	73.33	0.351132544	-
2.353	32	0.347674754	-
2.447	32	0.344748931	-
3.765	54.67	0.344349956	-
3.247	76	0.343684996	-
4.188	60	0.343419012	-
3.788	54.67	0.343419012	-
2.424	32	0.339429255	-

3.765	29.33	0.338099336	-
			-
3.482	77.33	0.338099336	-
			-
2.188	29.33	0.338099336	-
			-
2.188	28	0.338099336	-
			-
2.024	30.67	0.336769416	-
			-
2.329	30.67	0.335439497	-
			-
2.047	28	0.335439497	-
			-
2.047	30.67	0.326130063	-
			-
2.024	25.33	0.326130063	-
			-
5.247	94.67	0.316820629	-
			-
2.4	33.33	0.316820629	-
			-
2.071	28	0.316820629	-
4.141	70.67	-0.31549071	-
			-
3.435	72	0.310171033	-
			-
2.494	33.33	0.310171033	-
			-
2.282	36	0.304851356	-
			-
2.047	36	0.296871841	-
			-
2.376	36	0.284902568	-
			-
3.812	73.33	0.283572649	-
3.412	72	-0.28224273	-
			-
3.365	48	0.280912811	-
			-
2.471	33.33	0.278252972	-
			-
2.094	36	0.270273457	-
			-
2.565	33.33	0.268943538	-
			-
2.353	34.67	0.264953781	-
			-
3.788	64	0.263623861	-
			-
3.976	62.67	0.262293942	-
4.141	64		-

		0.259634104	-
1.482	22.67	0.259634104	-
4.282	68	0.258304185	-
2.024	26.67	0.252984508	-
3.388	72	-0.25032467	-
8.471	142.67	0.248994751	-
5.506	96	0.248994751	-
7.906	145.33	0.246334912	-
3.741	46.67	0.246334912	-
3.318	48	0.245004993	-
4.094	22.67	0.243675074	-
2.329	37.33	0.243675074	-
3.388	49.33	0.242345155	-
3.341	49.33	0.242345155	-
3.906	62.67	0.239685316	-
3.412	49.33	0.239685316	-
3.459	72	0.238355397	-
6.141	89.33	0.237025478	-
3.482	78.67	0.235695559	-
3.459	78.67	-0.23303572	-
4.188	66.67	0.230375882	-
4.047	74.67	0.230375882	-
1.459	22.67	0.230375882	-
4.141	66.67	0.229045963	-
2	29.33	0.226386124	-
3.647	65.33	0.225056205	-
3.553	73.33	0.225056205	-
3.812	53.33	0.223726286	-

		-
3.412	48	0.218406609
1.459	20	-0.21707669
		-
1.976	26.67	0.215746771
		-
2	25.33	0.214416852
		-
3.388	48	0.213086933
		-
2.071	25.33	0.211757013
		-
3.341	48	0.209097175
		-
7.906	144	0.206437337
		-
3.529	73.33	0.206437337
		-
2.518	33.33	0.206437337
		-
2.094	28	0.206437337
		-
2	24	0.206437337
		-
3.788	73.33	0.205107418
		-
3.694	64	0.205107418
		-
4.259	86.67	0.203777498
		-
4.165	66.67	0.199787741
		-
3.741	45.33	0.194468064
		-
4.118	64	0.193138145
		-
3.788	18.67	0.191808226
		-
3.765	46.67	0.191808226
		-
2.165	28	0.191808226
		-
2	26.67	0.191808226
		-
4.282	72	0.190478307
		-
1.435	22.67	0.190478307
		-
2.165	29.33	0.186488549
		-
1.529	18.67	0.186488549
		-
3.882	64	0.182498792

3.976	56	-0.1691996	-
3.694	62.67	0.167869681	-
3.812	64	0.165209842	-
3.835	64	0.163879923	-
4.329	76	-0.15191065	-
4.376	76	0.145261054	-
4.282	86.67	0.143931135	-
3.788	52	0.142601216	-
3.741	56	0.141271297	-
6.118	89.33	0.138611459	-
2.071	24	0.134621701	-
4.071	72	0.130631944	-
4.118	22.67	0.129302024	-
4.235	66.67	0.126642186	-
3.788	57.33	0.118662671	-
3.953	56	0.116002833	-
3.882	76	0.114672913	-
2.541	33.33	0.114672913	-
3.765	45.33	0.113342994	-
2.306	34.67	0.112013075	-
3.765	52	0.105363479	-
2.306	29.33	0.105363479	-
5.976	90.67	0.102703641	-
5.529	97.33	0.100043802	-
3.788	56	0.098713883	-
3.859	64	0.093394206	-
4.353	77.33	0.089404449	-
5.976	92	-	-

		0.086744611	-
2.118	28	0.086744611	-
1.412	22.67	0.086744611	-
3.906	76	0.084084772	-
1.294	24	0.084084772	-
3.765	64	0.069455661	-
4.212	66.67	0.061476146	-
3.553	42.67	0.061476146	-
3.553	45.33	0.058816308	-
3.718	64	0.050836793	-
2.141	28	0.045517116	-
3.718	62.67	0.034877763	-
1.318	24	0.033547843	-
3.953	62.67	-0.00694946	-
2.447	33.33	0.001629783	-
2.424	33.33	0.012999328	-
1.506	18.67	0.018319005	-
4.353	72	0.028958358	-
1.388	22.67	0.051566984	-
3.882	62.67	0.052896903	-
4.306	72	0.067526014	-
2.329	34.67	0.068855933	-
3.765	62.67	0.071515772	-
3.741	62.67	0.083485044	-
4.141	68	0.086144883	-
2.141	29.33	0.100773994	-
4.071	70.67	0.10742359	-
2.329	29.33	0.111413347	-
3.741	64	0.112743266	-
4.259	85.33	0.118062943	-
2.024	29.33	0.142001488	-
5.482	97.33	0.143331408	-
5.224	94.67	0.143331408	-
4.188	68	0.145991246	-
3.788	53.33	0.165940034	-
4.094	72	0.18854866	-
4.165	68	0.189878579	-
4.282	85.33	0.212487205	-

4.329	72	0.215147043
2.353	36	0.22046672
3.788	62.67	0.221796639
4.259	68	0.243075346
3.765	56	0.26967373
3.765	53.33	0.284302841
1.365	22.67	0.320210658
4.353	76	0.326860254
5.506	97.33	0.341489365
3.859	62.67	0.358778315
3.812	62.67	0.406655405
5.953	90.67	0.419954597
2.118	29.33	0.43059395
5.953	92	0.458522253
4.118	72	0.458522253
2.071	29.33	0.466501768
2.047	29.33	0.481130879
3.741	57.33	0.497089909
1.459	17.33	0.522358374
3.835	62.67	0.548956757
2.094	29.33	0.558266192
4.094	70.67	0.582204737
4.212	68	0.635401504
2.047	25.33	0.735145442
4.235	68	0.787012291
2.306	36	0.866807441
1.318	21.33	0.9333034
4.118	70.67	0.999799359
1.435	18.67	0.999799359
1.294	21.33	1.066295318
3.765	57.33	1.106192894
1.341	22.67	1.106192894
2.047	24	1.279082387
2.329	36	1.491869456
1.482	18.67	1.731254908
3.553	44	3.313858732
1.459	18.67	5.760910023
1.294	22.67	8.500543533
1.318	22.67	10.48212311

## Supplementary Table 2 – Statistics of *PHGDH* amplification across cancer types

Cancer Subset	Nearest Peak	#Genes in Peak	Q-value
Overall	High-level		
all_cancers	chr1:120041950-120269948	5	1.18E-09
all_epithelial	chr1:120041950-120269948	5	2.16E-10
Melanoma	chr1:120041950-120160448	3	1.93E-05
all_neural	chr1:97553627-143814988	166	0.219
Breast	chr1:113522920-120992603	55	0.319
Lung SC	chr1:44531979-143798352	450	1

### Notes:

Summary of cancers containing *PHGDH* copy number gain

Column 1                      Cancer subset considered  
Column 2                      Chromosome region containing peak region

Q -value of false discovery rate, Frequency of Amplification pertaining to Overall, Focal, and High-level are defined in: Beroukhi R et al. Nature. 2010 Feb 18;463(7283):899-905.

**Supplementary Table 3 – Metabolite intensities in control (shPHGDH) and knockdown (shPHGDH) Sk-Mel28 cells**

nega – denotes negative ionization fragment  
 posi – denotes positive ionization fragment

shPHGDH knockdown

Name	ID	Fold Change	p value
Atrolactic acid	HMDB00475	0.021606272	0.056109
2.oxo.4-methylthiobutanoate	C01180	0.026183491	0.070294
Phenyllactic acid	C01479	0.062565619	0.05522
phenylpyruvate	C00166	0.081688782	0.025158
Glycerophosphocholine	C00670	0.111222815	0.278722
4-aminobutyrate	C00334	0.12101063	0.128122
trehalose-sucrose	C00089	0.140091797	0.042378
4-Pyridoxic acid	C00847	0.141790909	0.113
propionyl-CoA-posi	C00100	0.161716882	0.373900
orotidine.5-phosphate	C01103	0.171186588	0.235532
adenine	C00147	0.17152741	0.0012
5.phosphoribosyl.1-pyrophosphate	C00119	0.183016392	0.260597
cyclic-AMP	C00575	0.197807588	0.011438
Ng,NG-dimethyl-L-arginine	C03626	0.202853608	0.020057
inosine	C00294	0.203651083	0.007768
S.ribosyl.L.homocysteine-nega	C03539	0.213038301	0.009608
Methylcysteine	C00155	0.215780856	0.00373
deoxyadenosine	HMDB02108	0.227153294	0.020352
GMP	C06193	0.229898053	0.006699
sn.glycerol.3-phosphate	C00093	0.26563377	0.00085
CDP-choline	C00307	0.298155297	0.006331
deoxyribose-phosphate	C00673	0.329260631	0.023510
Pyridoxamine	C00534	0.337805912	0.069313
CMP	C00055	0.361715454	0.057562
Citraconic acid	C02226	0.366938302	0.046992
taurine	C00245	0.383747214	0.011413
IMP	C00130	0.383957495	0.010085
FAD	C00016	0.388331296	0.054405
adenosine	C00212	0.393468797	0.008510
3-phospho-serine	C01005	0.405005913	0.015313
Hydroxyisocaproic acid	HMDB00746	0.419542443	0.018624
2-ketohaxanoic acid	HMDB01864	0.441535924	0.061182
citrulline	C00327	0.45375765	0.159443
arginine	C00062	0.459958879	0.323754
deoxyguanosine	C00212	0.468313899	0.249856
AMP	C00020	0.482992311	0.096584
Hydroxyphenylacetic acid	C05852	0.484211353	0.464005
adenosine 5-phosphosulfate	C00224	0.485594266	0.003666

L-arginino-succinate	C03406	0.505594004	0.014214
aconitate	C00417	0.510704428	0.001202
Thiamine pyrophosphate	C00068	0.520568899	0.002655
dCMP	C00239	0.523297331	0.113913
hypoxanthine	C00262	0.538488064	0.060575
Uric acid	C00366	0.54007971	0.00128
dGTP	C00286	0.547011425	0.425227
NAD+_posi	C00003	0.55220101	0.144070
ribose-phosphate	C00117	0.562855044	0.010560
dTMP-nega	C00364	0.573116965	0.166341
uridine	C00299	0.574792369	0.077107
isocitrate	C00311	0.575046798	0.046676
nicotinate	C00253	0.580393186	0.367386
glutathione	C00051	0.583961112	0.223389
homocysteic acid	C16511	0.5916659	0.421515
D-glucarate	C00767	0.615066115	0.022634
thymine	C00178	0.616470553	0.031721
D-gluconate	C00257	0.617870417	0.00406
NAD+_nega	C00003	0.633500028	0.001782
deoxyinosine	C05512	0.640339501	0.021717
proline	C00148	0.641492738	0.463907
biotin	C00120	0.641587976	0.338630
Carbamoyl phosphate	C00169	0.64532623	0.201794
CDP-ethanolamine	C00570	0.648148816	0.215898
quinolinate	C03722	0.657979545	0.107109
choline	C00114	0.661863686	0.104813
dGMP	C00362	0.68024357	0.562894
Acetyllysine	C02727	0.693540856	0.378814
D.erythrose.4-phosphate	C00279	0.697031884	0.091956
cysteine	C00491	0.700112326	0.235912
D-glucosamine-6-phosphate	C00352	0.700521781	0.050612
glucose.1-phosphate	C00103	0.703031203	0.012284
DL-Pipecolic acid	C00408	0.715659235	0.274798
histidinol	C00860	0.720942905	0.048954
D.sedoheptulose.1.7-phosphate	C05382	0.722374554	0.013551
fructose.6-phosphate	C00085	0.733078165	0.202067
glucose.6-phosphate	C00092	0.75072558	0.250662
anthranilate	C00108	0.751575803	0.1026
3.S-methylthiopropionate	C08276	0.753869834	0.764929
myo-inositol	C00137	0.75878187	0.147690
deoxyuridine	C00526	0.761927815	0.129667
N-Acetylputrescine	C02714	0.761972391	0.009939
dCDP-nega	C00705	0.769264344	0.667644
N-acetyl-glutamine	HMDB06029	0.77175004	0.513792
dimethylglycine	C01026	0.772854328	0.666767
N6-Acetyl-L-lysine	C02727	0.791104279	0.521458
p-hydroxybenzoate	C00156	0.793018673	0.018719
carnitine	C00318	0.797959851	0.554906
threonine	C00188	0.810289298	0.162954

serine	C00065	0.811071039	0.153429
hexose-phosphate	C00085	0.821440639	0.197197
alanine	C00041	0.824158303	0.536781
O-acetyl-L-serine	C00979	0.82908318	0.571964
guanine	C00242	0.836346545	0.488813
N.acetyl.glucosamine.1-phosphate	C03783	0.837696606	0.014145
hydroxyproline	C01157	0.838596927	0.165385
S-ribosyl-L-homocysteine-posi	C03539	0.839210087	0.224202
glycolate	C00160	0.841886008	0.478102
S-adenosyl-L-methionine	C00019	0.844655883	0.530817
glycerate	C00258	0.857078115	0.524184
Pyroglutamic acid	C01879	0.857184302	0.064389
S-adenosyl-L-homoCysteine-posi	C00021	0.863314511	0.513253
Ascorbic acid	C00072	0.865193935	0.669034
glutamate	C00025	0.871031938	0.341607
2-Aminooctanoic acid	HMDB00991	0.871844925	0.759090
cytidine	C00475	0.89405413	0.670705
acetoacetate	C00164	0.904289744	0.077859
Amino adipic acid	C00956	0.910447064	0.250044
oxaloacetate	C00036	0.921545537	0.308547
2-oxobutanoate	C00109	0.937345541	0.759797
Indole.3-carboxylic acid	HMDB03320	0.939350509	0.440945
NADH	C00004	0.941421595	0.745870
2-Hydroxy.2-methylbutanedioic acid	C02612	0.94184607	0.327579
2.dehydro.D-gluconate	C00629	0.942246814	0.522979
ATP-nega	C00002	0.949631671	0.9370
histidine	C00135	0.958021473	0.832661
NADP+_posi	C00006	0.960275785	0.815279
lysine	C00047	0.973254133	0.84858
aspartate	C00049	0.98286118	0.92188
betaine	C00719	0.984686484	0.868553
ethanolamine	C00189	0.990433054	0.936944
allantoin	C01551	0.991881543	0.913983
Urea	C00086	0.992825693	0.933642
leucine-isoleucine	C00123	0.998645735	0.986577
N-acetyl-glucosamine	C00140	1.004157707	0.988367
UDP.N.acetyl-glucosamine	C00043	1.005779782	0.927679
Kynurenine	C00328	1.007050555	0.987631
dAMP	C00360	1.013860171	0.960905
shikimate.3-phosphate	C03175	1.016578928	0.934635
tyrosine	C00082	1.017933779	0.932427
NADP+_nega	C00006	1.018245417	0.932002
NADH-nega	C00004	1.044248128	0.855132
tryptophan	C00078	1.056665914	0.82069
Flavone	C15608	1.061132953	0.866960
methylnicotinamide	C02918	1.061338847	0.473451
Taurodeoxycholic acid	C05463	1.074636213	0.711715
D.glucono.?.lactone.6-phosphate	C01236	1.1175004	0.575287
cystathionine	C00542	1.119159352	0.445686

N-acetyl-L-ornithine	C00437	1.119710497	0.809876
Indoleacrylic acid	HMDB00734	1.135803822	0.744033
thymidine	C00214	1.137037094	0.340861
Pyrophosphate	C00013	1.139790742	0.774118
ornithine	C00077	1.143263242	0.396842
orotate	C00295	1.146659587	0.775696
Xanthurenic acid	C02470	1.162587028	0.725284
dephospho.CoA-nega	C00882	1.172927891	0.720004
cytosine	C00380	1.18783499	0.394340
pantothenate	C00864	1.190141494	0.694328
acetylphosphate	C00227	1.201758114	0.676437
Creatinine	C00300	1.207291389	0.21586
glutamine	C00064	1.226651305	0.152954
betaine aldehyde	C00576	1.255336189	0.056760
malate	C00149	1.283801116	0.031872
UMP	C00105	1.284028013	0.192170
Maleic acid	C01384	1.284309896	0.012277
uracil	C00106	1.294592088	0.008391
fumarate	C00122	1.2958764	0.005531
2.keto-isovalerate	C00141	1.29743739	0.008940
riboflavin	C00255	1.29898878	0.064166
pyridoxine	C00314	1.305893373	0.056540
acadesine	D02742	1.308698742	0.061439
Guanidoacetic acid	C00581	1.340128246	0.080670
5-methyl-THF	C00440	1.340481378	0.582499
CTP-nega-IS	C00063	1.349211102	0.01835
OBP		1.36126557	0.232438
1-Methyl-Histidine	C01152	1.365465039	0.051421
shikimate	C04236	1.365692678	0.278475
thiamine	C00378	1.369879666	0.035133
glucono.-lactone	C00198	1.373925777	0.464235
lactate	C00186	1.37409423	0.000485
2,3-Diphosphoglyceric acid	C01159	1.375811625	0.650415
1-Methyladenosine	C02494	1.388716119	0.073630
O8P-O1P		1.411101085	0.040518
xanthosine	C01762	1.413026375	0.367625
valine	C00183	1.416302576	0.468606
S-methyl-5-thioadenosine	C00170	1.439981105	0.064511
glutathione-nega	C00051	1.442149954	0.0023
p-aminobenzoate	C00568	1.448617345	0.192808
N.Acetyl.L-alanine	C01073	1.449137455	0.206767
Methylmalonic acid	C02170	1.455667494	0.019456
Kynurenic acid	C01717	1.459103416	0.004759
homocysteine	C00155	1.462796036	0.299397
succinate	C00042	1.46475698	0.018926
Geranyl-PP	C00341	1.482285377	0.373900
D-glucosamine-1-phosphate	C03783	1.514677693	0.229960
2,3-dihydroxybenzoic acid	C00196	1.517200705	0.283599
Nicotinamide ribotide	C00455	1.520725245	0.461343

phenylalanine	C00079	1.525324196	0.129771
UDP.D-glucose	C00029	1.55149874	0.002994
a-ketoglutarate	C00026	1.554031413	0.001605
homoserine	C00263	1.566295348	0.203193
Phenylpropionic acid	HMDB00563	1.577506085	0.000140
indole	C16074	1.580861918	0.270401
2-Isopropylmalic acid	C02504	1.611862763	0.082727
methionine	C00073	1.62909124	0.279552
phosphoenolpyruvate	C00074	1.636504134	0.008829
Imidazole	C01589	1.640515186	0.163196
guanosine	C00387	1.654386952	0.373900
propionyl.CoA-nega	C00100	1.674336133	0.126339
pyruvate	C00022	1.680222923	0.054583
Acetylcarnitine DL	C02571	1.748850348	0.00852
dihydroorotate	C00337	1.813906501	0.257423
dUMP-nega	C00365	1.822333025	0.023484
7-methylguanosine	HMDB01107	1.858861352	0.009893
glucosamine	C00329	1.892189813	0.177020
cholesteryl sulfate	HMDB00653	1.918011097	0.06881
N-acetyl-glutamate	C00624	1.918329203	0.090551
glutathione disulfide-nega	C00127	1.935628547	0.014978
purine	C00465	1.965981318	0.045391
glutathione disulfide-posi	C00127	1.992352278	0.017737
6.phospho.D-gluconate	C00345	2.114810411	0.005935
trehalose.6-Phosphate	C00689	2.156254101	0.001956
Phosphorylcholine	C00588	2.289760331	0.000451
3-phosphoglycerate	C00197	2.538339016	0.000850
Methionine sulfoxide	HMDB02005	2.608094359	0.148873
asparagine	C00152	2.800383204	0.004677
dihydroxy.acetone-phosphate	C00111	2.855539084	5.33E
GDP-nega	C00035	2.90639825	0.160152
nicotinamide	C00153	2.917005446	0.002917
SBP	C00447	3.306501137	0.044213
FMN	C00061	3.550843839	0.000267
Cystine	C00491	3.671567508	0.116240
CTP-nega	C00063	3.782300978	0.118470
1,3-diphosphoglycerate	C00236	4.286014007	0.17094
UDP.D-glucuronate	C00167	4.788776398	0.009423
aminoimidazole carboxamide			
ribonucleotide	C04677	4.959823594	0.000159
UTP-nega	C00075	5.11662588	0.00639
dTMP	C00364	6.377011232	0.002402
Imidazoleacetic acid	C05828	6.614466076	0.060758
glyoxylate	C00048	7.107820407	0.000384
5-methoxytryptophan	HMDB02339	7.233714978	0.001681
N-carbamoyl-L-aspartate	C00438	8.301085665	0.00035
hydroxyphenylpyruvate	C01179	8.701793414	0.000715
allantoate	C00499	10.37454142	1.24E
Cellobiose	C00185	10.94795599	9.44E

xanthine	C00385	11.65684869	0.000151
N.carbamoyl.L.aspartate-nega	C00438	11.94992087	1.89E
fructose.1,6-bisphosphate	C00354	13.47404445	5.72E
CDP-nega	C00112	15.76647263	0.000461
D.glyceraldehydye.3-phosphate	C00118	19.95741779	2.92E
dTDP-nega	C00363	35.09456066	5.42E
UDP-nega	C00015	86.04323539	7.26E
IDP-nega	C00104	137.0096775	7.20E
citrate-isocitrate	C00158	177.1416191	0.001241
folate	C00504	231.9839163	0.001535
citrate	C00158	240.3178056	0.001552
dGDP-nega	C00361	1116.880639	6.82E
ADP-nega	C00008	1122.059179	5.71E

**Supplementary Table 4 – PHGDH statistical associations and references for breast cancer tumor microarray data sets**

PHGDH Expression

Name	p-value	Statistic	Probe (reporter)
ER- (vandeVijver)	7.00E-23	t-test	NM_006623
ER- (Lu)	6.76E-19	t-test	NM_006623
ER- (Wang)	1.58E-15	t-test	NM_006623
HER2-/ER-/PR- (Hess)	9.69E-05	t-test	NM_006623
Her2-/ER-/PR- (Chin)	1.20E-05	t-test	NM_006623
5-year survival (vandeVijver)	2.00E-07	t-test	NM_006623
3-year survival (vandeVijver)	1.59E-05	t-test	NM_006623
3-year metastasis (vandeVijver)	2.72E-06	t-test	NM_006623
3-year recurrence (vandeVijver)	9.51E-07	t-test	NM_006623
Grade 3 (Hess)	5.33E-06	t-test	NM_006623
Grade 3 (vantVeer)	2.33E-09	t-test	NM_006623
Grade 3 Bloom Richardson (Lu)	7.53E-09	t-test	NM_006623
BRCA (vantVeer)	3.15E-07	t-test	NM_006623

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