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# Appendix A

## Sample Quality

### A.1 Sample Correlation

Samples were excluded from expression analysis based on sample correlations and the clustering analysis presented below, as described in section 2.2.2.

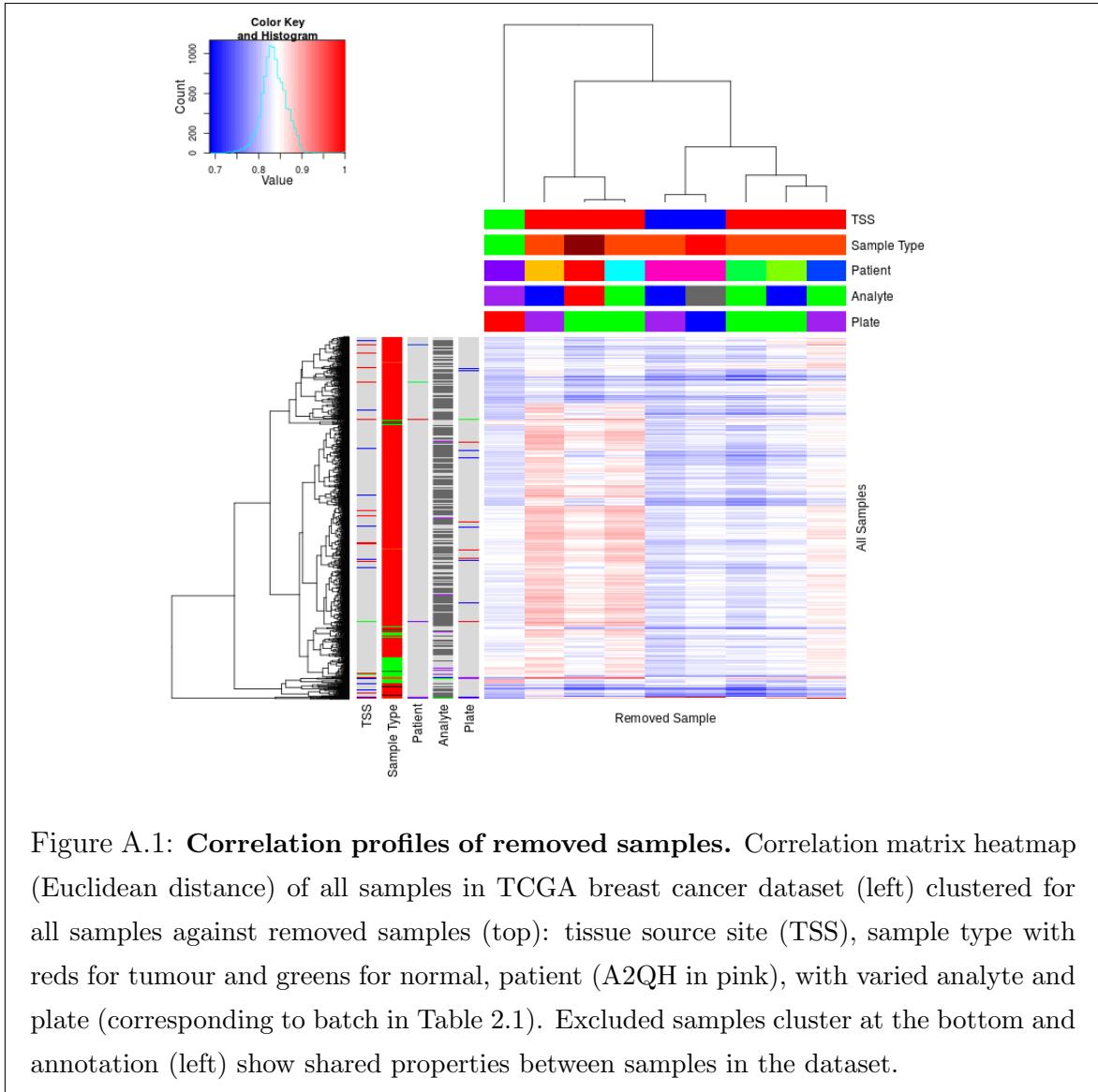
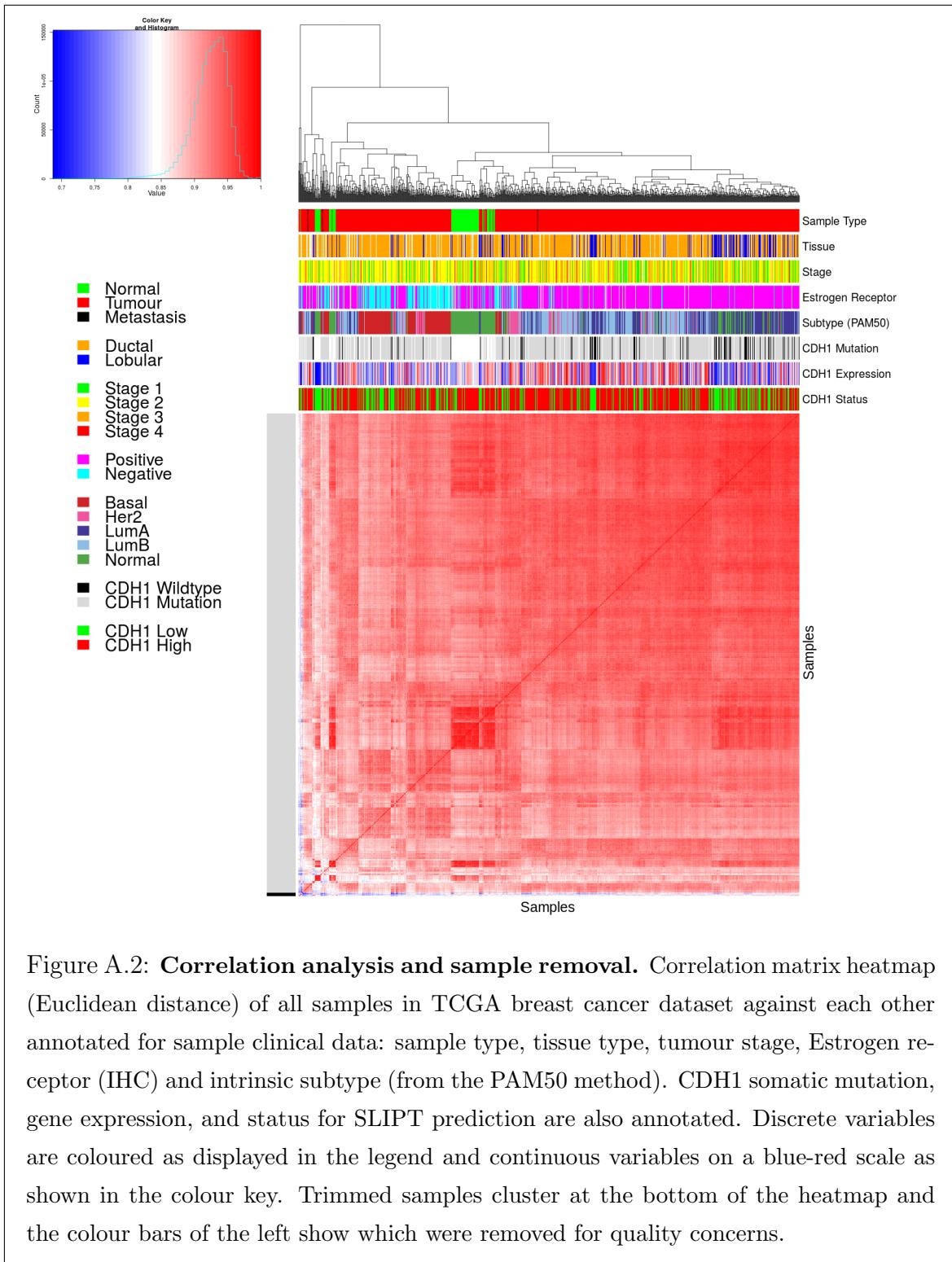


Figure A.1: **Correlation profiles of removed samples.** Correlation matrix heatmap (Euclidean distance) of all samples in TCGA breast cancer dataset (left) clustered for all samples against removed samples (top): tissue source site (TSS), sample type with reds for tumour and greens for normal, patient (A2QH in pink), with varied analyte and plate (corresponding to batch in Table 2.1). Excluded samples cluster at the bottom and annotation (left) show shared properties between samples in the dataset.



## A.2 Replicate Samples in TCGA Breast

Replicate samples were picked where possible from the TCGA breast cancer gene expression data to examine for sample quality. Independent samples of the same tumour are expected to have very high Pearson's correlation between their expression profiles unless there were issues with sample collection or preparation and are thus an indicator of sample quality. The log-transformed raw read counts for replicate samples were examined in Figures A.3–A.5. These were examined before normalisation which would be expected to increase sample concordance.

Another consideration are the samples which were removed for quality concerns (in section 2.2.2). While these were selected by unbiased hierarchical clustering (See Figure A.2), it is notable that many of the excluded (tumour) samples were performed in replicate despite relatively few replicate samples in the overall dataset. These samples correlate poorly with the rest of the dataset, in addition to with replicate samples.

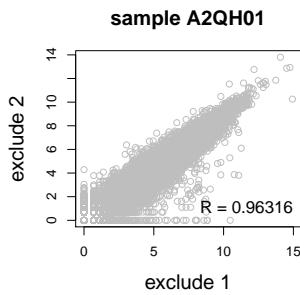


Figure A.3: **Replicate excluded samples.** Both tumour samples of patient A2QH were excluded as they were poorly correlated with other samples, although they are highly similar to each other as shown by Pearson's correlation of log-raw counts.

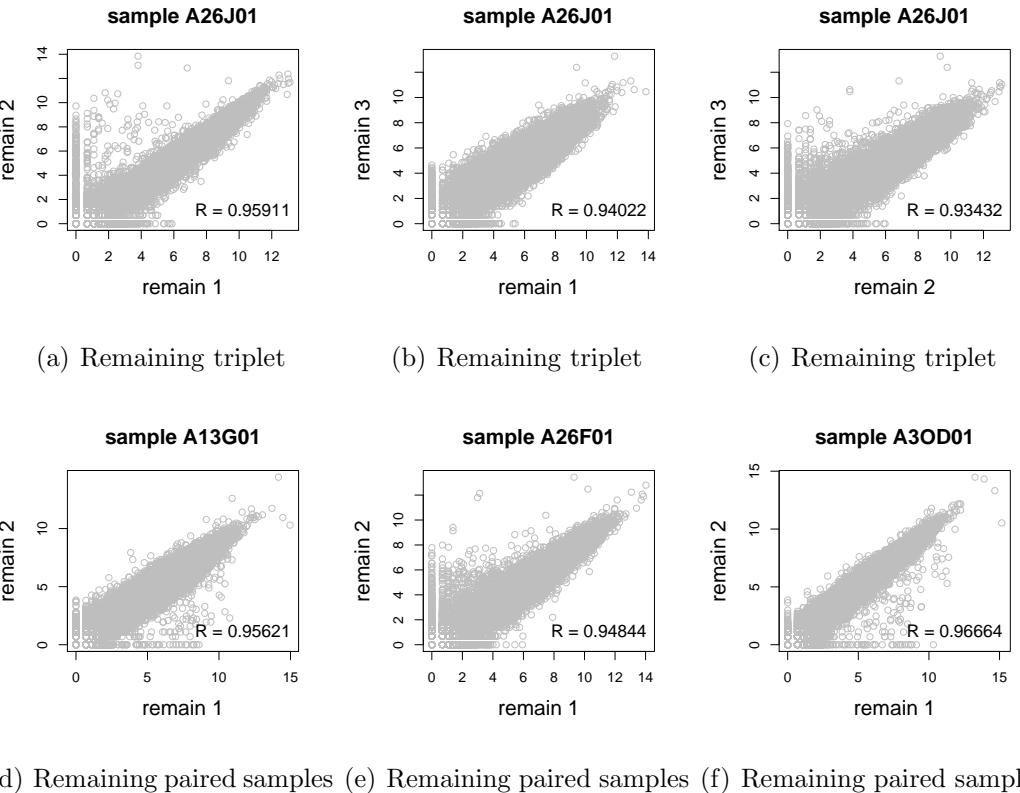


Figure A.4: **Replicate samples with all remaining.** Patient A26J was sampled 3 times and compared pairwise. Pairs of samples were also compared for other patients with replicate samples. In all cases, replicate samples remaining in the dataset were highly concordant as shown by Pearson's correlation of log-raw counts.

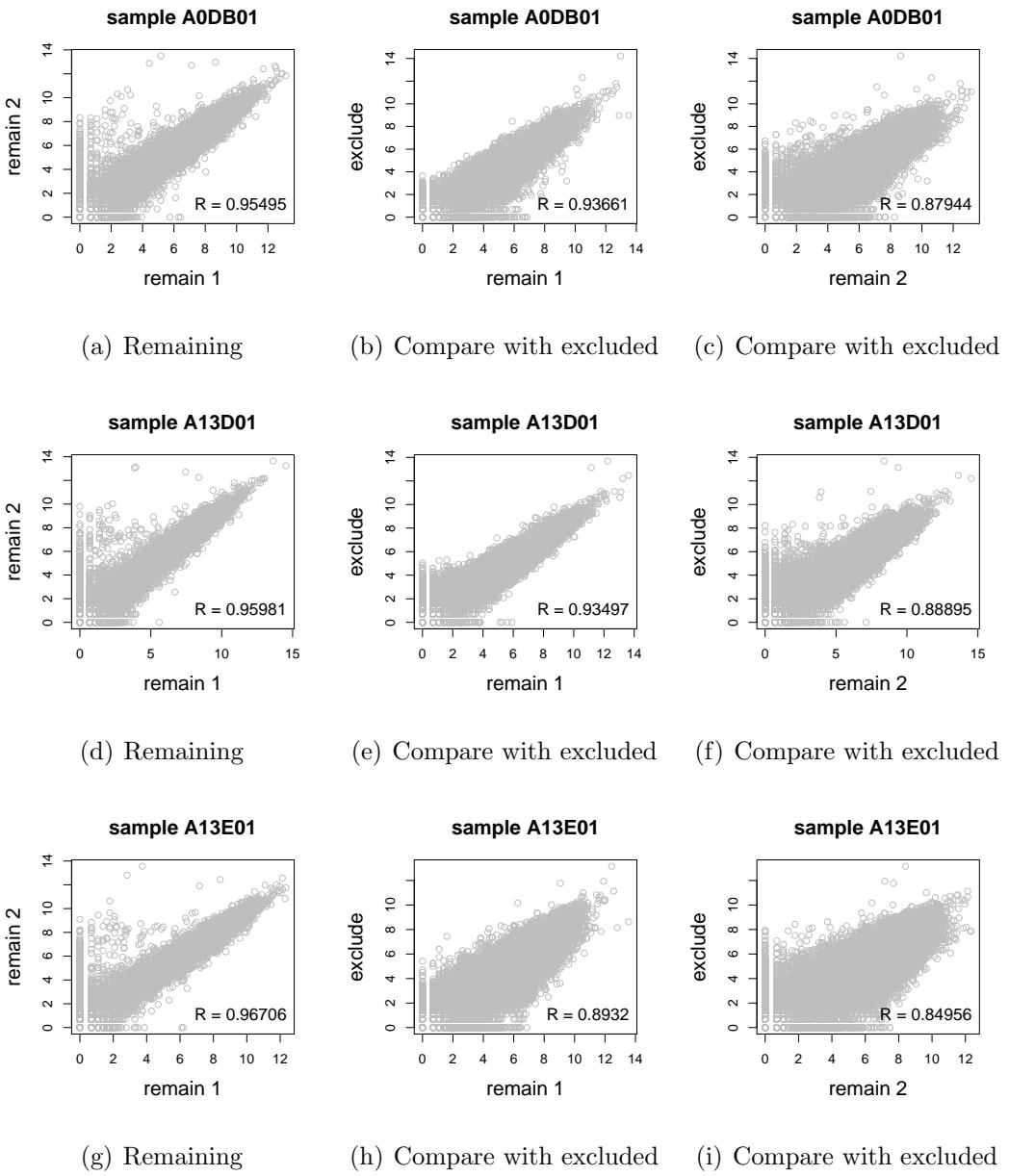
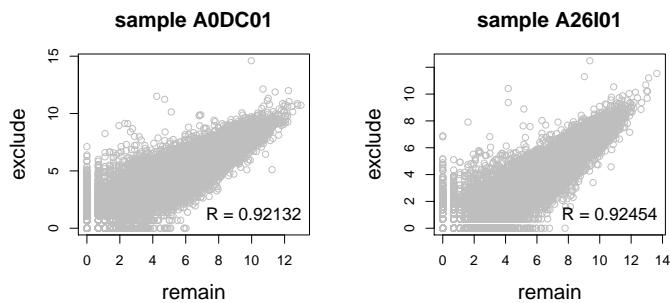
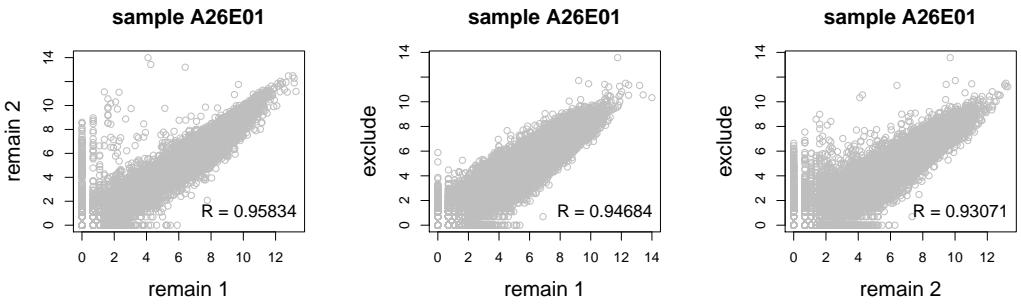


Figure A.5: **Replicate samples with some excluded.** Patients A0DB, A13D, A13E, and A26E were each sampled 3 times and compared pairwise. Pairs of samples were also compared for other patients with replicate samples. In all cases, the replicate samples remaining in the dataset more were highly concordant (as shown by Pearson's correlation of log-log raw counts) than those excluded from the analysis.



**Figure A.5: Replicate samples with some excluded.** Patients A0DB, A13D, A13E, and A26E were each sampled 3 times and compared pairwise. Pairs of samples were also compared for other patients with replicate samples. In all cases, the replicate samples remaining in the dataset more were highly concordant (as shown by Pearson's correlation of log-raw counts) than those excluded from the analysis.

# Appendix B

## Software Used for Thesis

Table B.1: R Packages used during Thesis

Package	Repository	Laptop	Lab	Server	NeSI
base	base	3.3.2	3.3.2	3.3.1	3.3.0
abind	CRAN		1.4-5		1.4-3
acepack	CRAN		1.4.1		1.3-3.3
ade4	CRAN		1.7-5		
annaffy	Bioconductor		1.46.0		
AnnotationDbi	Bioconductor		1.36.0	1.36.0	1.34.4
apComplex	CRAN		2.40.0		
ape	CRAN		4		3.4
arm	CRAN		1.9-3		
assertthat	CRAN	0.1	0.1	0.1	0.1
backports	CRAN	1.0.5	1.0.4	1.0.5	1.0.2
base64	CRAN			2	2
base64enc	CRAN		0.1-3		0.1-3
beanplot	CRAN		1.2	1.2	1.2
BH	CRAN	1.60.0-2	1.62.0-1	1.62.0-1	1.60.0-2
Biobase	Bioconductor		2.34.0	2.34.0	2.32.0
BiocGenerics	Bioconductor		0.20.0	0.20.0	0.18.0
BiocInstaller	Bioconductor		1.24.0	1.20.3	1.22.3
BiocParallel	Bioconductor		1.8.1	1.8.1	
Biostings	Bioconductor		2.42.1	2.42.0	
BiSEp	Bioconductor		2.0.1	2.0.1	2.0.1
bitops	CRAN	1.0-6	1.0-6	1.0-6	1.0-6
boot	base	1.3-18	1.3-18	1.3-18	1.3-18
brew	CRAN	1.0-6	1.0-6	1.0-6	1.0-6
broom	CRAN	0.4.1			

caTools	CRAN	1.17.1	1.17.1	1.17.1	1.17.1
cgdsr	CRAN		1.2.5		
checkmate	CRAN		1.8.2		1.7.4
chron	CRAN	2.3-47	2.3-48	2.3-50	2.3-47
class	base	7.3-14	7.3-14	7.3-14	7.3-14
cluster	base	2.0.5	2.0.5	2.0.5	2.0.4
coda	CRAN		0.19-1		0.18-1
codetools	base	0.2-15	0.2-15	0.2-15	0.2-14
colorRamps	CRAN		2.3		
colorspace	CRAN	1.2-6	1.3-2	1.3-2	1.2-6
commonmark	CRAN	1.1		1.2	
compiler	base	3.3.2	3.3.2	3.3.1	3.3.0
corpcor	CRAN		1.6.8	1.6.8	1.6.8
Cprob	CRAN		1.2.4		
crayon	CRAN	1.3.2	1.3.2	1.3.2	1.3.2
crop	CRAN		0.0-2	0.0-2	
curl	CRAN	1.2	2.3	2.3	0.9.7
d3Network	CRAN		0.5.2.1		
data.table	CRAN	1.9.6	1.10.0	1.10.1	1.9.6
data.tree	CRAN		0.7.0	0.7.0	
datasets	base	3.3.2	3.3.2	3.3.1	3.3.0
DBI	CRAN	0.5-1	0.5-1	0.5-1	0.5-1
dendextend	CRAN	1.4.0	1.4.0	1.4.0	
DEoptimR	CRAN	1.0-8	1.0-8	1.0-8	1.0-4
desc	CRAN	1.1.0		1.1.0	
devtools	CRAN	1.12.0	1.12.0	1.12.0	1.12.0
DiagrammeR	CRAN		0.9.0	0.9.0	
dichromat	CRAN	2.0-0	2.0-0	2.0-0	2.0-0
digest	CRAN	0.6.10	0.6.11	0.6.12	0.6.9
diptest	CRAN	0.75-7	0.75-7	0.75-7	
doParallel	CRAN	1.0.10	1.0.10	1.0.10	1.0.10
dplyr	CRAN	0.5.0	0.5.0	0.5.0	0.5.0
ellipse	CRAN		0.3-8	0.3-8	0.3-8
evaluate	CRAN		0.1	0.1	0.9
fdrtool	CRAN		1.2.15		

fields	CRAN		8.1		
flexmix	CRAN	2.3-13	2.3-13	2.3-13	
forcats	CRAN	0.2.0			
foreach	CRAN	1.4.3	1.4.3	1.4.3	1.4.3
foreign	base	0.8-67	0.8-67	0.8-67	0.8-66
formatR	CRAN		1.4	1.4	1.4
Formula	CRAN		1.2-1		1.2-1
fpc	CRAN	2.1-10	2.1-10	2.1-10	
futile.logger	CRAN		1.4.3	1.4.3	1.4.1
futile.options	CRAN		1.0.0	1.0.0	1.0.0
gdata	CRAN	2.17.0	2.17.0	2.17.0	2.17.0
geepack	CRAN		1.2-1		
GenomeInfoDb	Bioconductor		1.10.2	1.10.1	
GenomicAlignments	Bioconductor		1.10.0	1.10.0	
GenomicRanges	Bioconductor		1.26.2	1.26.1	
ggm	CRAN		2.3		
ggplot2	CRAN	2.1.0	2.2.1	2.2.1	2.1.0
git2r	CRAN	0.15.0	0.18.0	0.16.0	0.15.0
glasso	CRAN		1.8		
GO.db	Bioconductor		3.4.0	3.2.2	3.3.0
GOSemSim	Bioconductor		2.0.3	1.28.2	1.30.3
gplots	CRAN	3.0.1	3.0.1	3.0.1	3.0.1
graph	Bioconductor		1.52.0		
graphics	base	3.3.2	3.3.2	3.3.1	3.3.0
graphsim	GitHub TomKellyGenetics	0.1.0	0.1.0	0.1.0	0.1.0
grDevices	base	3.3.2	3.3.2	3.3.1	3.3.0
grid	base	3.3.2	3.3.2	3.3.1	3.3.0
gridBase	CRAN	0.4-7	0.4-7	0.4-7	0.4-7
gridExtra	CRAN	2.2.1	2.2.1	2.2.1	2.2.1
gridGraphics	CRAN		0.1-5		
gtable	CRAN	0.2.0	0.2.0	0.2.0	0.2.0
gtools	CRAN	3.5.0	3.5.0	3.5.0	3.5.0
haven	CRAN	1.0.0			

heatmap.2x	GitHub TomKellyGenetics	0.0.0.9000	0.0.0.9000	0.0.0.9000	0.0.0.9000
hgu133plus2.db	Bioconductor	3.2.3			
highr	CRAN	0.6	0.6	0.6	
Hmisc	CRAN		4.0-2	4.0-2	3.17-4
hms	CRAN	0.2	0.3		
htmlTable	CRAN		1.8	1.9	
htmltools	CRAN	0.3.5	0.3.5	0.3.5	0.3.5
htmlwidgets	CRAN		0.8	0.8	
httpuv	CRAN	1.3.3		1.3.3	
httr	CRAN	1.2.1	1.2.1	1.2.1	1.1.0
huge	CRAN		1.2.7		
hunspell	CRAN		2.3		2
hypergraph	CRAN		1.46.0		
igraph	CRAN	1.0.1	1.0.1	1.0.1	1.0.1
igraph.extensions	GitHub TomKellyGenetics	0.1.0.9001	0.1.0.9001	0.1.0.9001	0.1.0.9001
influenceR	CRAN		0.1.0	0.1.0	
info.centrality	GitHub TomKellyGenetics	0.1.0	0.1.0	0.1.0	0.1.0
IRanges	Bioconductor		2.8.1	2.8.1	2.6.1
irlba	CRAN	2.1.1	2.1.2	2.1.2	2.0.0
iterators	CRAN	1.0.8	1.0.8	1.0.8	1.0.8
jpeg	CRAN		0.1-8		
jsonlite	CRAN	1.1	1.2	1.3	0.9.20
KEGG.db	Bioconductor		3.2.3		
kernlab	CRAN	0.9-25	0.9-25	0.9-25	
KernSmooth	base	2.23-15	2.23-15	2.23-15	2.23-15
knitr	CRAN		1.15.1	1.15.1	1.14
labeling	CRAN	0.3	0.3	0.3	0.3
lambda.r	CRAN		1.1.9	1.1.9	1.1.7
lattice	base	0.20-34	0.20-34	0.20-34	0.20-33
latticeExtra	CRAN		0.6-28		0.6-28
lava	CRAN		1.4.6		
lavaan	CRAN		0.5-22		

lazyeval	CRAN	0.2.0	0.2.0	0.2.0	0.2.0
les	CRAN		1.24.0		
lgtdl	CRAN		1.1.3		
limma	Bioconductor		3.30.7	3.30.3	
lme4	CRAN		1.1-12		1.1-12
lubridate	CRAN	1.6.0			
magrittr	CRAN	1.5	1.5	1.5	1.5
maps	CRAN		3.1.1		
markdown	CRAN		0.7.7	0.7.7	0.7.7
MASS	base	7.3-45	7.3-45	7.3-45	7.3-45
Matrix	base	1.2-7.1	1.2-7.1	1.2-8	1.2-6
matrixcalc	CRAN	1.0-3	1.0-3	1.0-3	1.0-3
mclust	CRAN	5.2	5.2.1	5.2.2	5.2
memoise	CRAN	1.0.0	1.0.0	1.0.0	1.0.0
methods	base	3.3.2	3.3.2	3.3.1	3.3.0
mgcv	base	1.8-16	1.8-16	1.8-17	1.8-12
mi	CRAN		1		
mime	CRAN	0.5	0.5	0.5	0.4
minqa	CRAN		1.2.4		1.2.4
mnormt	CRAN	1.5-5	1.5-5		1.5-4
modelr	CRAN	0.1.0			
modeltools	CRAN	0.2-21	0.2-21	0.2-21	
multtest	Bioconductor		2.30.0	2.30.0	
munsell	CRAN	0.4.3	0.4.3	0.4.3	0.4.3
mvtnorm	CRAN	1.0-5	1.0-5	1.0-6	1.0-5
network	CRAN		1.13.0		
nlme	base	3.1-128	3.1-128	3.1-131	3.1-128
nloptr	CRAN		1.0.4		1.0.4
NMF	CRAN	0.20.6	0.20.6	0.20.6	0.20.6
nnet	base	7.3-12	7.3-12	7.3-12	7.3-12
numDeriv	CRAN		2016.8-1		2014.2-1
openssl	CRAN	0.9.4	0.9.6	0.9.6	0.9.4
org.Hs.eg.db	Bioconductor		3.1.2		3.3.0
org.Sc.sgd.db	Bioconductor		3.4.0		
parallel	base	3.3.2	3.3.2	3.3.1	3.3.0

pathway.structure	GitHub				
.permutation	TomKellyGenetics	0.1.0	0.1.0	0.1.0	0.1.0
pbivnorm	CRAN		0.6.0		
PGSEA	Bioconductor		1.48.0		
pkgmaker	CRAN	0.22	0.22	0.22	0.22
PKI	CRAN		0.1-3		
plogr	CRAN		0.1-1	0.1-1	
plot.igraph	GitHub				
	TomKellyGenetics	0.0.0.9001	0.0.0.9001	0.0.0.9001	0.0.0.9001
plotrix	CRAN		3.6-4		
plyr	CRAN	1.8.4	1.8.4	1.8.4	1.8.3
png	CRAN		0.1-7		0.1-7
prabclus	CRAN	2.2-6	2.2-6	2.2-6	
praise	CRAN	1.0.0	1.0.0		1.0.0
pROC	CRAN		1.8	1.9.1	
prodlim	CRAN		1.5.7		
prof.tree	CRAN		0.1.0		
protoools	CRAN		0.99-2		
progress	CRAN			1.1.2	
psych	CRAN	1.6.12	1.6.12		
purrr	CRAN	0.2.2	0.2.2	0.2.2	0.2.2
qgraph	CRAN		1.4.1		
quadprog	CRAN		1.5-5	1.5-5	1.5-5
R.methodsS3	CRAN		1.7.1		1.7.1
R.oo	CRAN		1.21.0		1.20.0
R.utils	CRAN		2.5.0		
R6	CRAN	2.1.3	2.2.0	2.2.0	2.1.3
RBGL	CRAN		1.50.0		
RColorBrewer	CRAN	1.1-2	1.1-2	1.1-2	1.1-2
Rcpp	CRAN	0.12.7	0.12.9	0.12.9	0.12.7
RcppArmadillo	CRAN			0.7.700.0.0	0.6.700.6.0
RcppEigen	CRAN		0.3.2.9.0		0.3.2.8.1
RCurl	CRAN		1.95-4.8	1.95-4.8	1.95-4.8
reactome.db	Bioconductor		1.52.1	1.52.1	

		GitHub			
		TomKellyGenetics	0.1		
reactometree					
readr	CRAN	1.0.0	1.0.0		
readxl	CRAN	0.1.1			
registry	CRAN	0.3	0.3	0.3	0.3
reshape2	CRAN	1.4.1	1.4.2	1.4.2	1.4.1
rgexf	CRAN		0.15.3	0.15.3	
rgl	CRAN			0.97.0	0.95.1441
Rgraphviz	CRAN		2.18.0		
rjson	CRAN		0.2.15		
RJSONIO	CRAN		1.3-0		
rmarkdown	CRAN		1.3	1.3	1
Rmpi	CRAN		0.6-6		0.6-5
rngtools	CRAN	1.2.4	1.2.4	1.2.4	1.2.4
robustbase	CRAN	0.92-7	0.92-7	0.92-7	0.92-5
ROCR	CRAN	1.0-7	1.0-7	1.0-7	1.0-7
Rook	CRAN		1.1-1	1.1-1	
roxygen2	CRAN	6.0.1	5.0.1	6.0.1	5.0.1
rpart	base	4.1-10	4.1-10	4.1-10	4.1-10
rprojroot	CRAN	1.2	1.1	1.2	
Rsamtools	Bioconductor		1.26.1	1.26.1	
rsconnect	CRAN		0.7		
RSQLite	CRAN		1.1-2	1.1-2	1.0.0
rstudioapi	CRAN	0.6	0.6	0.6	0.6
rvest	CRAN	0.3.2			
S4Vectors	Bioconductor		0.12.1	0.12.0	0.10.3
safe	Bioconductor		3.14.0	3.10.0	
scales	CRAN	0.4.0	0.4.1	0.4.1	0.4.0
selectr	CRAN	0.3-1			
sem	CRAN		3.1-8		
shiny	CRAN	0.14		1.0.0	
slpt	GitHub TomKellyGenetics	0.1.0	0.1.0	0.1.0	0.1.0
sm	CRAN	2.2-5.4	2.2-5.4		
sna	CRAN		2.4		

snow	CRAN	0.4-1	0.4-2	0.4-2	0.3-13
sourcetools	CRAN	0.1.5		0.1.5	
SparseM	CRAN		1.74		1.7
spatial	base	7.3-11	7.3-11	7.3-11	7.3-11
splines	base	3.3.2	3.3.2	3.3.1	3.3.0
statnet.common	CRAN		3.3.0		
stats	base	3.3.2	3.3.2	3.3.1	3.3.0
stats4	base	3.3.2	3.3.2	3.3.1	3.3.0
stringi	CRAN	1.1.1	1.1.2	1.1.2	1.0-1
stringr	CRAN	1.1.0	1.1.0	1.2.0	1.0.0
Summarized Experiment	Bioconductor		1.4.0	1.4.0	
survival	base	2.39-4	2.40-1	2.40-1	2.39-4
tcltk	base	3.3.2	3.3.2	3.3.1	3.3.0
testthat	CRAN	1.0.2	1.0.2		1.0.2
tibble	CRAN	1.2	1.2	1.2	1.2
tidyR	CRAN	0.6.1	0.6.1	0.6.1	
tidyverse	GitHub hadley	1.1.1			
timeline	CRAN		0.9		
tools	base	3.3.2	3.3.2	3.3.1	3.3.0
tpr	CRAN		0.3-1		
trimcluster	CRAN	0.1-2	0.1-2	0.1-2	
Unicode	CRAN	9.0.0-1	9.0.0-1	9.0.0-1	
utils	base	3.3.2	3.3.2	3.3.1	3.3.0
vioplot	CRAN		0.2		
vioplotx	GitHub TomKellyGenetics	0.0.0.9000	0.0.0.9000		
viridis	CRAN	0.3.4	0.3.4	0.3.4	
visNetwork	CRAN		1.0.3	1.0.3	
whisker	CRAN	0.3-2	0.3-2	0.3-2	0.3-2
withr	CRAN	1.0.2	1.0.2	1.0.2	1.0.2
XML	base	3.98-1.3	3.98-1.1	3.98-1.5	3.98-1.4
xml2	CRAN	1.1.1		1.1.1	1.0.0
xtable	CRAN	1.8-2	1.8-2	1.8-2	1.8-2

XVector	Bioconductor	0.14.0	0.14.0	
yaml	CRAN	2.1.14	2.1.14	2.1.13
zlibbioc	CRAN	1.20.0	1.20.0	
zoo	CRAN	1.7-13	1.7-14	1.7-13

# Appendix C

## Secondary Screen Data

A series of experimental genome-wide siRNA screens have been performed on synthetic lethal partners of *CDH1* (Telford *et al.*, 2015). The strongest candidates from a primary screen were subject to a further secondary screen for validation by independent replication with 4 gene knockdowns with different targeting siRNA. As shown in Table C.1, there is significant ( $p = 7.49 \times 10^{-3}$  by Fisher’s exact test) association between SLIPT candidates and stronger validations of siRNA candidates. Since there were more SLIPT $-$  genes among those not validated and more SLIPT $+$  genes among those validated with several siRNAs, this supports the use of SLIPT as a synthetic lethal discovery procedure which may augment such screening experiments.

Table C.1: Comparing SLIPT genes against Secondary siRNA Screen in breast cancer

		Secondary Screen					<b>Total</b>	
		0/4	1/4	2/4	3/4	4/4		
<b>SLIPT<math>+</math></b>	Observed	70	46	31	8	2	157	
	Expected	85	44	10	4	2		
<b>SLIPT<math>-</math></b>	Observed	190	90	31	10	4	325	
	Expected	175	91	42	12	4		
		<b>Total</b>	280	136	52	18	6	482

Similar analysis with mtSLIPT, comparing SLIPT against *CDH1* somatic mutation with siRNA validation results was not significant ( $p = 7.02 \times 10^{-1}$  by Fisher’s exact test). However, as shown in Table C.2, the observed and expected values were in a direction consistent with that observed above for SLIPT against low *CDH1* expression. It is not unexpected that this result does not have comparable statistical support due to the lower sample size for mutation data.

This analysis was replicated on a (smaller) stomach cancer dataset but it was less conclusive ( $p = 2.36 \times 10^{-1}$  by Fisher’s exact test). As shown in Table C.3, fewer

Table C.2: Comparing mtSLIPT genes against Secondary siRNA Screen in breast cancer

		Secondary Screen					<b>Total</b>
		0/4	1/4	2/4	3/4	4/4	
<b>mtSLIPT+</b>	Observed	54	35	17	4	6	<b>111</b>
	Expected	60	31	14	4	1	
<b>mtSLIPT-</b>	Observed	206	101	45	14	5	<b>371</b>
	Expected	200	105	48	14	4	
<b>Total</b>		269	143	63	19	6	<b>482</b>

SLIPT candidates were validated than expected statistically. However, these results in stomach cancer may not be directly comparable to experiments in a breast cell line. Genes validated by 0 or 1 siRNA behave consistently with the results above.

Table C.3: Comparing SLIPT genes against Secondary siRNA Screen in stomach cancer

		Secondary Screen					<b>Total</b>
		0/4	1/4	2/4	3/4	4/4	
<b>SLIPT+</b>	Observed	67	47	13	4	1	<b>132</b>
	Expected	71	37	17	5	2	
<b>SLIPT-</b>	Observed	195	90	50	14	5	<b>354</b>
	Expected	190	100	46	13	4	
<b>Total</b>		262	137	63	19	6	<b>486</b>

# Appendix D

## Mutation Analysis in Breast Cancer

### D.1 Synthetic Lethal Genes and Pathways

SLIPT expression analysis (described in section 3.1) on TCGA breast cancer data ( $n = 969$ ) found the following genes and pathways, described in sections 4.1 and 4.1.1.

Table D.1: Candidate synthetic lethal genes against E-cadherin from mtSLIPT

Gene	Observed	Expected	$\chi^2$ value	p-value	p-value (FDR)
<i>TFAP2B</i>	8	36.7	89.5	$3.60 \times 10^{-20}$	$8.37 \times 10^{-17}$
<i>ZNF423</i>	15	36.7	78.8	$7.89 \times 10^{-18}$	$1.22 \times 10^{-14}$
<i>CALCOCO1</i>	11	36.7	76.8	$2.09 \times 10^{-17}$	$2.59 \times 10^{-14}$
<i>RBM5</i>	13	36.7	75.7	$3.65 \times 10^{-17}$	$4.00 \times 10^{-14}$
<i>BTG2</i>	7	36.7	71.7	$2.72 \times 10^{-16}$	$1.81 \times 10^{-13}$
<i>RXRA</i>	6	36.7	70.5	$5.00 \times 10^{-16}$	$2.97 \times 10^{-13}$
<i>SLC27A1</i>	11	36.7	70.3	$5.42 \times 10^{-16}$	$2.97 \times 10^{-13}$
<i>MEF2D</i>	12	36.7	69.6	$7.86 \times 10^{-16}$	$3.95 \times 10^{-13}$
<i>NISCH</i>	12	36.7	69.6	$7.86 \times 10^{-16}$	$3.95 \times 10^{-13}$
<i>AVPR2</i>	9	36.7	69.2	$9.36 \times 10^{-16}$	$4.58 \times 10^{-13}$
<i>CRY2</i>	13	36.7	68.9	$1.07 \times 10^{-15}$	$4.98 \times 10^{-13}$
<i>RAPGEF3</i>	13	36.7	68.9	$1.07 \times 10^{-15}$	$4.98 \times 10^{-13}$
<i>NRIP2</i>	10	36.7	68.2	$1.58 \times 10^{-15}$	$7.18 \times 10^{-13}$
<i>DARC</i>	12	36.7	66.4	$3.76 \times 10^{-15}$	$1.54 \times 10^{-12}$
<i>SFRS5</i>	12	36.7	66.4	$3.76 \times 10^{-15}$	$1.54 \times 10^{-12}$
<i>NOSTRIN</i>	5	36.7	65.1	$7.40 \times 10^{-15}$	$2.70 \times 10^{-12}$
<i>KIF13B</i>	12	36.7	63.4	$1.69 \times 10^{-14}$	$5.16 \times 10^{-12}$
<i>TENC1</i>	10	36.7	62.5	$2.67 \times 10^{-14}$	$7.40 \times 10^{-12}$
<i>MFAP4</i>	12	36.7	60.5	$7.17 \times 10^{-14}$	$1.67 \times 10^{-11}$
<i>ELN</i>	13	36.7	59.7	$1.07 \times 10^{-13}$	$2.32 \times 10^{-11}$
<i>SGK223</i>	14	36.7	59	$1.51 \times 10^{-13}$	$3.05 \times 10^{-11}$
<i>KIF12</i>	11	36.7	58.8	$1.74 \times 10^{-13}$	$3.34 \times 10^{-11}$
<i>SELP</i>	11	36.7	58.8	$1.74 \times 10^{-13}$	$3.34 \times 10^{-11}$
<i>CIRBP</i>	9	36.7	58.7	$1.83 \times 10^{-13}$	$3.41 \times 10^{-11}$
<i>CTDSP1</i>	9	36.7	58.7	$1.83 \times 10^{-13}$	$3.41 \times 10^{-11}$

Strongest candidate SL partners for *CDH1* by mtSLIPT with observed and expected mutant samples with low expression of partner genes

Table D.2: Pathways for *CDH1* partners from mtSLIPT

Pathways Over-represented	Pathway Size	SL Genes	p-value (FDR)
Eukaryotic Translation Elongation	86	60	$2.0 \times 10^{-128}$
Peptide chain elongation	83	59	$2.0 \times 10^{-128}$
Eukaryotic Translation Termination	83	58	$2.3 \times 10^{-125}$
Viral mRNA Translation	81	57	$2.5 \times 10^{-124}$
Nonsense Mediated Decay independent of the Exon Junction Complex	88	59	$8.6 \times 10^{-124}$
Nonsense-Mediated Decay	103	61	$5.2 \times 10^{-117}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex	103	61	$5.2 \times 10^{-117}$
Formation of a pool of free 40S subunits	93	58	$1.6 \times 10^{-116}$
L13a-mediated translational silencing of Ceruloplasmin expression	103	59	$1.3 \times 10^{-111}$
3' -UTR-mediated translational regulation	103	59	$1.3 \times 10^{-111}$
GTP hydrolysis and joining of the 60S ribosomal subunit	104	59	$6.2 \times 10^{-111}$
SRP-dependent cotranslational protein targeting to membrane	104	58	$2.9 \times 10^{-108}$
Eukaryotic Translation Initiation	111	59	$3.0 \times 10^{-106}$
Cap-dependent Translation Initiation	111	59	$3.0 \times 10^{-106}$
Influenza Viral RNA Transcription and Replication	108	57	$5.1 \times 10^{-103}$
Influenza Infection	117	59	$1.5 \times 10^{-102}$
Translation	141	64	$3.7 \times 10^{-101}$
Influenza Life Cycle	112	57	$1.4 \times 10^{-100}$
GPCR downstream signaling	472	116	$1.0 \times 10^{-80}$
Hemostasis	422	105	$1.4 \times 10^{-78}$

Gene set over-representation analysis (hypergeometric test) for Reactome pathways in mtSLIPT partners for *CDH1*

The genes and pathways identified in Tables D.1 and D.2 were derived from comparing the expression profiles of potential partners to the mutation status of *CDH1* (as shown in Figure 3.2). Thus the following analysis is only limited the samples for which TCGA provides both expression and somatic mutation data.

## D.2 Synthetic Lethal Expression Profiles

Similar to the analysis of synthetic lethal partners against low *CDH1* expression in 4.1.2, the partners detected from *CDH1* were also examined for their expression profiles and the pathway composition of gene clusters. Hierarchical clustering was performed on mtSLIPT partners for *CDH1* as showing in Figure D.1. Over-representation for Reactome pathways for each of the gene clusters identified is given in Table D.3.

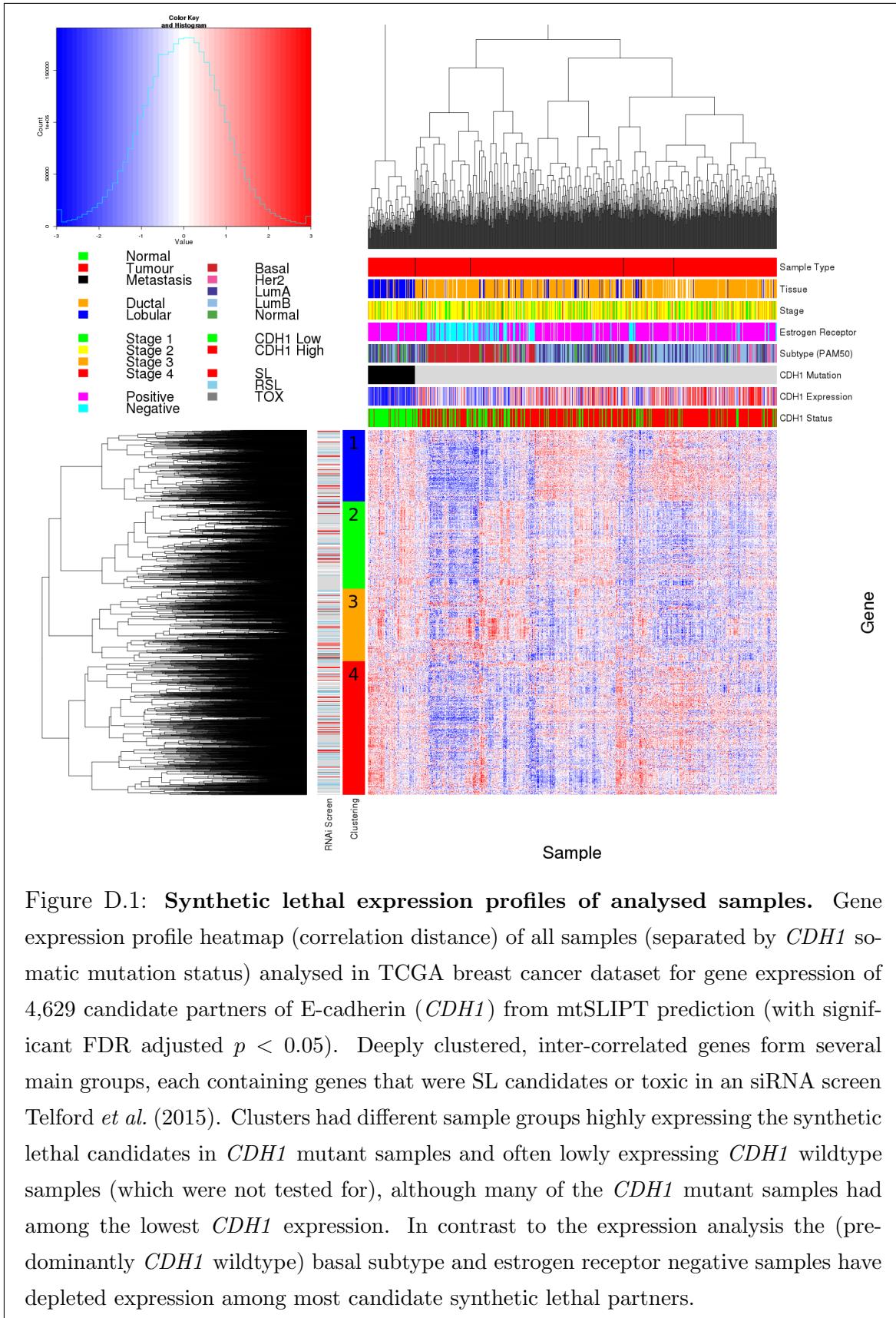


Table D.3: Pathway composition for clusters of *CDH1* partners from mtSLIPT

Pathways Over-represented in Cluster 1	Pathway Size	Cluster Genes	p-value (FDR)
Olfactory Signaling Pathway	57	8	$7.1 \times 10^{-9}$
Assembly of the primary cilium	149	14	$8.0 \times 10^{-9}$
Sphingolipid metabolism	62	8	$9.6 \times 10^{-9}$
Signaling by ERBB4	133	12	$5.1 \times 10^{-8}$
PI3K Cascade	65	7	$4.9 \times 10^{-7}$
Circadian Clock	33	5	$4.9 \times 10^{-7}$
Nuclear signaling by ERBB4	34	5	$4.9 \times 10^{-7}$
Intraflagellar transport	35	5	$4.9 \times 10^{-7}$
PI3K events in ERBB4 signaling	87	8	$4.9 \times 10^{-7}$
PIP3 activates AKT signaling	87	8	$4.9 \times 10^{-7}$
PI3K events in ERBB2 signaling	87	8	$4.9 \times 10^{-7}$
PI-3K cascade:FGFR1	87	8	$4.9 \times 10^{-7}$
PI-3K cascade:FGFR2	87	8	$4.9 \times 10^{-7}$
PI-3K cascade:FGFR3	87	8	$4.9 \times 10^{-7}$
PI-3K cascade:FGFR4	87	8	$4.9 \times 10^{-7}$
Deadenylation of mRNA	22	4	$5.6 \times 10^{-7}$
PI3K/AKT activation	90	8	$5.6 \times 10^{-7}$
Cargo trafficking to the periciliary membrane	38	5	$5.6 \times 10^{-7}$
Signaling by Hedgehog	108	9	$5.6 \times 10^{-7}$
Downstream signal transduction	143	11	$5.6 \times 10^{-7}$

Pathways Over-represented in Cluster 2	Pathway Size	Cluster Genes	p-value (FDR)
G <sub>αs</sub> signalling events	83	19	$5.1 \times 10^{-25}$
Extracellular matrix organization	238	30	$1.4 \times 10^{-18}$
Hemostasis	422	46	$2.7 \times 10^{-16}$
Aquaporin-mediated transport	32	9	$2.7 \times 10^{-16}$
Transcriptional regulation of white adipocyte differentiation	56	11	$1.7 \times 10^{-15}$
Degradation of the extracellular matrix	102	15	$1.7 \times 10^{-15}$
Integration of energy metabolism	84	13	$8.8 \times 10^{-15}$
GPCR downstream signaling	472	48	$2.8 \times 10^{-14}$
G <sub>αs</sub> signalling events	15	6	$5.0 \times 10^{-14}$
Molecules associated with elastic fibres	33	8	$5.4 \times 10^{-14}$
Phase 1 - Functionalization of compounds	67	11	$5.6 \times 10^{-14}$
Platelet activation, signaling and aggregation	179	20	$5.6 \times 10^{-14}$
Vasopressin regulates renal water homeostasis via Aquaporins	24	7	$6.1 \times 10^{-14}$
Elastic fibre formation	37	8	$.03 \times 10^{-13}$
Calmodulin induced events	27	7	$3.3 \times 10^{-13}$
CaM pathway	27	7	$3.3 \times 10^{-13}$
cGMP effects	18	6	$3.6 \times 10^{-13}$
G <sub>αs</sub> signalling events	167	18	$6.3 \times 10^{-13}$
Ca-dependent events	29	7	$8.2 \times 10^{-13}$
Binding and Uptake of Ligands by Scavenger Receptors	40	8	$8.2 \times 10^{-13}$

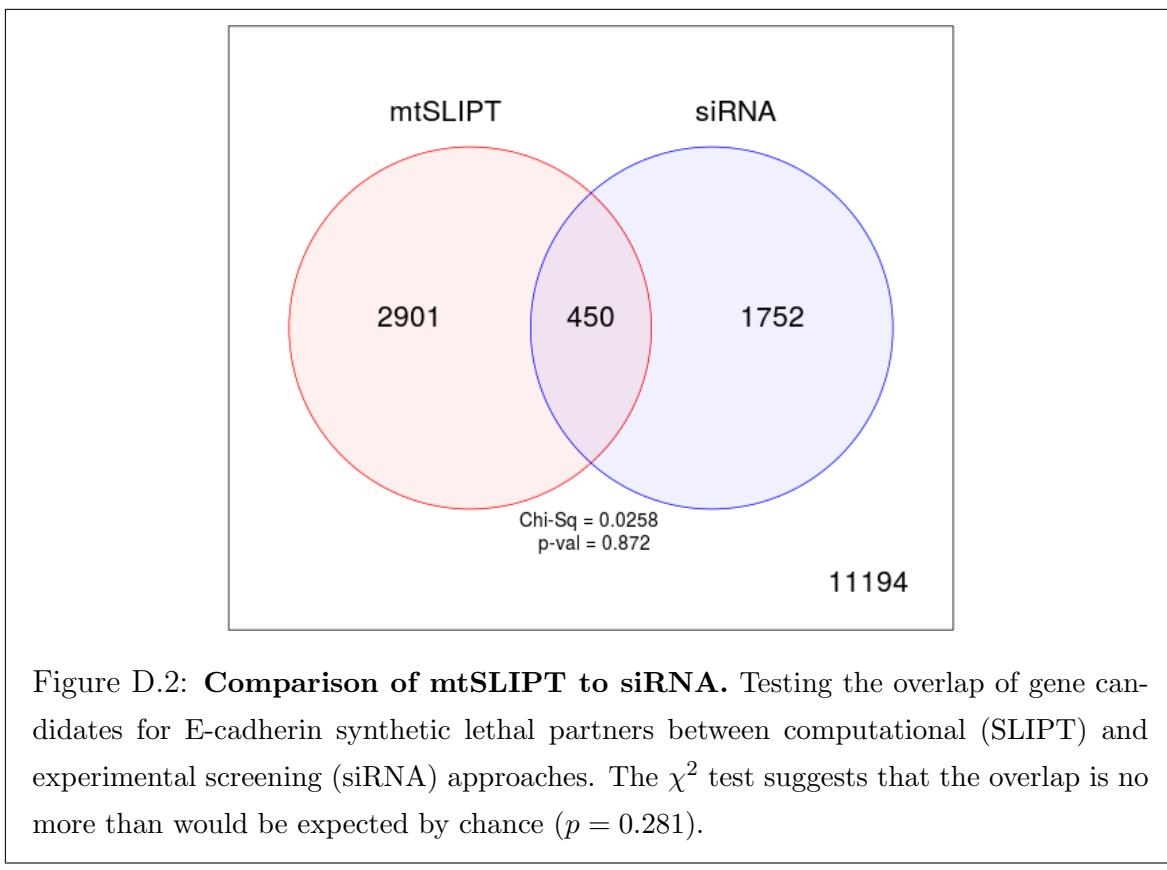
Pathways Over-represented in Cluster 3	Pathway Size	Cluster Genes	p-value (FDR)
Eukaryotic Translation Elongation	86	55	$1.1 \times 10^{-112}$
Peptide chain elongation	83	54	$1.3 \times 10^{-112}$
Viral mRNA Translation	81	53	$1.6 \times 10^{-111}$
Eukaryotic Translation Termination	83	53	$7.1 \times 10^{-110}$
Nonsense Mediated Decay independent of the Exon Junction Complex	88	54	$1.0 \times 10^{-108}$
Formation of a pool of free 40S subunits	93	53	$4.1 \times 10^{-102}$
Nonsense-Mediated Decay	103	54	$3.9 \times 10^{-98}$
Nonsense-Mediated Decay enhanced by the Exon Junction Complex	103	54	$3.9 \times 10^{-98}$
L13a-mediated translational silencing of Ceruloplasmin expression	103	53	$1.2 \times 10^{-95}$
3' -UTR-mediated translational regulation	103	53	$1.2 \times 10^{-95}$
SRP-dependent cotranslational protein targeting to membrane	104	53	$4.3 \times 10^{-95}$
GTP hydrolysis and joining of the 60S ribosomal subunit	104	53	$4.3 \times 10^{-95}$
Influenza Viral RNA Transcription and Replication	108	53	$9.6 \times 10^{-93}$
Eukaryotic Translation Initiation	111	53	$4.2 \times 10^{-91}$
Cap-dependent Translation Initiation	111	53	$4.2 \times 10^{-91}$
Influenza Life Cycle	112	53	$1.4 \times 10^{-90}$
Influenza Infection	117	53	$6.2 \times 10^{-88}$
Translation	141	55	$3 \times 10^{-81}$
Formation of the ternary complex, and subsequently, the 43S complex	47	23	$2.3 \times 10^{-48}$
Translation initiation complex formation	54	23	$9.1 \times 10^{-45}$

Pathways Over-represented in Cluster 4	Pathway Size	Cluster Genes	p-value (FDR)
ECM proteoglycans	66	10	$2.9 \times 10^{-11}$
deactivation of the beta-catenin transactivating complex	38	7	$5.1 \times 10^{-10}$
Arachidonic acid metabolism	41	7	$1.1 \times 10^{-9}$
Gαq signalling events	149	14	$4.0 \times 10^{-9}$
HS-GAG degradation	21	5	$4.5 \times 10^{-9}$
Uptake and actions of bacterial toxins	22	5	$6.1 \times 10^{-9}$
Gastrin-CREB signalling pathway via PKC and MAPK	170	15	$6.1 \times 10^{-9}$
RNA Polymerase I, RNA Polymerase III, and Mitochondrial Transcription	64	8	$6.1 \times 10^{-9}$
Non-integrin membrane-ECM interactions	53	7	$1.5 \times 10^{-8}$
Syndecan interactions	25	5	$1.5 \times 10^{-8}$
NOTCH1 Intracellular Domain Regulates Transcription	40	6	$2.3 \times 10^{-8}$
Synthesis of Leukotrienes and Exoxins	15	4	$3.2 \times 10^{-8}$
Signaling by NOTCH1	59	7	$5.3 \times 10^{-8}$
Regulation of insulin secretion	44	6	$6.0 \times 10^{-8}$
Metabolism of lipids and lipoproteins	471	37	$8.2 \times 10^{-8}$
Signaling by NOTCH	80	8	$1.2 \times 10^{-7}$
Platelet activation, signaling and aggregation	179	14	$1.2 \times 10^{-7}$
Recruitment of mitotic centrosome proteins and complexes	64	7	$1.2 \times 10^{-7}$
Centrosome maturation	64	7	$1.2 \times 10^{-7}$
Biological oxidations	133	11	$1.5 \times 10^{-7}$

### D.3 Comparison to Primary Screen

The mutation synthetic lethal partners with *CDH1* were also compared to siRNA primary screen data (Telford *et al.*, 2015), as performed in section 4.2.2. These are expected to be more concordant with the experimental results performed on a null mutant, however this is not the case at the gene level: less genes overlapped with experimental candidates in Figure D.2. This may be affected by lower sample size for mutations in TCGA data or lower frequency (expected value) of *CDH1* mutations compared to low expression.



Despite a lower sample size (and low number of predicted partners) for mutation analysis, the pathway composition (Tables D.2 and D.4) is similar to expression analysis, as described in section 4.2.2.3. In particular, the resampling analysis (section D.3.1) supported many of the results of expression analysis (section 4.2.2.3.1) with Tables D.5 and D.6 detecting many of the same or functionally-related pathways.

Table D.4: Pathway composition for *CDH1* partners from mtSLIPT and siRNA

Predicted only by SLIPT (2901 genes)	Pathway	Size	Genes Identified	p-value (FDR)
Eukaryotic Translation Elongation		87	57	$2.8 \times 10^{-120}$
Peptide chain elongation		84	56	$3.1 \times 10^{-120}$
Eukaryotic Translation Termination		84	55	$2.8 \times 10^{-117}$
Viral mRNA Translation		82	54	$4.1 \times 10^{-116}$
Nonsense Mediated Decay independent of the Exon Junction Complex		89	55	$3.7 \times 10^{-113}$
Formation of a pool of free 40S subunits		94	55	$2.8 \times 10^{-109}$
Nonsense-Mediated Decay		104	57	$8.4 \times 10^{-108}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex		104	57	$8.4 \times 10^{-108}$
L13a-mediated translational silencing of Ceruloplasmin expression		104	56	$3.4 \times 10^{-105}$
3' -UTR-mediated translational regulation		104	56	$3.4 \times 10^{-105}$
GTP hydrolysis and joining of the 60S ribosomal subunit		105	56	$1.4 \times 10^{-104}$
Eukaryotic Translation Initiation		112	56	$2.8 \times 10^{-100}$
Cap-dependent Translation Initiation		112	56	$2.8 \times 10^{-100}$
SRP-dependent cotranslational protein targeting to membrane		105	54	$2.2 \times 10^{-99}$
Influenza Viral RNA Transcription and Replication		109	54	$5.3 \times 10^{-97}$
Influenza Life Cycle		113	54	$9.6 \times 10^{-95}$
Influenza Infection		118	55	$1.7 \times 10^{-94}$
Translation		142	60	$3.5 \times 10^{-94}$
Infectious disease		349	77	$5.9 \times 10^{-62}$
Extracellular matrix organization		241	54	$3.0 \times 10^{-52}$

Detected only by siRNA screen (1752 genes)	Pathway	Size	Genes Identified	p-value (FDR)
Class A/1 (Rhodopsin-like receptors)		282	69	$1.9 \times 10^{-59}$
GPCR ligand binding		363	78	$2.7 \times 10^{-54}$
Peptide ligand-binding receptors		175	41	$1.5 \times 10^{-42}$
$G_{\alpha i}$ signalling events		184	41	$1.1 \times 10^{-40}$
Gastrin-CREB signalling pathway via PKC and MAPK		180	37	$1.5 \times 10^{-35}$
$G_{\alpha q}$ signalling events		159	34	$3.7 \times 10^{-35}$
DAP12 interactions		159	27	$1.1 \times 10^{-24}$
VEGFA-VEGFR2 Pathway		91	19	$1.0 \times 10^{-23}$
Downstream signal transduction		146	24	$1.9 \times 10^{-22}$
Signaling by VEGF		99	19	$2.6 \times 10^{-22}$
DAP12 signaling		149	24	$4.2 \times 10^{-22}$
Organelle biogenesis and maintenance		264	34	$4.3 \times 10^{-20}$
Downstream signaling of activated FGFR1		134	21	$4.3 \times 10^{-20}$
Downstream signaling of activated FGFR2		134	21	$4.3 \times 10^{-20}$
Downstream signaling of activated FGFR3		134	21	$4.3 \times 10^{-20}$
Downstream signaling of activated FGFR4		134	21	$4.3 \times 10^{-20}$
Signaling by ERBB2		146	22	$5.3 \times 10^{-20}$
Signaling by FGFR		146	22	$5.3 \times 10^{-20}$
Signaling by FGFR1		146	22	$5.3 \times 10^{-20}$
Signaling by FGFR2		146	22	$5.3 \times 10^{-20}$

Intersection of SLIPT and siRNA screen (450 genes)	Pathway	Size	Genes Identified	p-value (FDR)
HS-GAG degradation		21	4	$4.9 \times 10^{-6}$
Retinoid metabolism and transport		39	5	$4.9 \times 10^{-6}$
Platelet activation, signaling and aggregation		186	13	$4.9 \times 10^{-6}$
Signaling by NOTCH4		11	3	$4.9 \times 10^{-6}$
$G_{\alpha s}$ signalling events		100	8	$5.0 \times 10^{-6}$
Defective EXT2 causes exostoses 2		12	3	$5.0 \times 10^{-6}$
Defective EXT1 causes exostoses 1, TRPS2 and CHDS		12	3	$5.0 \times 10^{-6}$
Class A/1 (Rhodopsin-like receptors)		289	18	$2.2 \times 10^{-5}$
Signaling by PDGF		173	11	$2.9 \times 10^{-5}$
Circadian Clock		34	4	$2.9 \times 10^{-5}$
Signaling by ERBB4		139	9	$4.3 \times 10^{-5}$
Role of LAT2/NTAL/LAB on calcium mobilization		99	7	$4.4 \times 10^{-5}$
Peptide ligand-binding receptors		181	11	$4.5 \times 10^{-5}$
Defective B4GALT7 causes EDS, progeroid type		19	3	$4.5 \times 10^{-5}$
Defective B3GAT3 causes JDSSDHD		19	3	$4.5 \times 10^{-5}$
Signaling by NOTCH		80	6	$4.5 \times 10^{-5}$
$G_{\alpha q}$ signalling events		164	10	$5.1 \times 10^{-5}$
Response to elevated platelet cytosolic $\text{Ca}^{2+}$		84	6	$7.1 \times 10^{-5}$
Signaling by ERBB2		148	9	$7.1 \times 10^{-5}$
Signaling by SCF-KIT		129	8	$8.3 \times 10^{-5}$

### D.3.1 Resampling Analysis

Table D.5: Pathways for *CDH1* partners from mtSLIPT

Reactome Pathway	Over-representation	Permutation
<b>Eukaryotic Translation Elongation</b>	$3.2 \times 10^{-128}$	$< 7.035 \times 10^{-4}$
Peptide chain elongation	$3.2 \times 10^{-128}$	$< 7.035 \times 10^{-4}$
<b>Eukaryotic Translation Termination</b>	$3.7 \times 10^{-125}$	$< 7.035 \times 10^{-4}$
Viral mRNA Translation	$4.1 \times 10^{-124}$	$< 7.035 \times 10^{-4}$
Nonsense Mediated Decay independent of the Exon Junction Complex	$1.4 \times 10^{-123}$	$< 7.035 \times 10^{-4}$
Nonsense-Mediated Decay	$8.4 \times 10^{-117}$	$< 7.035 \times 10^{-4}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex	$8.4 \times 10^{-117}$	$< 7.035 \times 10^{-4}$
Formation of a pool of free 40S subunits	$2.6 \times 10^{-116}$	$< 7.035 \times 10^{-4}$
L13a-mediated translational silencing of Ceruloplasmin expression	$2.0 \times 10^{-111}$	$< 7.035 \times 10^{-4}$
3' -UTR-mediated translational regulation	$2.0 \times 10^{-111}$	$< 7.035 \times 10^{-4}$
GTP hydrolysis and joining of the 60S ribosomal subunit	$9.9 \times 10^{-111}$	$< 7.035 \times 10^{-4}$
SRP-dependent cotranslational protein targeting to membrane	$4.7 \times 10^{-108}$	$< 7.035 \times 10^{-4}$
<b>Eukaryotic Translation Initiation</b>	$4.8 \times 10^{-106}$	$< 7.035 \times 10^{-4}$
Cap-dependent Translation Initiation	$4.8 \times 10^{-106}$	$< 7.035 \times 10^{-4}$
<b>Influenza Viral RNA Transcription and Replication</b>	$8.1 \times 10^{-103}$	$< 7.035 \times 10^{-4}$
<b>Influenza Infection</b>	$2.4 \times 10^{-102}$	$< 7.035 \times 10^{-4}$
<b>Translation</b>	$6.0 \times 10^{-101}$	$< 7.035 \times 10^{-4}$
<b>Influenza Life Cycle</b>	$2.2 \times 10^{-100}$	$< 7.035 \times 10^{-4}$
<b>Disease</b>	$2.1 \times 10^{-90}$	0.013347
<b>GPCR downstream signaling</b>	$1.6 \times 10^{-80}$	0.095478
Hemostasis	$2.1 \times 10^{-78}$	0.2671
Signaling by GPCR	$1.2 \times 10^{-73}$	0.44939
<i>Extracellular matrix organization</i>	$2.2 \times 10^{-67}$	0.054008
Metabolism of proteins	$1.4 \times 10^{-66}$	0.9607
Signal Transduction	$2.1 \times 10^{-66}$	0.48184
Developmental Biology	$2.5 \times 10^{-66}$	0.54075
Innate Immune System	$5.3 \times 10^{-66}$	0.9589
Infectious disease	$9.6 \times 10^{-66}$	0.21075
Signalling by NGF	$1.1 \times 10^{-62}$	0.43356
Immune System	$2.8 \times 10^{-62}$	0.23052

Over-representation (hypergeometric test) and Permutation p-values adjusted for multiple tests across pathways (FDR). Significant pathways are marked in bold (FDR < 0.05) and italics (FDR < 0.1).

Table D.6: Pathways for *CDH1* partners from mtSLIPT and siRNA primary screen

Reactome Pathway	Over-representation	Permutation
Visual phototransduction	$1.2 \times 10^{-9}$	0.86279
<b>G<sub>αs</sub> signalling events</b>	$2.9 \times 10^{-7}$	0.023066
Retinoid metabolism and transport	$2.9 \times 10^{-7}$	0.299
Acylic chain remodelling of PS	$1.1 \times 10^{-5}$	0.42584
Transcriptional regulation of white adipocyte differentiation	$1.1 \times 10^{-5}$	0.53928
Chemokine receptors bind chemokines	$1.1 \times 10^{-5}$	0.95259
<i>Signaling by NOTCH4</i>	$1.2 \times 10^{-5}$	0.079229
Defective EXT2 causes exostoses 2	$1.2 \times 10^{-5}$	0.22292
Defective EXT1 causes exostoses 1, TRPS2 and CHDS	$1.2 \times 10^{-5}$	0.22292
Platelet activation, signaling and aggregation	$1.2 \times 10^{-5}$	0.48853
Serotonin receptors	$1.4 \times 10^{-5}$	0.34596
Nicotinamide salvaging	$1.4 \times 10^{-5}$	0.70881
Phase 1 - Functionalization of compounds	$2 \times 10^{-5}$	0.31142
Amine ligand-binding receptors	$2.5 \times 10^{-5}$	0.34934
Acylic chain remodelling of PE	$3.8 \times 10^{-5}$	0.42615
Signaling by GPCR	$3.8 \times 10^{-5}$	0.93888
<b>Molecules associated with elastic fibres</b>	$3.9 \times 10^{-5}$	0.017982
DAP12 interactions	$3.9 \times 10^{-5}$	0.71983
Beta defensins	$3.9 \times 10^{-5}$	0.91458
Cytochrome P <sub>450</sub> - arranged by substrate type	$4.7 \times 10^{-5}$	0.83493
GPCR ligand binding	$5.7 \times 10^{-5}$	0.95258
Acylic chain remodelling of PC	$6.1 \times 10^{-5}$	0.42584
Response to elevated platelet cytosolic Ca <sup>2+</sup>	$6.4 \times 10^{-5}$	0.54046
<b>Arachidonic acid metabolism</b>	$6.7 \times 10^{-5}$	0.026696
Defective B4GALT7 causes EDS, progeroid type	$7.3 \times 10^{-5}$	0.24921
Defective B3GAT3 causes JDSSDHD	$7.3 \times 10^{-5}$	0.24921
Hydrolysis of LPC	$7.3 \times 10^{-5}$	0.80663
<b>Elastic fibre formation</b>	$7.4 \times 10^{-5}$	0.0058768
<b>HS-GAG degradation</b>	$9.4 \times 10^{-5}$	0.0083179
<i>Bile acid and bile salt metabolism</i>	$9.4 \times 10^{-5}$	0.079905
Netrin-1 signaling	0.00011	0.92216
<b>Integration of energy metabolism</b>	0.00011	0.011152
Dectin-2 family	0.00012	0.10385
Platelet sensitization by LDL	0.00012	0.34596
DAP12 signaling	0.00012	0.62787
Defensins	0.00012	0.77542
GPCR downstream signaling	0.00012	0.79454
<i>Diseases associated with glycosaminoglycan metabolism</i>	0.00013	0.065927
<i>Diseases of glycosylation</i>	0.00013	0.065927
Signaling by Retinoic Acid	0.00013	0.22292
Signaling by Leptin	0.00013	0.34596
Signaling by SCF-KIT	0.00013	0.70881
Opioid Signalling	0.00013	0.96053
Signaling by NOTCH	0.00015	0.26884
Platelet homeostasis	0.00015	0.4878
Signaling by NOTCH1	0.00016	0.13043
Class B/2 (Secretin family receptors)	0.00016	0.13994
<i>Diseases of Immune System</i>	0.0002	0.0795
<i>Diseases associated with the TLR signaling cascade</i>	0.0002	0.0795
A tetrasaccharide linker sequence is required for GAG synthesis	0.0002	0.42615

Over-representation (hypergeometric test) and Permutation p-values adjusted for multiple tests across pathways (FDR). Significant pathways are marked in bold (FDR < 0.05) and italics (FDR < 0.1).

## D.4 Compare SLIPT genes

The mutation synthetic lethal partners with *CDH1* were also compared to siRNA primary screen data (Telford *et al.*, 2015), by correlation and siRNA viability as described in sections 4.2.2.1 and 4.2.2.2.

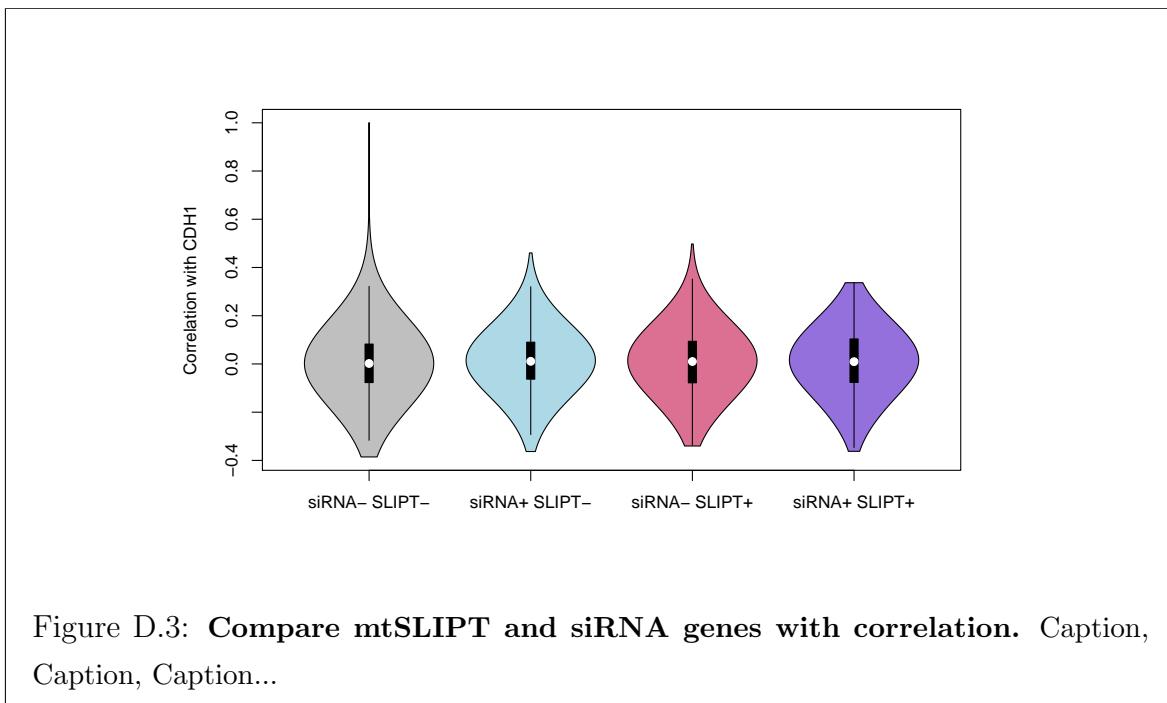


Figure D.3: **Compare mtSLIPT and siRNA genes with correlation.** Caption, Caption, Caption...

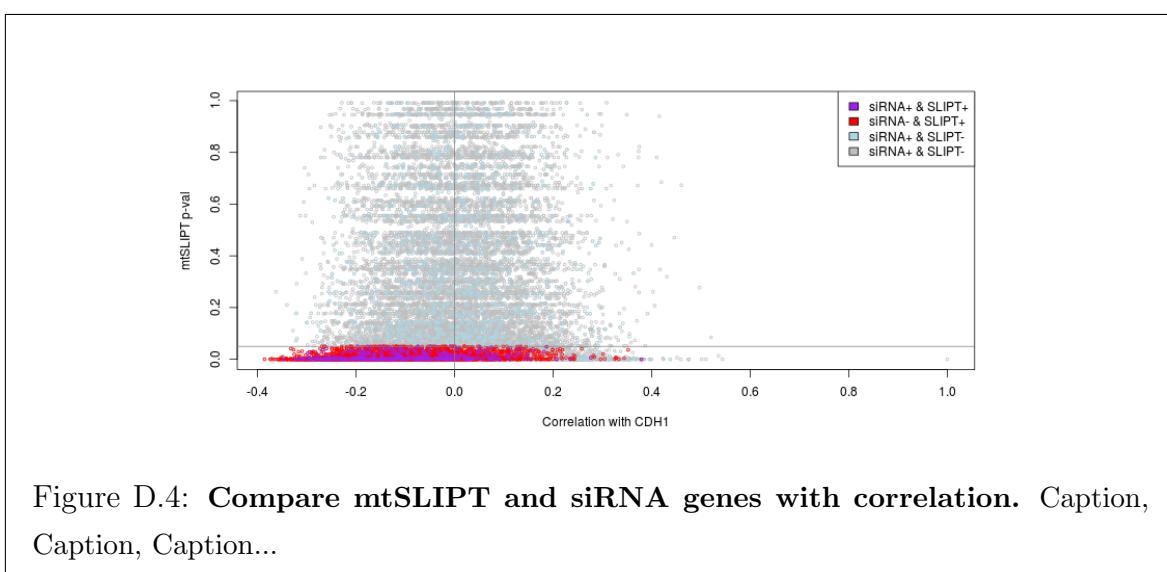
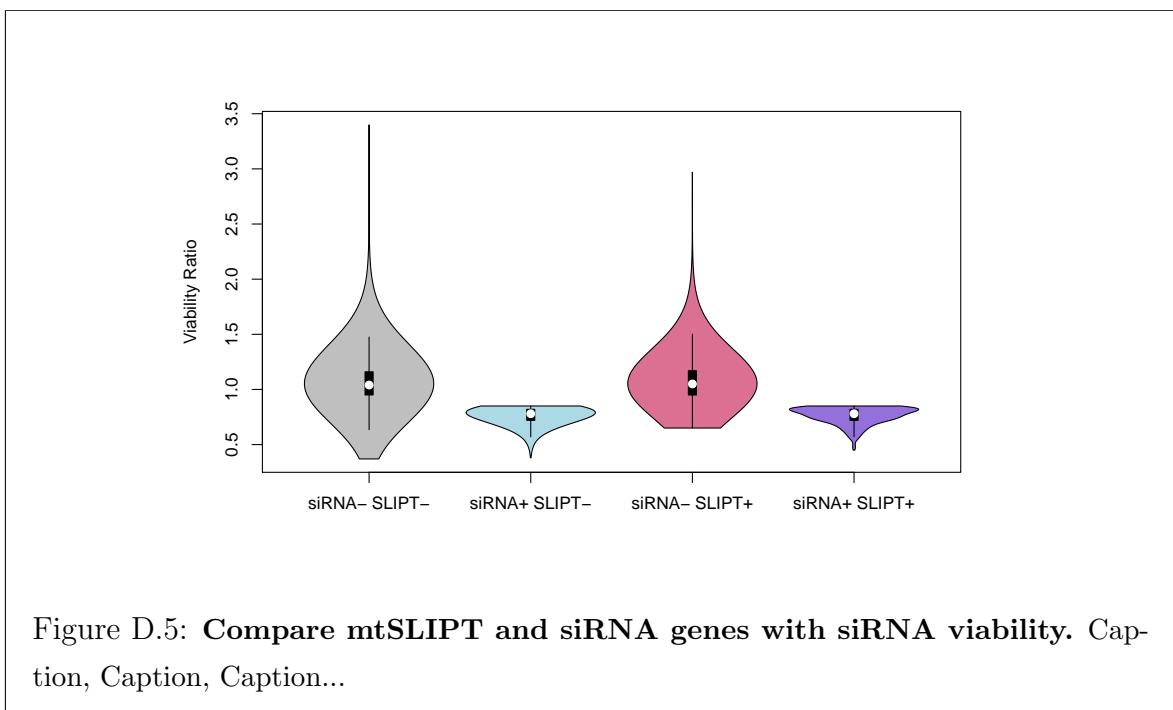


Figure D.4: **Compare mtSLIPT and siRNA genes with correlation.** Caption, Caption, Caption...



## D.5 Metagene Analysis

Metagene analysis was also performed for synthetic lethal candidates for *CDH1* mutation. These are described and compared to mutation analysis in section 4.4.3.

Table D.7: Candidate synthetic lethal metagenes against *CDH1* from mtSLIPT

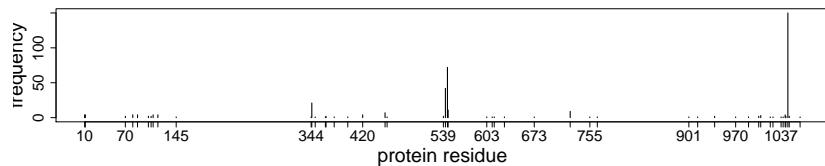
Pathway	ID	Observed	Expected	$\chi^2$ value	p-value	p-value (FDR)
Linoleic acid (LA) metabolism	2046105	79	36.70	87.03	$1.2637 \times 10^{-19}$	$2.0839 \times 10^{-160}$
ATF6-alpha activates chaperone genes	381183	78	36.70	80.25	$3.7449 \times 10^{-18}$	$3.0877 \times 10^{-150}$
Neurotoxicity of clostridium toxins	168799	8	36.70	79.41	$5.7092 \times 10^{-18}$	$3.1382 \times 10^{-150}$
Aquaporin-mediated transport	445717	8	36.70	76.28	$2.7327 \times 10^{-17}$	$9.0124 \times 10^{-150}$
Toxicity of botulinum toxin type G (BoNTG)	5250989	8	36.70	76.278	$2.7327 \times 10^{-17}$	$9.0124 \times 10^{-150}$
Purine metabolism	73847	75	36.70	75.86	$3.3623 \times 10^{-17}$	$9.2407 \times 10^{-150}$
Chk1Chk2(Cds1) mediated inactivation of Cyclin B:Cdk1 complex	75035	74	36.70	71.68	$2.7211 \times 10^{-16}$	$6.41 \times 10^{-140}$
Scavenging by Class F Receptors	3000484	75	36.70	69.56	$7.8573 \times 10^{-16}$	$1.4396 \times 10^{-130}$
Cytosolic tRNA aminoacylation	379716	75	36.70	69.56	$7.8573 \times 10^{-16}$	$1.4396 \times 10^{-130}$
G1S Transition	69206	74	36.70	69.21	$9.3593 \times 10^{-16}$	$1.5433 \times 10^{-130}$
ABC-family proteins mediated transport	382556	10	36.70	68.16	$1.5826 \times 10^{-15}$	$1.8641 \times 10^{-130}$
MG1 Transition	68874	74	36.70	68.16	$1.5826 \times 10^{-15}$	$1.8641 \times 10^{-130}$
DNA Replication Pre-Initiation	69002	74	36.70	68.16	$1.5826 \times 10^{-15}$	$1.8641 \times 10^{-130}$
Cell Cycle Checkpoints	69620	74	36.70	68.16	$1.5826 \times 10^{-15}$	$1.8641 \times 10^{-130}$
Basigin interactions	210991	74	36.70	67.23	$2.5162 \times 10^{-15}$	$2.7661 \times 10^{-130}$
Mitotic G1-G1S phases	453279	72	36.70	64.98	$7.7471 \times 10^{-15}$	$7.9843 \times 10^{-130}$
Metabolism of folate and pterines	196757	73	36.70	63.42	$1.6932 \times 10^{-14}$	$1.6424 \times 10^{-120}$
Tetrahydrobiopterin (BH4) synthesis, recycling, salvage and regulation	1474151	73	36.70	62.68	$2.4547 \times 10^{-14}$	$2.0427 \times 10^{-120}$
DNA Replication	69306	72	36.70	62.51	$2.6652 \times 10^{-14}$	$2.0427 \times 10^{-120}$
Separation of Sister Chromatids	2467813	71	36.70	62.47	$2.7252 \times 10^{-14}$	$2.0427 \times 10^{-120}$
M Phase	68886	71	36.70	62.47	$2.7252 \times 10^{-14}$	$2.0427 \times 10^{-120}$
Cell Cycle, Mitotic	69278	71	36.70	62.47	$2.7252 \times 10^{-14}$	$2.0427 \times 10^{-120}$
G0 and Early G1	1538133	70	36.70	61.62	$4.1658 \times 10^{-14}$	$2.8623 \times 10^{-120}$
Regulation of PLK1 Activity at G2M Transition	2565942	70	36.70	61.62	$4.1658 \times 10^{-14}$	$2.8623 \times 10^{-120}$
alpha-linolenic (omega3) and linoleic (omega6) acid metabolism	2046104	70	36.70	60.07	$9.0139 \times 10^{-14}$	$5.1255 \times 10^{-120}$

Strongest candidate SL partners for *CDH1* by mtSLIPT with observed and expected mutant samples with low expression of partner metagenes

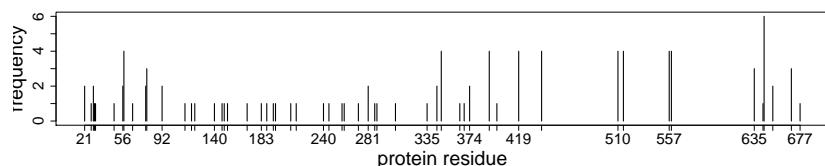
## D.6 Mutation Variation

Mutations have different effects as shown by the following examples in cancer genes.

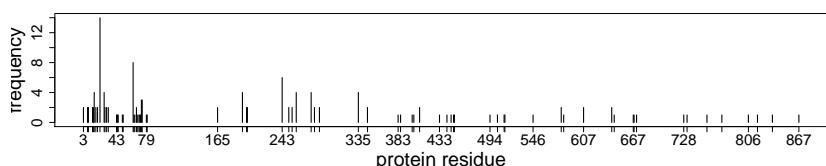
### D.6.1 Mutation Frequency



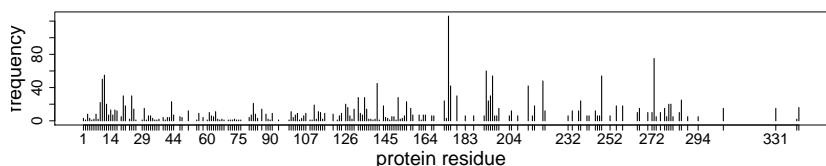
(a) *PI3KCA*



(b) *PI3KR1*



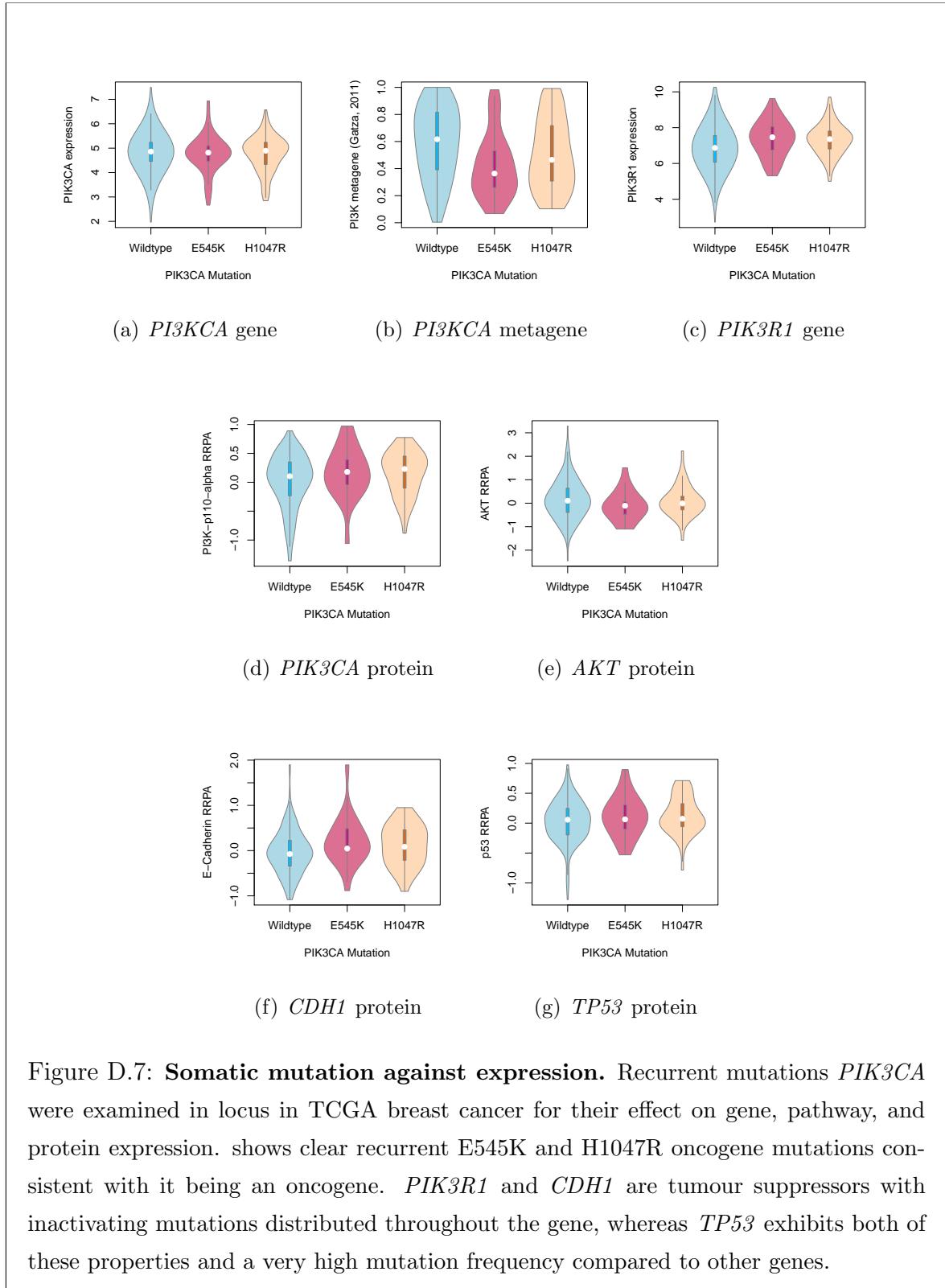
(c) *CDH1*



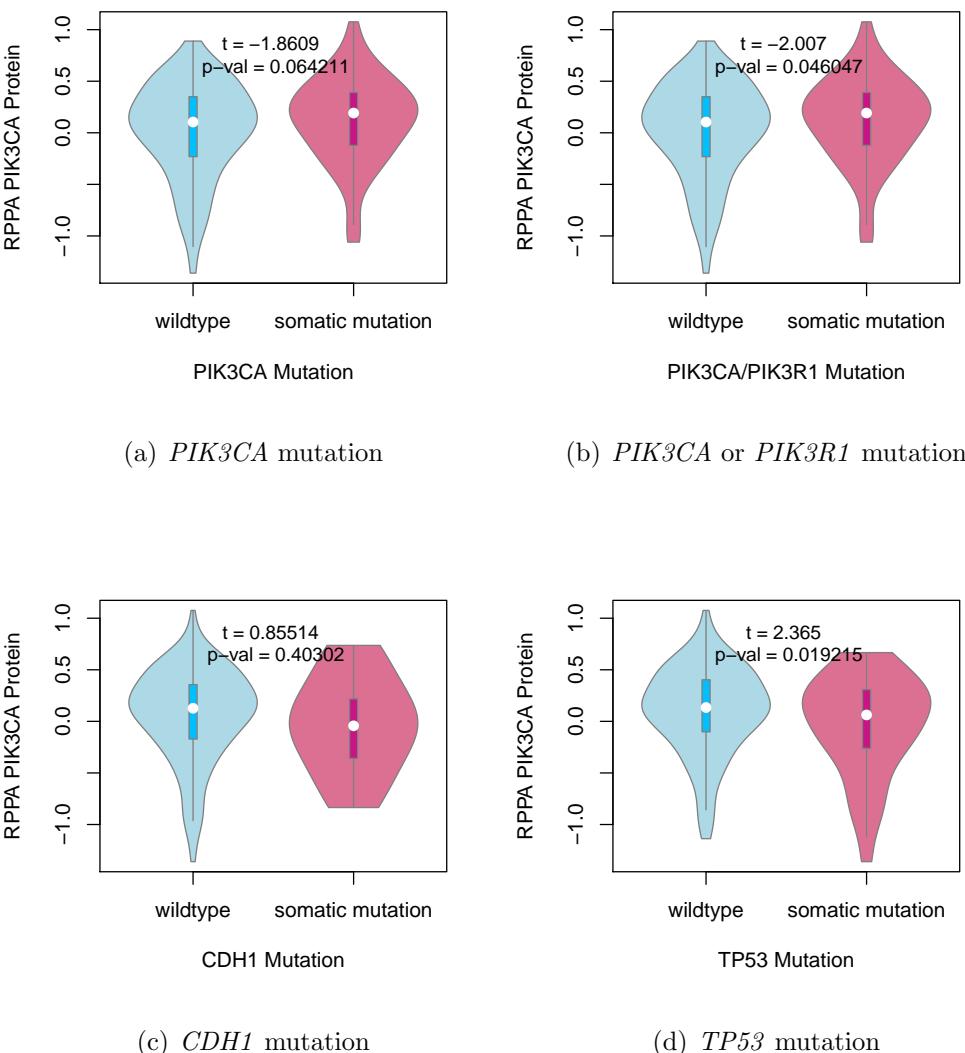
(d) *TP53*

Figure D.6: **Somatic mutation locus.** Mutation frequency at each locus in TCGA breast cancer. *PIK3CA* shows clear recurrent E545K and H1047R oncogene mutations consistent with it being an oncogene. *PIK3R1* and *CDH1* are tumour suppressors with inactivating mutations distributed throughout the gene, whereas *TP53* exhibits both of these properties and a very high mutation frequency compared to other genes.

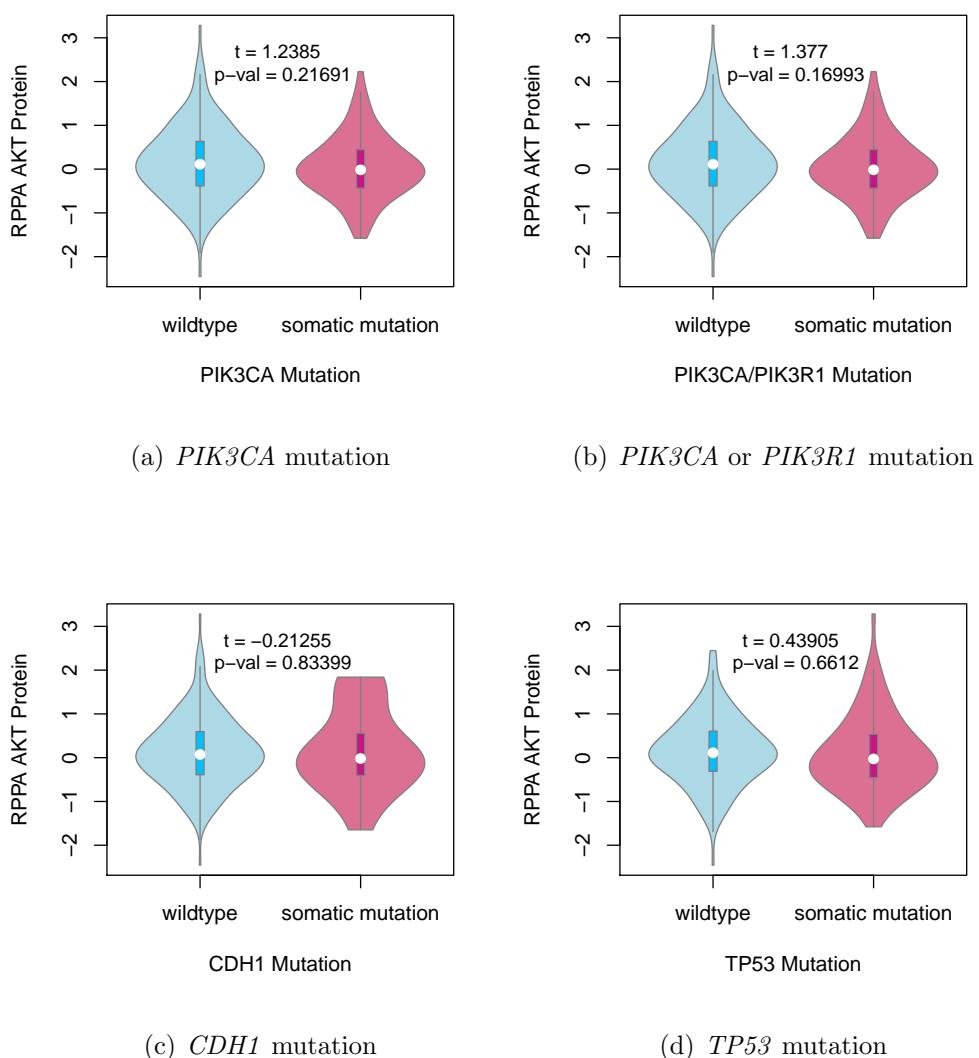
## D.6.2 PI3K Mutation Expression



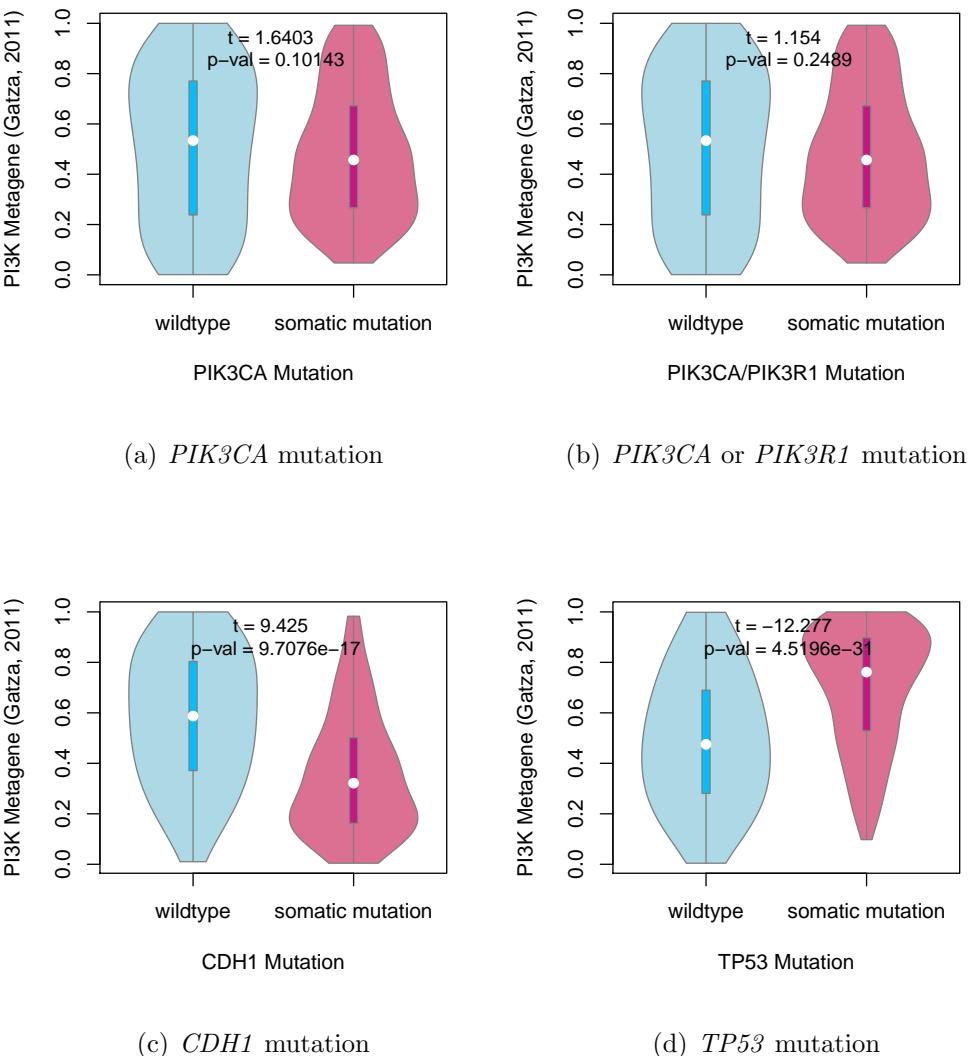
**Figure D.7: Somatic mutation against expression.** Recurrent mutations *PIK3CA* were examined in locus in TCGA breast cancer for their effect on gene, pathway, and protein expression. shows clear recurrent E545K and H1047R oncogene mutations consistent with it being an oncogene. *PIK3R1* and *CDH1* are tumour suppressors with inactivating mutations distributed throughout the gene, whereas *TP53* exhibits both of these properties and a very high mutation frequency compared to other genes.



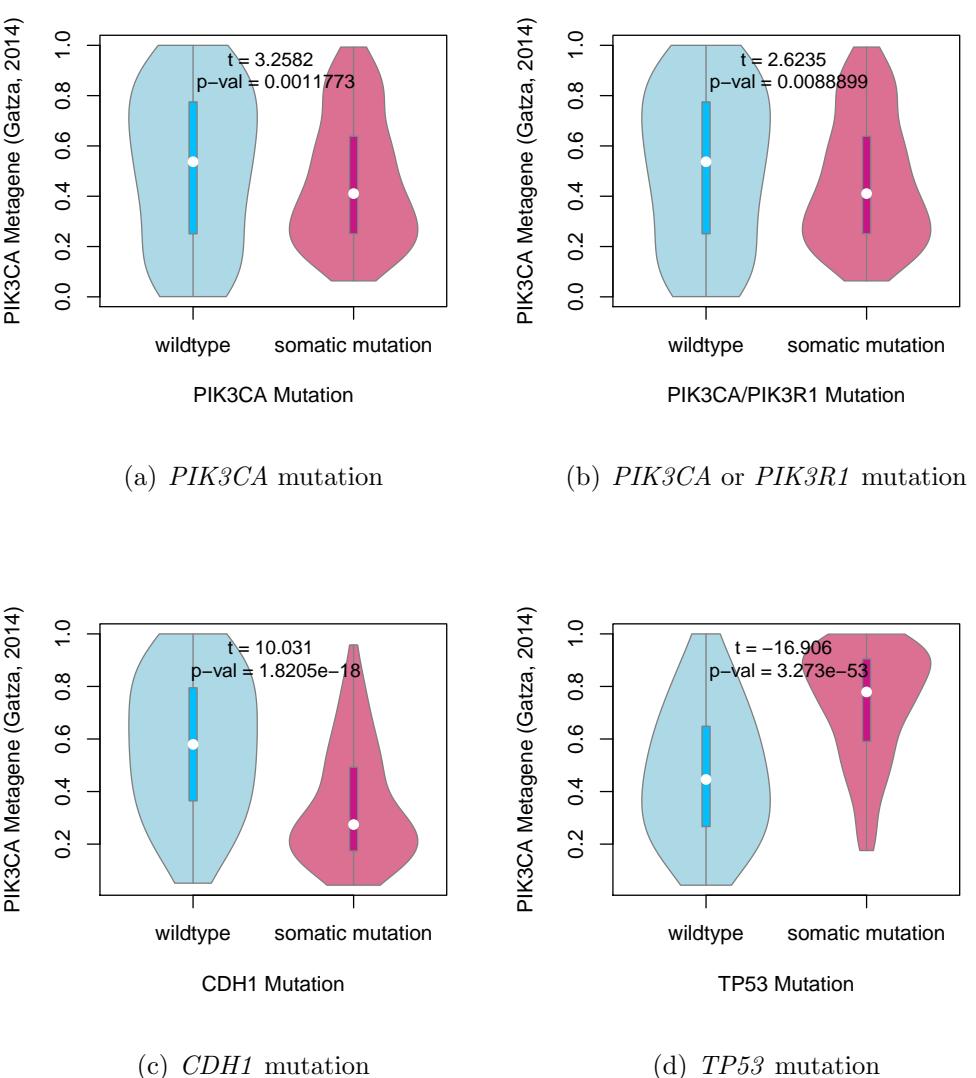
**Figure D.8: Somatic mutation against PI3K protein.** Recurrent mutations *PIK3CA* were examined in locus in TCGA breast cancer for their effect on gene, pathway, and protein expression (p110 $\alpha$  protein). shows clear recurrent E545K and H1047R oncogene mutations consistent with it being an oncogene. *PIK3R1* and *CDH1* are tumour suppressors with inactivating mutations distributed throughout the gene, whereas *TP53* exhibits both of these properties and a very high mutation frequency compared to other genes.



**Figure D.9: Somatic mutation against AKT protein.** Recurrent mutations *PIK3CA* were examined in locus in TCGA breast cancer for their effect on gene, pathway, and protein expression. shows clear recurrent E545K and H1047R oncogene mutations consistent with it being an oncogene. *PIK3R1* and *CDH1* are tumour suppressors with inactivating mutations distributed throughout the gene, whereas *TP53* exhibits both of these properties and a very high mutation frequency compared to other genes.



**Figure D.10: Somatic mutation against PI3K metagene.** Recurrent mutations *PIK3CA* were examined in locus in TCGA breast cancer for their effect on gene, pathway, and protein expression. shows clear recurrent E545K and H1047R oncogene mutations consistent with it being an oncogene. *PIK3R1* and *CDH1* are tumour suppressors with inactivating mutations distributed throughout the gene, whereas *TP53* exhibits both of these properties and a very high mutation frequency compared to other genes.



**Figure D.11: Somatic mutation against PIK3CA metagene.** Recurrent mutations *PIK3CA* were examined in locus in TCGA breast cancer for their effect on gene, pathway, and protein expression. shows clear recurrent E545K and H1047R oncogene mutations consistent with it being an oncogene. *PIK3R1* and *CDH1* are tumour suppressors with inactivating mutations distributed throughout the gene, whereas *TP53* exhibits both of these properties and a very high mutation frequency compared to other genes.

# **Appendix E**

## **Metagene Expression Profiles**

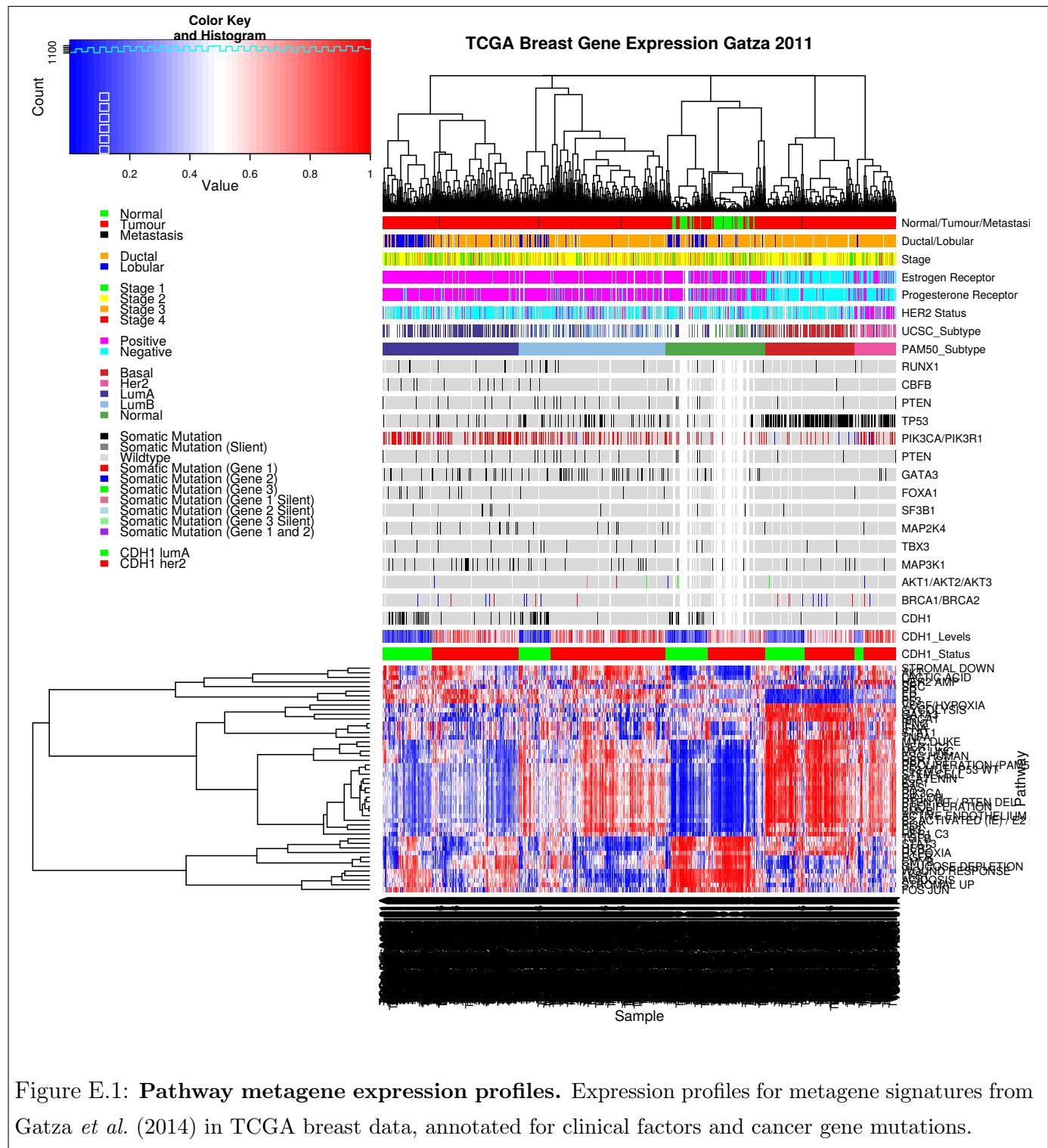
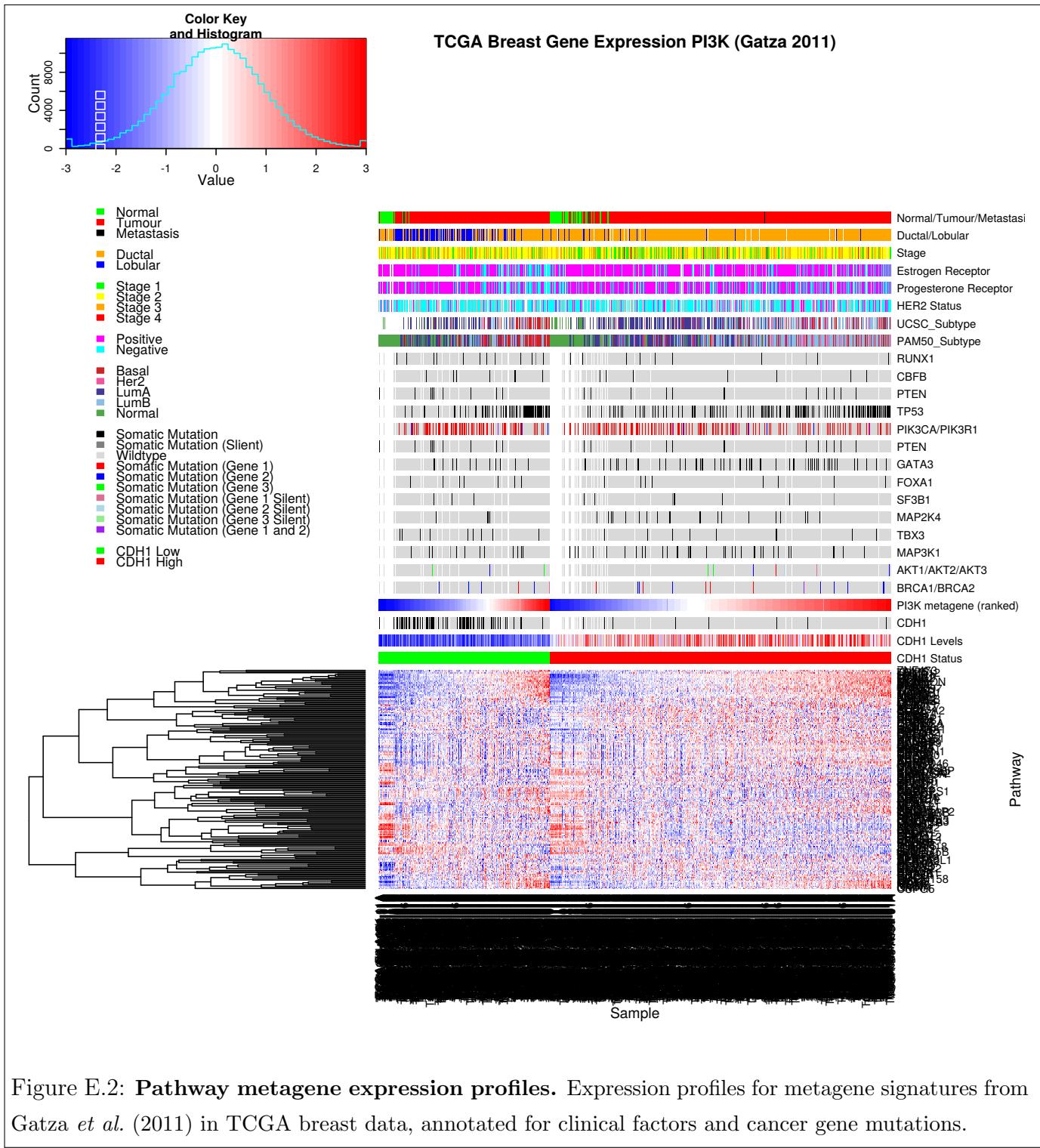
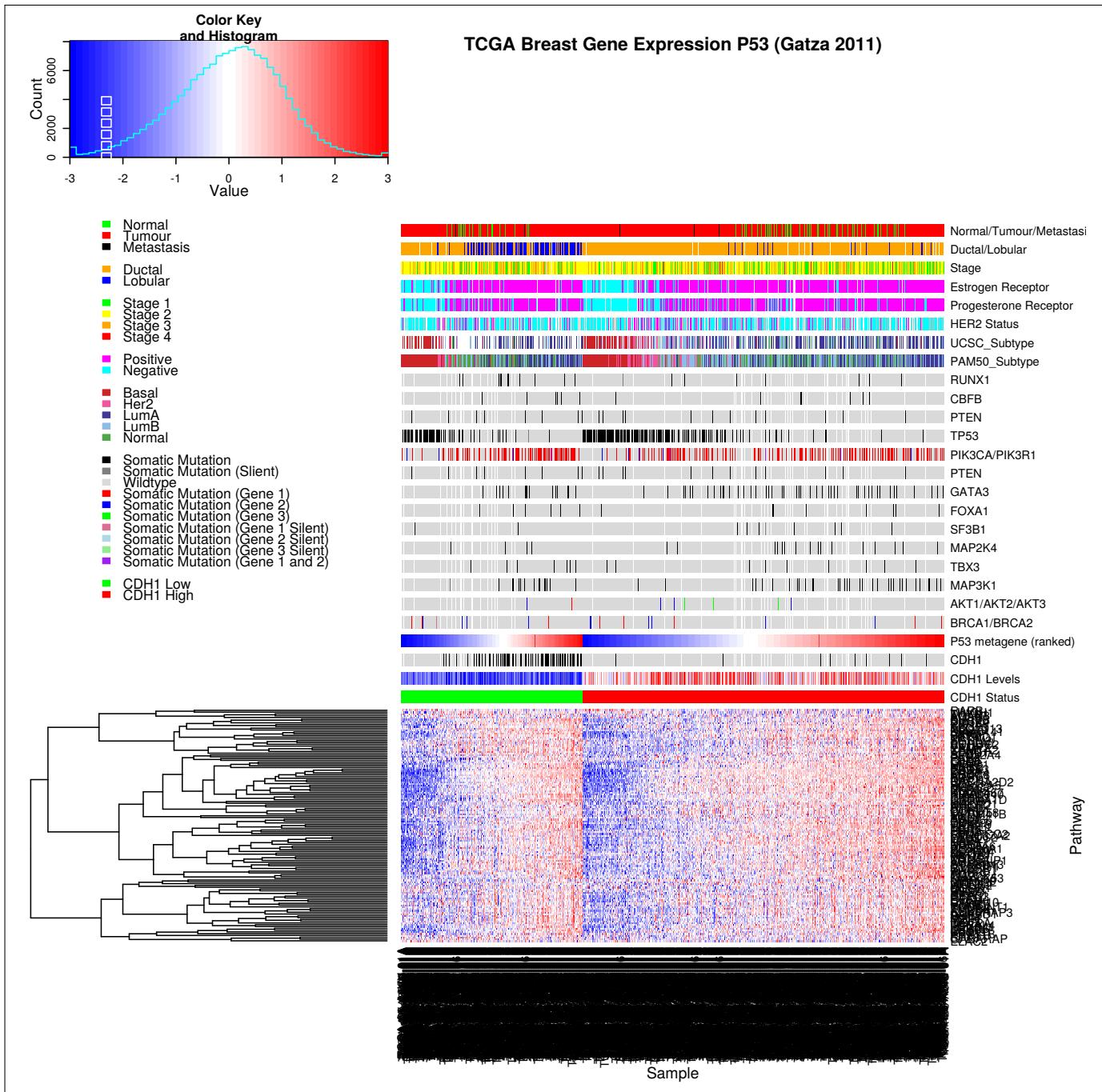
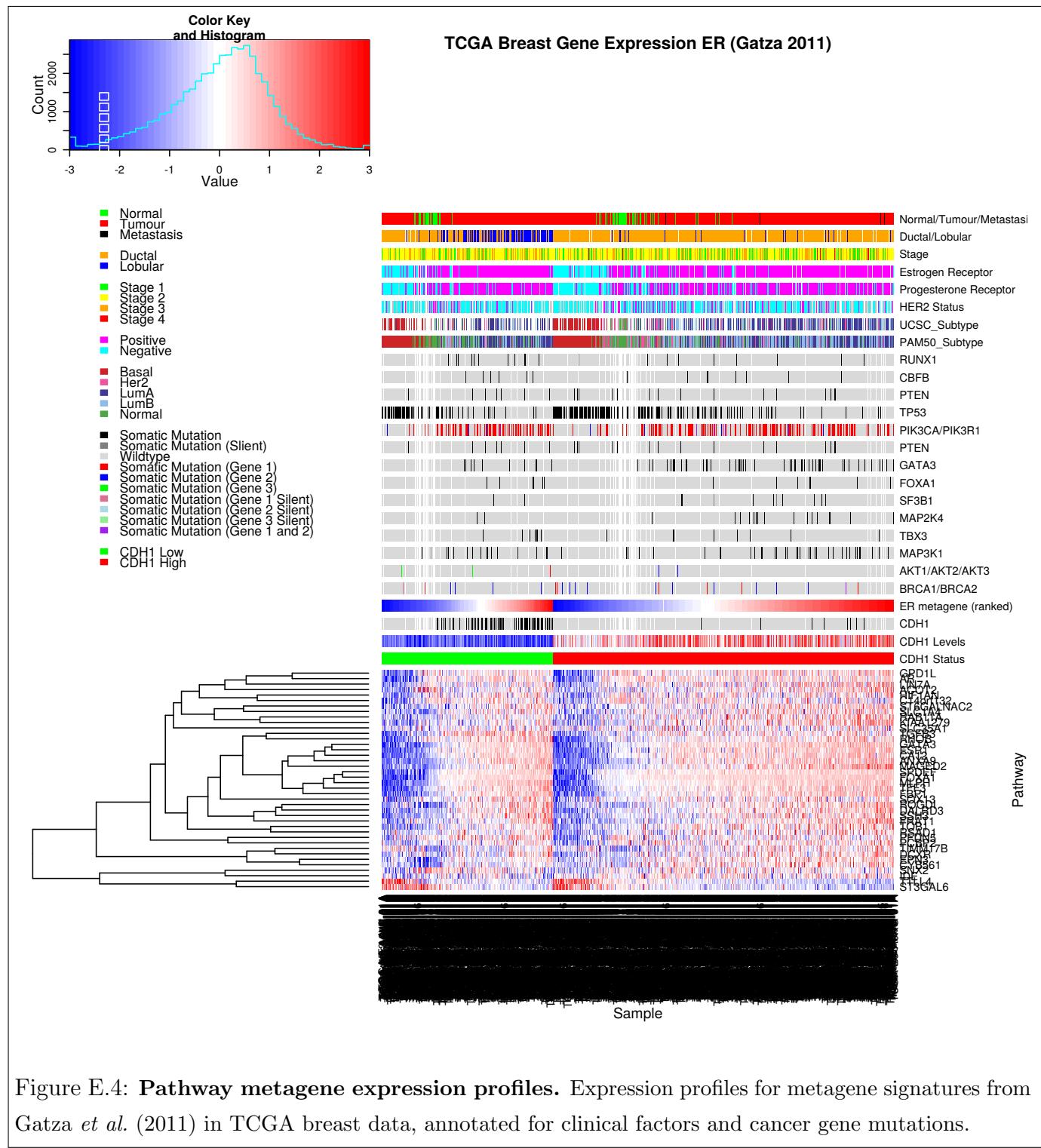


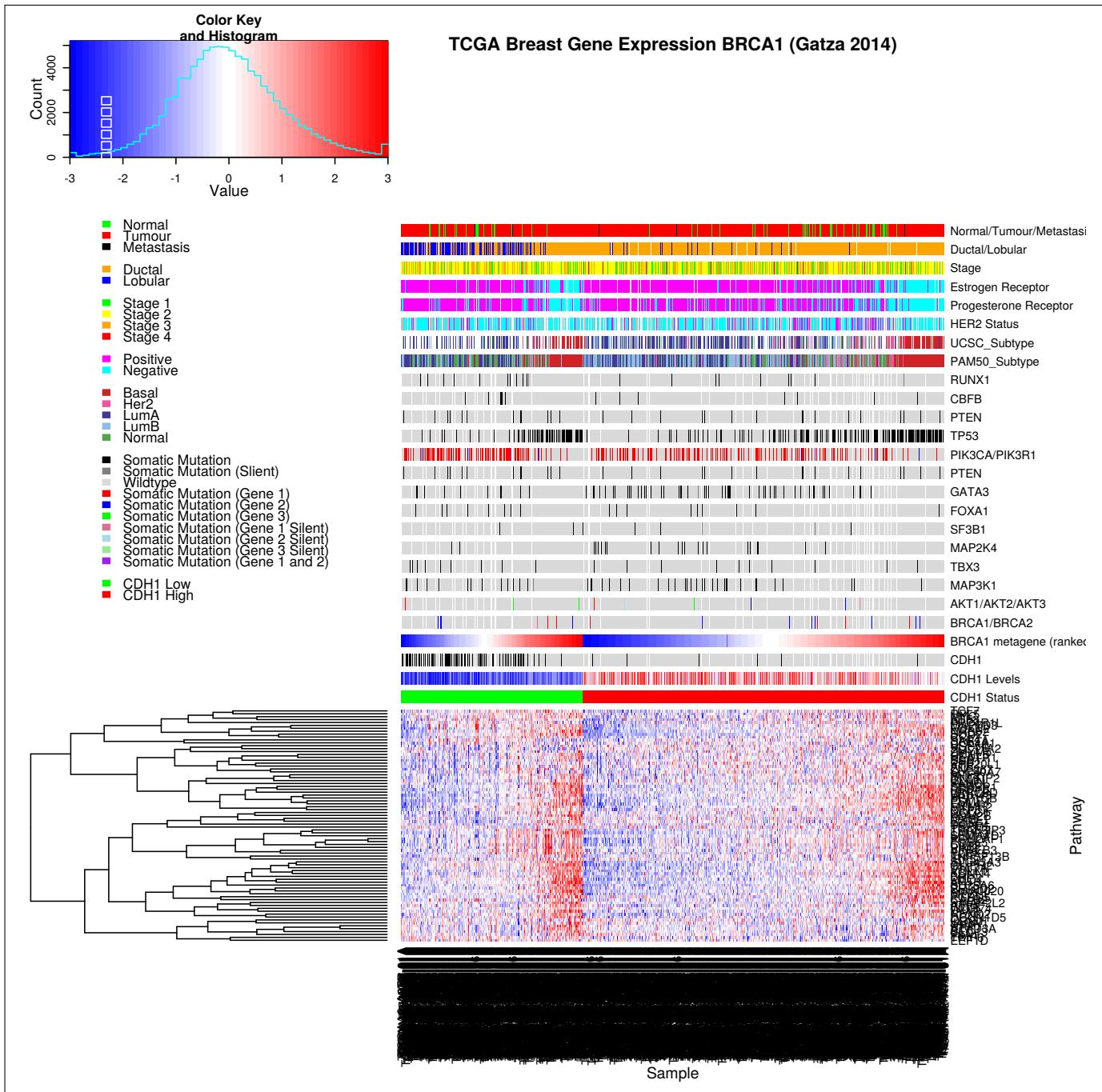
Figure E.1: **Pathway metagene expression profiles.** Expression profiles for metagene signatures from Gatza *et al.* (2014) in TCGA breast data, annotated for clinical factors and cancer gene mutations.





**Figure E.3: Pathway metagene expression profiles.** Expression profiles for metagene signatures from Gatza *et al.* (2011) in TCGA breast data, annotated for clinical factors and cancer gene mutations.





**Figure E.5: Pathway metagene expression profiles.** Expression profiles for metagene signatures from Gatza *et al.* (2014) in TCGA breast data, annotated for clinical factors and cancer gene mutations.

## **Appendix F**

# **Stomach Cancer Expression Analysis**

**F.1 Synthetic Lethal Genes and Pathways**

**F.2 Synthetic Lethal Expression Profiles**

**F.3 Comparison to Primary Screen**

**F.3.1 Resampling Analysis**

**F.4 Metagene Analysis**

# Appendix G

## Stomach Cancer Mutation Analysis

### G.1 Synthetic Lethal Genes and Pathways

Table G.1: Candidate synthetic lethal genes against E-cadherin from mtSLIPT in stomach cancer

Gene	Observed	Expected	$\chi^2$ value	p-value	p-value (FDR)
<i>OLFML1</i>	5	10.1	29.2	$4.53 \times 10^{-7}$	0.0031
<i>NRIP2</i>	6	10.1	25.4	$3.11 \times 10^{-6}$	0.00706
<i>VIM</i>	3	10.1	24.7	$4.29 \times 10^{-6}$	0.00706
<i>TCF4</i>	5	10.1	24.7	$4.33 \times 10^{-6}$	0.00706
<i>ZEB2</i>	5	10.1	24.7	$4.33 \times 10^{-6}$	0.00706
<i>BCL2</i>	2	10.1	22	$1.66 \times 10^{-5}$	0.0155
<i>SMARCA2</i>	2	10.1	22	$1.66 \times 10^{-5}$	0.0155
<i>CCND2</i>	3	10.1	21.1	$2.61 \times 10^{-5}$	0.0155
<i>MMP19</i>	3	10.1	21.1	$2.61 \times 10^{-5}$	0.0155
<i>NEURL1B</i>	3	10.1	21.1	$2.61 \times 10^{-5}$	0.0155
<i>IGFBP6</i>	6	10.1	21.1	$2.65 \times 10^{-5}$	0.0155
<i>OGN</i>	6	10.1	21.1	$2.65 \times 10^{-5}$	0.0155
<i>THY1</i>	6	10.2	21	$2.7 \times 10^{-5}$	0.0155
<i>DZIP1</i>	4	10.1	20.6	$3.29 \times 10^{-5}$	0.0155
<i>LOC650368</i>	4	10.1	20.6	$3.29 \times 10^{-5}$	0.0155
<i>PCOLCE</i>	4	10.1	20.6	$3.29 \times 10^{-5}$	0.0155
<i>PTGFR</i>	4	10.1	20.6	$3.29 \times 10^{-5}$	0.0155
<i>RUNX1T1</i>	4	10.1	20.6	$3.29 \times 10^{-5}$	0.0155
<i>CLEC2B</i>	5	10.1	20.6	$3.3 \times 10^{-5}$	0.0155
<i>MSC</i>	5	10.1	20.6	$3.3 \times 10^{-5}$	0.0155
<i>NISCH</i>	5	10.1	20.6	$3.3 \times 10^{-5}$	0.0155
<i>TSPAN11</i>	5	10.1	20.6	$3.3 \times 10^{-5}$	0.0155
<i>KCTD12</i>	2	10.1	19.1	$7.19 \times 10^{-5}$	0.0246
<i>LRRC55</i>	2	10.1	19.1	$7.19 \times 10^{-5}$	0.0246
<i>PCBP3</i>	2	10.1	19.1	$7.19 \times 10^{-5}$	0.0246

Strongest candidate SL partners for *CDH1* by mtSLIPT with observed and expected mutant samples with low expression of partner genes

Table G.2: Pathways for *CDH1* partners from mtSLIPT in stomach cancer

Pathways Over-represented	Pathway Size	SL Genes	p-value (FDR)
Extracellular matrix organization	241	20	$9.6 \times 10^{-9}$
Elastic fibre formation	38	6	$3.7 \times 10^{-8}$
Diseases associated with glycosaminoglycan metabolism	26	5	$3.7 \times 10^{-8}$
Diseases of glycosylation	26	5	$3.7 \times 10^{-8}$
Nitric oxide stimulates guanylate cyclase	24	4	$3.1 \times 10^{-6}$
Molecules associated with elastic fibres	34	4	$3.7 \times 10^{-5}$
Platelet homeostasis	54	5	$3.7 \times 10^{-5}$
Initial triggering of complement	17	3	$3.7 \times 10^{-5}$
Regulation of IGF transport and uptake by IGFBPs	17	3	$3.7 \times 10^{-5}$
Collagen degradation	58	5	$5.6 \times 10^{-5}$
Defective B4GALT7 causes EDS, progeroid type	19	3	$5.6 \times 10^{-5}$
Defective B3GAT3 causes JDSSDHD	19	3	$5.6 \times 10^{-5}$
Degradation of the extracellular matrix	104	7	$8.0 \times 10^{-5}$
ECM proteoglycans	66	5	0.00017
A tetrasaccharide linker sequence is required for GAG synthesis	25	3	0.00025
RHO GTPases Activate WASPs and WAVEs	29	3	0.00059
Non-integrin membrane-ECM interactions	53	4	0.00065
Creation of C4 and C2 activators	11	2	0.00079
Dermatan sulfate biosynthesis	11	2	0.00079
Integrin cell surface interactions	82	5	0.00098

Gene set over-representation analysis (hypergeometric test) for Reactome pathways in mtSLIPT partners for *CDH1*

## G.2 Synthetic Lethal Expression Profiles

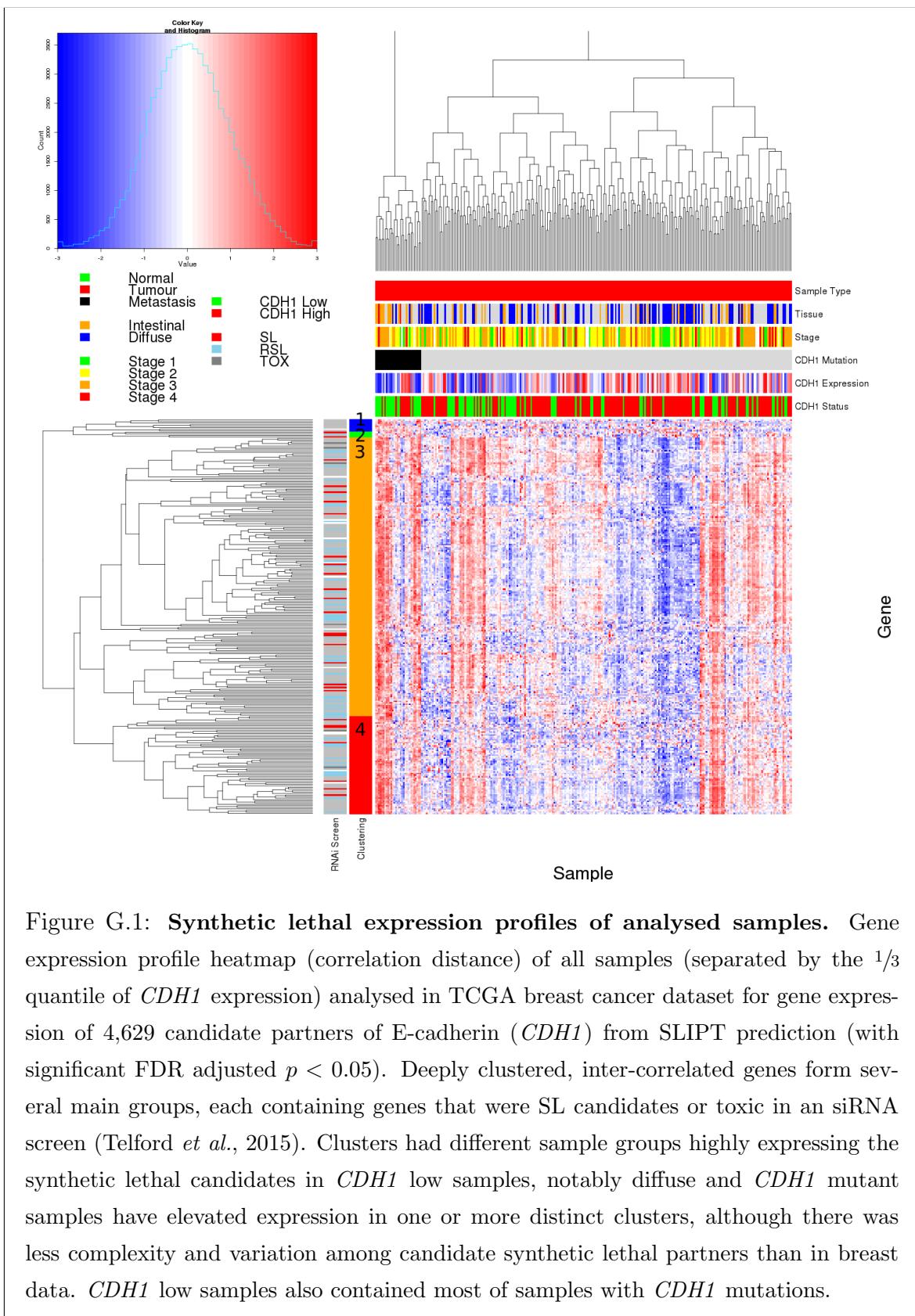


Table G.3: Pathway composition for clusters of *CDH1* partners in stomach mtSLIPT

Pathways Over-represented in Cluster 1	Pathway Size	Cluster Genes	p-value (FDR)
CD28 dependent PI3K/Akt signaling	15	1	1
Hormone-sensitive lipase (HSL)-mediated triacylglycerol hydrolysis	19	1	1
CD28 co-stimulation	26	1	1
Lipid digestion, mobilization, and transport	48	1	1
Costimulation by the CD28 family	51	1	1
Dectin-1 mediated noncanonical NF- $\kappa$ B signaling	58	1	1
CLEC7A (Dectin-1) signaling	99	1	1
C-type lectin receptors (CLRs)	123	1	1
Adaptive Immune System	418	1	1
Metabolism of lipids and lipoproteins	494	1	1
Interleukin-6 signaling	10	0	1
Apoptosis	150	0	1
Hemostasis	445	0	1
Intrinsic Pathway for Apoptosis	36	0	1
Cleavage of Growing Transcript in the Termination Region	33	0	1
PKB-mediated events	28	0	1
PI3K Cascade	68	0	1
RAF/MAP kinase cascade	10	0	1
Global Genomic NER (GG-NER)	35	0	1
Repair synthesis for gap-filling by DNA polymerase in TC-NER	15	0	1

Pathways Over-represented in Cluster 2	Pathway Size	Cluster Genes	p-value (FDR)
Kinesins	22	1	1
O-linked glycosylation of mucins	49	1	1
O-linked glycosylation	59	1	1
MHC class II antigen presentation	85	1	1
Factors involved in megakaryocyte development and platelet production	120	1	1
Post-translational protein modification	303	1	1
Adaptive Immune System	418	1	1
Hemostasis	445	1	1
Interleukin-6 signaling	10	0	1
Apoptosis	150	0	1
Intrinsic Pathway for Apoptosis	36	0	1
Cleavage of Growing Transcript in the Termination Region	33	0	1
PKB-mediated events	28	0	1
PI3K Cascade	68	0	1
RAF/MAP kinase cascade	10	0	1
Global Genomic NER (GG-NER)	35	0	1
Repair synthesis for gap-filling by DNA polymerase in TC-NER	15	0	1
Gap-filling DNA repair synthesis and ligation in TC-NER	17	0	1
Formation of transcription-coupled NER (TC-NER) repair complex	29	0	1
Dual incision reaction in TC-NER	29	0	1

Pathways Over-represented in Cluster 3	Pathway Size	Cluster Genes	p-value (FDR)
Extracellular matrix organization	241	20	$9.6 \times 10^{-9}$
Elastic fibre formation	38	6	$3.7 \times 10^{-8}$
Diseases associated with glycosaminoglycan metabolism	26	5	$3.7 \times 10^{-8}$
Diseases of glycosylation	26	5	$3.7 \times 10^{-8}$
Molecules associated with elastic fibres	34	4	$4.8 \times 10^{-5}$
Initial triggering of complement	17	3	$4.8 \times 10^{-5}$
Regulation of IGF transport and uptake by IGFBPs	17	3	$4.8 \times 10^{-5}$
Collagen degradation	58	5	$6.7 \times 10^{-5}$
Defective B4GALT7 causes EDS, progeroid type	19	3	$6.7 \times 10^{-5}$
Defective B3GAT3 causes JDSSDH	19	3	$6.7 \times 10^{-5}$
Degradation of the extracellular matrix	104	7	$9.5 \times 10^{-5}$
ECM proteoglycans	66	5	0.0002
A tetrasaccharide linker sequence is required for GAG synthesis	25	5	0.00029
Non-integrin membrane-ECM interactions	53	4	0.00079
Creation of C4 and C2 activators	11	2	0.00093
Dermatan sulfate biosynthesis	11	2	0.00093
Integrin cell surface interactions	82	5	0.0012
Keratan sulfate degradation	12	2	0.0012
Complement cascade	34	3	0.0013
CS/DS degradation	13	2	0.0015

Pathways Over-represented in Cluster 4	Pathway Size	Cluster Genes	p-value (FDR)
cGMP effects	18	2	0.11
Nitric oxide stimulates guanylate cyclase	24	2	0.19
Neurotoxicity of clostridium toxins	10	1	1
Platelet homeostasis	54	2	1
Eicosanoid ligand-binding receptors	14	1	1
Prolactin receptor signaling	15	1	1
Acyl chain remodelling of PI	15	1	1
Signaling by FGFR1 fusion mutants	15	1	1
PKA activation	16	1	1
PKA-mediated phosphorylation of CREB	17	1	1
Synthesis of glycosylphosphatidylinositol (GPI)	17	1	1
PKA activation in glucagon signalling	17	1	1
Butyrate Response Factor 1 (BRF1) destabilizes mRNA	17	1	1
Other semaphorin interactions	19	1	1
Acyl chain remodelling of PE	21	1	1
Signaling by Leptin	21	1	1
DARPP-32 events	22	1	1
Glucagon-like Peptide-1 (GLP1) regulates insulin secretion	22	1	1
Uptake and actions of bacterial toxins	22	1	1
Acyl chain remodelling of PC	23	1	1

### G.3 Comparison to Primary Screen

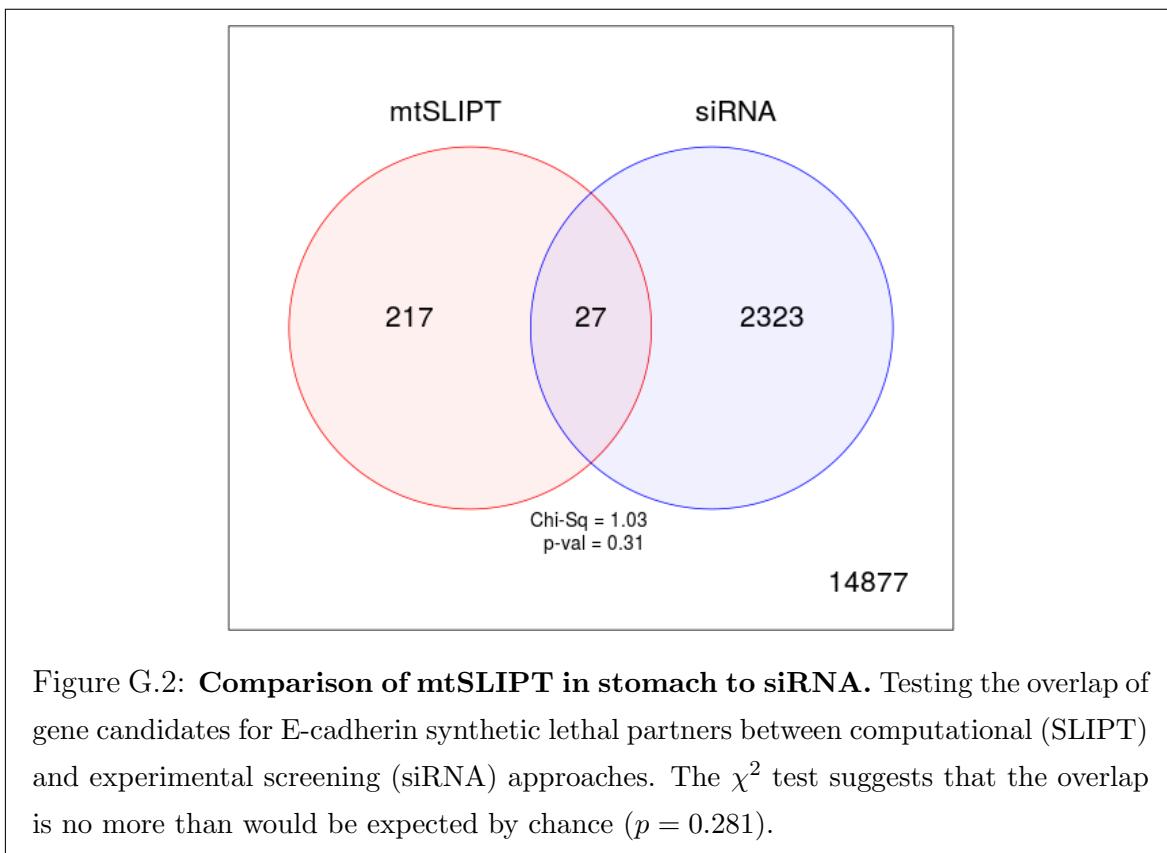


Table G.4: Pathway composition for *CDH1* partners from mtSLIPT and siRNA

Predicted only by SLIPT (217 genes)	Pathway	Size	Genes Identified	p-value (FDR)
Eukaryotic Translation Elongation		87	57	$2.8 \times 10^{-120}$
Peptide chain elongation		84	56	$3.1 \times 10^{-120}$
Eukaryotic Translation Termination		84	55	$2.8 \times 10^{-117}$
Viral mRNA Translation		82	54	$4.1 \times 10^{-116}$
Nonsense Mediated Decay independent of the Exon Junction Complex		89	55	$3.7 \times 10^{-113}$
Formation of a pool of free 40S subunits		94	55	$2.8 \times 10^{-109}$
Nonsense-Mediated Decay		104	57	$8.4 \times 10^{-108}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex		104	57	$8.4 \times 10^{-108}$
L13a-mediated translational silencing of Ceruloplasmin expression		104	56	$3.4 \times 10^{-105}$
3' -UTR-mediated translational regulation		104	56	$3.4 \times 10^{-105}$
GTP hydrolysis and joining of the 60S ribosomal subunit		105	56	$1.4 \times 10^{-104}$
Eukaryotic Translation Initiation		112	56	$2.8 \times 10^{-100}$
Cap-dependent Translation Initiation		112	56	$2.8 \times 10^{-100}$
SRP-dependent cotranslational protein targeting to membrane		105	54	$2.2 \times 10^{-99}$
Influenza Viral RNA Transcription and Replication		109	54	$5.3 \times 10^{-97}$
Influenza Life Cycle		113	54	$9.6 \times 10^{-95}$
Influenza Infection		118	55	$1.7 \times 10^{-94}$
Translation		142	60	$3.5 \times 10^{-94}$
Infectious disease		349	77	$5.9 \times 10^{-62}$
Extracellular matrix organization		241	54	$3 \times 10^{-52}$

Detected only by siRNA screen (2323 genes)	Pathway	Size	Genes Identified	p-value (FDR)
Class A/1 (Rhodopsin-like receptors)		282	69	$1.9 \times 10^{-59}$
GPCR ligand binding		363	78	$2.7 \times 10^{-54}$
Peptide ligand-binding receptors		175	41	$1.5 \times 10^{-42}$
G <sub>αi</sub> signalling events		184	41	$1.1 \times 10^{-40}$
Gastrin-CREB signalling pathway via PKC and MAPK		180	37	$1.5 \times 10^{-35}$
G <sub>αq</sub> signalling events		159	34	$3.7 \times 10^{-35}$
DAP12 interactions		159	27	$1.1 \times 10^{-24}$
VEGFA-VEGFR2 Pathway		91	19	$1.0 \times 10^{-23}$
Downstream signal transduction		146	24	$1.9 \times 10^{-22}$
Signaling by VEGF		99	19	$2.6 \times 10^{-22}$
DAP12 signaling		149	24	$4.2 \times 10^{-22}$
Organelle biogenesis and maintenance		264	34	$4.3 \times 10^{-20}$
Downstream signaling of activated FGFR1		134	21	$4.3 \times 10^{-20}$
Downstream signaling of activated FGFR2		134	21	$4.3 \times 10^{-20}$
Downstream signaling of activated FGFR3		134	21	$4.3 \times 10^{-20}$
Downstream signaling of activated FGFR4		134	21	$4.3 \times 10^{-20}$
Signaling by ERBB2		146	22	$5.3 \times 10^{-20}$
Signaling by FGFR		146	22	$5.3 \times 10^{-20}$
Signaling by FGFR1		146	22	$5.3 \times 10^{-20}$
Signaling by FGFR2		146	22	$5.3 \times 10^{-20}$

Intersection of SLIPT and siRNA screen (23 genes)	Pathway	Size	Genes Identified	p-value (FDR)
HS-GAG degradation		21	4	$4.9 \times 10^{-6}$
Retinoid metabolism and transport		39	5	$4.9 \times 10^{-6}$
Platelet activation, signaling and aggregation		186	13	$4.9 \times 10^{-6}$
Signaling by NOTCH4		11	3	$4.9 \times 10^{-6}$
G <sub>αs</sub> signalling events		100	8	$5 \times 10^{-6}$
Defective EXT2 causes exostoses 2		12	3	$5 \times 10^{-6}$
Defective EXT1 causes exostoses 1, TRPS2 and CHDS		12	3	$5 \times 10^{-6}$
Class A/1 (Rhodopsin-like receptors)		289	18	$2.2 \times 10^{-5}$
Signaling by PDGF		173	11	$2.9 \times 10^{-5}$
Circadian Clock		34	4	$2.9 \times 10^{-5}$
Signaling by ERBB4		139	9	$4.3 \times 10^{-5}$
Role of LAT2/NTAL/LAB on calcium mobilization		99	7	$4.4 \times 10^{-5}$
Peptide ligand-binding receptors		181	11	$4.5 \times 10^{-5}$
Defective B4GALT7 causes EDS, progeroid type		19	3	$4.5 \times 10^{-5}$
Defective B3GAT3 causes JDSSDH		19	3	$4.5 \times 10^{-5}$
Signaling by NOTCH		80	6	$4.5 \times 10^{-5}$
G <sub>αq</sub> signalling events		164	10	$5.1 \times 10^{-5}$
Response to elevated platelet cytosolic Ca <sup>2+</sup>		84	6	$7.1 \times 10^{-5}$
Signaling by ERBB2		148	9	$7.1 \times 10^{-5}$
Signaling by SCF-KIT		129	8	$8.3 \times 10^{-5}$

### G.3.1 Resampling Analysis

Table G.5: Pathways for *CDH1* partners from mtSLIPT in stomach cancer

Reactome Pathway	Over-representation	Permutation
Eukaryotic Translation Elongation	$2 \times 10^{-128}$	$< 8.802 \times 10^{-4}$
Peptide chain elongation	$2 \times 10^{-128}$	$< 8.802 \times 10^{-4}$
Eukaryotic Translation Termination	$2.3 \times 10^{-125}$	$< 8.802 \times 10^{-4}$
Viral mRNA Translation	$2.5 \times 10^{-124}$	$< 8.802 \times 10^{-4}$
Nonsense Mediated Decay independent of the Exon Junction Complex	$8.6 \times 10^{-124}$	$< 8.802 \times 10^{-4}$
Nonsense-Mediated Decay	$5.2 \times 10^{-117}$	$< 8.802 \times 10^{-4}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex	$5.2 \times 10^{-117}$	$< 8.802 \times 10^{-4}$
Formation of a pool of free 40S subunits	$1.6 \times 10^{-116}$	$< 8.802 \times 10^{-4}$
L13a-mediated translational silencing of Ceruloplasmin expression	$1.3 \times 10^{-111}$	$< 8.802 \times 10^{-4}$
3' -UTR-mediated translational regulation	$1.3 \times 10^{-111}$	$< 8.802 \times 10^{-4}$
GTP hydrolysis and joining of the 60S ribosomal subunit	$6.2 \times 10^{-111}$	$< 8.802 \times 10^{-4}$
SRP-dependent cotranslational protein targeting to membrane	$2.9 \times 10^{-108}$	$< 8.802 \times 10^{-4}$
Eukaryotic Translation Initiation	$3 \times 10^{-106}$	$< 8.802 \times 10^{-4}$
Cap-dependent Translation Initiation	$3 \times 10^{-106}$	$< 8.802 \times 10^{-4}$
Influenza Viral RNA Transcription and Replication	$5.1 \times 10^{-103}$	$< 8.802 \times 10^{-4}$
Influenza Infection	$1.5 \times 10^{-102}$	$< 8.802 \times 10^{-4}$
Translation	$3.7 \times 10^{-101}$	$< 8.802 \times 10^{-4}$
Influenza Life Cycle	$1.4 \times 10^{-100}$	$< 8.802 \times 10^{-4}$
GPCR downstream signaling	$1 \times 10^{-80}$	0.034498
Hemostasis	$1.4 \times 10^{-78}$	0.086519
Extracellular matrix organization	$1.5 \times 10^{-67}$	0.040016
Developmental Biology	$1.8 \times 10^{-66}$	0.18385
Infectious disease	$7.3 \times 10^{-66}$	0.068426
Signalling by NGF	$8.5 \times 10^{-63}$	0.16798
Metabolism of lipids and lipoproteins	$4.9 \times 10^{-58}$	0.51411
Platelet activation, signaling and aggregation	$2.7 \times 10^{-55}$	0.081717
GPCR ligand binding	$7.3 \times 10^{-55}$	0.28898
Signaling by PDGF	$8.4 \times 10^{-55}$	0.16025
Class A/1 (Rhodopsin-like receptors)	$3.2 \times 10^{-54}$	0.22801
Fc epsilon receptor (FCER1) signaling	$6.2 \times 10^{-53}$	0.15229
Adaptive Immune System	$5.1 \times 10^{-52}$	0.037698
Signaling by ERBB4	$5.9 \times 10^{-52}$	0.10088
Axon guidance	$8.8 \times 10^{-52}$	0.40234
Formation of the ternary complex, and subsequently, the 43S complex	$1.6 \times 10^{-51}$	0.00088017
Ribosomal scanning and start codon recognition	$2.2 \times 10^{-50}$	0.00088017
Translation initiation complex formation	$2.2 \times 10^{-50}$	0.0017305
NGF signalling via TRKA from the plasma membrane	$6.7 \times 10^{-50}$	0.28811
Activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to 43S	$7.1 \times 10^{-50}$	0.0017305
Transmembrane transport of small molecules	$1.8 \times 10^{-49}$	0.081229
Signaling by ERBB2	$5.9 \times 10^{-49}$	0.11896
Rho GTPase cycle	$3.6 \times 10^{-48}$	0.035735
Gαs signalling events	$1.1 \times 10^{-47}$	0.0088487
Downstream signal transduction	$1.7 \times 10^{-47}$	0.11909
Signaling by FGFR	$1.7 \times 10^{-47}$	0.11896
Signaling by FGFR1	$1.7 \times 10^{-47}$	0.11896
Signaling by FGFR2	$1.7 \times 10^{-47}$	0.11896
Signaling by FGFR3	$1.7 \times 10^{-47}$	0.11896
Signaling by FGFR4	$1.7 \times 10^{-47}$	0.11896
DAP12 interactions	$1.9 \times 10^{-47}$	0.28811
DAP12 signaling	$1 \times 10^{-46}$	0.12442

Over-representation (hypergeometric test) and Permutation p-values adjusted for multiple tests across pathways (FDR).

Significant pathways are marked in bold (FDR < 0.05) and italics (FDR < 0.1).

Table G.6: Pathways for *CDH1* partners from mtSLIPT in stomach and siRNA screen

Reactome Pathway	Over-representation	Permutation
Signaling by NOTCH4	$4.9 \times 10^{-6}$	0.050121
HS-GAG degradation	$4.9 \times 10^{-6}$	0.013193
Platelet activation, signaling and aggregation	$4.9 \times 10^{-6}$	0.28053
Retinoid metabolism and transport	$4.9 \times 10^{-6}$	0.0927
Defective EXT2 causes exostoses 2	$5 \times 10^{-6}$	0.14898
Defective EXT1 causes exostoses 1, TRPS2 and CHDS	$5 \times 10^{-6}$	0.14898
<i>Gαs</i> signalling events	$5 \times 10^{-6}$	0.048426
Class A/1 (Rhodopsin-like receptors)	$2.2 \times 10^{-5}$	0.60435
Signaling by PDGF	$2.9 \times 10^{-5}$	0.43907
Circadian Clock	$2.9 \times 10^{-5}$	0.012519
Signaling by ERBB4	$4.3 \times 10^{-5}$	0.12835
Role of LAT2/NTAL/LAB on calcium mobilization	$4.4 \times 10^{-5}$	0.27344
Defective B4GALT7 causes EDS, progeroid type	$4.5 \times 10^{-5}$	0.23536
Defective B3GAT3 causes JDSSDHD	$4.5 \times 10^{-5}$	0.23536
Peptide ligand-binding receptors	$4.5 \times 10^{-5}$	0.41193
Signaling by NOTCH	$4.5 \times 10^{-5}$	0.10912
<i>Gαq</i> signalling events	$5.1 \times 10^{-5}$	0.28937
Signaling by ERBB2	$7.1 \times 10^{-5}$	0.50797
Response to elevated platelet cytosolic $\text{Ca}^{2+}$	$7.1 \times 10^{-5}$	0.38513
Signaling by SCF-KIT	$8.3 \times 10^{-5}$	0.55412
PI3K events in ERBB4 signaling	0.0001	0.24486
PIP3 activates AKT signaling	0.0001	0.24486
Collagen formation	0.0001	0.15296
PI3K events in ERBB2 signaling	0.0001	0.24486
PI-3K cascade:FGFR1	0.0001	0.24486
PI-3K cascade:FGFR2	0.0001	0.24486
PI-3K cascade:FGFR3	0.0001	0.24486
PI-3K cascade:FGFR4	0.0001	0.24486
Growth hormone receptor signaling	0.0001	0.057494
PI3K Cascade	0.00011	0.20906
Effects of PIP2 hydrolysis	0.00012	0.14898
A tetrasaccharide linker sequence is required for GAG synthesis	0.00012	0.29766
PI3K/AKT activation	0.00013	0.24486
GAB1 signalosome	0.00013	0.4648
Diseases associated with glycosaminoglycan metabolism	0.00013	0.050121
Diseases of glycosylation	0.00013	0.050121
Heparan sulfate/heparin (HS-GAG) metabolism	0.00016	0.19
HS-GAG biosynthesis	0.00016	0.29681
Integrin alphaIIb beta3 signaling	0.00016	0.63007
Interferon gamma signaling	0.00018	0.43088
Gastrin-CREB signalling pathway via PKC and MAPK	0.00018	0.77958
Chemokine receptors bind chemokines	0.00023	0.62702
Downstream signal transduction	0.00027	0.54921
Platelet homeostasis	0.00029	0.24577
IRS-mediated signalling	0.00029	0.31766
<i>Gαi</i> signalling events	0.00029	$< 2.749 \times 10^{-4}$
Diseases of signal transduction	0.00029	0.65733
Signaling by activated point mutants of FGFR1	0.00029	0.24892
FGFR1c ligand binding and activation	0.00029	0.24892
Signaling by NOTCH3	0.00029	0.017419

Over-representation (hypergeometric test) and Permutation p-values adjusted for multiple tests across pathways (FDR). Significant pathways are marked in bold (FDR < 0.05) and italicics (FDR < 0.1).

## G.4 Metagene Analysis

Table G.7: Candidate synthetic lethal metagenes against *CDH1* from mtSLIPT in stomach cancer

Pathway	ID	Observed	Expected	$\chi^2$ value	p-value	p-value (FDR)
Prostacyclin signalling through prostacyclin receptor	392851	1	10.07	26.53	$1.7307 \times 10^{-6}$	0.0028590
Cell surface interactions at the vascular wall	202733	3	10.07	21.11	$2.6107 \times 10^{-5}$	0.00642330
The NLRP1 inflammasome	844455	3	10.07	21.11	$2.6107 \times 10^{-5}$	0.00642330
Innate Immune System	168249	6	10.07	21.07	$2.6548 \times 10^{-5}$	0.00642330
Keratan sulfatekeratin metabolism	1638074	4	10.07	20.65	$3.2861 \times 10^{-5}$	0.00642330
Keratan sulfate biosynthesis	2022854	4	10.07	20.65	$3.2861 \times 10^{-5}$	0.00642330
Signaling by SCF-KIT	1433557	5	10.07	20.64	$3.3045 \times 10^{-5}$	0.00642330
VEGFA-VEGFR2 Pathway	4420097	5	10.07	20.64	$3.3045 \times 10^{-5}$	0.00642330
ERK1 activation	110056	21	10.07	20.12	$4.277 \times 10^{-5}$	0.00642330
Cholesterol biosynthesis	191273	21	10.07	20.12	$4.277 \times 10^{-5}$	0.00642330
G2 Phase	68911	21	10.07	20.12	$4.277 \times 10^{-5}$	0.00642330
p130Cas linkage to MAPK signaling for integrins	372708	2	10.07	19.08	$7.1872 \times 10^{-5}$	0.00651340
cGMP effects	418457	8	10.07	19.01	$7.4597 \times 10^{-5}$	0.00651340
Regulation of cytoskeletal remodeling and cell spreading by IPP complex components	446388	8	10.07	19.01	$7.4597 \times 10^{-5}$	0.00651340
Post-translational modification: synthesis of GPI-anchored proteins	163125	20	10.07	18.59	$9.1878 \times 10^{-5}$	0.00651340
Fcgamma receptor (FCGR) dependent phagocytosis	2029480	3	10.07	17.95	0.00012676	0.00651340
A third proteolytic cleavage releases NICD	157212	7	10.07	17.90	0.00012995	0.00651340
Signalling by NGF	166520	7	10.07	17.90	0.00012995	0.00651340
Signaling by VEGF	194138	7	10.07	17.90	0.00012995	0.00651340
Regulation of thyroid hormone activity	350864	7	10.07	17.90	0.00012995	0.00651340
Nitric oxide stimulates guanylate cyclase	392154	7	10.07	17.90	0.00012995	0.00651340
Platelet homeostasis	418346	7	10.07	17.90	0.00012995	0.00651340
Termination of translesion DNA synthesis	5656169	20	10.07	17.46	0.00016155	0.00651340
PI3K events in ERBB4 signaling	1250342	4	10.07	17.26	0.00017862	0.00651340
PIP3 activates AKT signaling	1257604	4	10.07	17.26	0.00017862	0.00651340

Strongest candidate SL partners for *CDH1* by mtSLIPT with observed and expected mutant samples with low expression of partner metagenes

# Appendix H

## Global Synthetic Lethality in Stomach Cancer

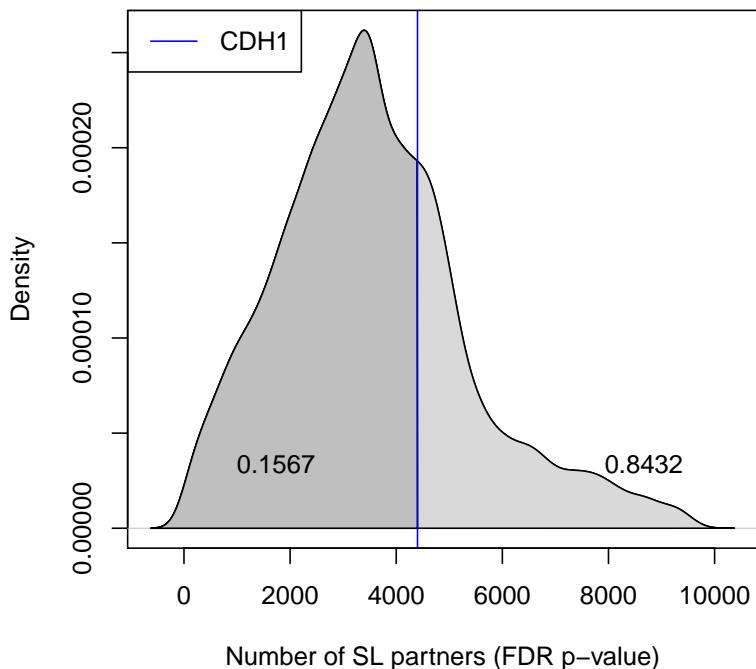


Figure H.1: **Synthetic lethal partners across query genes.** Global synthetic lethal pairs were examined across the genome in TCGA stomach expression data by applying SLIPT across query genes. The high number of predicted partners for *CDH1* was typical for a human gene and lower than many other genes.

## H.1 Hub Genes

Table H.1: Query synthetic lethal genes with the most SLIPT partners

Gene	Direction	raw p-value	p-value (FDR)	SLIPT raw p-value	SLIPT (FDR)
<i>HEG1</i>	10719	16956	16724	9616	9532
<i>SYNE1</i>	10755	17210	16984	9749	9676
<i>A2M</i>	10743	16650	16378	9529	9433
<i>ANK2</i>	11008	16616	16355	9764	9653
<i>TTC28</i>	10757	16523	16248	9530	9429
<i>FAT4</i>	10451	16286	15978	9225	9115
<i>MRVI1</i>	10904	16967	16718	9775	9686
<i>PAPLN</i>	10483	16405	16104	9305	9193
<i>NFASC</i>	10773	16575	16307	9578	9475
<i>MACF1</i>	9697	16378	16058	8620	8540
<i>HMCN1</i>	10475	16101	15733	9156	9008
<i>MPDZ</i>	10878	16550	16299	9599	9491
<i>FLRT2</i>	10776	16760	16473	9590	9464
<i>SETBP1</i>	10869	16632	16349	9615	9489
<i>LAMA4</i>	10463	16447	16121	9273	9151
<i>IL1R1</i>	10611	16185	15803	9299	9174
<i>ABCA6</i>	10499	16573	16318	9260	9158
<i>LAMC1</i>	10238	15777	15392	8837	8691
<i>TNS1</i>	10920	17038	16806	9836	9751
<i>AMOTL1</i>	10612	16458	16178	9367	9250

Genes with the most candidate SL partners SLIPT in TCGA stomach expression data with the number of partner genes predicted by direction criteria and  $\chi^2$  testing separately and combined as a SLIPT analysis. Where specified, the p-values for the  $\chi^2$  test were adjusted for multiple tests (FDR).

## H.2 Hub Pathways

Table H.2: Pathways for genes with the most SLIPT partners

Pathways Over-represented	Pathway Size	SL Genes	p-value	p-value (FDR)
Molecules associated with elastic fibres	34	10	$4.6 \times 10^{-21}$	$2.7 \times 10^{-18}$
Extracellular matrix organization	241	29	$5.3 \times 10^{-21}$	$2.7 \times 10^{-18}$
Smooth Muscle Contraction	29	9	$5.6 \times 10^{-20}$	$1.6 \times 10^{-17}$
Elastic fibre formation	38	10	$6 \times 10^{-20}$	$1.6 \times 10^{-17}$
Nitric oxide stimulates guanylate cyclase	24	8	$6.9 \times 10^{-19}$	$1.4 \times 10^{-16}$
Muscle contraction	64	12	$8.3 \times 10^{-19}$	$1.4 \times 10^{-16}$
Platelet homeostasis	54	11	$1.3 \times 10^{-18}$	$1.9 \times 10^{-16}$
cGMP effects	18	6	$3.3 \times 10^{-15}$	$4.3 \times 10^{-13}$
Laminin interactions	30	7	$1.3 \times 10^{-14}$	$1.6 \times 10^{-12}$
Axon guidance	289	25	$5 \times 10^{-13}$	$5.2 \times 10^{-11}$
Signaling by BMP	23	5	$3.7 \times 10^{-11}$	$3.2 \times 10^{-9}$
RHO GTPases activate PAKs	23	5	$3.7 \times 10^{-11}$	$3.2 \times 10^{-9}$
Non-integrin membrane-ECM interactions	53	7	$7.2 \times 10^{-11}$	$5.8 \times 10^{-9}$
Rho GTPase cycle	120	11	$1.2 \times 10^{-10}$	$8.7 \times 10^{-9}$
Degradation of the extracellular matrix	104	10	$1.3 \times 10^{-10}$	$8.8 \times 10^{-9}$
Netrin-1 signaling	42	6	$2.5 \times 10^{-10}$	$1.6 \times 10^{-8}$
Developmental Biology	432	32	$8.3 \times 10^{-10}$	$5 \times 10^{-8}$
L1CAM interactions	80	8	$8.7 \times 10^{-10}$	$5 \times 10^{-8}$
Semaphorin interactions	64	7	$1.1 \times 10^{-9}$	$6.1 \times 10^{-8}$
Cell-extracellular matrix interactions	18	4	$1.3 \times 10^{-9}$	$6.6 \times 10^{-8}$

Gene set over-representation analysis (hypergeometric test) for Reactome pathways in the top 500 “hub” genes with the most candidate synthetic lethal partners by SLIPT analysis of TCGA stomach expression data