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# Glossary

centrality	A network metric which identifies important vertices.
E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by <i>CDH1</i> .
essential	A gene which is required to be functional or expressed for a cell or organism to be viable, grow or develop.
gene expression	A measure of the relative expression of each gene from the mRNA extracted from (pooled) cells.
graph or network	A mathematical structure modelling or depicting the relationships between elements.
information centrality	A network centrality metric which uses the impact of removing a vertex or node on connections in the network.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.
mutation	A change in DNA sequence that disrupts gene function.
PageRank centrality	A network centrality metric which uses eigenvectors with a scaling factor (Brin and Page, 1998).
RNA-Seq	The generation of transcriptome data from sequencing RNA.
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.

vertex degree	A network metric of connectivity of vertices which uses the number of edges connected to each vertex or node.
vertex or node	An element of a graph structure or network.
wild-type	A natural phenotype of a trait or the normally functional allele which encodes it.

# Acronyms

ANOVA	Analysis of Variance.
CRAN	comprehensive R archive network.
ER	Estrogen Receptor.
FDR	False Discovery Rate.
GPCR	G Crotein Coupled Receptor.
mRNA	Messenger RNA.
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (against mutation).
NMD	Nonsense-Mediated Decay.
PAM50	Prediction Analysis of Microarray 50.
PI3K	Phosphoinositide 3-kinase.
RNA	Ribonucleic Acid.
ROC	Reciever Operating Characteristic (curve).
siRNA	Short Interfering RNA.
SLIPT	Synthetic Lethal Interaction Prediction Tool.
TCGA	The Cancer Genome Atlas (genomics project).
UCSC	University of California, Santa Cruz.
UTR	Untranslated Region (of mRNA).

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# Appendix A

## Sample Quality

### A.1 Sample Correlation

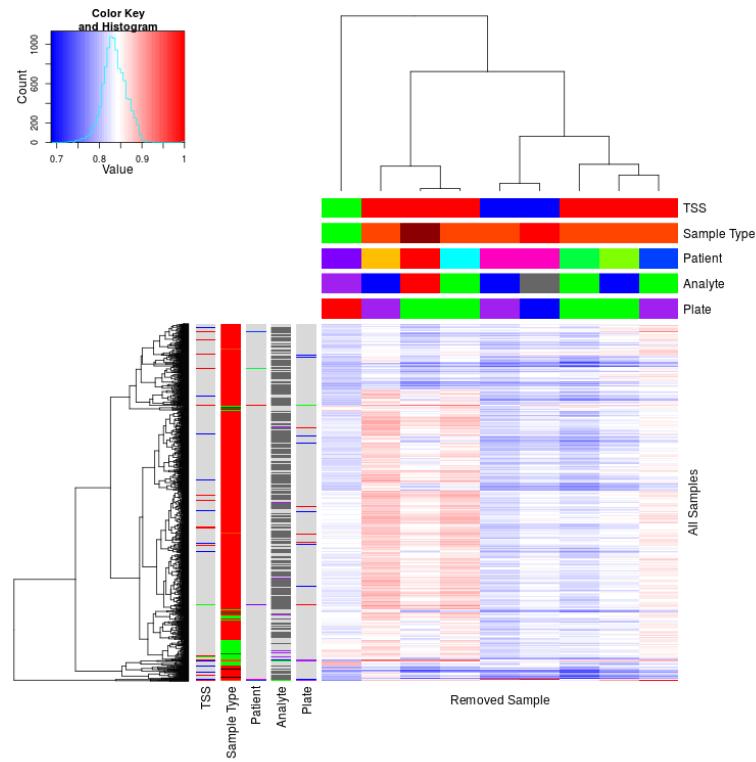
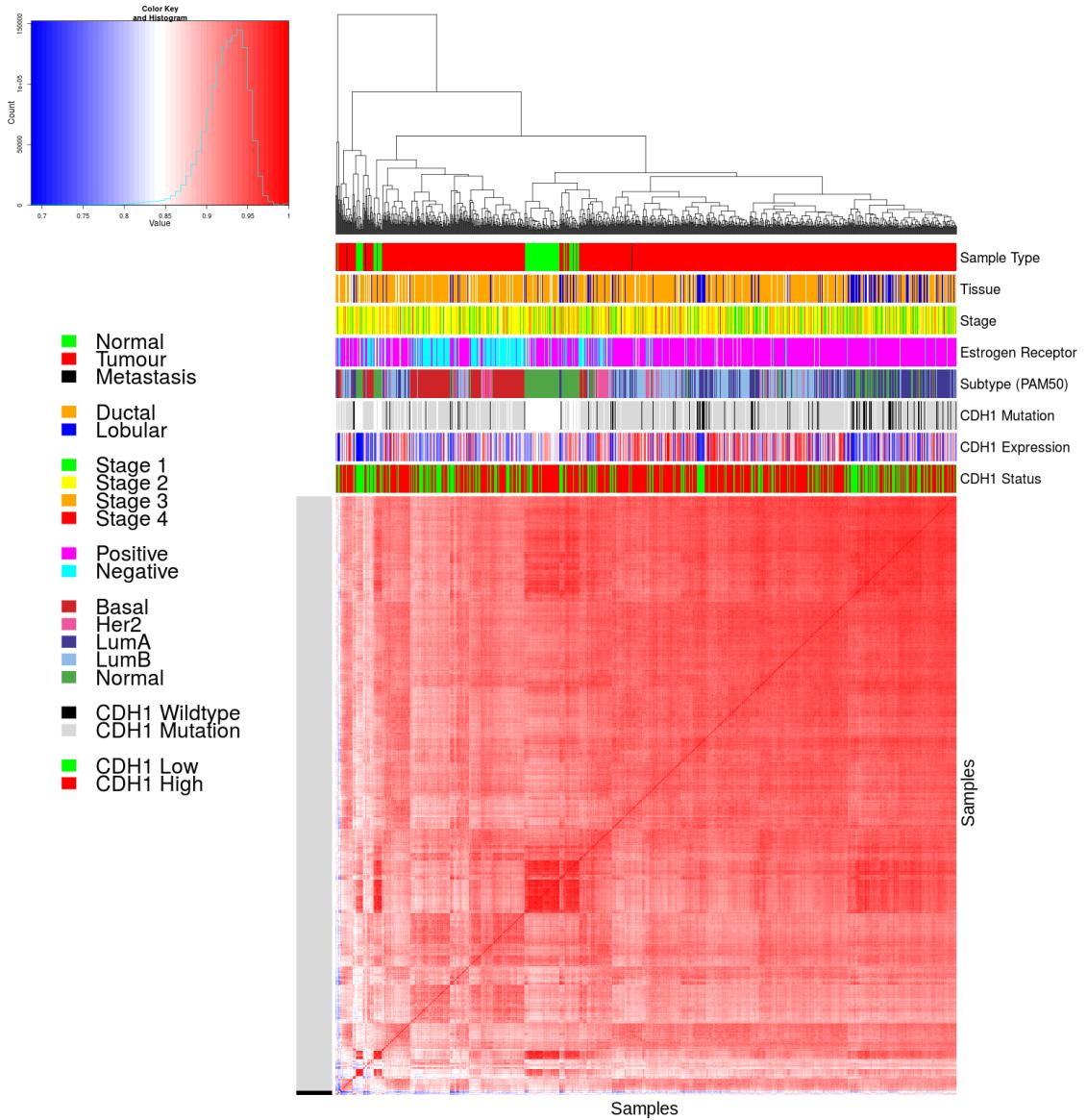


Figure A.1: **Correlation profiles of removed samples.** Heatmap (Euclidean distance) of samples in TCGA breast cancer dataset (left) clustered for all samples against removed samples (top): tissue source site (TSS), sample type with reds for tumour and greens for normal, patient (A2QH in pink), with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



**Figure A.2: Correlation analysis and sample removal.** Correlation matrix heatmap (Euclidean distance) of all samples in TCGA breast cancer dataset against each other annotated for sample clinical data: sample type, tissue type, tumour stage, Estrogen receptor (ER) and intrinsic subtype (from the PAM50 method). *CDH1* somatic mutation, gene expression, and status for SLIPT prediction were also annotated. Discrete variables were coloured as displayed in the legend and continuous variables on a blue–red scale as shown in the colour key. Trimmed samples cluster at the bottom of the heatmap and the colour bars of the left show which were removed for quality concerns.

## 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 were expected to have very high Pearson correlation between their expression profiles unless there were issues with sample collection or preparation and were 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 was 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), 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 correlation with replicate samples.

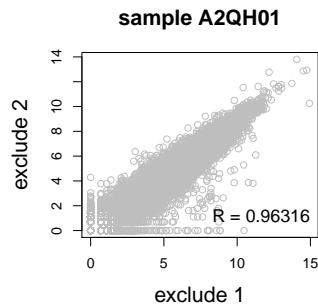


Figure A.3: **Replicate excluded samples.** Both tumour samples of patient A2QH were excluded as they were poorly correlated with other samples, although they were highly similar to each other as shown by Pearson correlation of log-raw counts.

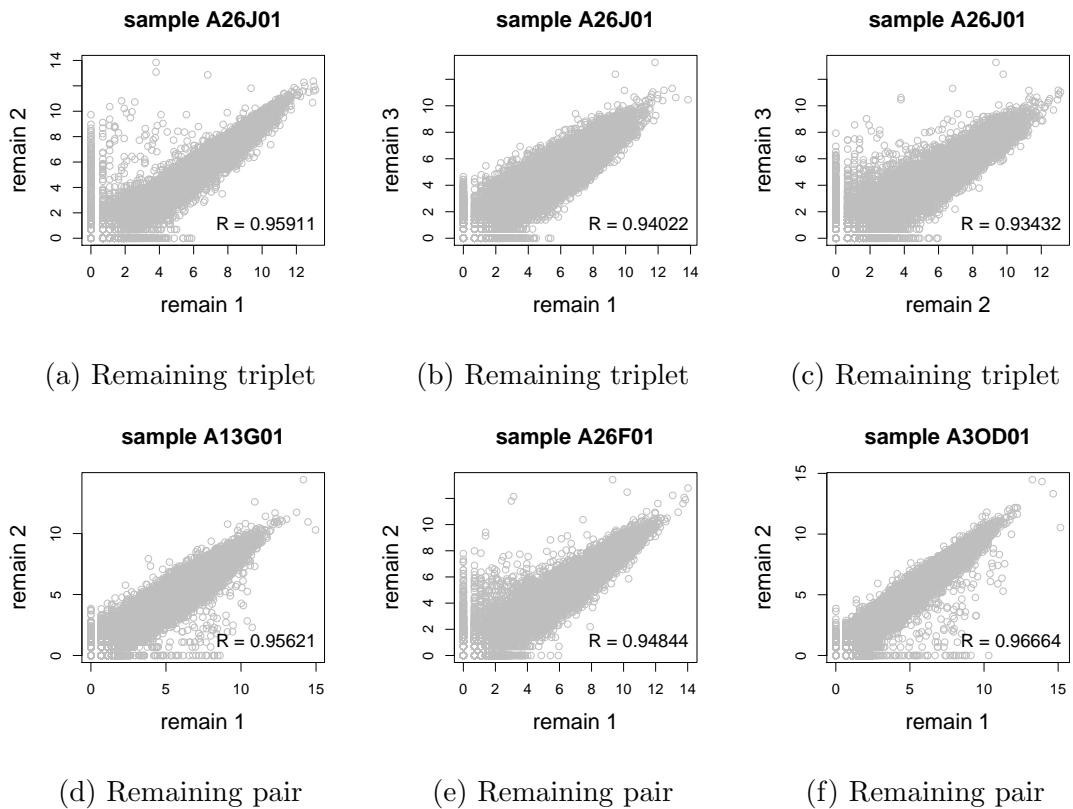


Figure A.4: **Replicate samples with all remaining.** Patient A26J was sampled 3 times and compared pairwise. Pairs of samples were also compared for other patients with replicate samples. In all cases, replicate samples remaining in the dataset were highly concordant, as shown by Pearson correlation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

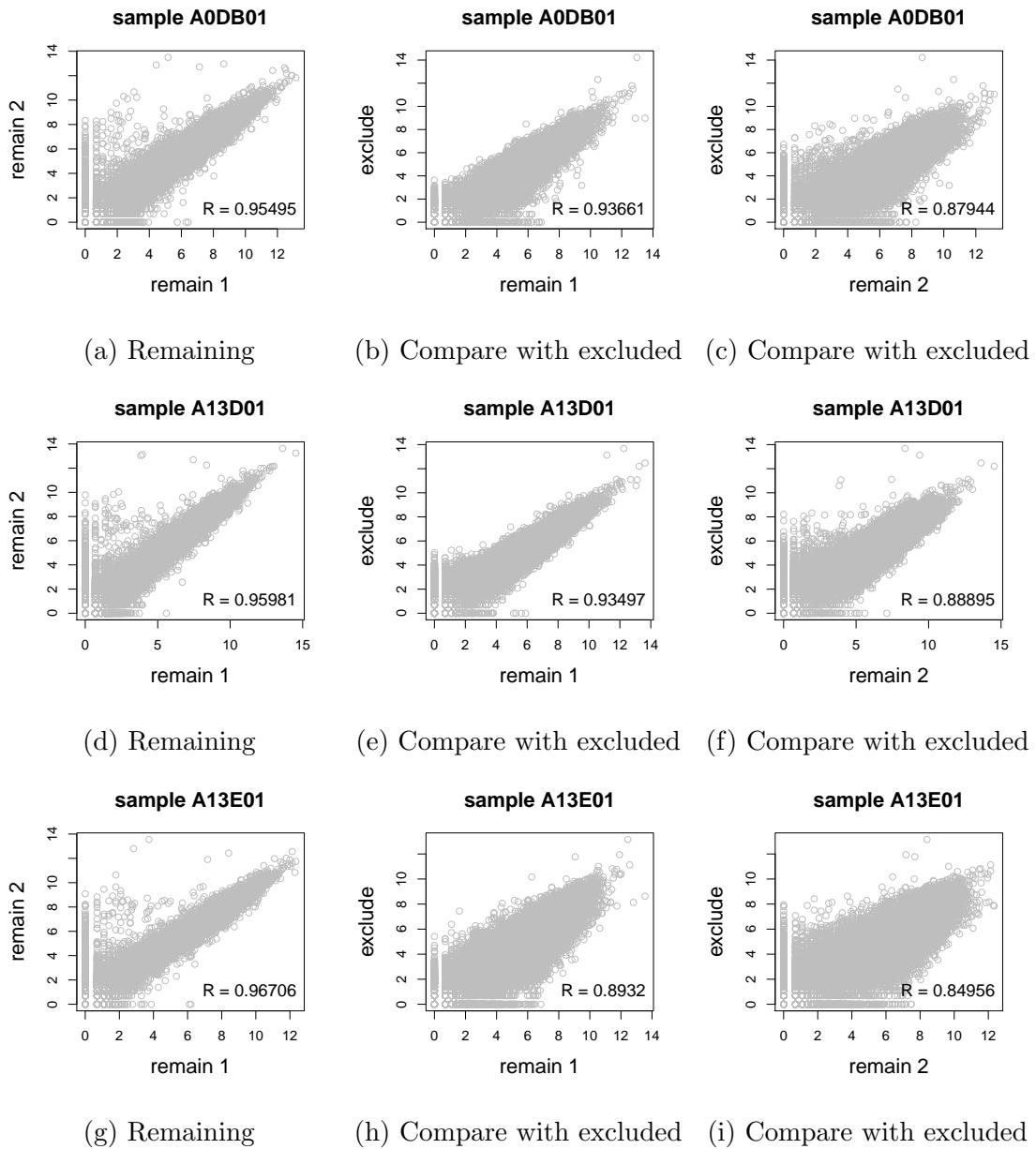


Figure A.5: **Replicate samples with some excluded.** (continued on next page)

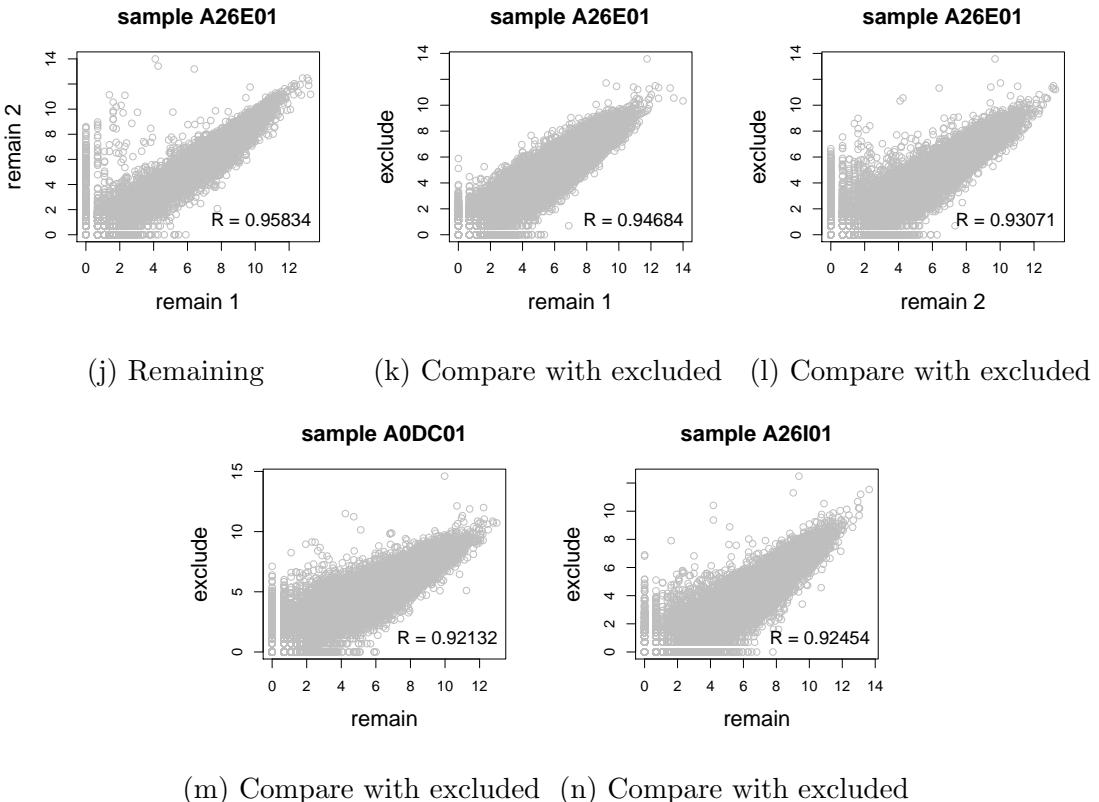


Figure A.5: **Replicate samples with some excluded.** Patients A0DB, A13D, A13E, and A26E were each sampled 3 times and compared pairwise. Pairs of samples were also compared for other patients with replicate samples. In all cases, the replicate samples remaining in the dataset more were highly concordant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

# Appendix B

## Software Used for Thesis

Table B.1: Complete list of R packages used during this 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	
Biostrings	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
cgdssr	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		0.0.0.9000	0.0.0.9000	0.0.0.9000
	TomKellyGenetics				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	0.1.0	0.1.0	0.1.0	0.1.0
.permutation	TomKellyGenetics				
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	0.0.0.9001	0.0.0.9001	0.0.0.9001	0.0.0.9001
	TomKellyGenetics				
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		
protools	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	
reactometree	GitHub		0.1		
	TomKellyGenetics				
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
rgeff	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	
slipt	GitHub	0.1.0	0.1.0	0.1.0	0.1.0
	TomKellyGenetics				

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

# Appendix C

## Mutation Analysis in Breast Cancer

### C.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 C.1: Candidate synthetic lethal gene partners of *CDH1* from mtSLIPT

Gene	Observed*	Expected*	$\chi^2$ value	p-value	p-value (False discovery rate (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 synthetic lethal partners for *CDH1* by mtSLIPT in TCGA in breast cancer expression and mutation data

\* Observed and expected numbers of *CDH1* mutant TCGA breast tumours with low expression of partner genes

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

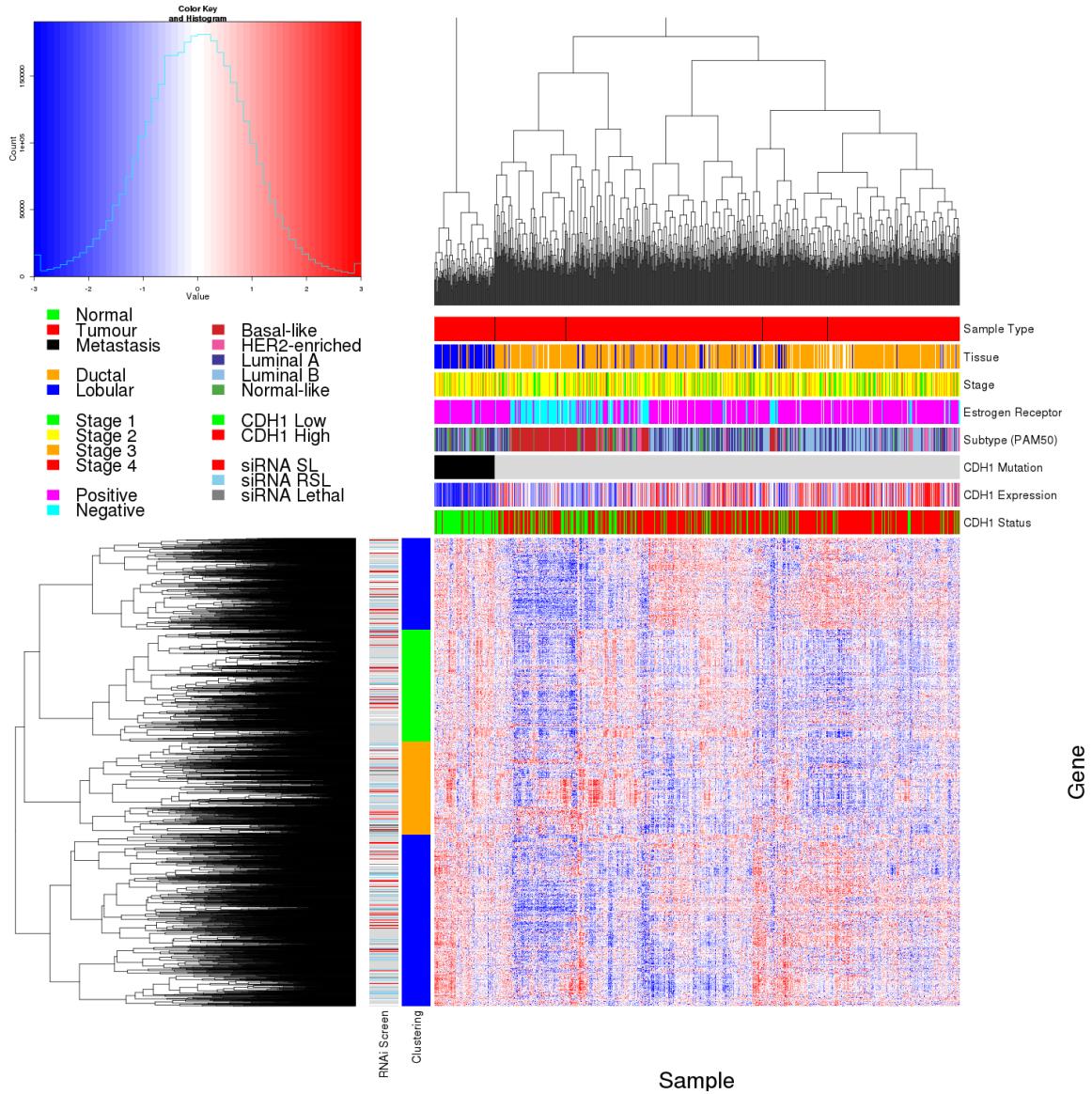
Pathways Over-represented	Pathway Size	SL Genes	p-value (FDR)
Eukaryotic Translation Elongation	86	60	$2.0 \times 10^{-128}$
Peptide chain elongation	83	59	$2.0 \times 10^{-128}$
Eukaryotic Translation Termination	83	58	$2.3 \times 10^{-125}$
Viral mRNA Translation	81	57	$2.5 \times 10^{-124}$
Nonsense 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 signalling	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 C.1 and C.2 were derived from comparing the expression profiles of potential partners to the mutation status of *CDH1* (as shown in Figure 3.2). The following analysis was limited to the samples for which both expression and somatic mutation data were available from TCGA.

## C.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* mutation 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 C.1. Over-representation for Reactome pathways for each of the gene clusters identified is given in Table C.3.



**Figure C.1: Synthetic lethal expression profiles of analysed samples.** Gene expression profile heatmap (correlation distance) of all samples (separated by *CDH1* somatic mutation status) analysed in TCGA breast cancer dataset for gene expression of 3743 candidate partners of E-cadherin (*CDH1*) from mtSLIPT prediction (with significant FDR adjusted  $p < 0.05$ ). Deeply clustered, inter-correlated genes form several main groups, each containing genes that were SL candidates or toxic in an siRNA screen Telford *et al.* (2015). Clusters had different sample groups highly expressing the synthetic lethal candidates in *CDH1* mutant samples and often lowly expressing *CDH1* wild-type samples (which were not tested for), although many of the *CDH1* mutant samples had among the lowest *CDH1* expression. In contrast to the expression analysis the (predominantly *CDH1* wild-type) basal subtype and ER negative samples have depleted expression among most candidate synthetic lethal partners.

Table C.3: Pathways for clusters of *CDH1* partners from mtSLIPT

Pathways Over-represented in Cluster 1	Pathway	Size	Cluster Genes	p-value (FDR)
Olfactory Signalling Pathway		57	8	$7.1 \times 10^{-9}$
Assembly of the primary cilium		149	14	$8.0 \times 10^{-9}$
Sphingolipid metabolism		62	8	$9.6 \times 10^{-9}$
Signalling 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 signalling by ERBB4		34	5	$4.9 \times 10^{-7}$
Intraflagellar transport		35	5	$4.9 \times 10^{-7}$
PI3K events in ERBB4 signalling		87	8	$4.9 \times 10^{-7}$
PIP3 activates AKT signalling		87	8	$4.9 \times 10^{-7}$
PI3K events in ERBB2 signalling		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	$5.6 \times 10^{-7}$
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 signalling		472	48	$2.8 \times 10^{-14}$
G <sub>αx</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, signalling 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>αi</sub> signalling events		167	18	$6.3 \times 10^{-13}$
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	$3 \times 10^{-81}$
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	$1.1 \times 10^{-9}$
G <sub>αq</sub> 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 Eoxins		15	4	$3.2 \times 10^{-8}$
Signalling 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	$8.2 \times 10^{-8}$
Signalling by NOTCH1		80	8	$1.2 \times 10^{-7}$
Platelet activation, signalling and aggregation		179	14	$1.2 \times 10^{-7}$
Recruitment of mitotic centrosome proteins and complexes		64	7	$1.2 \times 10^{-7}$

Pathway over-representation analysis for Reactome pathways with the number of genes in each pathway (Pathway Size), number of genes within the pathway identified (Cluster Genes), and the pathway over-representation p-value (adjusted by FDR) from the hypergeometric test.

### C.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 4.2.1. These were expected to be more concordant with the experimental results performed on a null mutant, however this was not the case at the gene level: less genes overlapped with experimental candidates in Figure C.2. This discrepancy was may be due to lower sample size for mutations in TCGA data or lower frequency (expected value) of *CDH1* mutations compared to low expression.

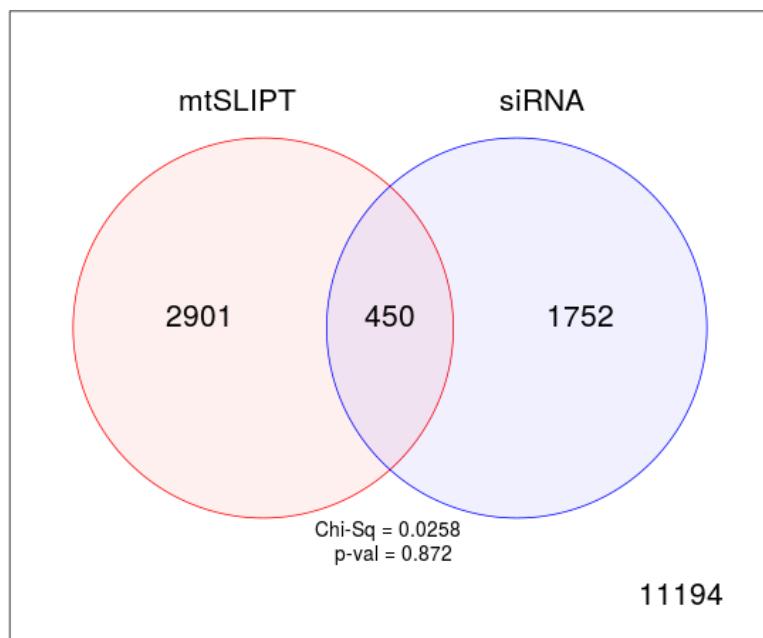


Figure C.2: **Comparison of mtSLIPT to siRNA.** Testing the overlap of gene candidates for E-cadherin synthetic lethal partners between computational (SLIPT) and experimental screening (siRNA) approaches. The  $\chi^2$  test suggests that the overlap is no more than would be expected by chance ( $p = 0.281$ ).

Despite a lower sample size (and low number of a predicted partners) for mutation analysis, the pathway composition (Tables C.2 and C.4) was similar to expression analysis, as described in Section 4.2.5. In particular, the resampling analysis (Section C.3.1) supported many of the results of expression analysis (Section 4.2.5.1). Tables C.5 and C.6 detected many of the same or functionally-related pathways.

Table C.4: Pathways 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	$1.9 \times 10^{-22}$
Signalling by VEGF	99	19	$2.6 \times 10^{-22}$
DAP12 signalling	149	24	$4.2 \times 10^{-22}$
Organelle biogenesis and maintenance	264	34	$4.3 \times 10^{-20}$
Downstream signalling of activated FGFR1	134	21	$4.3 \times 10^{-20}$
Downstream signalling of activated FGFR2	134	21	$4.3 \times 10^{-20}$
Downstream signalling of activated FGFR3	134	21	$4.3 \times 10^{-20}$
Downstream signalling of activated FGFR4	134	21	$4.3 \times 10^{-20}$
Signalling by ERBB2	146	22	$5.3 \times 10^{-20}$
Signalling by FGFR	146	22	$5.3 \times 10^{-20}$
Signalling by FGFR1	146	22	$5.3 \times 10^{-20}$
Signalling 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, signalling and aggregation	186	13	$4.9 \times 10^{-6}$
Signalling 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	$2.2 \times 10^{-5}$
Signalling by PDGF	173	11	$2.9 \times 10^{-5}$
Circadian Clock	34	4	$2.9 \times 10^{-5}$
Signalling 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	$4.5 \times 10^{-5}$
Signalling 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	$7.1 \times 10^{-5}$
Signalling by ERBB2	148	9	$7.1 \times 10^{-5}$
Signalling by SCF-KIT	129	8	$8.3 \times 10^{-5}$

### C.3.1 Resampling Analysis

Table C.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 signalling</b>	$1.6 \times 10^{-80}$	0.095478
Hemostasis	$2.1 \times 10^{-78}$	0.2671
Signalling 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 were marked in bold (FDR < 0.05) and italics (FDR < 0.1).

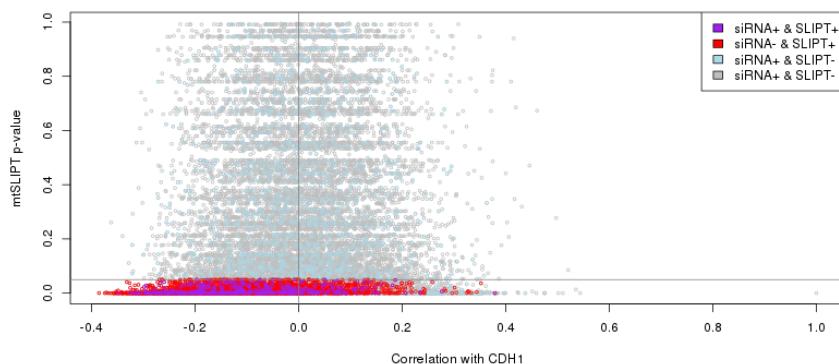
Table C.6: Pathways for *CDH1* partners from mtSLIPT and siRNA primary screen

Reactome Pathway	Over-representation	Permutation
Visual phototransduction	$1.2 \times 10^{-9}$	0.86279
<b>G<sub>as</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>Signalling 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, signalling 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
Signalling 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 signalling	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 signalling	0.00012	0.62787
Defensins	0.00012	0.77542
GPCR downstream signalling	0.00012	0.79454
<i>Diseases associated with glycosaminoglycan metabolism</i>	0.00013	0.065927
<i>Diseases of glycosylation</i>	0.00013	0.065927
Signalling by Retinoic Acid	0.00013	0.22292
Signalling by Leptin	0.00013	0.34596
Signalling by SCF-KIT	0.00013	0.70881
Opioid Signalling	0.00013	0.96053
Signalling by NOTCH	0.00015	0.26884
Platelet homeostasis	0.00015	0.4878
Signalling 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 signalling cascade</i>	0.0002	0.0795
A tetrasaccharide linker sequence is required for GAG synthesis	0.0002	0.42615

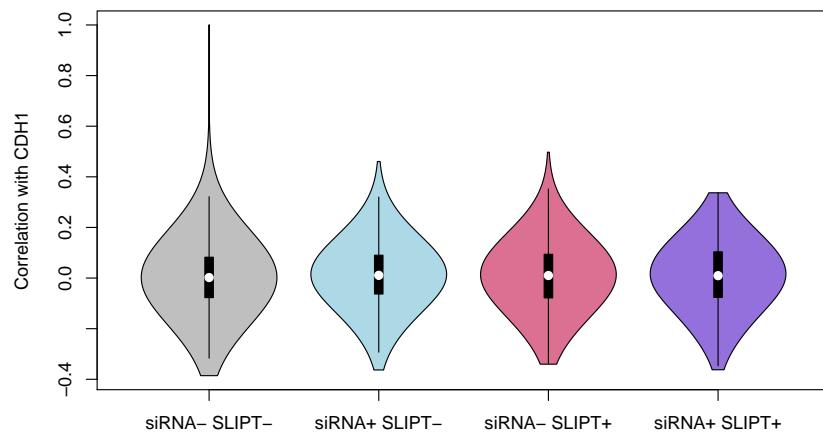
Over-representation (hypergeometric test) and Permutation p-values adjusted for multiple tests across pathways (FDR). Significant pathways were marked in bold (FDR < 0.05) and italics (FDR < 0.1).

## C.4 Compare SLIPT genes

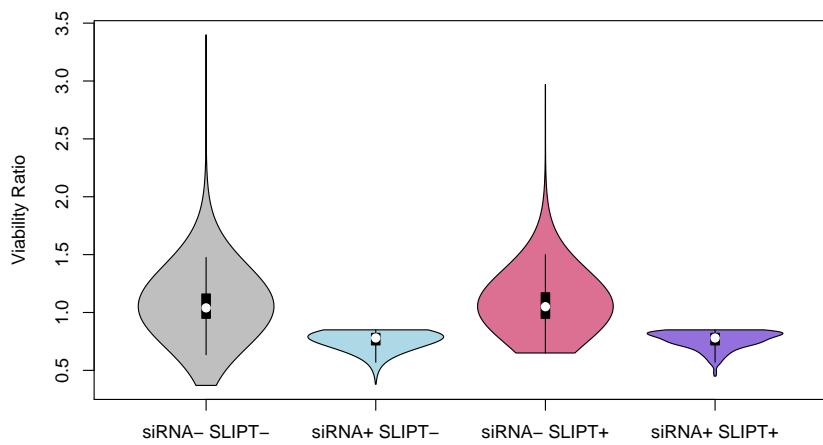
The mutation synthetic lethal partners with *CDH1* were also compared to siRNA primary screen data (Telford *et al.*, 2015), by correlation and siRNA viability as described in sections 4.2.2 and 4.2.3.



**Figure C.3: Compare mtSLIPT and siRNA genes with correlation.** The mtSLIPT p-values were compared against Pearson correlation of expression with *CDH1*. Genes detected by SLIPT or siRNA were coloured according to the legend.



**Figure C.4: Compare mtSLIPT and siRNA genes with correlation.** Genes detected by mtSLIPT against *CDH1* mutation and siRNA screening were compared against Pearson correlation of expression with *CDH1*. There were no differences in correlation between the gene groups.



**Figure C.5: Compare mtSLIPT and siRNA genes with siRNA viability.** Genes detected as candidate synthetic lethal partners by mtSLIPT (in TCGA breast cancer) expression analysis against *CDH1* mutation and experimental screening (with siRNA) were compared against the viability ratio of *CDH1* mutant and wild-type cells in the primary siRNA screen. There were clear no differences in viability between genes detected by mtSLIPT and those not with the differences being primarily due to viability thresholds that were used to detect synthetic lethality by Telford *et al.* (2015).

## C.5 Metagene Analysis

Metagene analysis was performed for synthetic lethal pathways against *CDH1* mutation. These were described and compared to expression analysis in Section 4.3.3.

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

Pathway	ID	Observed	Expected	$\chi^2$ value	p-value	p-value (FDR)
Neurotoxicity of clostridium toxins	168799	8	36.7	79.4	$5.71 \times 10^{-18}$	$3.14 \times 10^{-15}$
Aquaporin-mediated transport	445717	8	36.7	76.3	$2.73 \times 10^{-17}$	$9.01 \times 10^{-15}$
Toxicity of botulinum toxin type G (BoNT/G)	5250989	8	36.7	76.3	$2.73 \times 10^{-17}$	$9.01 \times 10^{-15}$
ABC-family proteins mediated transport	382556	10	36.7	68.2	$1.58 \times 10^{-15}$	$1.86 \times 10^{-13}$
G <sub>αz</sub> signalling events	418597	10	36.7	59.9	$9.97 \times 10^{-14}$	$5.48 \times 10^{-12}$
Regulation of IGF transport and uptake by IGFBPs	381426	9	36.7	56.3	$5.88 \times 10^{-13}$	$2.11 \times 10^{-11}$
GP1b-IX-V activation signalling	430116	8	36.7	55.7	$8.20 \times 10^{-13}$	$2.76 \times 10^{-11}$
GABA receptor activation	977443	12	36.7	55.1	$1.07 \times 10^{-12}$	$3.26 \times 10^{-11}$
Vasopressin regulates renal water homeostasis via Aquaporins	432040	9	36.7	54.1	$1.77 \times 10^{-12}$	$4.88 \times 10^{-11}$
Toxicity of botulinum toxin type D (BoNT/D)	5250955	14	36.7	53.4	$2.54 \times 10^{-12}$	$6.64 \times 10^{-11}$
Toxicity of botulinum toxin type F (BoNT/F)	5250981	14	36.7	53.4	$2.54 \times 10^{-12}$	$6.64 \times 10^{-11}$
STAT6-mediated induction of chemokines	3249367	16	36.7	52.2	$4.72 \times 10^{-12}$	$1.13 \times 10^{-10}$
Toxicity of botulinum toxin type B (BoNT/B)	5250958	14	36.7	50.8	$9.5 \times 10^{-12}$	$1.98 \times 10^{-10}$
S6K1 signalling	165720	12	36.7	50.2	$1.24 \times 10^{-11}$	$2.5 \times 10^{-10}$
G <sub>αs</sub> signalling events	418555	11	36.7	49.2	$2.08 \times 10^{-11}$	$3.85 \times 10^{-10}$
RHO GTPases activate CIT	5625900	14	36.7	48.2	$3.34 \times 10^{-11}$	$5.9 \times 10^{-10}$
NADE modulates death signalling	205025	15	36.7	47.4	$5.00 \times 10^{-11}$	$8.32 \times 10^{-10}$
Keratan sulfate degradation	2022857	10	36.7	46.6	$7.5 \times 10^{-11}$	$1.15 \times 10^{-9}$
Signalling by Retinoic Acid	5362517	10	36.7	46.6	$7.5 \times 10^{-11}$	$1.15 \times 10^{-9}$
Adenylate cyclase inhibitory pathway	170670	14	36.7	45.9	$1.11 \times 10^{-10}$	$1.59 \times 10^{-9}$
Inhibition of adenylate cyclase pathway	997269	14	36.7	45.9	$1.11 \times 10^{-10}$	$1.59 \times 10^{-9}$
Fatty acids	211935	6	36.7	45.7	$1.21 \times 10^{-10}$	$1.72 \times 10^{-9}$
Ionotropic activity of Kainate Receptors	451306	13	36.7	44.6	$2.03 \times 10^{-10}$	$2.58 \times 10^{-9}$
Activation of Ca-permeable Kainate Receptor	451308	13	36.7	44.6	$2.03 \times 10^{-10}$	$2.58 \times 10^{-9}$
RA biosynthesis pathway	5365859	13	36.7	44.6	$2.03 \times 10^{-10}$	$2.58 \times 10^{-9}$

Strongest candidate synthetic lethal partners for *CDH1* by mtSLIPT with observed and expected numbers of mutant *CDH1* TCGA breast cancer tumours with low expression of partner metagenes.

## C.6 Expression of Somatic Mutations

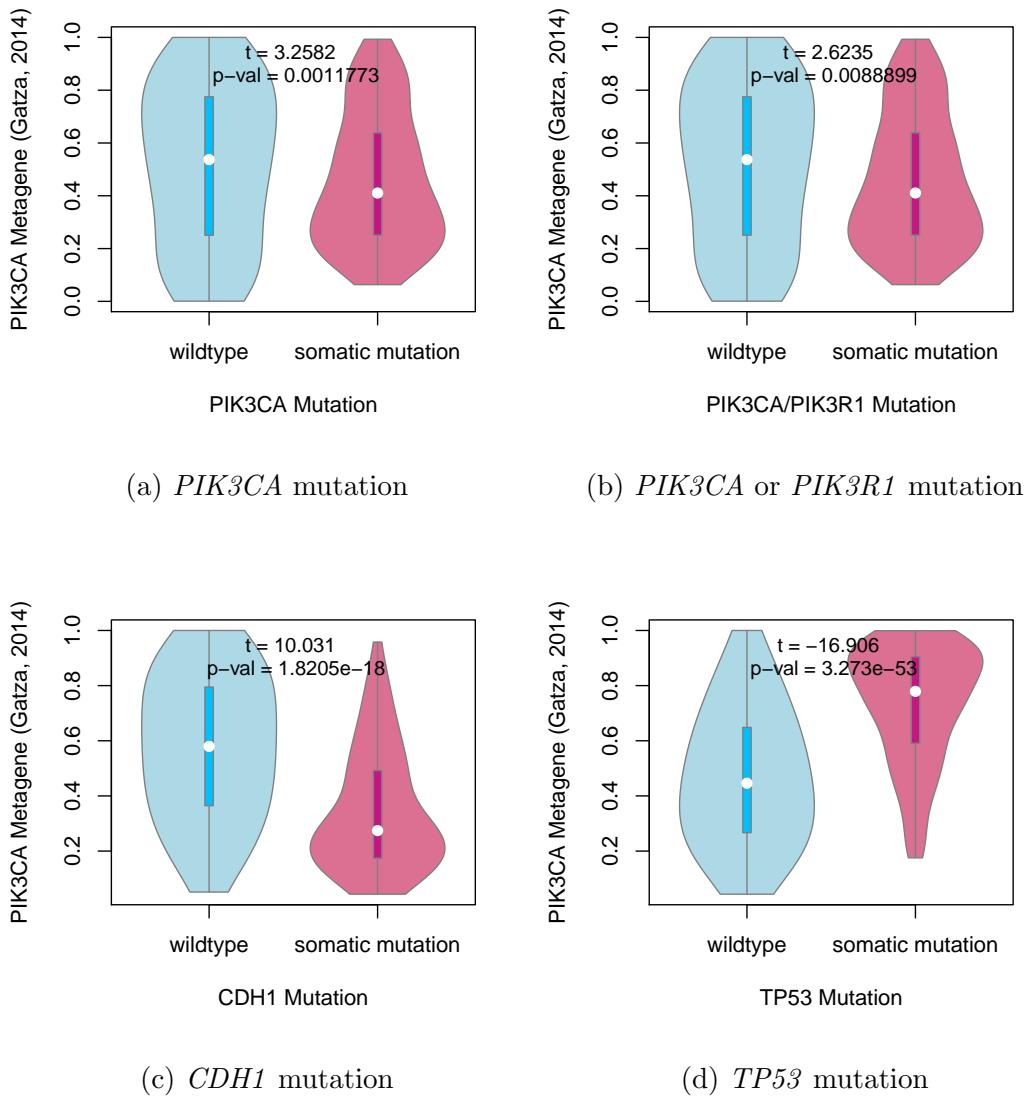
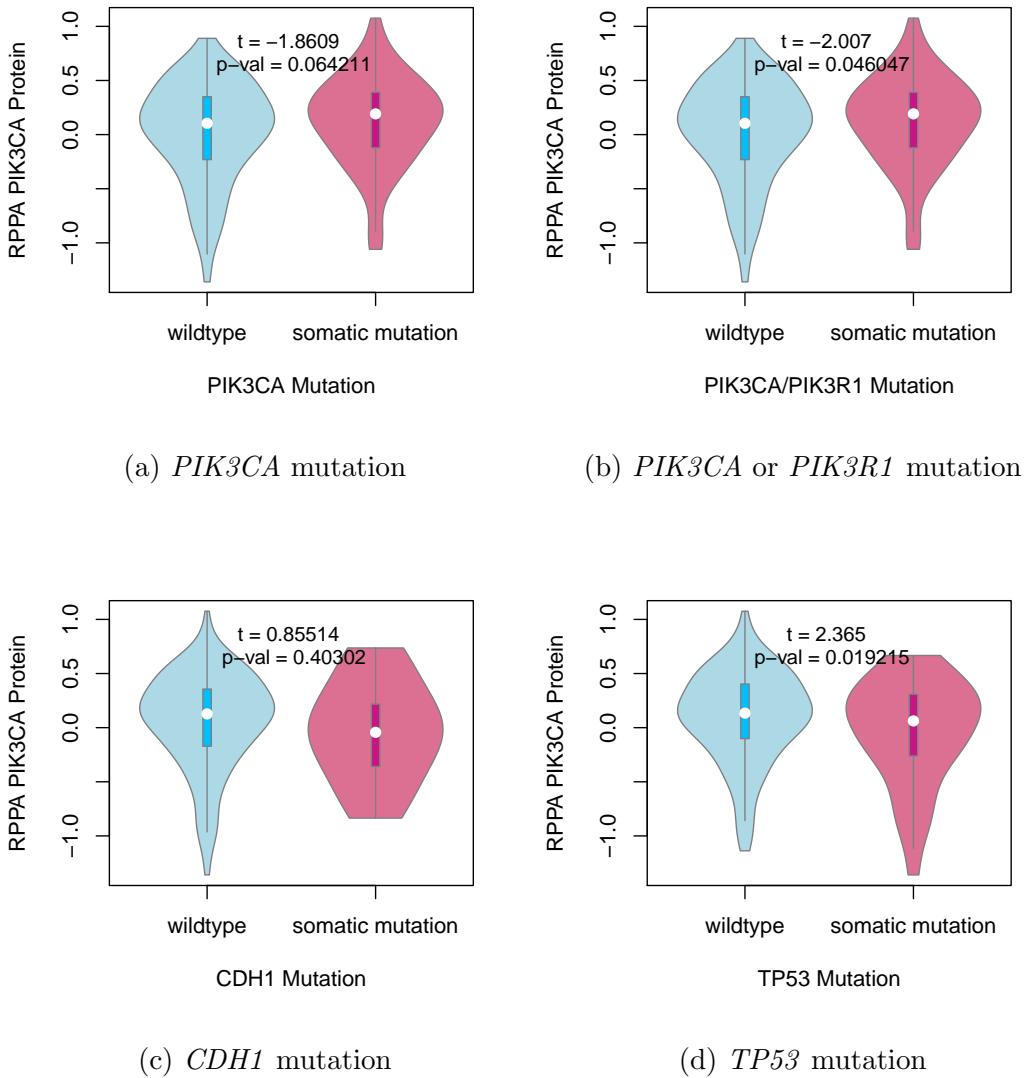
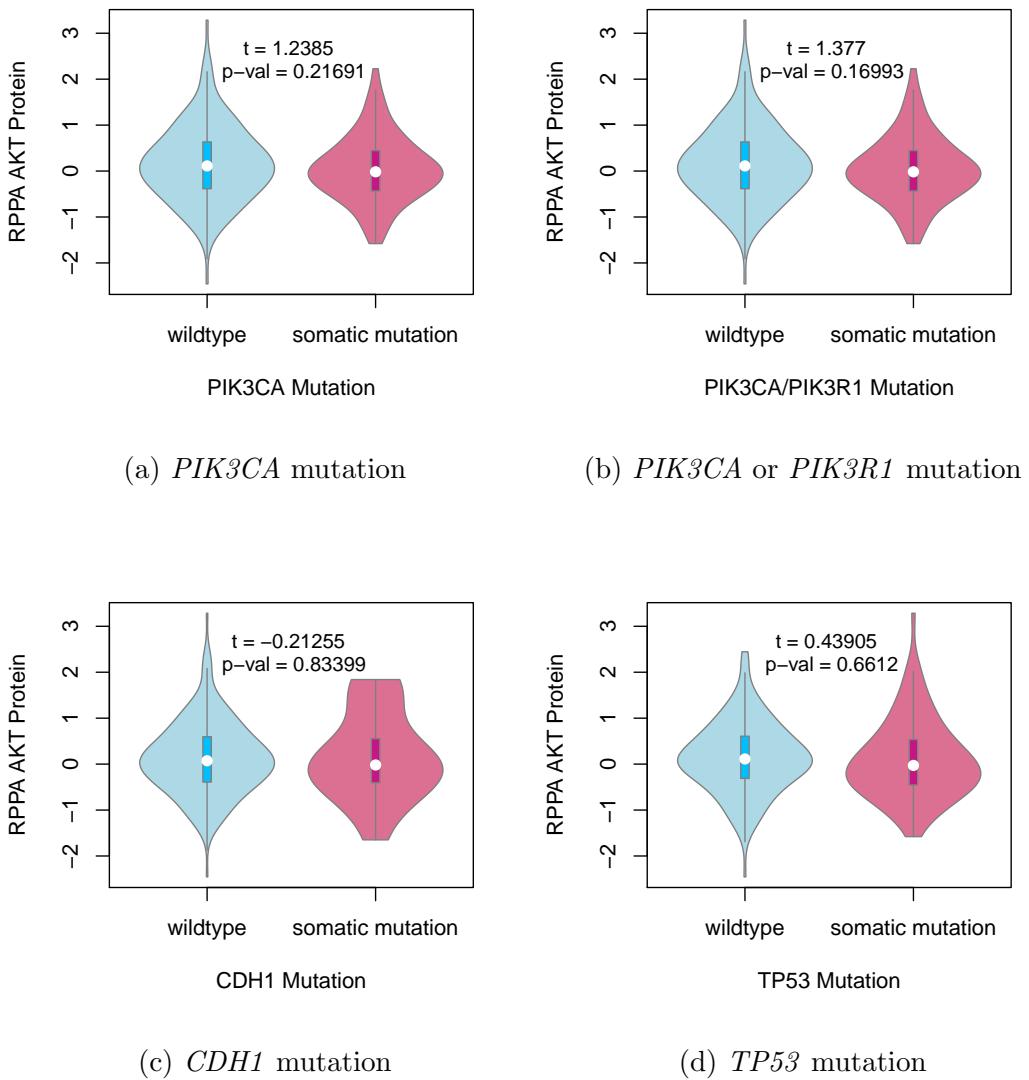


Figure C.6: **Somatic mutation against PIK3CA metagene.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the PIK3CA (Gatza *et al.*, 2014) pathway metagene. The tumour suppressors *CDH1* and *TP53* showed an increase and decrease in the metagene respectively, whereas *PIK3CA* and *PIK3R1* mutations weaker evidence of decrease in metagene levels.



**Figure C.7: Somatic mutation against PI3K protein.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the expression of the p110 $\alpha$  protein (encoded by *PIK3CA*). Protein levels were significantly elevated in samples with *PIK3CA* or *PIK3R1* mutations and lower in samples with *TP53* mutations.



**Figure C.8: Somatic mutation against AKT protein.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the expression of the AKT protein (a downstream target of *PIK3CA*). Protein levels were not significantly different in samples mutations in any of these cancer genes.

## C.7 Metagene Expression Profiles

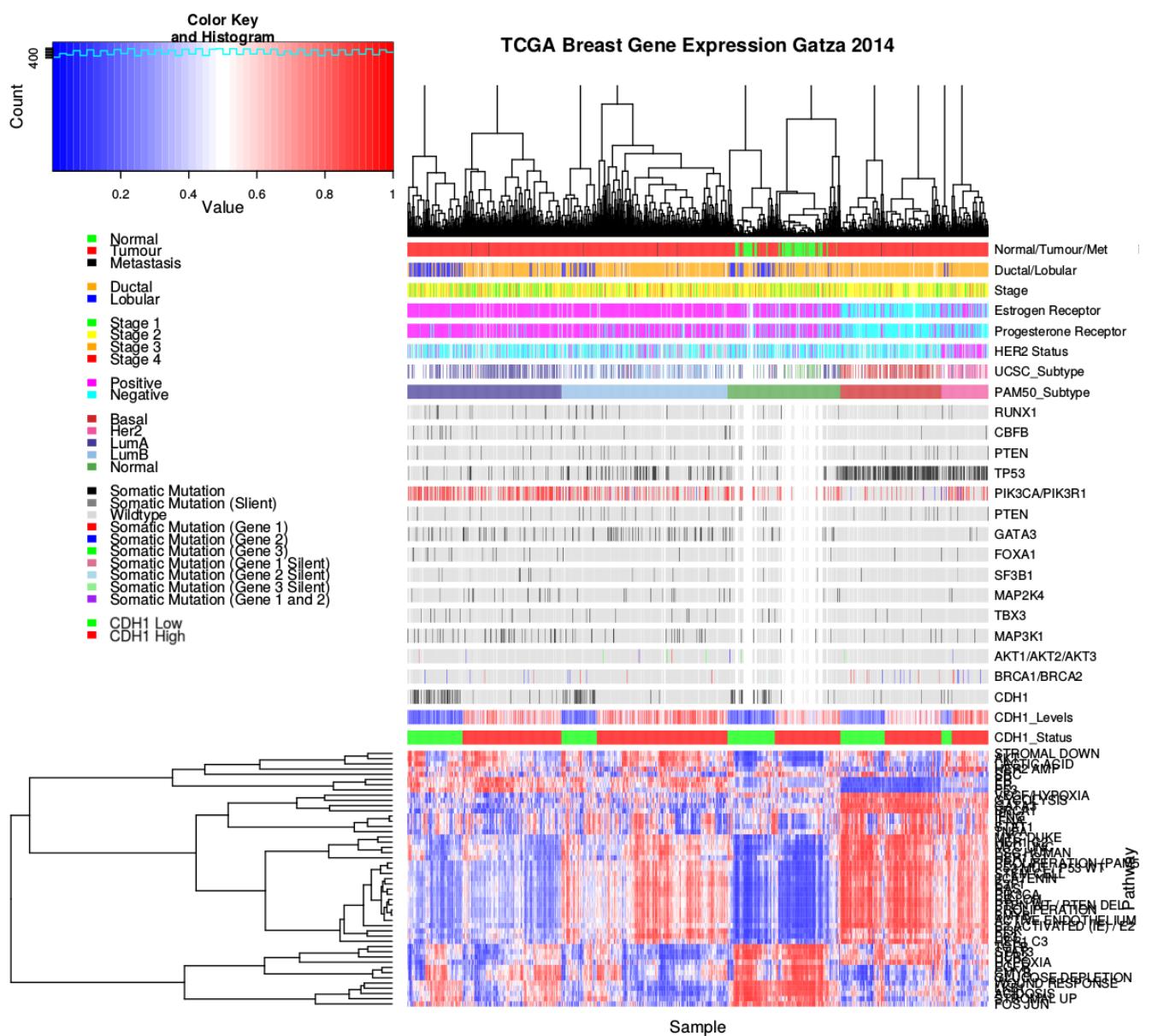
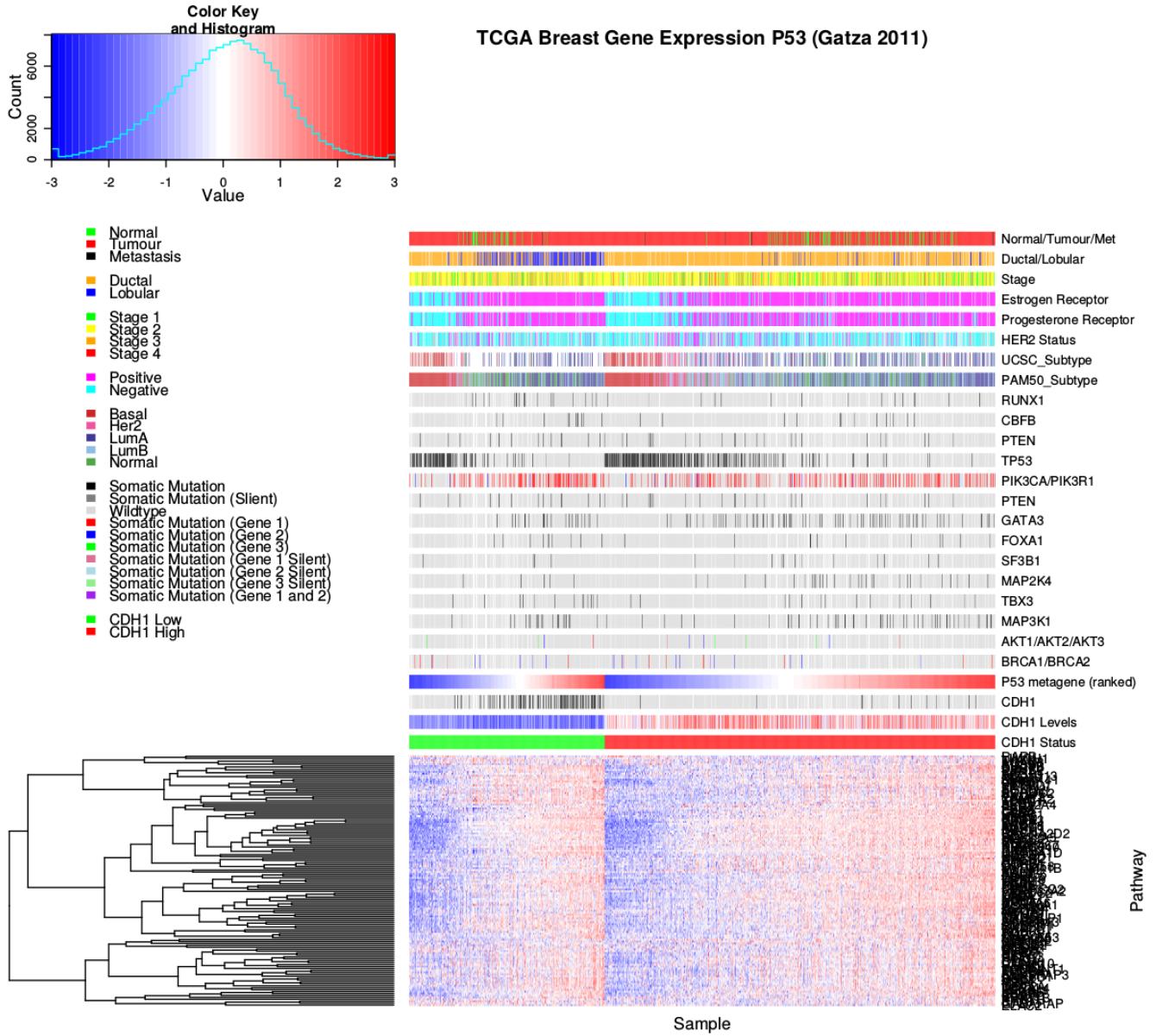


Figure C.9: **Pathway metagene expression profiles.** Expression profiles for metagene signatures from Gatza *et al.* (2014) in TCGA breast data, annotated for clinical factors and cancer gene mutations.



**Figure C.10: Expression profiles for p53 related genes.** Expression profiles the genes contained in the *TP53* gene signature from Gatza *et al.* (2011) in TCGA breast data, annotated for clinical factors and cancer gene mutations. Samples were separated by *CDH1* expression status and sorted by the metagene. In both cases, the majority of genes were consistent with the direction of the metagene, with few very exceptions. *TP53* mutant samples had low metagene expression, consistent with loss of tumour suppressor functions, and were less likely to have *CDH1* or *PIK3CA* mutations.

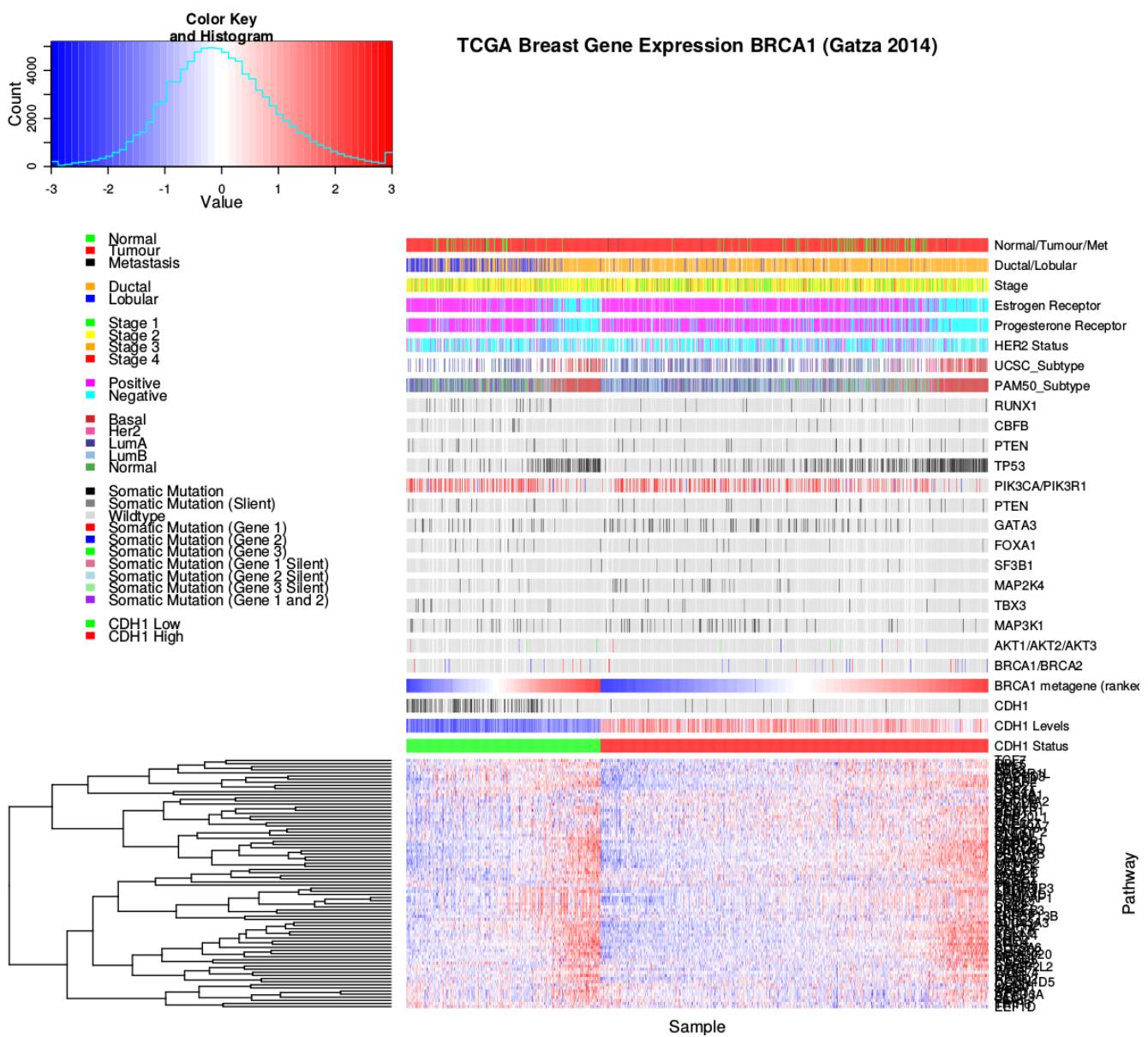


Figure C.11: **Expression profiles for BRCA related genes.** Expression profiles the genes contained in the gene signature related to *BRCA1* and *BRCA2* functions from Gatza *et al.* (2014) in TCGA breast data, annotated for clinical factors and cancer gene mutations. Samples were separated by *CDH1* expression status and sorted by the metagene. In both cases, the majority of genes were consistent with the direction of the metagene, with few very exceptions. *BRCA1* and *BRCA2* mutant samples had higher metagene expression than most samples for the ductal subtype, although this was not the case (for the lobular samples for which the metagene was lower). However, the metagene was higher for basal subtype and ER negative samples.

# Appendix D

## Intrinsic Subtyping

The intrinsic subtypes for TCGA breast cancer samples provided by University of California, Santa Cruz (UCSC) (Koboldt *et al.*, 2012; UCSC, 2012) that were derived from microarray analysis have been compared to the Prediction Analysis of Microarray 50 (PAM50) results for performing subtyping from RNA-Seq data (Parker *et al.*, 2009). As shown in Table D.1, these subtypes were highly concordant for samples which had both procedures performed upon them ( $\chi^2 = 1305.9$ ,  $p = 2.73 \times 10^{-268}$ ). The main exception were the luminal A samples some of which were reclassified as luminal B or “normal-like”.

Table D.1: Comparison of intrinsic subtypes

UCSC Subtype					
	Basal-like	HER2-enriched	Luminal A	Luminal B	Normal-like
	100	58	232	128	30

PAM50 Subtype					
	Basal-like	HER2-enriched	Luminal A	Luminal B	Normal-like
	208	94	314	334	227

		UCSC Subtype				
PAM50 Subtype		Basal-like	HER2-enriched	Luminal A	Luminal B	Normal-like
Basal-like		96	4	2	2	1
HER2-enriched		0	47	5	3	0
Luminal A		1	0	141	1	0
Luminal B		2	7	49	121	0
Normal-like		1	0	35	1	29

The intrinsic subtypes of TCGA breast samples were compared between those provided by UCSC (Koboldt *et al.*, 2012) from microarray expression to those derived from RNA-Seq data (Parker *et al.*, 2009). Comparisons between these were limited to samples for which both data types were available.

The PAM50 subtypes could be more accurate given similarity of these subtypes and that the remainder of the subtypes were accurately recapitulated with RNA-Seq data. Furthermore, UCSC subtypes correctly identified 22/22 normal samples as “normal-like” and PAM50 subtyping in RNA-Seq data had a success rate of 112/113 (including all of those identified from microarrays). Therefore the PAM50 subtypes (performed on a larger cohort of samples) are appropriate to use for further interpretation, superseding the UCSC subtypes available for a limited set of samples.

# Appendix E

## Stomach Expression Analysis

The following results are a replication of the TCGA results (in Chapter 4) with stomach cancer data, using synthetic lethality (SLIPT) against *CDH1*.

### E.1 Synthetic Lethal Genes and Pathways

Table E.1: Synthetic lethal gene partners of *CDH1* from SLIPT in stomach cancer

Gene	Observed*	Expected*	$\chi^2$ value	p-value	p-value (FDR)
<i>PRAF2</i>	17	50.4	121	$3.54 \times 10^{-25}$	$1.45 \times 10^{-21}$
<i>EMP3</i>	17	50.4	115	$5.06 \times 10^{-24}$	$1.48 \times 10^{-20}$
<i>PLEKHO1</i>	22	50.4	112	$2.14 \times 10^{-23}$	$4.75 \times 10^{-20}$
<i>SELM</i>	20	50.4	111	$5.13 \times 10^{-23}$	$8.09 \times 10^{-20}$
<i>GYPC</i>	20	50.4	110	$5.77 \times 10^{-23}$	$8.45 \times 10^{-20}$
<i>COX7A1</i>	18	50.4	109	$1.15 \times 10^{-22}$	$1.39 \times 10^{-19}$
<i>TNFSF12</i>	20	50.4	106	$4.06 \times 10^{-22}$	$4.38 \times 10^{-19}$
<i>SEPT4</i>	17	50.4	106	$6.58 \times 10^{-22}$	$5.91 \times 10^{-19}$
<i>LGALS1</i>	19	50.4	105	$6.64 \times 10^{-22}$	$5.91 \times 10^{-19}$
<i>RARRES2</i>	27	50.4	105	$8.02 \times 10^{-22}$	$6.85 \times 10^{-19}$
<i>VEGFB</i>	16	50.4	104	$1.19 \times 10^{-21}$	$9.74 \times 10^{-19}$
<i>PRR24</i>	22	50.4	102	$2.96 \times 10^{-21}$	$2.02 \times 10^{-18}$
<i>SYNC</i>	19	50.4	102	$3.73 \times 10^{-21}$	$2.39 \times 10^{-18}$
<i>MAGEH1</i>	17	50.4	100	$9.52 \times 10^{-21}$	$5.01 \times 10^{-18}$
<i>HSPB2</i>	23	50.4	99.6	$1.19 \times 10^{-20}$	$5.82 \times 10^{-18}$
<i>SMARCD3</i>	19	50.4	99	$1.59 \times 10^{-20}$	$7.57 \times 10^{-18}$
<i>CREM</i>	13	50.4	98.1	$2.48 \times 10^{-20}$	$1.13 \times 10^{-17}$
<i>GNG11</i>	20	50.4	97.3	$3.68 \times 10^{-20}$	$1.59 \times 10^{-17}$
<i>GNAI2</i>	17	50.4	96.4	$5.75 \times 10^{-20}$	$2.36 \times 10^{-17}$
<i>FUNDC2</i>	22	50.4	95.9	$7.39 \times 10^{-20}$	$2.91 \times 10^{-17}$
<i>CNRIP1</i>	21	50.4	95.3	$1.0 \times 10^{-19}$	$3.66 \times 10^{-17}$
<i>CALHM2</i>	22	50.4	93.1	$2.94 \times 10^{-19}$	$1.06 \times 10^{-16}$
<i>ARID5A</i>	18	50.4	92.7	$3.47 \times 10^{-19}$	$1.22 \times 10^{-16}$
<i>ST3GAL3</i>	27	50.4	92.2	$4.49 \times 10^{-19}$	$1.56 \times 10^{-16}$
<i>LOC339524</i>	21	50.4	92.1	$4.8 \times 10^{-19}$	$1.59 \times 10^{-16}$

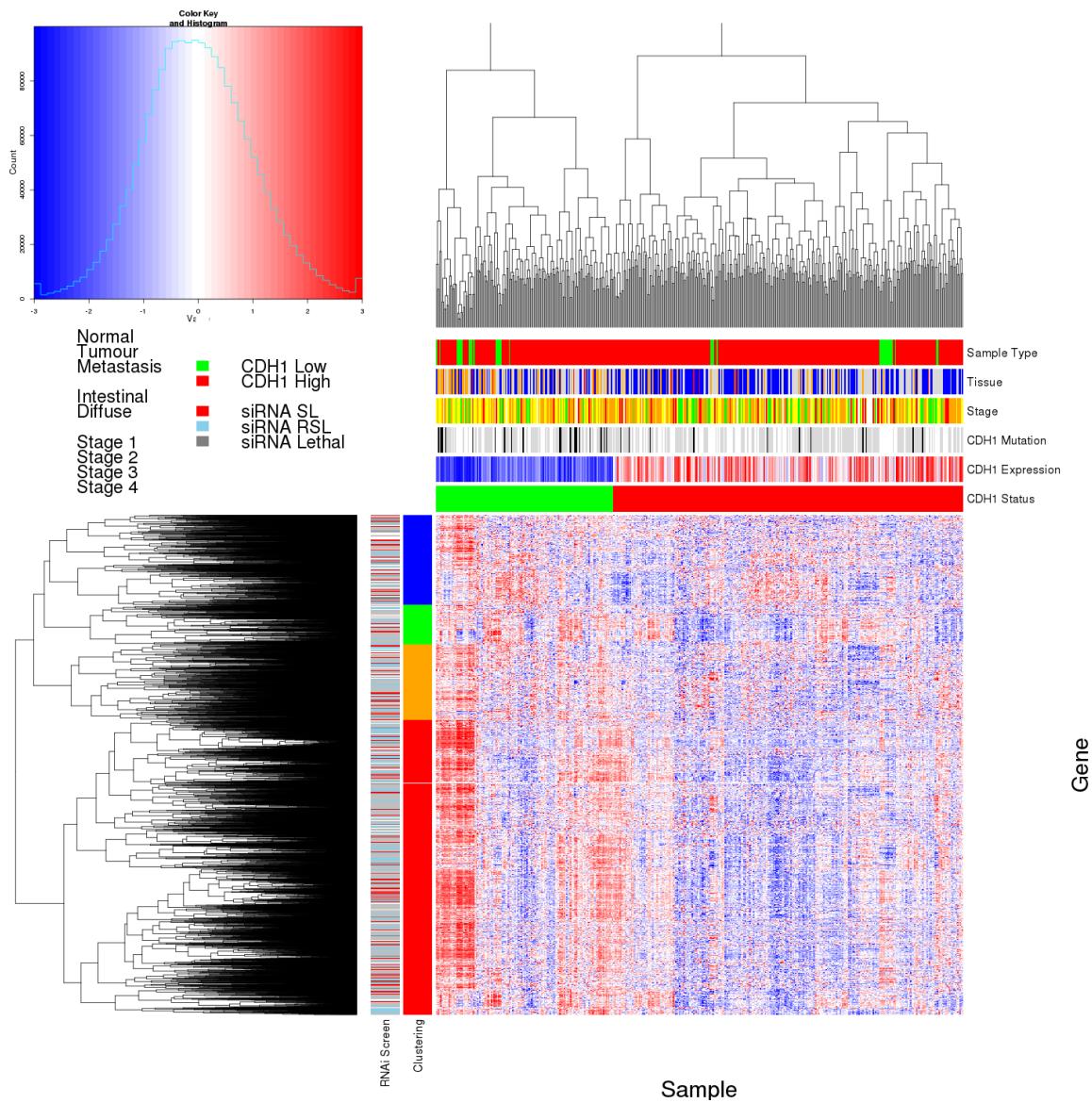
Strongest candidate synthetic lethal partners for *CDH1* by SLIPT in TCGA stomach cancer expression data

\* Observed and expected numbers of samples which had low expression of both genes

Table E.2: Pathways for *CDH1* partners from SLIPT in stomach cancer

Pathways Over-represented	Pathway Size	SL Genes	p-value (FDR)
Extracellular matrix organization	241	104	$7.5 \times 10^{-140}$
Hemostasis	445	138	$1.8 \times 10^{-121}$
Developmental Biology	432	125	$9.2 \times 10^{-107}$
Axon guidance	289	94	$1.5 \times 10^{-102}$
Eukaryotic Translation Termination	84	49	$1.9 \times 10^{-99}$
GPCR ligand binding	373	108	$3.8 \times 10^{-99}$
Viral mRNA Translation	82	48	$3.3 \times 10^{-98}$
Formation of a pool of free 40S subunits	94	51	$3.3 \times 10^{-98}$
Eukaryotic Translation Elongation	87	49	$1.6 \times 10^{-97}$
Peptide chain elongation	84	48	$7.2 \times 10^{-97}$
Class A/1 (Rhodopsin-like receptors)	289	90	$2.7 \times 10^{-96}$
Nonsense Mediated Decay independent of the Exon Junction Complex	89	49	$3.0 \times 10^{-96}$
Infectious disease	349	100	$2.6 \times 10^{-94}$
GTP hydrolysis and joining of the 60S ribosomal subunit	105	52	$3.4 \times 10^{-94}$
L13a-mediated translational silencing of Ceruloplasmin expression	104	51	$2.8 \times 10^{-92}$
3' -UTR-mediated translational regulation	104	51	$2.8 \times 10^{-92}$
Neuronal System	272	84	$8.4 \times 10^{-92}$
SRP-dependent cotranslational protein targeting to membrane	105	51	$9.5 \times 10^{-92}$
Eukaryotic Translation Initiation	112	52	$2.0 \times 10^{-90}$
Cap-dependent Translation Initiation	112	52	$2.0 \times 10^{-90}$

Gene set over-representation analysis (hypergeometric test) for Reactome pathways for *CDH1*.



**Figure E.1: Synthetic lethal expression profiles of analysed samples.** Gene expression profile heatmap (correlation distance) of all samples (separated by the  $1/3$  quantile of *CDH1* expression) analysed in TCGA stomach cancer dataset for gene expression of 4365 candidate partners of E-cadherin (*CDH1*) from SLIPT prediction (with significant FDR adjusted  $p < 0.05$ ). Deeply clustered, inter-correlated genes form several main groups, each containing genes that were SL candidates or toxic in an siRNA screen Telford *et al.* (2015). Clusters had different sample groups highly expressing the synthetic lethal candidates in *CDH1* low samples. Notably, diffuse and *CDH1* mutant samples had elevated expression in one or more distinct clusters, although there was less complexity and variation among candidate synthetic lethal partners than in breast data. *CDH1* low samples also contained most of samples with *CDH1* mutations.

Table E.3: Pathways for clusters of *CDH1* partners in stomach SLIPT

Pathways Over-represented in Cluster 1	Pathway Size	Cluster Genes	p-value (FDR)
Viral mRNA Translation	82	48	$1.3 \times 10^{-97}$
Formation of a pool of free 40S subunits	94	51	$1.3 \times 10^{-97}$
Eukaryotic Translation Elongation	87	49	$4.8 \times 10^{-97}$
Peptide chain elongation	84	48	$1.4 \times 10^{-96}$
Eukaryotic Translation Termination	84	48	$1.4 \times 10^{-96}$
GTP hydrolysis and joining of the 60S ribosomal subunit	105	52	$7.9 \times 10^{-94}$
Nonsense Mediated Decay independent of the Exon Junction Complex	89	48	$3.1 \times 10^{-93}$
L13a-mediated translational silencing of Ceruloplasmin expression	104	51	$5.1 \times 10^{-92}$
3' -UTR-mediated translational regulation	104	51	$5.1 \times 10^{-92}$
SRP-dependent cotranslational protein targeting to membrane	105	51	$1.7 \times 10^{-91}$
Eukaryotic Translation Initiation	112	52	$3.3 \times 10^{-90}$
Cap-dependent Translation Initiation	112	52	$3.3 \times 10^{-90}$
Translation	142	56	$3.6 \times 10^{-85}$
Nonsense-Mediated Decay	104	48	$1.2 \times 10^{-84}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex	104	48	$1.2 \times 10^{-84}$
Influenza Viral RNA Transcription and Replication	109	48	$4.1 \times 10^{-82}$
Influenza Life Cycle	113	48	$3.4 \times 10^{-80}$
Influenza Infection	118	48	$6.4 \times 10^{-78}$
Pathways Over-represented in Cluster 2	Pathway Size	Cluster Genes	p-value (FDR)
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	65	12	$1.3 \times 10^{-15}$
Phosphorylation of CD3 and TCR zeta chains	18	6	$1.7 \times 10^{-12}$
Generation of second messenger molecules	29	7	$2.7 \times 10^{-12}$
PD-1 signalling	21	6	$7.4 \times 10^{-12}$
TCR signalling	62	9	$4.3 \times 10^{-11}$
Translocation of ZAP-70 to Immunological synapse	16	5	$1.1 \times 10^{-10}$
Interferon alpha/beta signalling	68	9	$1.6 \times 10^{-10}$
Initial triggering of complement	17	5	$1.6 \times 10^{-10}$
IKK complex recruitment mediated by RIP1	19	5	$5.1 \times 10^{-10}$
TRIF-mediated programmed cell death	10	4	$6.2 \times 10^{-10}$
Creation of C4 and C2 activators	11	4	$1.3 \times 10^{-9}$
RHO GTPases Activate NADPH Oxidases	11	4	$1.3 \times 10^{-9}$
Interferon Signalling	175	15	$2.3 \times 10^{-9}$
Chemokine receptors bind chemokines	52	7	$4.0 \times 10^{-9}$
Interferon gamma signalling	74	8	$1.6 \times 10^{-8}$
TRAF6 mediated induction of TAK1 complex	15	4	$1.6 \times 10^{-8}$
Activation of IRF3/IRF7 mediated by TBK1/IKK epsilon	16	4	$2.7 \times 10^{-8}$
Downstream TCR signalling	45	6	$3.5 \times 10^{-8}$
Pathways Over-represented in Cluster 3	Pathway Size	Cluster Genes	p-value (FDR)
Uptake and actions of bacterial toxins	22	4	$3.5 \times 10^{-6}$
Neurotoxicity of clostridium toxins	10	3	$3.5 \times 10^{-6}$
Activation of PPARGC1A (PGC-1alpha) by phosphorylation	10	3	$3.5 \times 10^{-6}$
SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	28	4	$1.4 \times 10^{-5}$
Assembly of the primary cilium	149	10	$2.5 \times 10^{-5}$
Serotonin Neurotransmitter Release Cycle	15	3	$2.5 \times 10^{-5}$
Glycosaminoglycan metabolism	114	8	$3.3 \times 10^{-5}$
Platelet homeostasis	54	5	$3.3 \times 10^{-5}$
Norepinephrine Neurotransmitter Release Cycle	17	3	$3.3 \times 10^{-5}$
Acetylcholine Neurotransmitter Release Cycle	17	3	$3.3 \times 10^{-5}$
G <sub>αs</sub> signalling events	100	7	$5.5 \times 10^{-5}$
GABA synthesis, release, reuptake and degradation	19	3	$5.6 \times 10^{-5}$
deactivation of the beta-catenin transactivating complex	39	4	$6.7 \times 10^{-5}$
Dopamine Neurotransmitter Release Cycle	20	3	$6.7 \times 10^{-5}$
IRS-related events triggered by IGF1R	83	6	$7.1 \times 10^{-5}$
Generic Transcription Pathway	186	11	$7.1 \times 10^{-5}$
Termination of O-glycan biosynthesis	21	3	$7.4 \times 10^{-5}$
Kinesins	22	3	$8.5 \times 10^{-5}$
Pathways Over-represented in Cluster 4	Pathway Size	Cluster Genes	p-value (FDR)
Extracellular matrix organization	241	97	$8.8 \times 10^{-126}$
Axon guidance	289	75	$8.3 \times 10^{-72}$
Hemostasis	445	101	$8.3 \times 10^{-72}$
Developmental Biology	432	95	$3.0 \times 10^{-67}$
Response to elevated platelet cytosolic Ca <sup>2+</sup>	84	37	$5.8 \times 10^{-67}$
Platelet degranulation	79	36	$5.8 \times 10^{-67}$
Degradation of the extracellular matrix	104	39	$6.7 \times 10^{-63}$
Platelet activation, signalling and aggregation	186	52	$6.6 \times 10^{-62}$
ECM proteoglycans	66	31	$8.1 \times 10^{-61}$
Neuronal System	272	64	$5.1 \times 10^{-60}$
Signalling by PDGF	173	47	$9.7 \times 10^{-57}$
Integrin cell surface interactions	82	31	$1.9 \times 10^{-53}$
Collagen biosynthesis and modifying enzymes	56	26	$1.1 \times 10^{-52}$
Collagen formation	67	28	$1.4 \times 10^{-52}$
Class A/1 (Rhodopsin-like receptors)	289	61	$2.3 \times 10^{-52}$
GPCR ligand binding	373	73	$2.8 \times 10^{-52}$
Elastic fibre formation	38	22	$4.7 \times 10^{-52}$
Non-integrin membrane-ECM interactions	53	24	$7.0 \times 10^{-49}$

Pathway over-representation analysis for Reactome pathways with the number of genes in each pathway (Pathway Size), number of genes within the pathway identified (Cluster Genes), and the pathway over-representation p-value (adjusted by FDR) from the hypergeometric test.

## E.2 Comparison to Primary Screen

The synthetic lethal partners with *CDH1* expression in stomach cancers were also compared to siRNA primary screen data (Telford *et al.*, 2015), as performed in Section 4.2.1. These were expected to be more concordant with the experimental results performed on a null mutant, however this was not the case at the gene level: less genes overlapped with experimental candidates in Figure E.2. This may be due to lower sample size for mutations in TCGA data or lower frequency (expected value) of *CDH1* mutations compared to low expression.

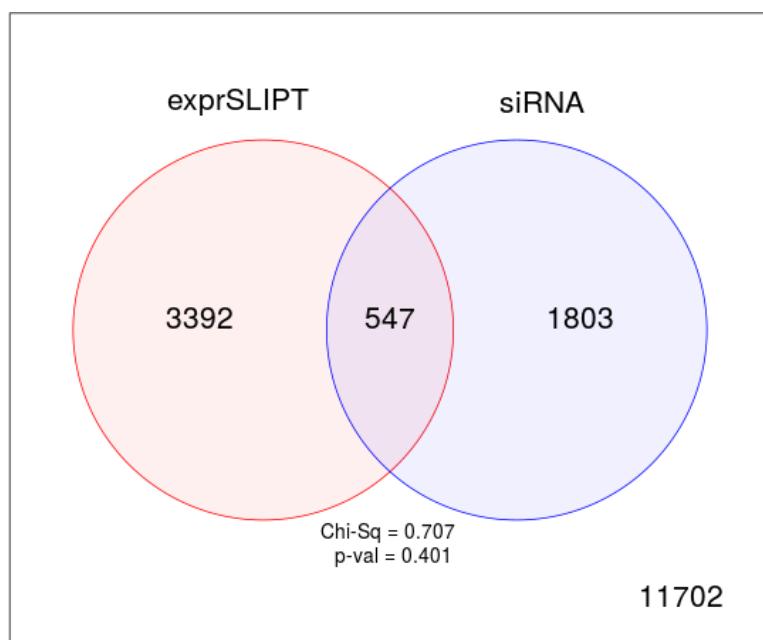


Figure E.2: **Comparison of SLIPT in stomach to siRNA.** The overlap of gene candidates for E-cadherin synthetic lethal partners between computational (SLIPT) and experimental screening (siRNA) approaches. The  $\chi^2$  test suggests that the overlap is no more than would be expected by chance ( $p = 0.281$ ).

Table E.4: Pathways for *CDH1* partners from SLIPT and siRNA

Predicted only by SLIPT (3392 genes)	Pathway	Size	Genes Identified	p-value (FDR)
Extracellular matrix organization		238	90	$3.4 \times 10^{-107}$
Eukaryotic Translation Termination		79	46	$7.6 \times 10^{-91}$
Viral mRNA Translation		77	45	$1.2 \times 10^{-89}$
Eukaryotic Translation Elongation		82	46	$5.8 \times 10^{-89}$
Peptide chain elongation		79	45	$2.1 \times 10^{-88}$
Nonsense Mediated Decay independent of the Exon Junction Complex		84	46	$9.4 \times 10^{-88}$
Formation of a pool of free 40S subunits		89	47	$3.3 \times 10^{-87}$
GTP hydrolysis and joining of the 60S ribosomal subunit		100	48	$3.2 \times 10^{-83}$
Axon guidance		284	84	$3.9 \times 10^{-82}$
Developmental Biology		426	111	$4.2 \times 10^{-82}$
L13a-mediated translational silencing of Ceruloplasmin expression		99	47	$1.4 \times 10^{-81}$
3' -UTR-mediated translational regulation		99	47	$1.4 \times 10^{-81}$
SRP-dependent cotranslational protein targeting to membrane		99	47	$1.4 \times 10^{-81}$
Nonsense-Mediated Decay		99	47	$1.4 \times 10^{-81}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex		99	47	$1.4 \times 10^{-81}$
Hemostasis		438	112	$1.2 \times 10^{-80}$
Eukaryotic Translation Initiation		107	48	$8.0 \times 10^{-80}$
Cap-dependent Translation Initiation		107	48	$8.0 \times 10^{-80}$
Infectious disease		338	90	$1.6 \times 10^{-76}$
Neuronal System		267	77	$1.6 \times 10^{-76}$

Detected only by siRNA screen (1803 genes)	Pathway	Size	Genes Identified	p-value (FDR)
Class A/1 (Rhodopsin-like receptors)		282	62	$8.1 \times 10^{-50}$
GPCR ligand binding		363	71	$4.9 \times 10^{-46}$
Peptide ligand-binding receptors		175	38	$7.9 \times 10^{-38}$
G <sub>αi</sub> signalling events		184	37	$1.1 \times 10^{-34}$
Gastrin-CREB signalling pathway via PKC and MAPK		180	35	$1.4 \times 10^{-32}$
G <sub>αq</sub> signalling events		159	32	$4.8 \times 10^{-32}$
DAP12 interactions		159	29	$1.4 \times 10^{-27}$
Downstream signal transduction		146	26	$2.4 \times 10^{-25}$
DAP12 signalling		149	26	$6.4 \times 10^{-25}$
VEGFA-VEGFR2 Pathway		91	19	$8.1 \times 10^{-24}$
Signalling by PDGF		172	27	$5.7 \times 10^{-23}$
Signalling by ERBB2		146	24	$1.4 \times 10^{-22}$
Signalling by VEGF		99	19	$2.0 \times 10^{-22}$
Visual phototransduction		85	17	$1.3 \times 10^{-21}$
Downstream signalling of activated FGFR1		134	22	$1.3 \times 10^{-21}$
Downstream signalling of activated FGFR2		134	22	$1.3 \times 10^{-21}$
Downstream signalling of activated FGFR3		134	22	$1.3 \times 10^{-21}$
Downstream signalling of activated FGFR4		134	22	$1.3 \times 10^{-21}$
Signalling by FGFR		146	23	$2.0 \times 10^{-21}$
Signalling by FGFR1		146	23	$2.0 \times 10^{-21}$

Intersection of SLIPT and siRNA screen (547 genes)	Pathway	Size	Genes Identified	p-value (FDR)
Class A/1 (Rhodopsin-like receptors)		282	25	$3.9 \times 10^{-9}$
Platelet activation, signalling and aggregation		182	17	$3.9 \times 10^{-9}$
Response to elevated platelet cytosolic Ca <sup>2+</sup>		82	9	$5.5 \times 10^{-8}$
Platelet homeostasis		53	7	$5.7 \times 10^{-8}$
Nucleotide-like (purinergic) receptors		16	4	$1.8 \times 10^{-7}$
Platelet degranulation		77	8	$2.8 \times 10^{-7}$
Peptide ligand-binding receptors		175	14	$3.8 \times 10^{-7}$
Molecules associated with elastic fibres		34	5	$7.1 \times 10^{-7}$
Amine ligand-binding receptors		35	5	$8.6 \times 10^{-7}$
G <sub>αi</sub> signalling events		184	14	$9.8 \times 10^{-7}$
GPCR ligand binding		363	27	$1.1 \times 10^{-6}$
Elastic fibre formation		38	5	$1.5 \times 10^{-6}$
G <sub>αq</sub> signalling events		159	12	$1.9 \times 10^{-6}$
Serotonin receptors		12	3	$3.8 \times 10^{-6}$
P2Y receptors		12	3	$3.8 \times 10^{-6}$
Signal amplification		16	3	$2.3 \times 10^{-5}$
Gastrin-CREB signalling pathway via PKC and MAPK		180	12	$2.3 \times 10^{-5}$
Complement cascade		33	4	$2.4 \times 10^{-5}$
Glycosaminoglycan metabolism		110	8	$2.5 \times 10^{-5}$
Glycogen breakdown (glycogenolysis)		17	3	$2.7 \times 10^{-5}$

### E.2.1 Resampling Analysis

Table E.5: Pathways for *CDH1* partners from SLIPT in stomach cancer

Reactome Pathway	Over-representation	Permutation
<i>Extracellular matrix organization</i>	$7.5 \times 10^{-140}$	0.070215
Hemostasis	$1.8 \times 10^{-121}$	0.25804
Developmental Biology	$9.2 \times 10^{-107}$	0.53032
Axon guidance	$1.5 \times 10^{-102}$	0.6704
<b>Eukaryotic Translation Termination</b>	$1.9 \times 10^{-99}$	$> 1.031 \times 10^{-5}$
GPCR ligand binding	$3.8 \times 10^{-99}$	0.54914
<b>Viral mRNA Translation</b>	$3.3 \times 10^{-98}$	$> 1.031 \times 10^{-5}$
Formation of a pool of free 40S subunits	$3.3 \times 10^{-98}$	$> 1.031 \times 10^{-5}$
<b>Eukaryotic Translation Elongation</b>	$1.6 \times 10^{-97}$	$> 1.031 \times 10^{-5}$
Peptide chain elongation	$7.2 \times 10^{-97}$	$> 1.031 \times 10^{-5}$
Class A/1 (Rhodopsin-like receptors)	$2.7 \times 10^{-96}$	0.58174
<b>Nonsense Mediated Decay independent of the Exon Junction Complex</b>	$3 \times 10^{-96}$	$> 1.031 \times 10^{-5}$
Infectious disease	$2.6 \times 10^{-94}$	0.25484
GTP hydrolysis and joining of the 60S ribosomal subunit	$3.4 \times 10^{-94}$	$> 1.031 \times 10^{-5}$
L13a-mediated translational silencing of Ceruloplasmin expression	$2.8 \times 10^{-92}$	$> 1.031 \times 10^{-5}$
<b>3' -UTR-mediated translational regulation</b>	$2.8 \times 10^{-92}$	$> 1.031 \times 10^{-5}$
Neuronal System	$8.4 \times 10^{-92}$	0.53433
SRP-dependent cotranslational protein targeting to membrane	$9.5 \times 10^{-92}$	$> 1.031 \times 10^{-5}$
<b>Eukaryotic Translation Initiation</b>	$2.0 \times 10^{-90}$	$> 1.031 \times 10^{-5}$
Cap-dependent Translation Initiation	$2.0 \times 10^{-90}$	$> 1.031 \times 10^{-5}$
<b>Nonsense-Mediated Decay</b>	$7.4 \times 10^{-90}$	$> 1.031 \times 10^{-5}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex	$7.4 \times 10^{-90}$	$> 1.031 \times 10^{-5}$
Adaptive Immune System	$8.1 \times 10^{-88}$	0.14116
<b>Translation</b>	$1.3 \times 10^{-87}$	$> 1.031 \times 10^{-5}$
Platelet activation, signalling and aggregation	$1.3 \times 10^{-86}$	0.28959
<b>Influenza Infection</b>	$1 \times 10^{-82}$	$> 1.031 \times 10^{-5}$
<b>Influenza Viral RNA Transcription and Replication</b>	$2.4 \times 10^{-82}$	$> 1.031 \times 10^{-5}$
<b>Influenza Life Cycle</b>	$2 \times 10^{-80}$	$> 1.031 \times 10^{-5}$
Response to elevated platelet cytosolic Ca <sup>2+</sup>	$4.9 \times 10^{-78}$	0.50817
Signalling by NGF	$1.6 \times 10^{-75}$	0.38518
Rho GTPase cycle	$5.1 \times 10^{-75}$	0.14864
Signalling by PDGF	$7.4 \times 10^{-74}$	0.40493
<i>Signalling by Rho GTPases</i>	$5.1 \times 10^{-73}$	0.077217
Glycosaminoglycan metabolism	$1.4 \times 10^{-68}$	0.52984
<i>G<sub>ai</sub> signalling events</i>	$1.8 \times 10^{-66}$	0.9254
Metabolism of carbohydrates	$1.1 \times 10^{-65}$	0.39501
<b>G<sub>as</sub> signalling events</b>	$2.7 \times 10^{-65}$	0.0050293
Potassium Channels	$2.7 \times 10^{-65}$	0.53359
Transmission across Chemical Synapses	$1.8 \times 10^{-64}$	0.81833
ECM proteoglycans	$3.4 \times 10^{-64}$	0.083482
Peptide ligand-binding receptors	$4.8 \times 10^{-64}$	0.62817
Degradation of the extracellular matrix	$1.1 \times 10^{-63}$	0.80879
Platelet homeostasis	$5.3 \times 10^{-63}$	0.53134
NGF signalling via TRKA from the plasma membrane	$6.1 \times 10^{-63}$	0.57117
Integration of energy metabolism	$4.5 \times 10^{-61}$	0.10889
Collagen formation	$5.4 \times 10^{-61}$	0.29896
Integrin cell surface interactions	$7 \times 10^{-59}$	0.18167
Collagen biosynthesis and modifying enzymes	$7 \times 10^{-59}$	0.30208
Neurotransmitter Receptor Binding And Downstream Transmission	$8.7 \times 10^{-57}$	0.82522
In The Postsynaptic Cell		
Signalling by Wnt	$8.7 \times 10^{-57}$	0.25468

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

Table E.6: Pathways for *CDH1* partners from SLIPT in stomach and siRNA

Reactome Pathway	Over-representation	Permutation
Platelet activation, signalling and aggregation	$3.9 \times 10^{-9}$	0.49557
Class A/1 (Rhodopsin-like receptors)	$3.9 \times 10^{-9}$	0.98432
Response to elevated platelet cytosolic Ca <sup>2+</sup>	$5.5 \times 10^{-8}$	0.54349
Platelet homeostasis	$5.7 \times 10^{-8}$	0.45017
Nucleotide-like (purinergic) receptors	$1.8 \times 10^{-7}$	0.36966
Peptide ligand-binding receptors	$3.8 \times 10^{-7}$	0.91294
<b>Molecules associated with elastic fibres</b>	$7.1 \times 10^{-7}$	0.0025868
Amine ligand-binding receptors	$8.6 \times 10^{-7}$	0.43303
G <sub>ai</sub> signalling events	$9.8 \times 10^{-7}$	0.99626
GPCR ligand binding	$1.1 \times 10^{-6}$	0.97733
<b>Elastic fibre formation</b>	$1.5 \times 10^{-6}$	0.0025868
G <sub>aq</sub> signalling events	$1.9 \times 10^{-6}$	0.86089
P2Y receptors	$3.8 \times 10^{-6}$	0.18795
Serotonin receptors	$3.8 \times 10^{-6}$	0.37853
Signal amplification	$2.3 \times 10^{-5}$	0.47856
Gastrin-CREB signalling pathway via PKC and MAPK	$2.3 \times 10^{-5}$	0.98567
<b>Complement cascade</b>	$2.4 \times 10^{-5}$	$> 3.4628 \times 10^{-6}$
Glycosaminoglycan metabolism	$2.5 \times 10^{-5}$	0.38953
Glycogen breakdown (glycogenolysis)	$2.7 \times 10^{-5}$	0.83772
Defective B4GALT7 causes EDS, progeroid type	$4.9 \times 10^{-5}$	0.10792
Defective B3GAT3 causes JDSSDHD	$4.9 \times 10^{-5}$	0.10792
Role of LAT2/NTAL/LAB on calcium mobilization	$5.6 \times 10^{-5}$	0.35373
Cell surface interactions at the vascular wall	$5.6 \times 10^{-5}$	0.47642
<b>G<sub>as</sub> signalling events</b>	$6 \times 10^{-5}$	0.019858
Signalling by NOTCH	$6 \times 10^{-5}$	0.19008
A tetrasaccharide linker sequence is required for GAG synthesis	0.00017	0.47642
<b>Extracellular matrix organization</b>	0.00018	0.0047308
Collagen formation	0.00018	0.19245
Effects of PIP2 hydrolysis	0.0002	0.37779
Syndecan interactions	0.0002	0.37779
<b>Diseases associated with glycosaminoglycan metabolism</b>	0.00023	0.01028
<b>Diseases of glycosylation</b>	0.00023	0.01028
<i>Chondroitin sulfate/dermatan sulfate metabolism</i>	0.00023	0.085541
Integrin alphaIIb beta3 signalling	0.00028	0.76936
Keratan sulfate biosynthesis	0.00034	0.68744
Rho GTPase cycle	0.00034	0.15675
Creation of C4 and C2 activators	0.00035	0.12275
Abacavir transport and metabolism	0.00035	0.12443
Amine compound SLC transporters	0.00037	0.69773
FCER1 mediated NF-κB activation	0.00037	0.69846
Fc epsilon receptor (FCER1) signalling	0.00056	0.43303
Defective EXT2 causes exostoses 2	0.00067	0.16053
Defective EXT1 causes exostoses 1, TRPS2 and CHDS	0.00067	0.16053
<i>Collagen biosynthesis and modifying enzymes</i>	0.00071	0.052911
Keratan sulfate/keratin metabolism	0.00073	0.46533
G alpha (12/13) signalling events	0.00078	0.59164
<b>SEMA3A-Plexin repulsion signalling by inhibiting Integrin adhesion</b>	0.00084	0.038504
Signal attenuation	0.00084	0.37779
Eicosanoid ligand-binding receptors	0.0011	0.11117
SOS-mediated signalling	0.0011	0.25387

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

### E.3 Metagene Analysis

Metagenes used to detect synthetic lethal pathways with *CDH1* in stomach cancer.

Table E.7: Synthetic lethal metagenes against *CDH1* in stomach cancer

Pathway	ID	Observed	Expected	$\chi^2$ value	p-value	p-value (FDR)
Cell-Cell communication	1500931	18	50.4	110	$7.43 \times 10^{-23}$	$1.53 \times 10^{-20}$
VEGFR2 mediated vascular permeability	5218920	19	50.4	109	$1.36 \times 10^{-22}$	$2.49 \times 10^{-20}$
Sema4D in semaphorin signalling	400685	20	50.4	104	$1.62 \times 10^{-21}$	$2.12 \times 10^{-19}$
Ion transport by P-type ATPases	936837	17	50.4	100	$8.29 \times 10^{-21}$	$8.06 \times 10^{-19}$
Sialic acid metabolism	4085001	19	50.4	95.3	$9.95 \times 10^{-20}$	$7.82 \times 10^{-18}$
Synthesis of pyrophosphates in the cytosol	1855167	26	50.4	94	$1.86 \times 10^{-19}$	$1.23 \times 10^{-17}$
Keratan sulfate/keratin metabolism	1638074	25	50.4	93.5	$2.36 \times 10^{-19}$	$1.44 \times 10^{-17}$
Ion channel transport	983712	19	50.4	92.8	$3.37 \times 10^{-19}$	$1.99 \times 10^{-17}$
Keratan sulfate biosynthesis	2022854	26	50.4	91.4	$6.79 \times 10^{-19}$	$3.62 \times 10^{-17}$
Arachidonic acid metabolism	2142753	22	50.4	90.6	$9.81 \times 10^{-19}$	$5.07 \times 10^{-17}$
RHO GTPases activate CIT	5625900	22	50.4	87	$5.80 \times 10^{-18}$	$2.66 \times 10^{-16}$
Stimuli-sensing channels	2672351	25	50.4	85.8	$1.03 \times 10^{-17}$	$4.58 \times 10^{-16}$
Synthesis of PI	1483226	19	50.4	85.6	$1.15 \times 10^{-17}$	$4.89 \times 10^{-16}$
G-protein activation	202040	19	50.4	85.3	$1.34 \times 10^{-17}$	$5.53 \times 10^{-16}$
NrCAM interactions	447038	22	50.4	84.3	$2.1 \times 10^{-17}$	$8.27 \times 10^{-16}$
Inwardly rectifying $K^+$ channels	1296065	24	50.4	83.5	$3.19 \times 10^{-17}$	$1.22 \times 10^{-15}$
Calcitonin-like ligand receptors	419812	20	50.4	82.2	$6.07 \times 10^{-17}$	$2.13 \times 10^{-15}$
Prostacyclin signalling through prostacyclin receptor	392851	24	50.4	81.8	$7.27 \times 10^{-17}$	$2.5 \times 10^{-15}$
Presynaptic function of Kainate receptors	500657	26	50.4	79.7	$2.00 \times 10^{-16}$	$6.34 \times 10^{-15}$
ADP signalling through P2Y purinoceptor 12	392170	23	50.4	79.2	$2.57 \times 10^{-16}$	$7.71 \times 10^{-15}$
regulation of FZD by ubiquitination	4641263	22	50.4	78.8	$3.15 \times 10^{-16}$	$9.3 \times 10^{-15}$
Toxicity of tetanus toxin (TeNT)	5250982	27	50.4	78.7	$3.36 \times 10^{-16}$	$9.75 \times 10^{-15}$
Gap junction degradation	190873	21	50.4	78.5	$3.66 \times 10^{-16}$	$1.04 \times 10^{-14}$
Nephrin interactions	373753	25	50.4	78.2	$4.21 \times 10^{-16}$	$1.14 \times 10^{-14}$
GABA synthesis, release, reuptake and degradation	888590	26	50.4	77	$7.69 \times 10^{-16}$	$1.95 \times 10^{-14}$

Strongest candidate synthetic lethal partners for *CDH1* by SLIPT with observed and expected numbers of TCGA stomach cancer samples with low expression of both genes.

## Appendix F

# Synthetic Lethal Genes in Pathways

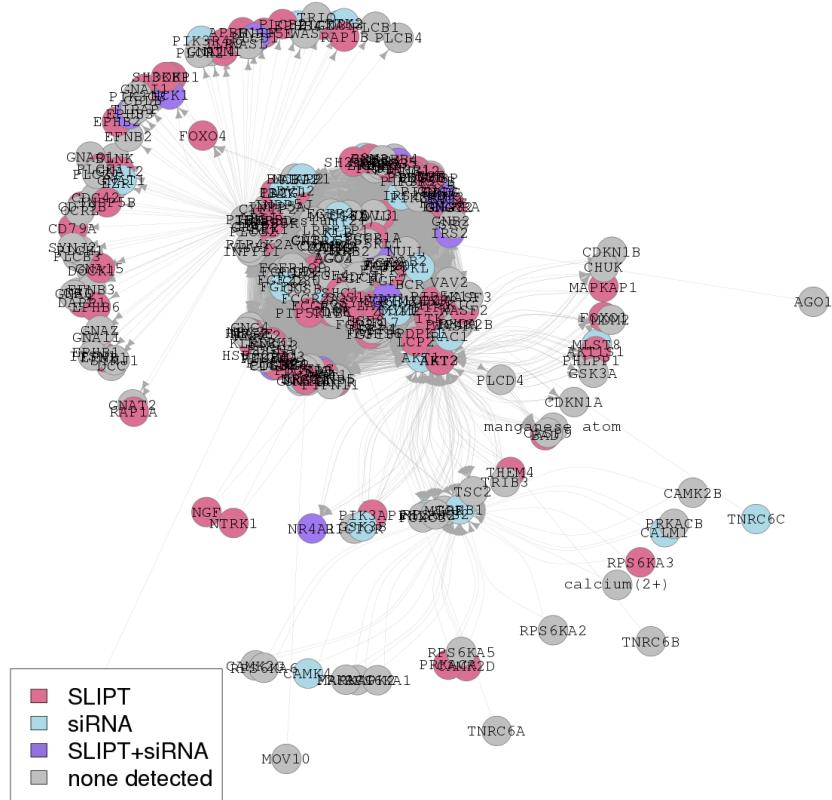
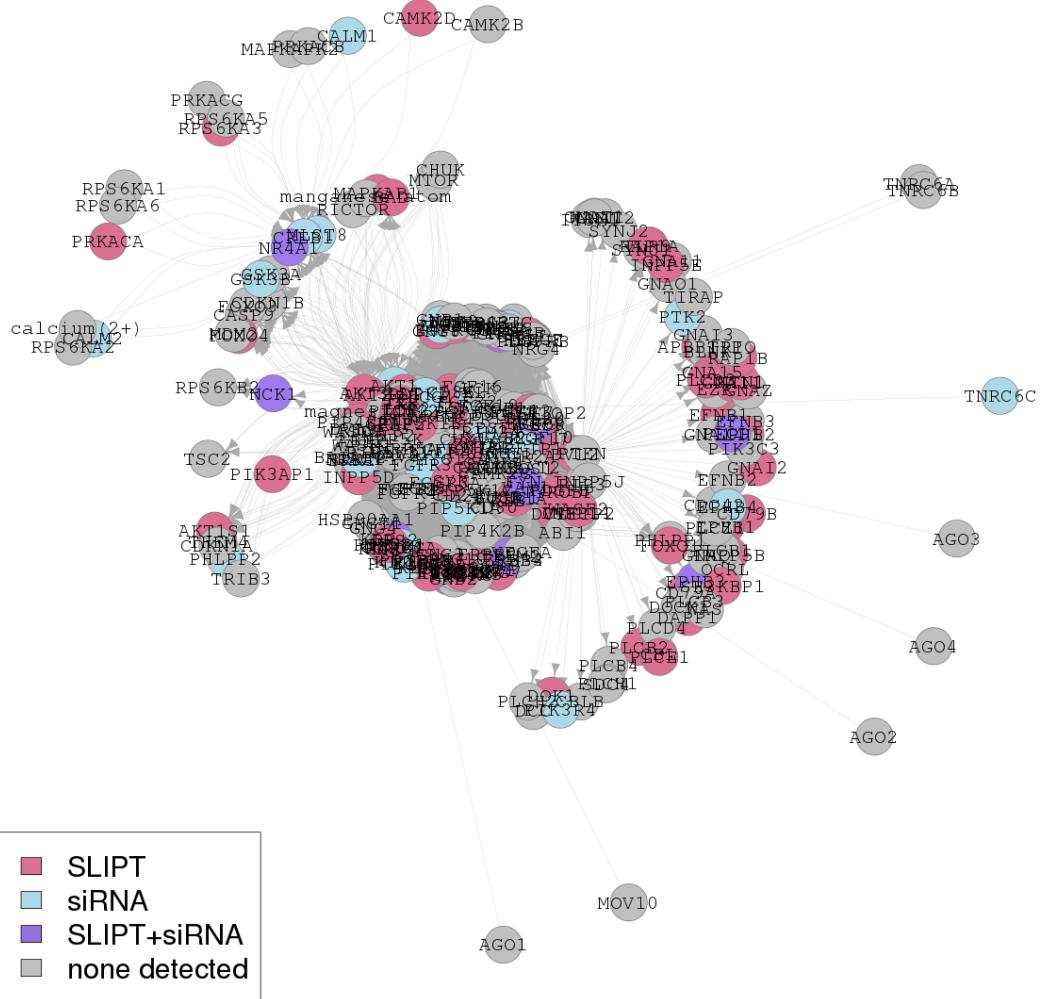
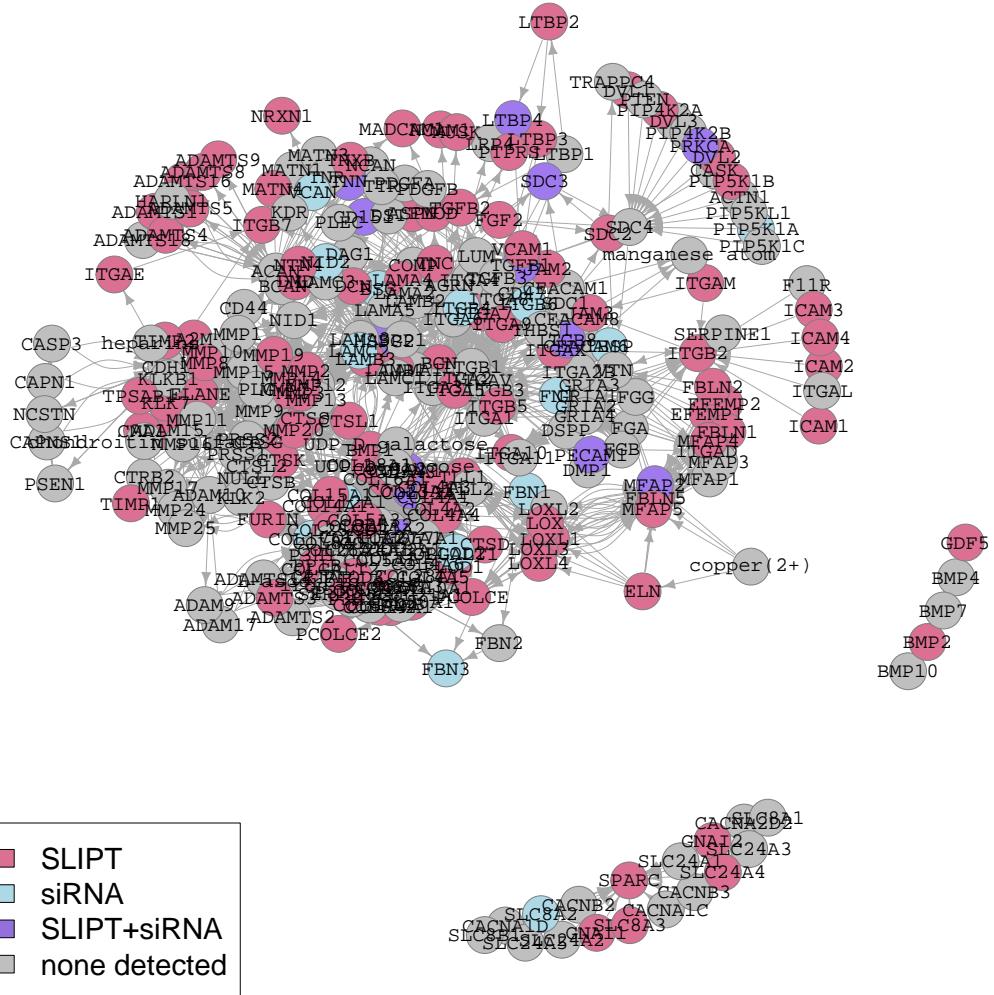


Figure F.1: **Synthetic lethality in the PI3K/AKT pathway.** The Reactome PI3K/AKT pathway with synthetic lethal candidates, coloured as shown in the legend.



**Figure F.2: Synthetic lethality in the PI3K/AKT pathway in cancer.** The Reactome PI3K/AKT in cancer pathway with synthetic lethal candidates, coloured as shown in the legend.



**Figure F.3: Synthetic lethality in the Extracellular Matrix.** The Reactome Extracellular Matrix pathway with synthetic lethal candidates, coloured as shown in the legend.

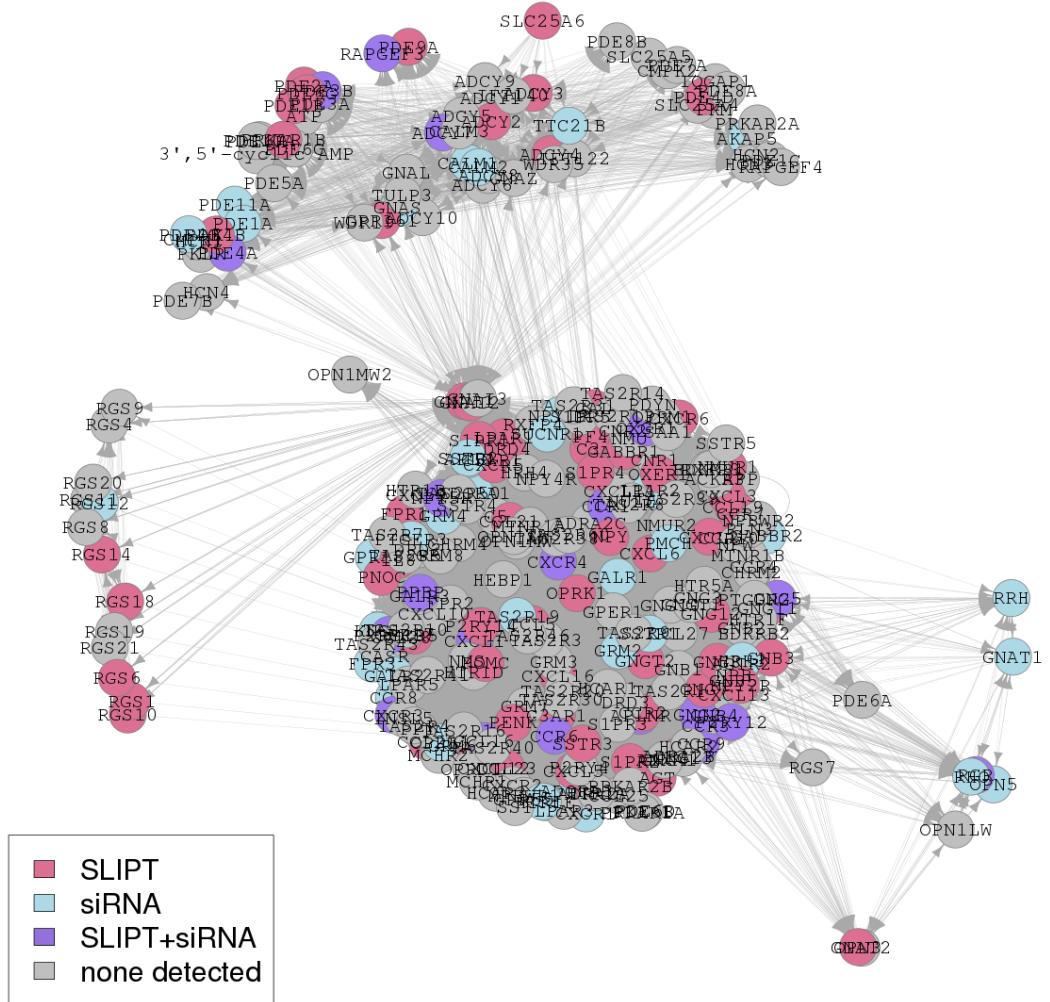


Figure F.4: **Synthetic lethality in the GPCRs.** The Reactome  $G_{\alpha i}$  pathway with synthetic lethal candidates, coloured as shown in the legend.

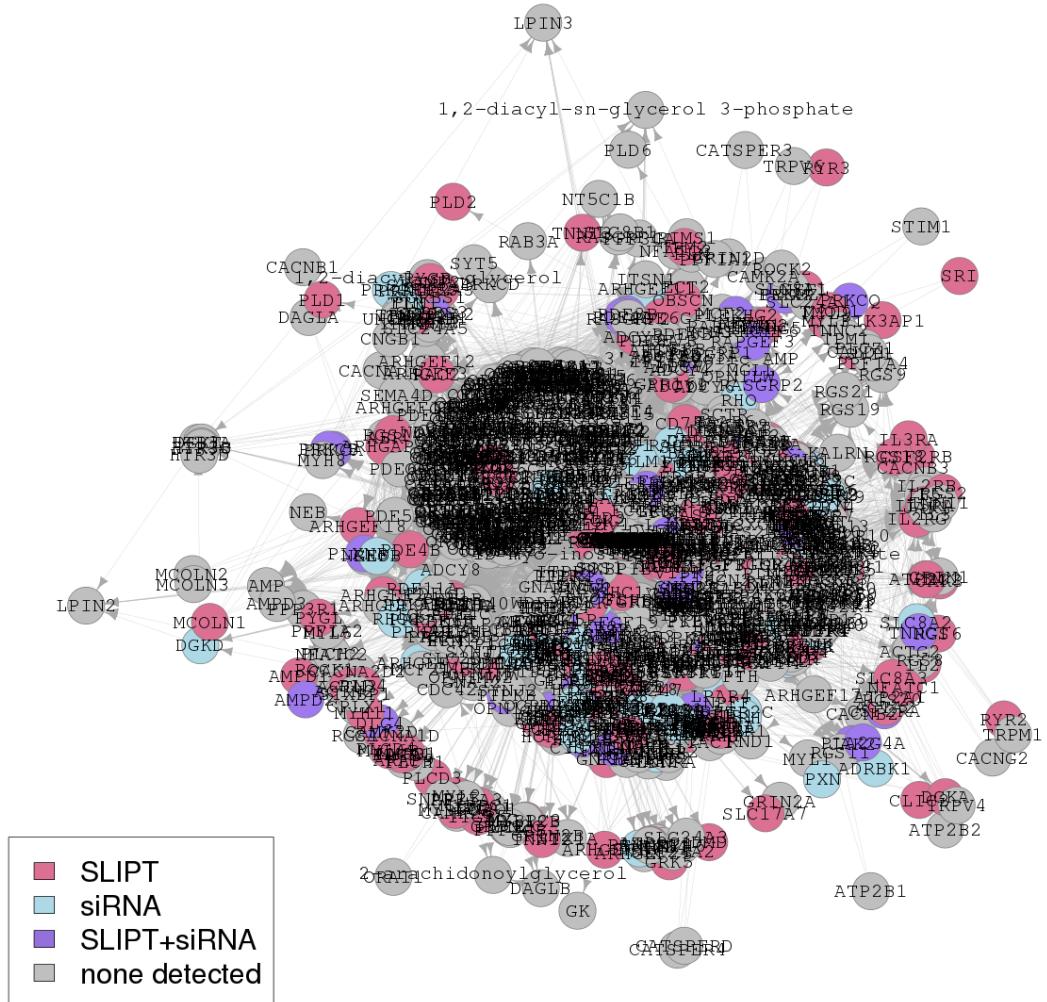


Figure F.5: **Synthetic lethality in the GPCR Downstream.** The Reactome G protein coupled receptor (GPCR) Downstream pathway with synthetic lethal candidates, coloured as shown in the legend.

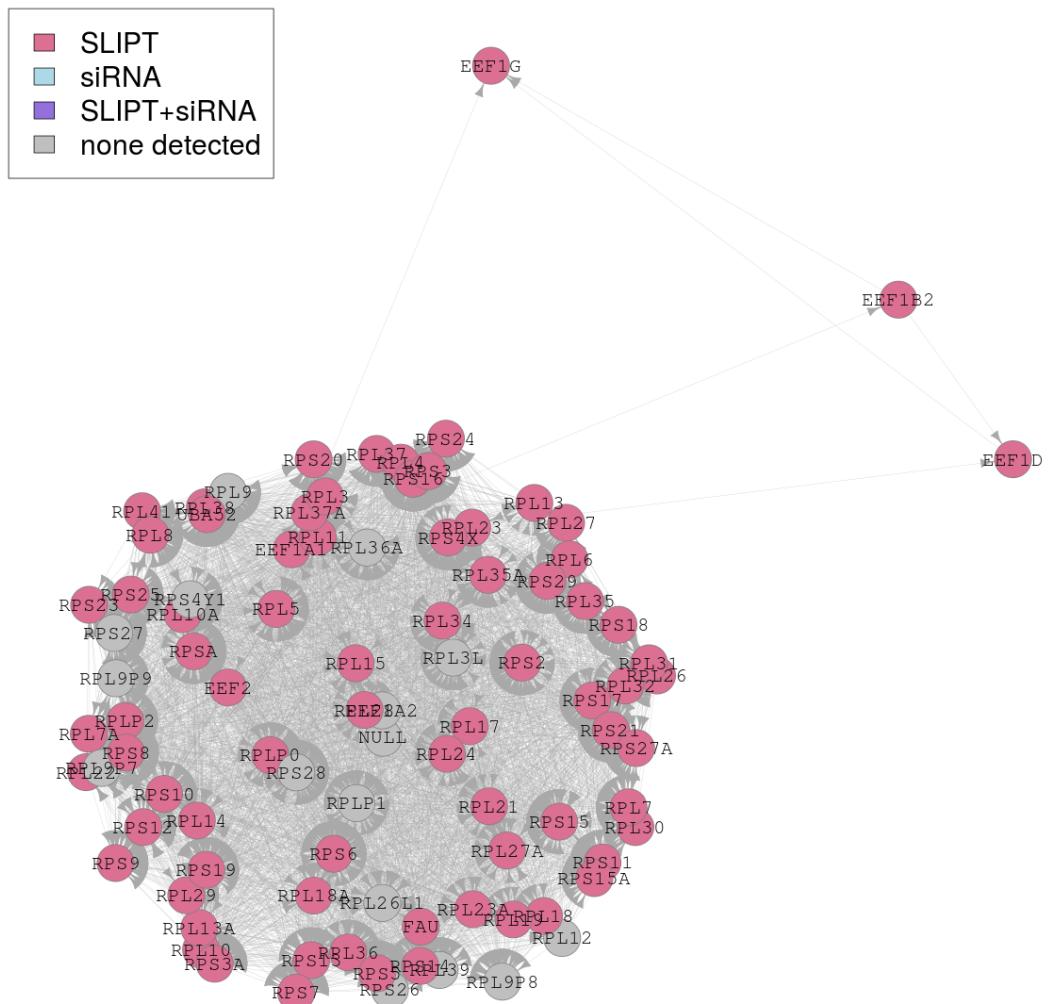
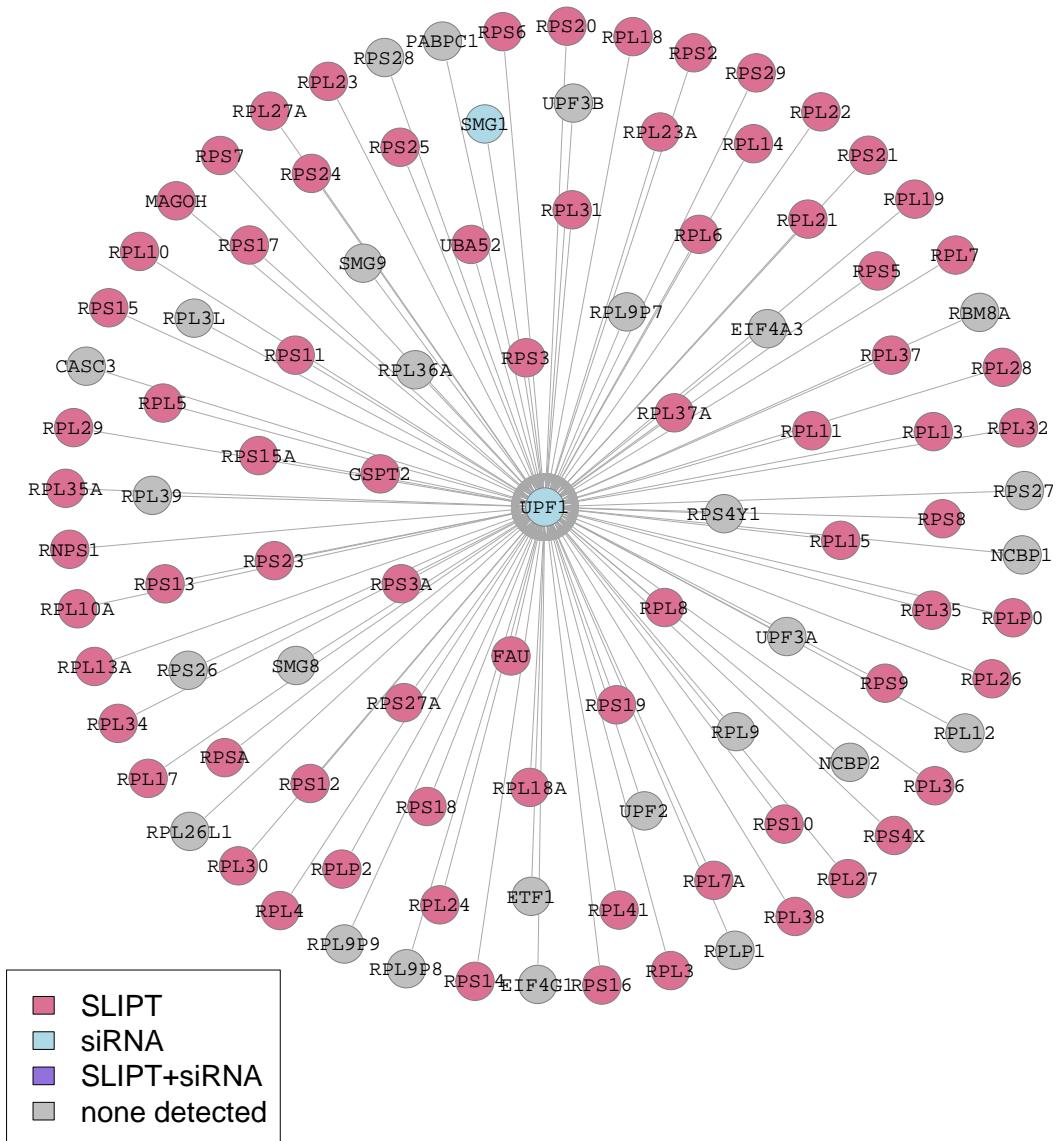


Figure F.6: **Synthetic lethality in the Translation Elongation**. The Reactome Translation Elongation pathway with synthetic lethal candidates, coloured as shown in the legend.



**Figure F.7: Synthetic lethality in the Nonsense-mediated Decay.** The Reactome nonsense-mediated decay (NMD) pathway with synthetic lethal candidates, coloured as shown in the legend.

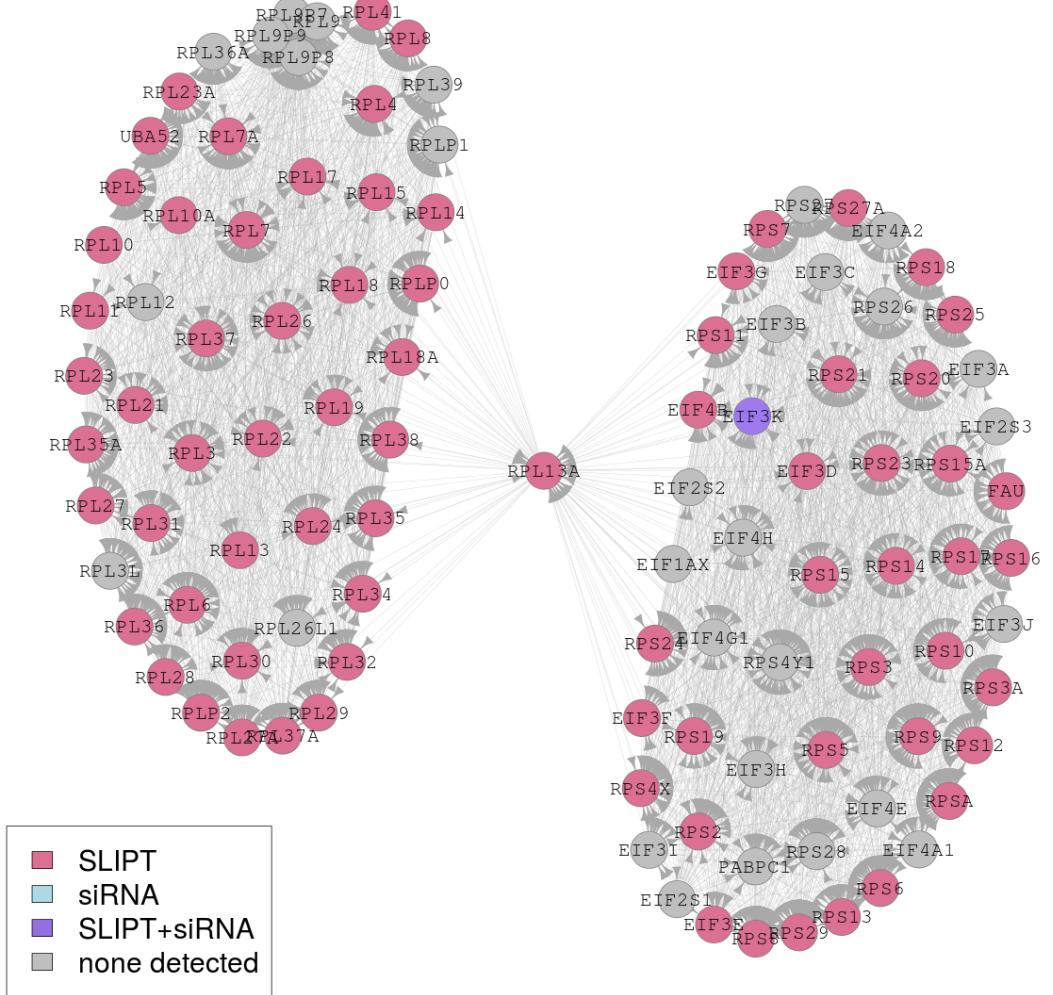


Figure F.8: **Synthetic lethality in the 3' UTR.** The Reactome 3' untranslated region (UTR) pathway with synthetic lethal candidates, coloured as shown in the legend.

## Appendix G

# Pathway Connectivity for Mutation SLIPT

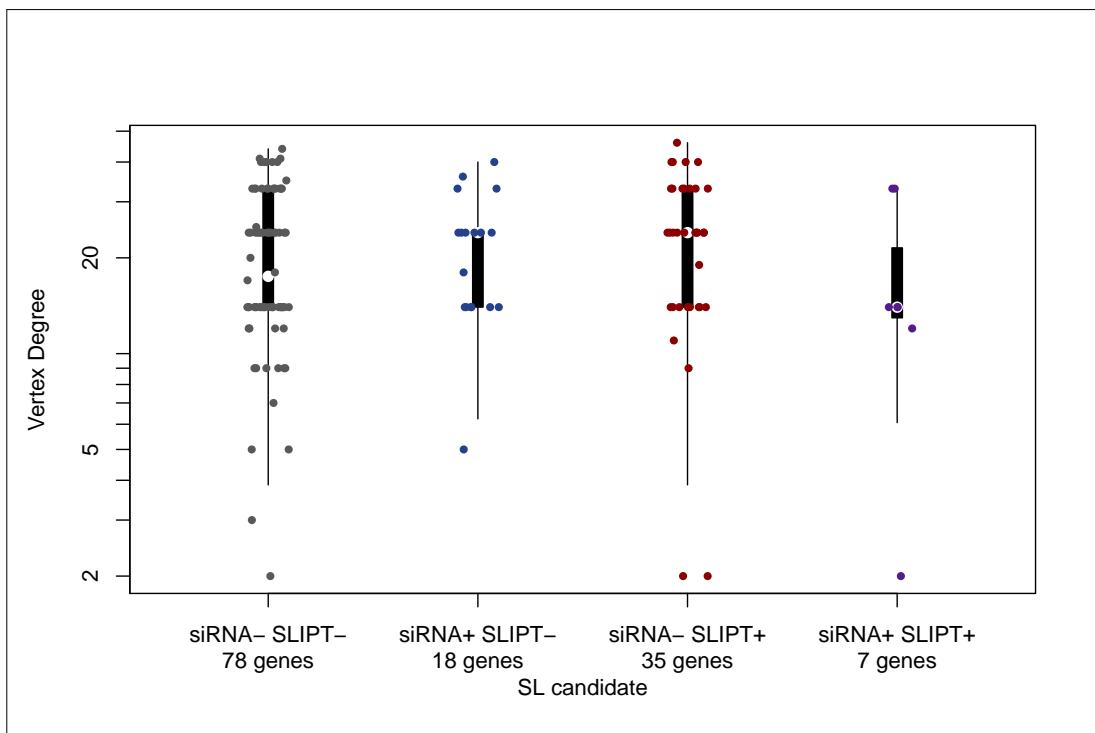


Figure G.1: **Synthetic lethality and vertex degree.** The number of connected genes (vertex degree) was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome phosphoinositide 3-kinase (PI3K) cascade pathway. There were very few differences in vertex degree between the groups, although genes detected by siRNA included those with the fewest connections.

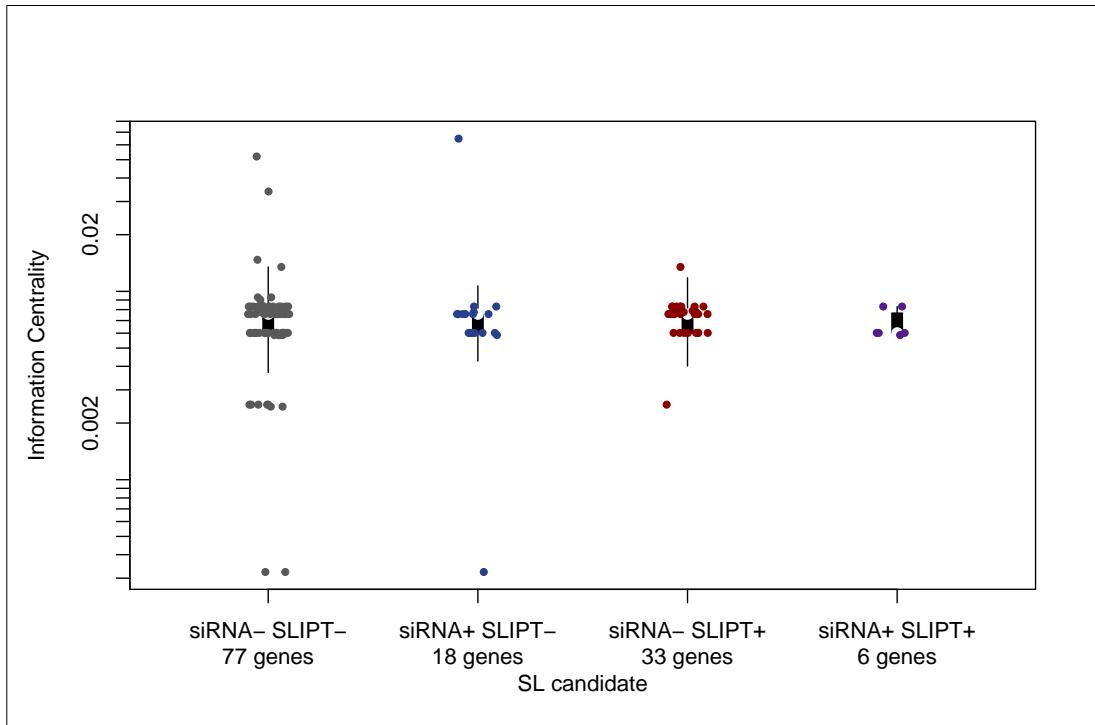
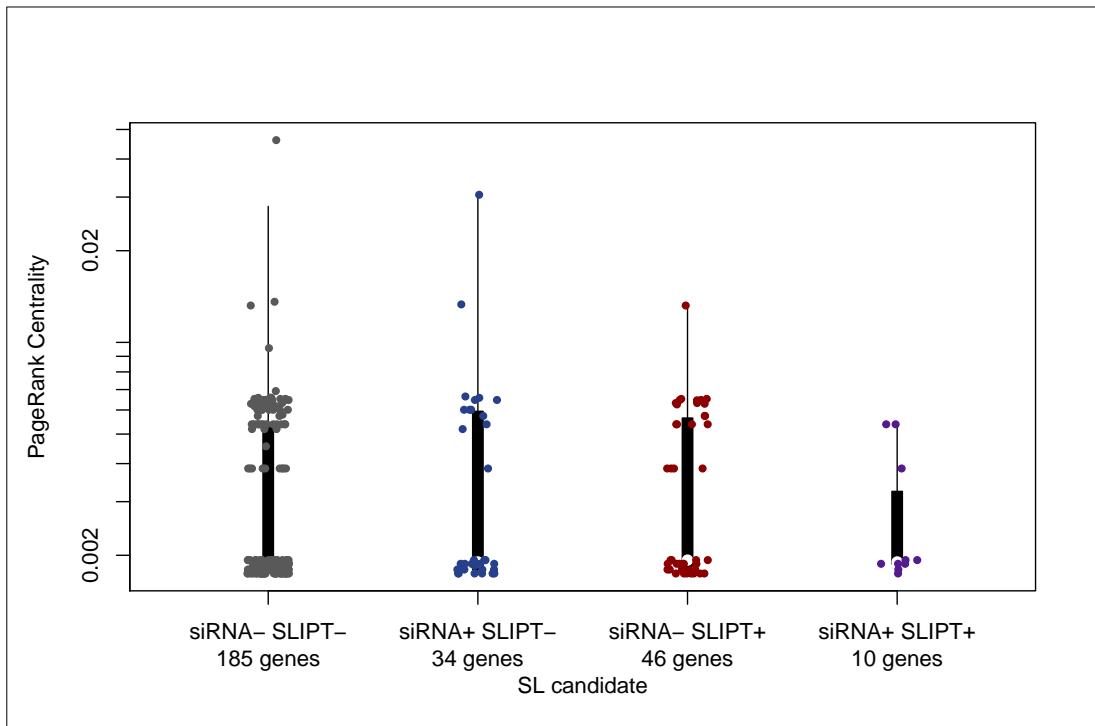


Figure G.2: **Synthetic lethality and centrality.** The information centrality was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. Genes detected by mtSLIPT or siRNA did not have higher connectivity than genes not detected by either approach. The gene with the highest centrality was detected by siRNA.



**Figure G.3: Synthetic lethality and PageRank.** The PageRank centrality was compared (on a log-scale) across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. Genes detected by siRNA had a more restricted range of centrality values than other genes not detected by either approach, although these groups also had fewer genes.

Table G.1: ANOVA for synthetic lethality and vertex degree

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	15	15.50	0.0134	0.9084
mtSLIPT	1	196	195.94	0.1689	0.6825
siRNA×mtSLIPT	1	9	9.17	0.0079	0.9294

Analysis of variance for vertex degree against synthetic lethal detection approaches (with an interaction term)

Table G.2: ANOVA for synthetic lethality and information centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.000256	0.0002561	0.1851	0.6685
mtSLIPT	1	0.003225	0.0032247	2.3308	0.1318
siRNA×mtSLIPT	1	0.001238	0.0012385	0.8952	0.3476

Analysis of variance for information centrality against synthetic lethal detection approaches (with an interaction term)

Table G.3: ANOVA for synthetic lethality and PageRank centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.0002038	$2.0385 \times 10^{-4}$	1.1423	0.2892
mtSLIPT	1	0.0000208	$2.0752 \times 10^{-5}$	0.1163	0.7342
siRNA×mtSLIPT	1	0.0000137	$1.3743 \times 10^{-5}$	0.0770	0.7823

Analysis of variance for PageRank centrality against synthetic lethal detection approaches (with an interaction term)

## Appendix H

# Information Centrality for Gene Essentiality

Network structure could be used to analyse gene function. This has been performed to investigate network properties of a network constructed from Reactome pathways (Croft *et al.*, 2014) imported via Pathway Commons with Paxtools (Cerami *et al.*, 2011; Demir *et al.*, 2013). Information centrality, which has been proposed as a measure of gene essentiality, was calculated as performed by Kranthi *et al.* (2013) using the efficiency and shortest path between each pair of nodes in the network before and after a node of interest is removed to test the importance of a node to network connectivity. Reactome contains substrates and cofactors in addition to genes or proteins. In support of centrality as a measure of essentiality, a number of nodes with the highest centrality (shown in Table H.1) were essential nutrients including Mg<sup>2+</sup>, Ca<sup>2+</sup>, Zn<sup>2+</sup>, and Fe. In addition, there were genes important in development of epithelial tissues and breast cancer such as *IL8*, *GATA3*, and *CTNNB1* detected with relatively high information centrality.

Table H.1: Information centrality for genes and molecules in the Reactome network

<b>Node</b>	<b>Centrality</b>
<i>ZNF473</i>	0.0510
Magnesium ( $Mg^{2+}$ )	0.0082
<i>XBP1</i>	0.0053
Calcium ( $Ca^{2+}$ )	0.0050
Zinc ( $Zn^{2+}$ )	0.0048
Iron atom (Fe)	0.0041
<i>FMN</i>	0.0040
<i>AGT</i>	0.0037
<i>HSP90AA1</i>	0.0029
Phosphatidyl-L-serine	0.0029
<i>P2RX7</i>	0.0026
<i>PANX1</i>	0.0024
<i>NCAM1</i>	0.0022
<i>NUDT1</i>	0.0021
<i>PLAUR</i>	0.0020
<i>IL8</i>	0.0020
<i>HSPA8</i>	0.0019
<i>TYROBP</i>	0.0019
<i>CASP3</i>	0.0017
<i>GNAL</i>	0.0015
<i>CBLB</i>	0.0015
<i>HBB</i>	0.0014
<i>GATA4</i>	0.0013
<i>TGS1</i>	0.0013
<i>CTNNB1</i>	0.0012

Highest information centrality for genes (proteins), cofactors, and minerals in the Reactome network

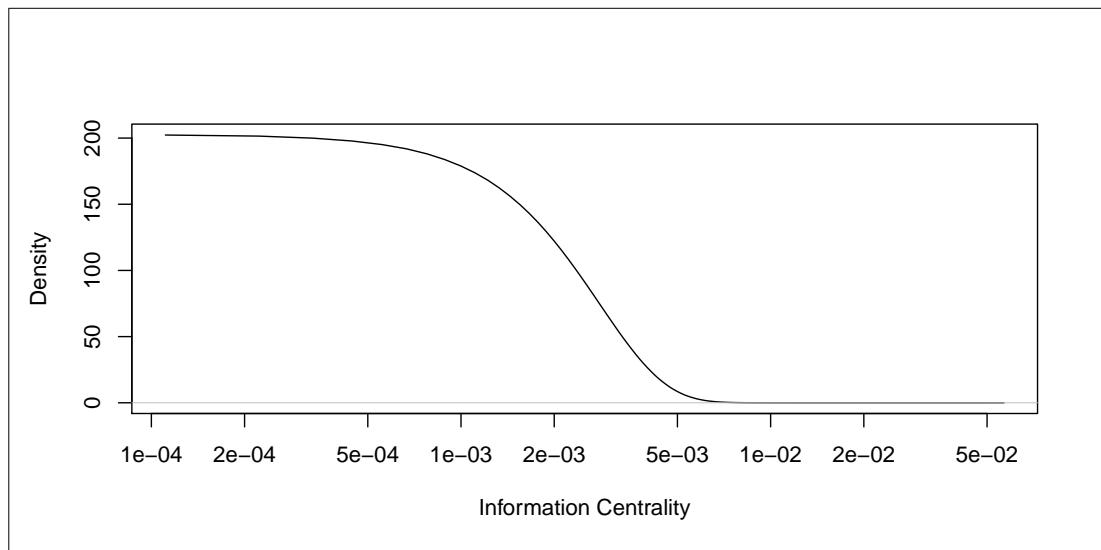


Figure H.1: **Information centrality distribution.** Information centrality in the Reactome network for nodes, including genes/proteins and other biomolecules.

# Appendix I

## Pathway Structure for Mutation SLIPT

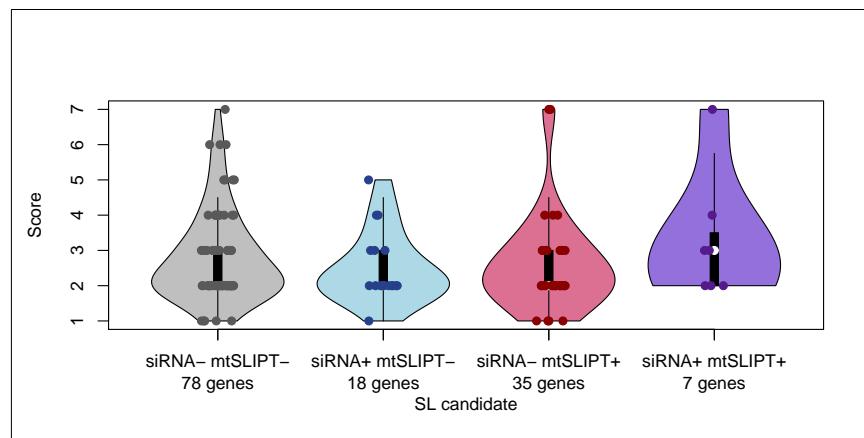
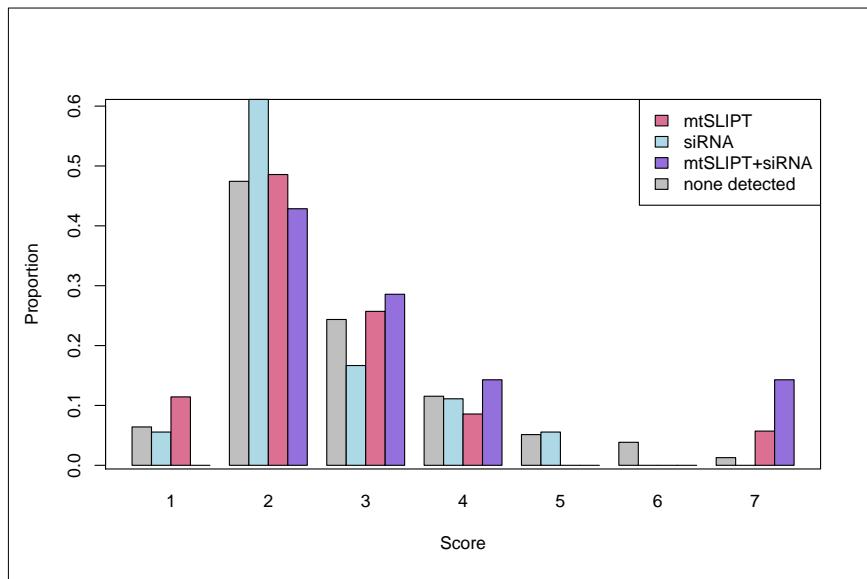


Figure I.1: **Synthetic lethality and heirarchy score in PI3K.** The hierarchical distance scores were similarly distributed across mtSLIPT and siRNA genes. Genes detected by both methods had a higher (downstream) median than either group.

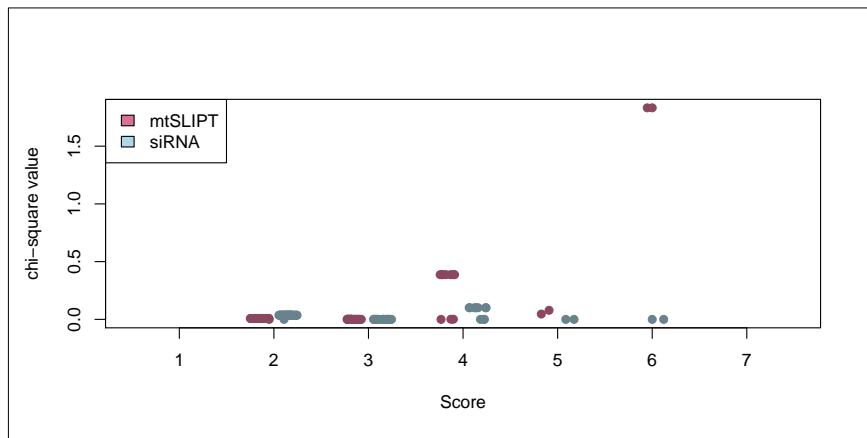
Table I.1: ANOVA for synthetic lethality and PI3K hierarchy

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.001	0.00070	0.0004	0.9841
mtSLIPT	1	0.007	0.0066	0.0040	0.9496
siRNA×mtSLIPT	1	3.906	3.9056	2.3829	0.1250

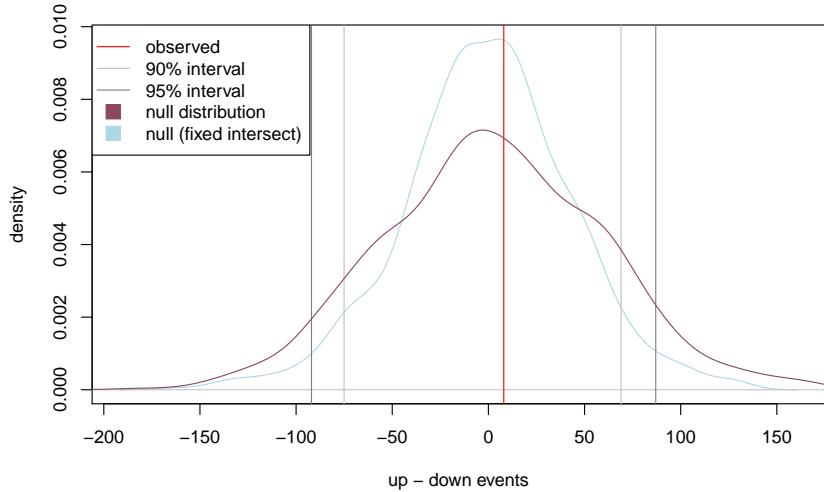
Analysis of variance for PI3K hierarchy score against synthetic lethal detection approaches (with an interaction term)



**Figure I.2: Hierarchy score in PI3K against synthetic lethality in PI3K.** The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities.



**Figure I.3: Structure of synthetic lethality in PI3K.** The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities. The number of mtSLIPT and siRNA genes upstream or downstream of each gene in the Reactome PI3K pathway were tested (by the  $\chi^2$ -test). These were plotted as a split jitter stripchart against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities.



**Figure I.4: Structure of synthetic lethality resampling.** A null distribution (10,000 iterations) of the siRNA genes upstream or downstream of mtSLIPT genes (shown by the difference) in the PI3K pathway. The observed events (red) were compared to the the distribution (violet) and were not significant. Genes detected by both methods were fixed for the distribution (blue). The genes detected by both approaches were used.

Table I.2: Resampling for pathway structure of synthetic lethal detection methods

Pathway	Graph		States		Observed				Permutation p-value	
	Nodes	Edges	mtSL	siRNA	Up	Down	Up-Down	Up/Down	Up-Down	Down-Up
PI3K Cascade	138	1495	42	25	131	123	8	1.065	0.4473	0.5466
PI3K/AKT Signalling in Cancer	275	12882	56	44	478	440	38	1.086	0.4163	0.5810
<b>G<sub>αi</sub> Signalling</b>	292	22003	57	58	543	866	-323	0.627	0.9507	0.0488
GPCR downstream	1270	142071	218	160	7632	6500	1132	1.174	0.1707	0.8291
Elastic fibre formation	42	175	16	7	6	7	-1	0.857	0.5512	0.3681
Extracellular matrix	299	3677	81	29	313	347	-34	0.902	0.5762	0.4215
Formation of Fibrin	52	243	11	5	8	19	-11	0.421	0.7993	0.1800
Nonsense-Mediated Decay	103	102	56	2	0	0	0		0.197	0.1373
3'-UTR-mediated translational regulation	107	2860	56	1	52	1	51	52	0.1210	0.8751
Eukaryotic Translation Elongation	92	3746	57	0	0	0	0		0.4952	0.4892

Pathways in the Reactome network tested for structural relationships between mtSLIPT and siRNA genes by resampling. The raw p-value (computed without adjusting for multiple comparisons over pathways) is given for the difference in upstream and downstream paths from mtSLIPT to siRNA gene candidate partners of CDH1 with significant pathways highlighted in bold. Sampling was performed only in the target pathway and shortest paths were computed within it. Loops or paths in either direction that could not be resolved were excluded from the analysis. The gene detected by both mtSLIPT and siRNA (or resampling for them) were included in the analysis and the number of these were fixed to the number observed.

## Appendix J

# Performance of SLIPT and $\chi^2$

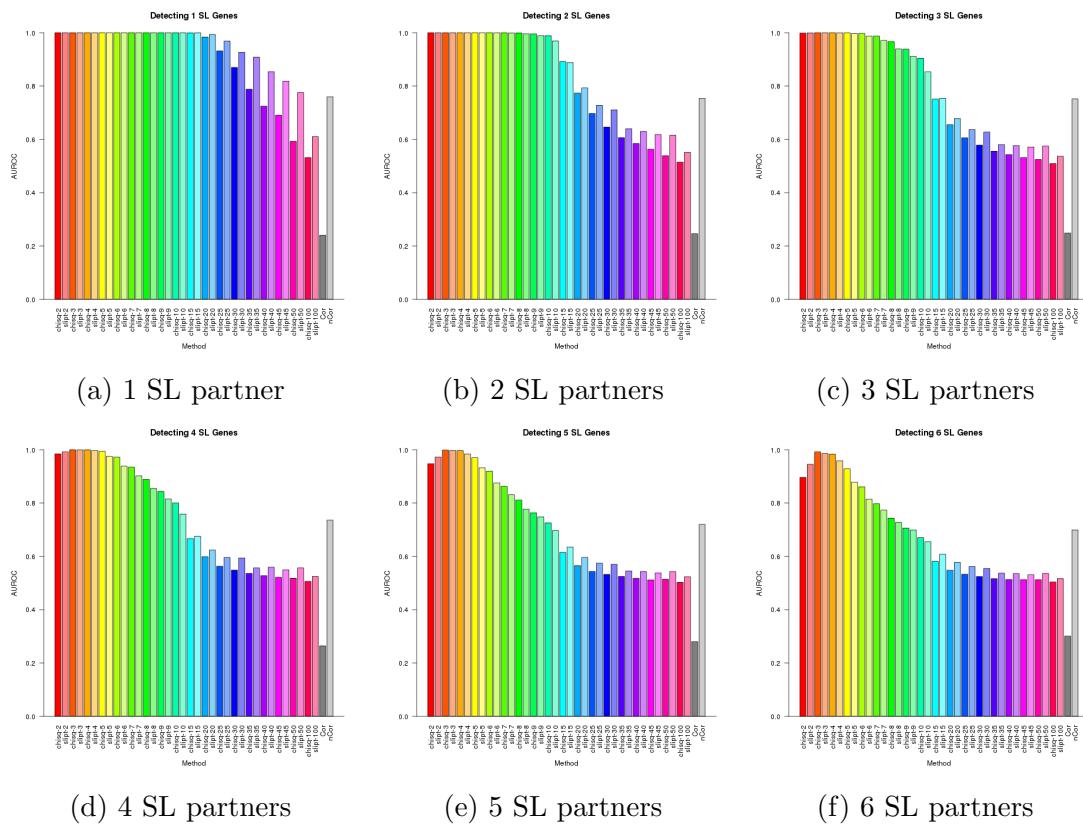
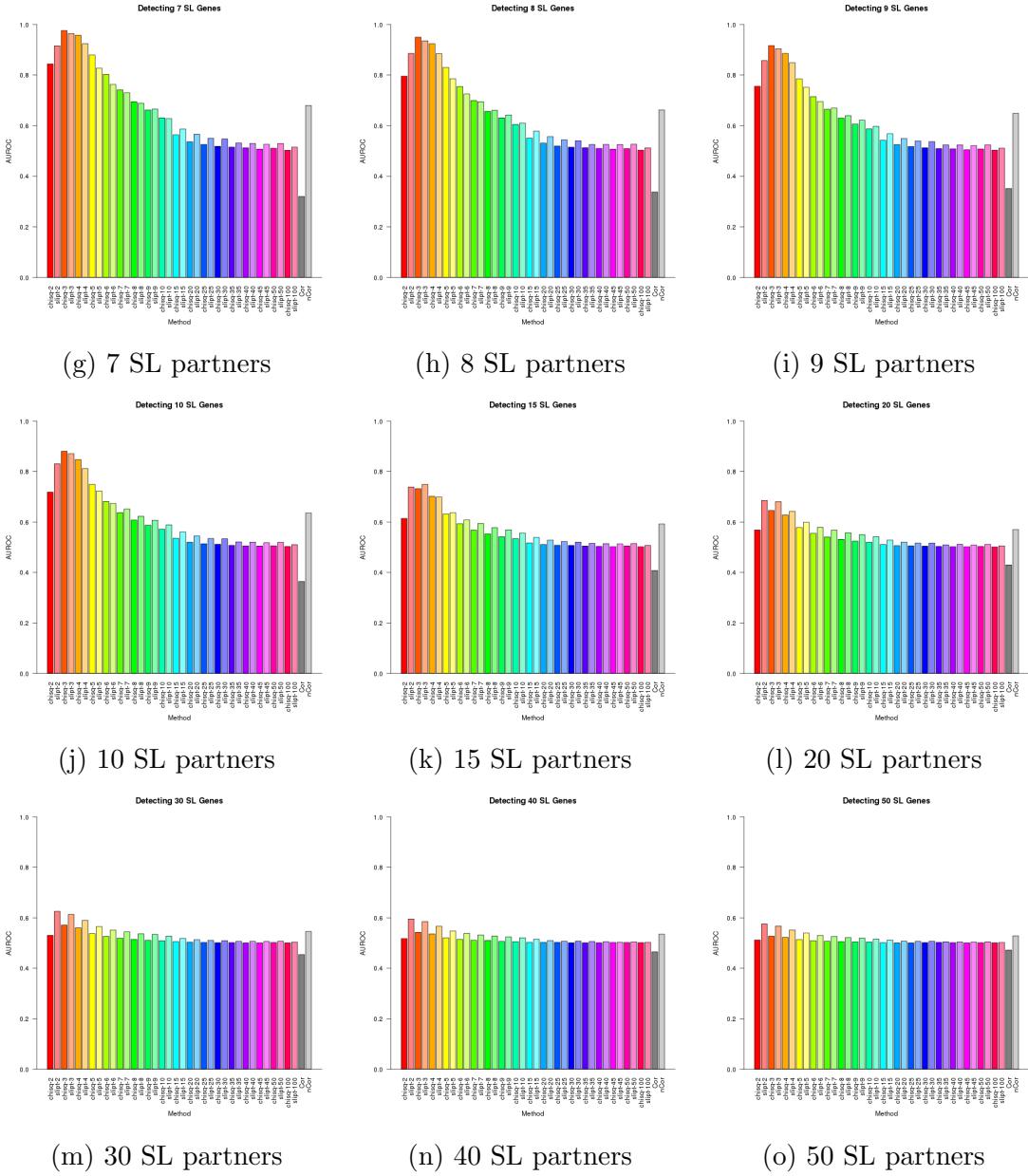


Figure J.1: **Performance of  $\chi^2$  and SLIPT across quantiles.** (continued on next page)



**Figure J.1: Performance of  $\chi^2$  and SLIPT across quantiles.** Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for  $\chi^2$  (and positive correlation). SLIPT and  $\chi^2$  performed similarly, peaking at  $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or  $\chi^2$ . These findings were robust across different numbers of underlying synthetic lethal genes in 10,000 simulations of 100 genes and 1000 samples. SLIPT performed better than  $\chi^2$  for higher numbers of synthetic lethal genes and finer quantiles.

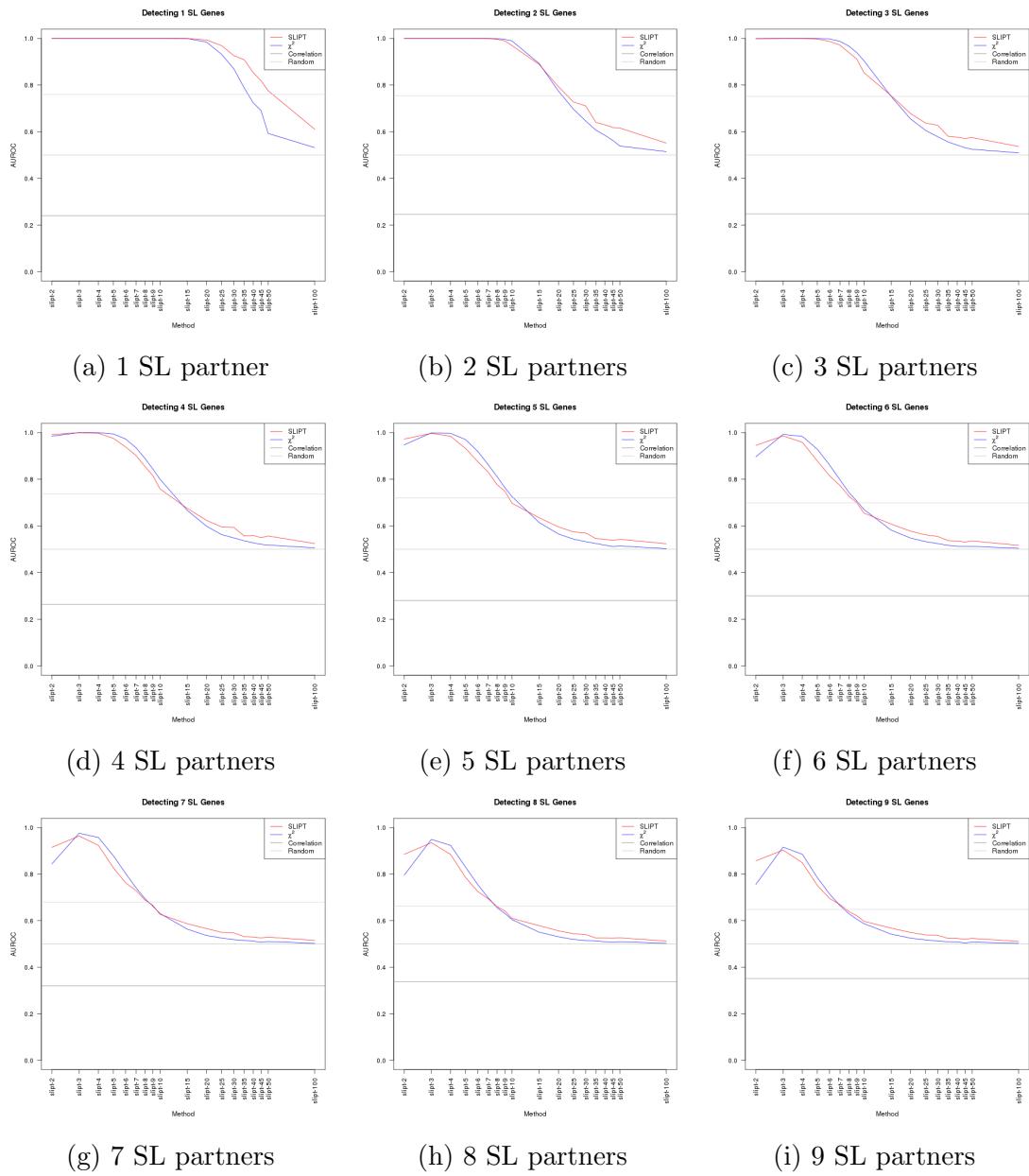
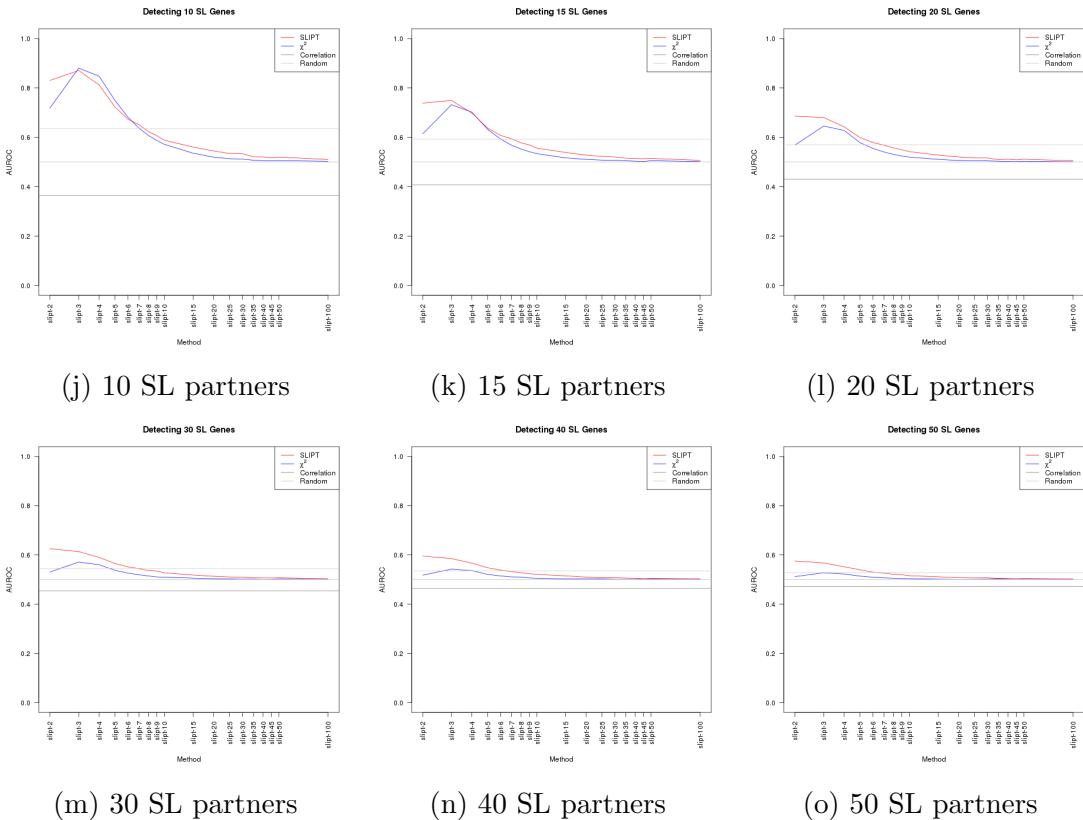


Figure J.2: **Performance of  $\chi^2$  and SLIPT across quantiles.** (continued on next page)



**Figure J.2: Performance of  $\chi^2$  and SLIPT across quantiles.** Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red),  $\chi^2$  (blue) and correlation (grey), according to the legend. SLIPT and  $\chi^2$  performed similarly, peaking at  $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or  $\chi^2$ . These findings were robust across different numbers of underlying synthetic lethal genes in 10,000 simulations of 100 genes and 1000 samples. SLIPT performed better than  $\chi^2$  for higher numbers of synthetic lethal genes and finer quantiles.

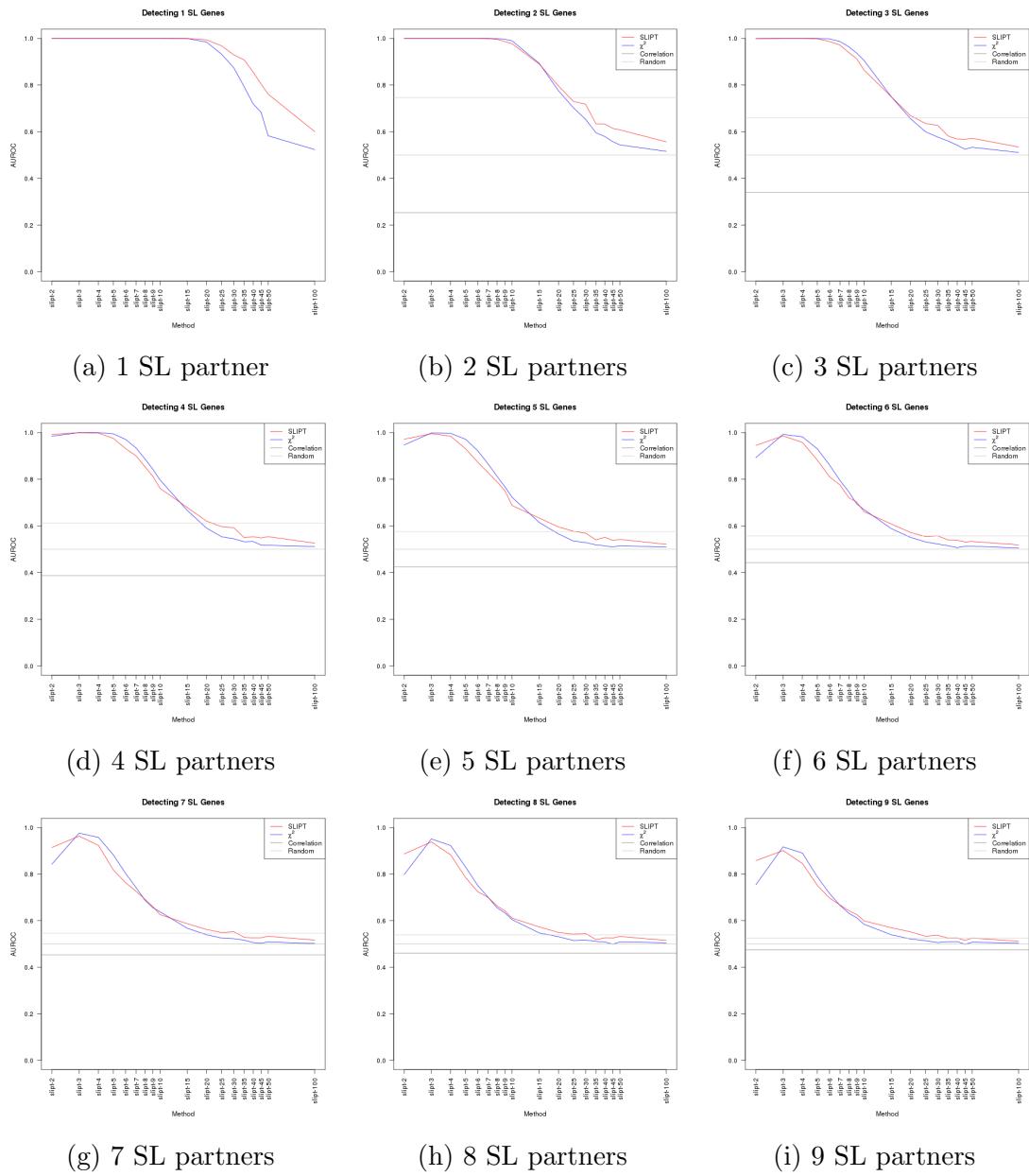
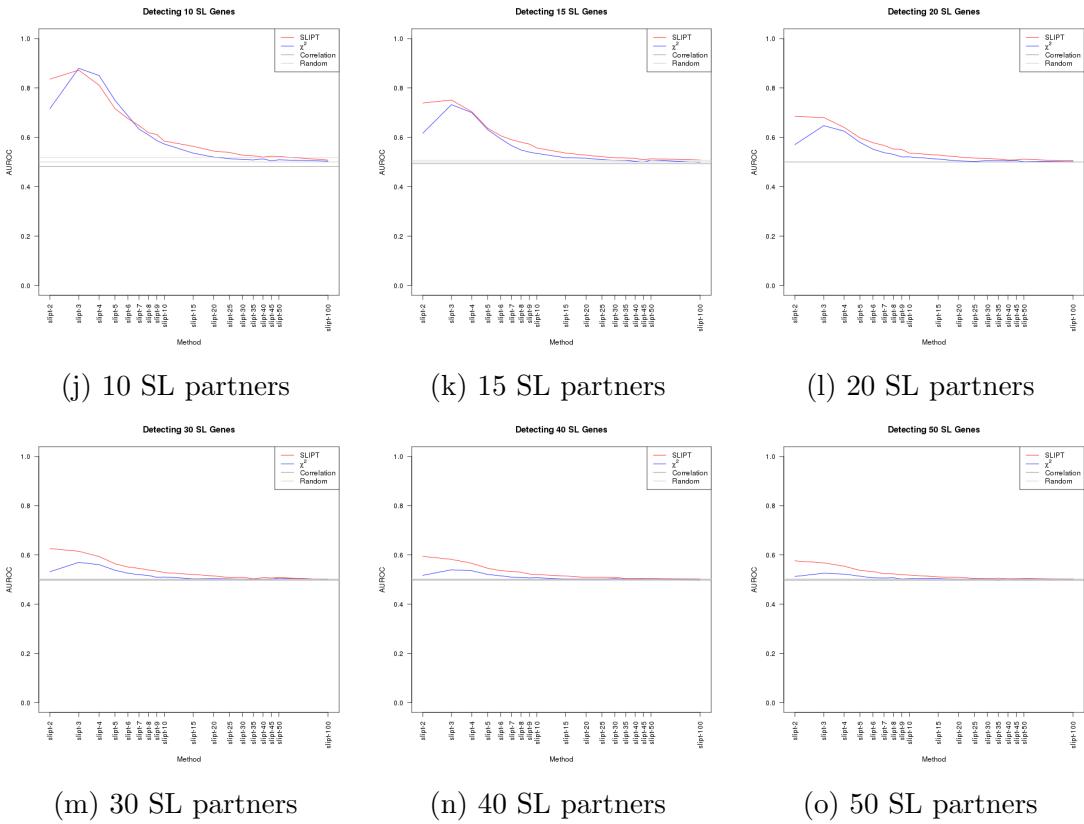


Figure J.3: **Performance of  $\chi^2$  and SLIPT across quantiles with more genes.**  
 (continued on next page)



**Figure J.3: Performance of  $\chi^2$  and SLIPT across quantiles with more genes.**  
 Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red),  $\chi^2$  (blue) and correlation (grey), according to the legend. SLIPT and  $\chi^2$  performed similarly, peaking at  $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or  $\chi^2$ . These findings were robust across different numbers of underlying synthetic lethal genes in 1000 simulations of 20,000 genes and 1000 samples. SLIPT performed better than  $\chi^2$  for higher numbers of synthetic lethal genes and finer quantiles.

## J.1 Correlated Query Genes affects Specificity

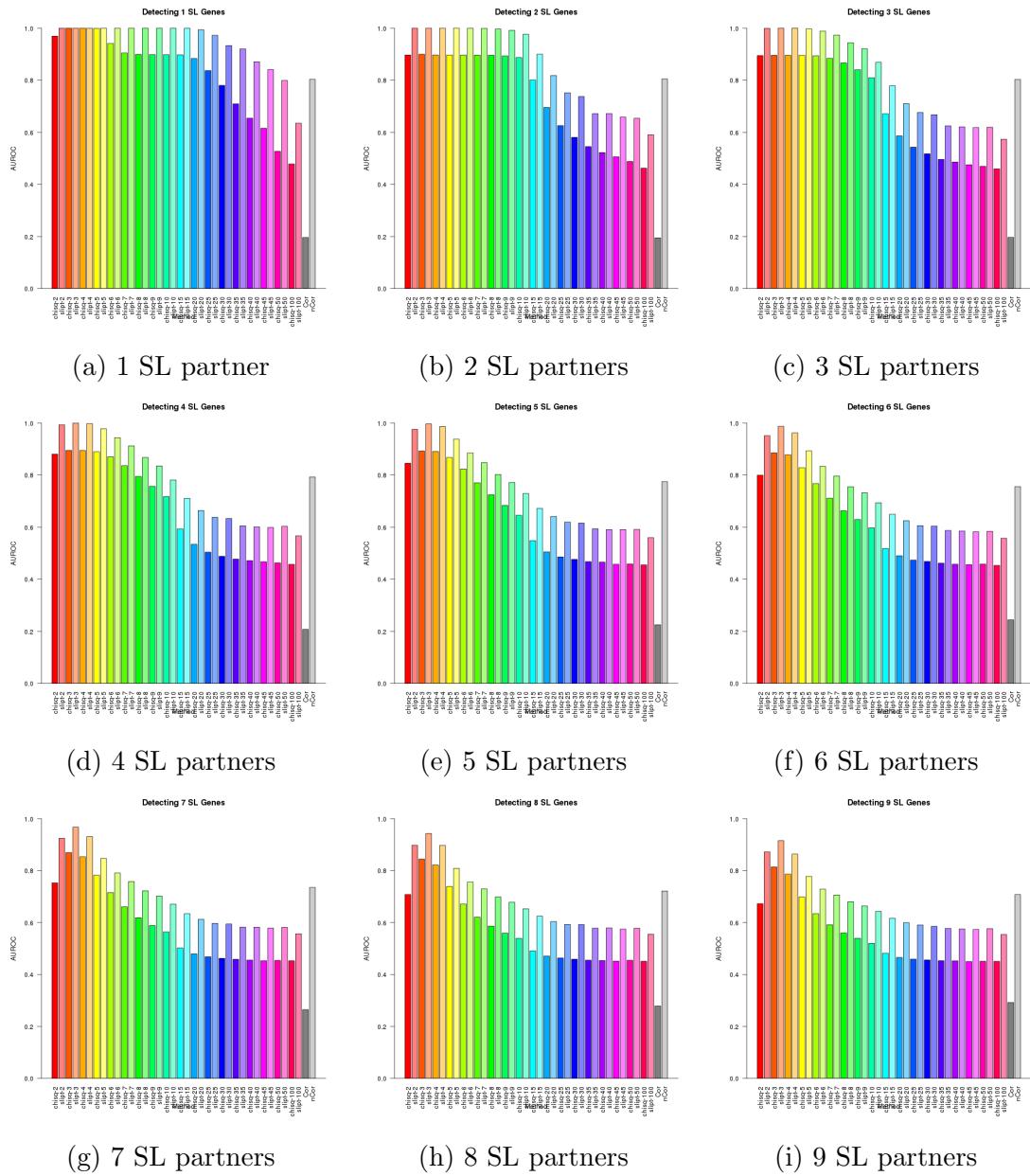
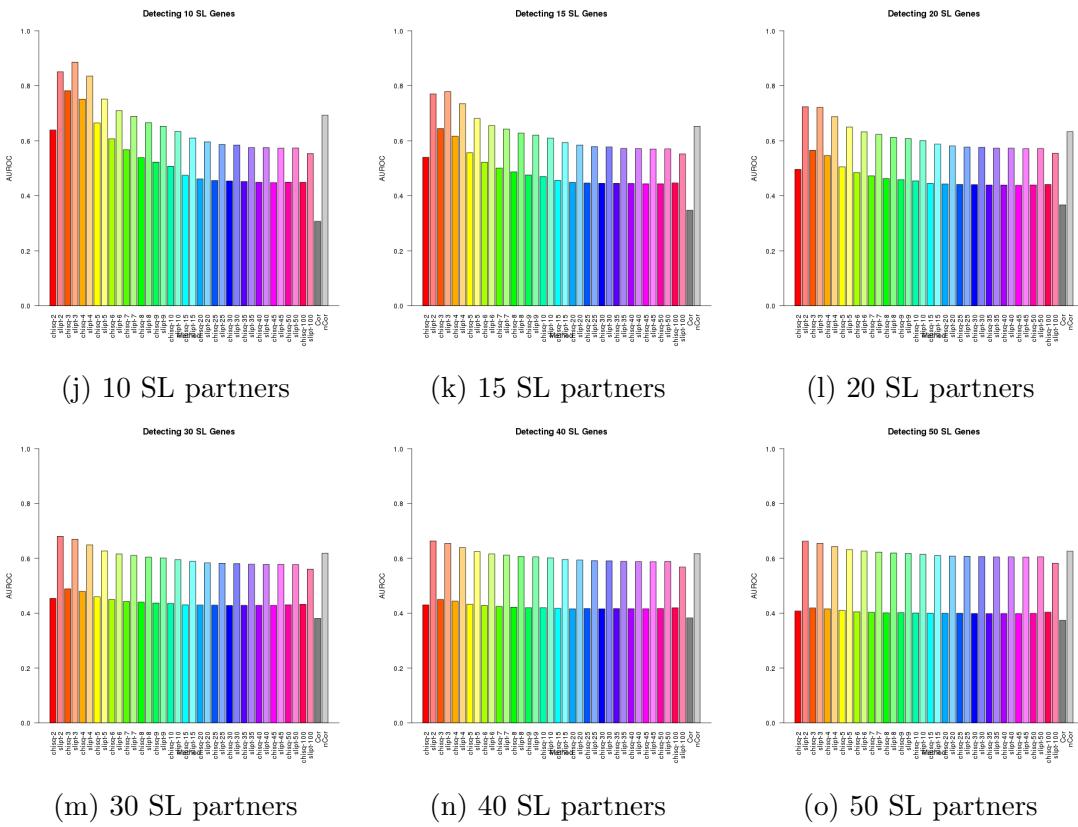


Figure J.4: Performance of  $\chi^2$  and SLIPT across quantiles with query correlation. (continued on next page)



**Figure J.4: Performance of  $\chi^2$  and SLIPT across quantiles with query correlation.** Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for  $\chi^2$  (and positive correlation). SLIPT and  $\chi^2$  performed similarly, peaking at  $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or  $\chi^2$ . These findings were robust across different numbers of underlying synthetic lethal genes in 10,000 simulations of 100 genes (including 10 correlated with the query) and 1000 samples. SLIPT performed consistently better than  $\chi^2$  with positively correlated genes.

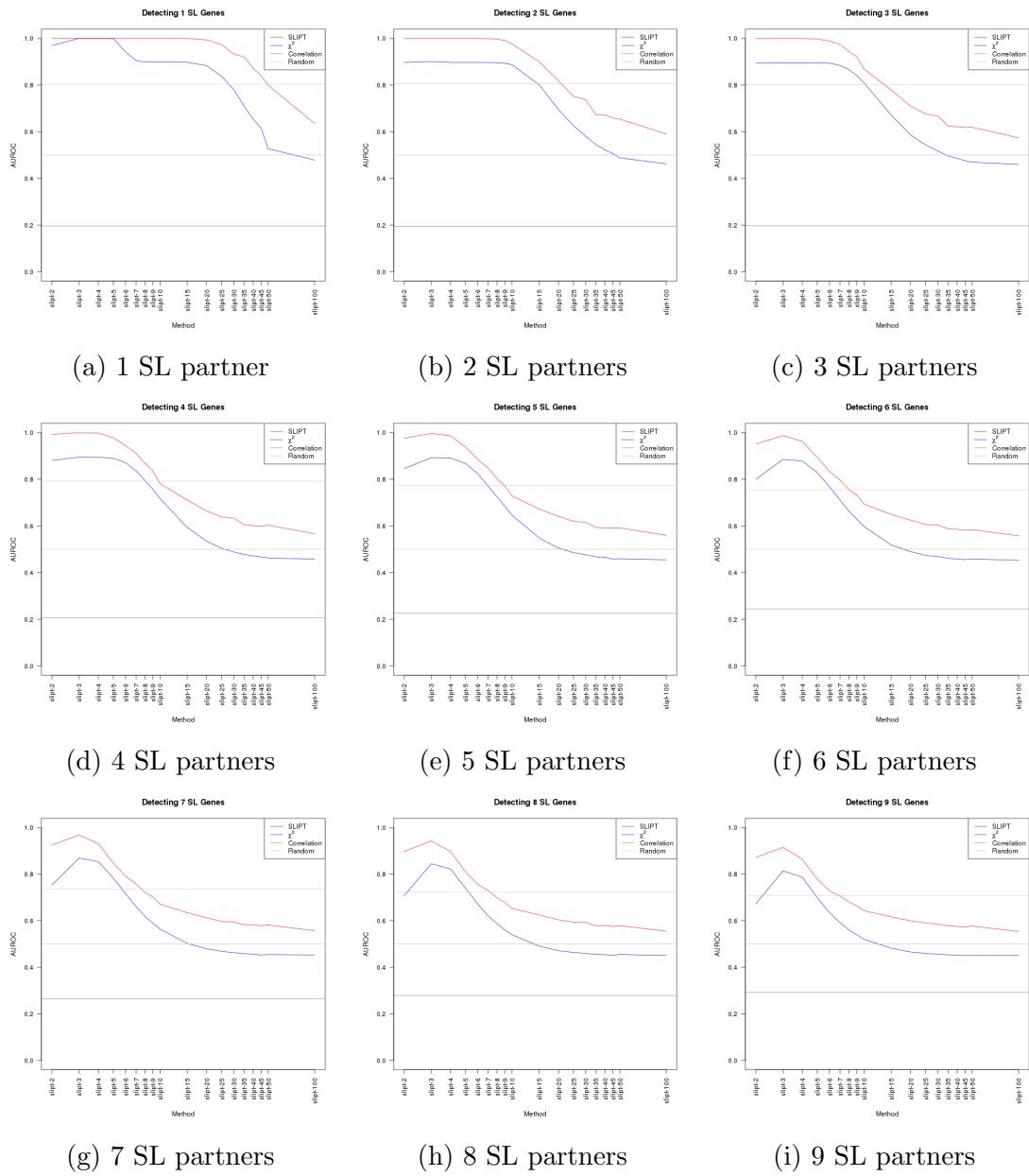
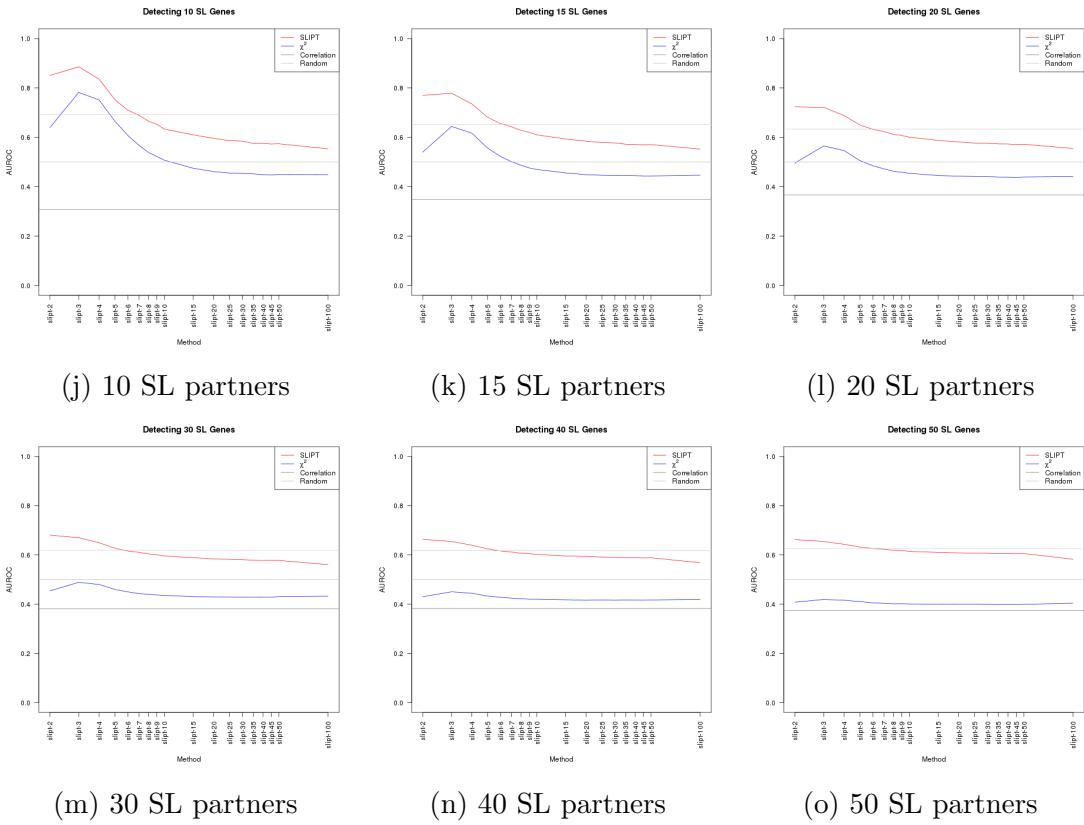


Figure J.5: **Performance of  $\chi^2$  and SLIPT across quantiles with query correlation.** (continued on next page)



**Figure J.5: Performance of  $\chi^2$  and SLIPT across quantiles with query correlation.** Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red),  $\chi^2$  (blue) and correlation (grey), according to the legend. SLIPT and  $\chi^2$  performed similarly, peaking at  $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or  $\chi^2$ . These findings were robust across different numbers of underlying synthetic lethal genes in 10,000 simulations of 100 genes (including 10 correlated with the query) and 1000 samples. SLIPT performed consistently better than  $\chi^2$  with positively correlated genes.

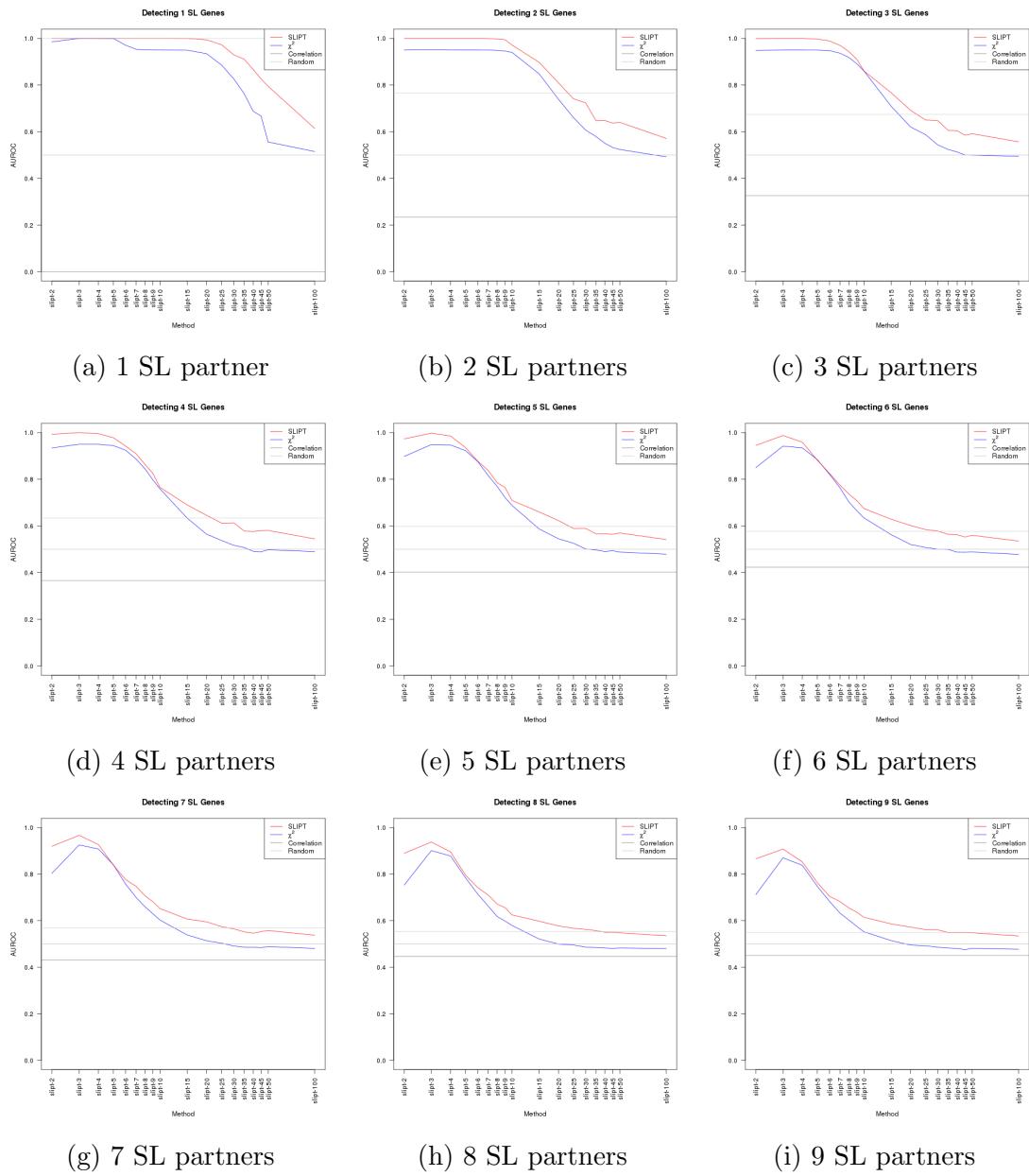
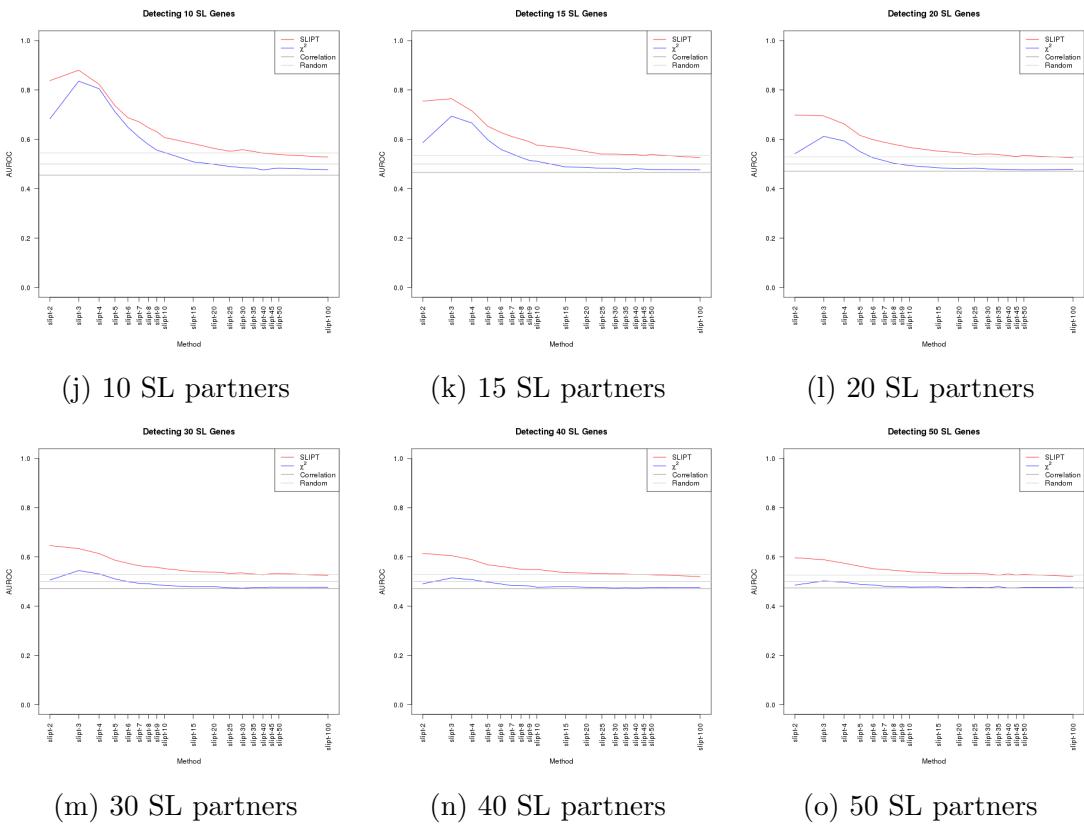


Figure J.6: **Performance of  $\chi^2$  and SLIPT across quantiles with query correlation and more genes.** (continued on next page)



**Figure J.6: Performance of  $\chi^2$  and SLIPT across quantiles with query correlation and more genes.** Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red),  $\chi^2$  (blue) and correlation (grey), according to the legend. SLIPT and  $\chi^2$  performed similarly, peaking at  $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or  $\chi^2$ . These findings were robust across different numbers of underlying synthetic lethal genes in 1000 simulations of 20,000 genes (including 1000 correlated with the query) and 1000 samples. SLIPT performed consistently better than  $\chi^2$  with positively correlated genes.

# Appendix K

## Simulations on Graph Structures

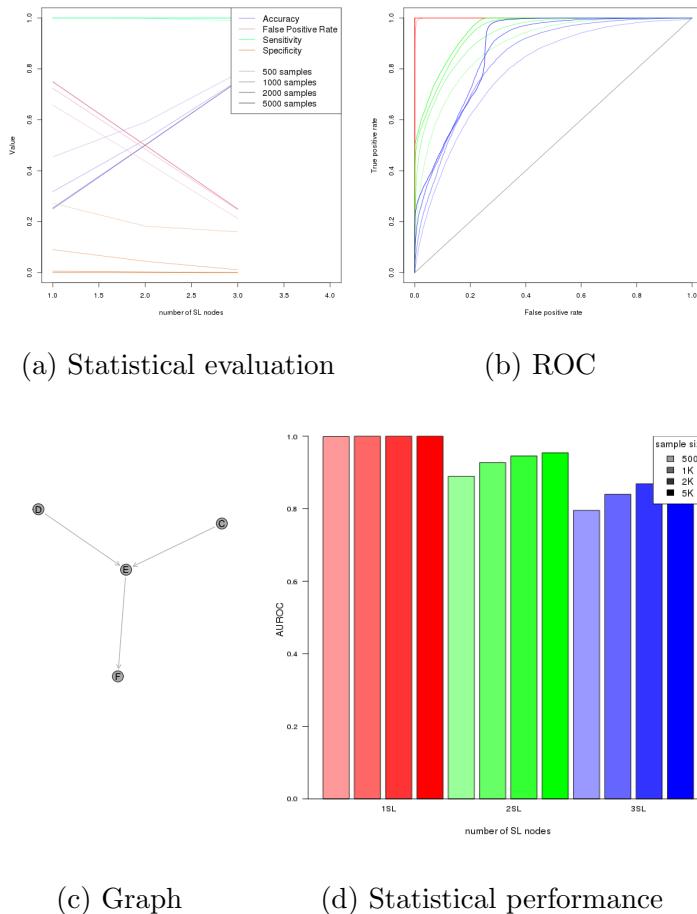
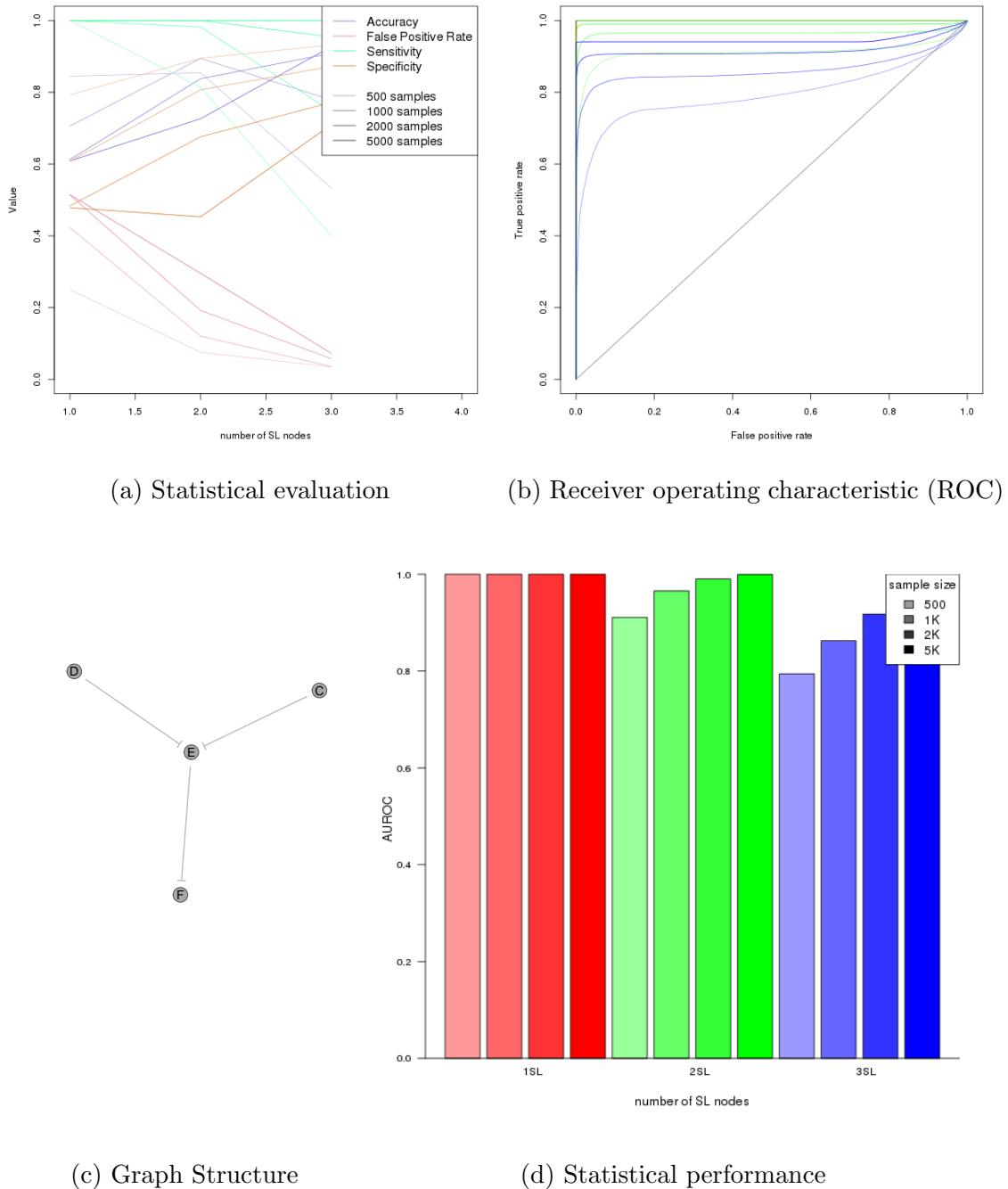
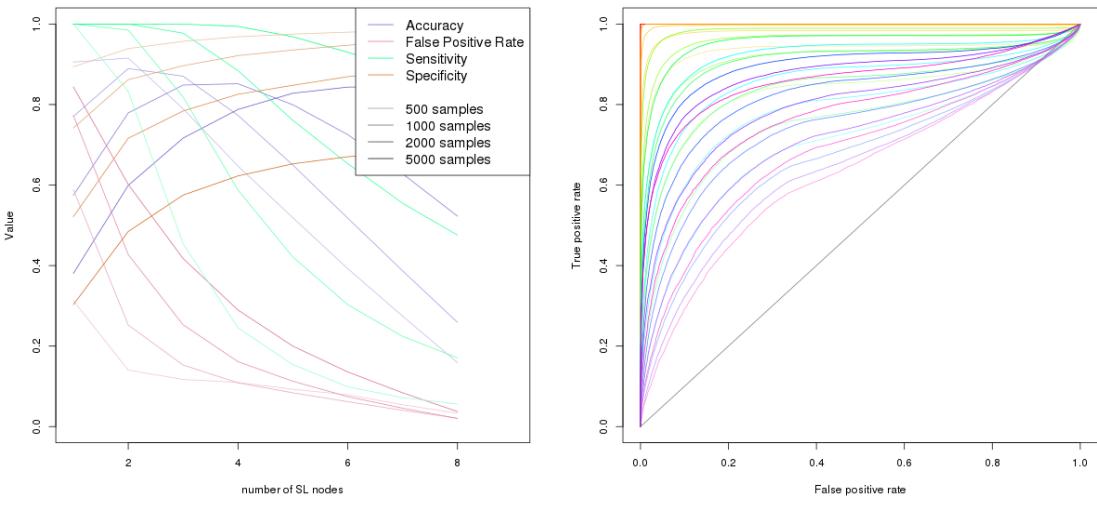


Figure K.1: **Performance of simulations on a simple graph.** Simulation of synthetic lethality was performed using a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.1b match Figure K.1d.

### K.0.1 Simulations from Inhibiting Graph Structures

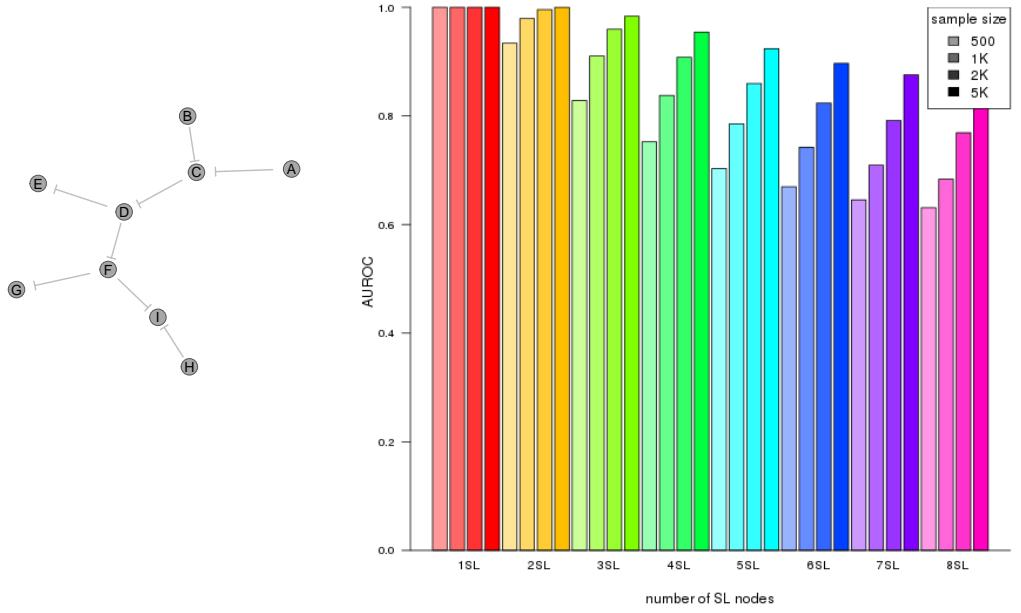


**Figure K.2: Performance of simulations on an inhibiting graph.** Simulation of synthetic lethality used a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.2b match Figure K.2d.



(a) Statistical evaluation

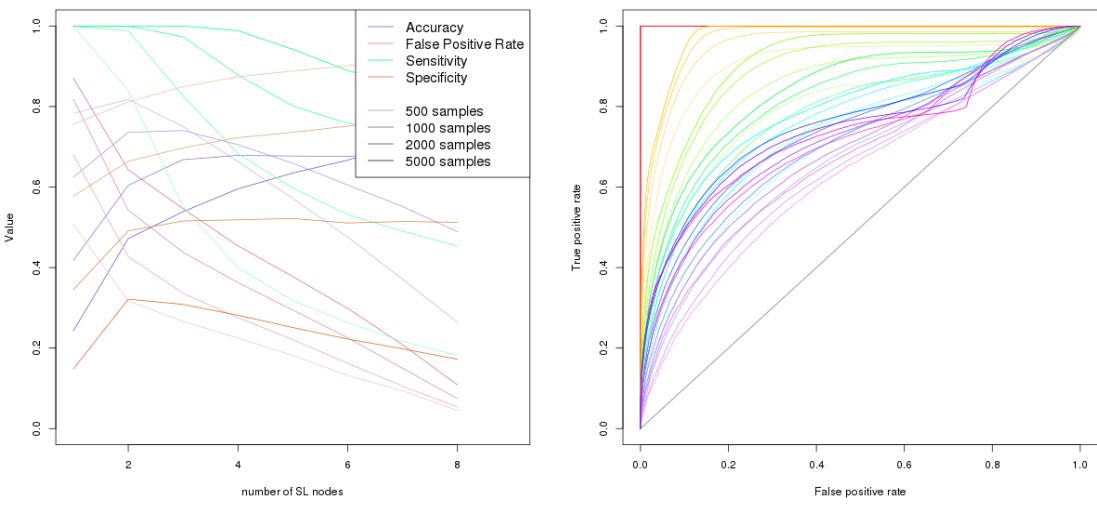
(b) ROC



(c) Graph Structure

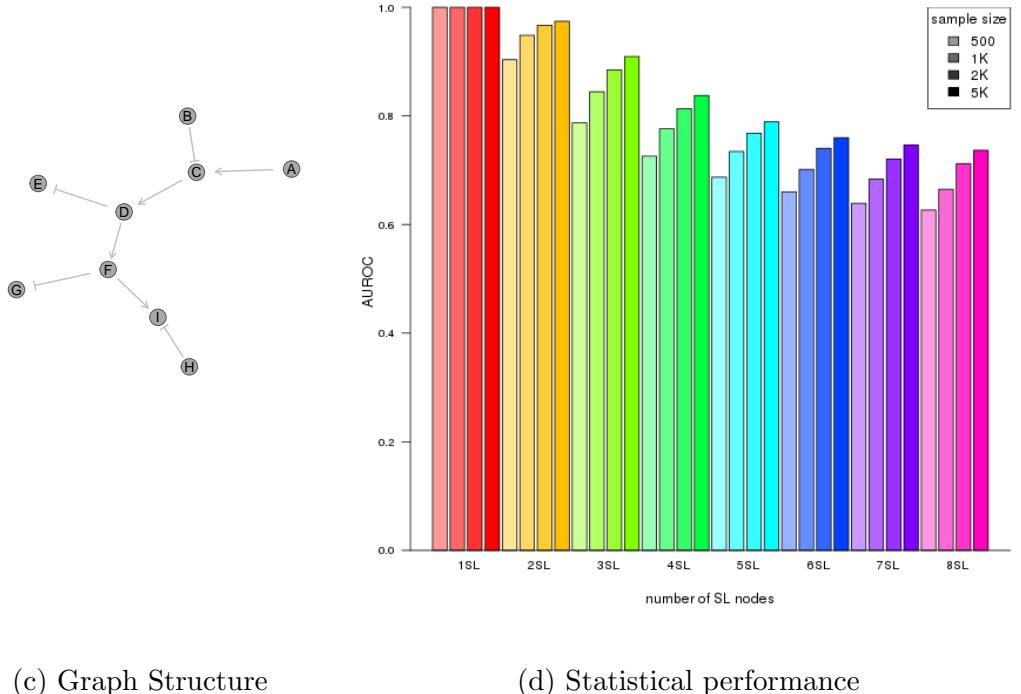
(d) Statistical performance

**Figure K.3: Performance of simulations on a constructed graph with inhibition.**  
 Simulation of synthetic lethality used a multivariate normal distribution from a pathway with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.3b match Figure K.3d.



(a) Statistical evaluation

(b) ROC

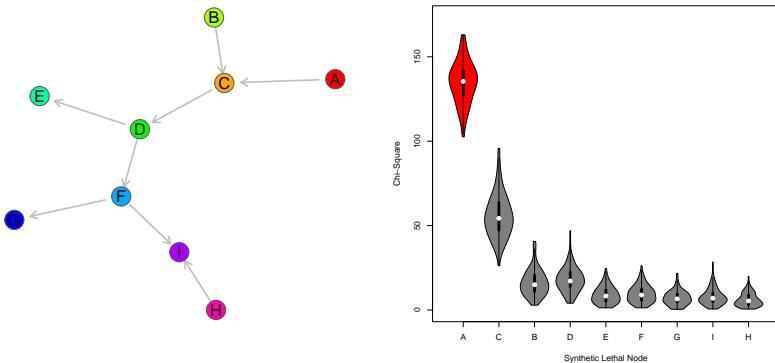


(c) Graph Structure

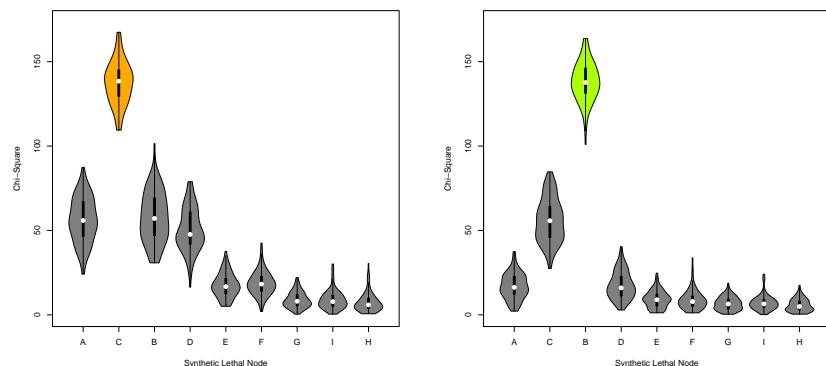
(d) Statistical performance

**Figure K.4: Performance of simulations on a constructed graph with inhibition.**  
 Simulation of synthetic lethality used a multivariate normal distribution from a pathway with a combination of inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.4b match Figure K.4d.

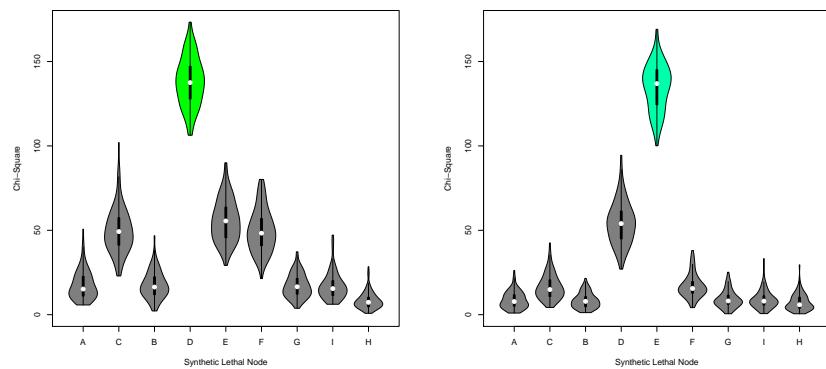
## K.1 Simulation across Graph Structures



(a) Activating Graph Structure      (b)  $\chi^2$  distribution for “A” SL

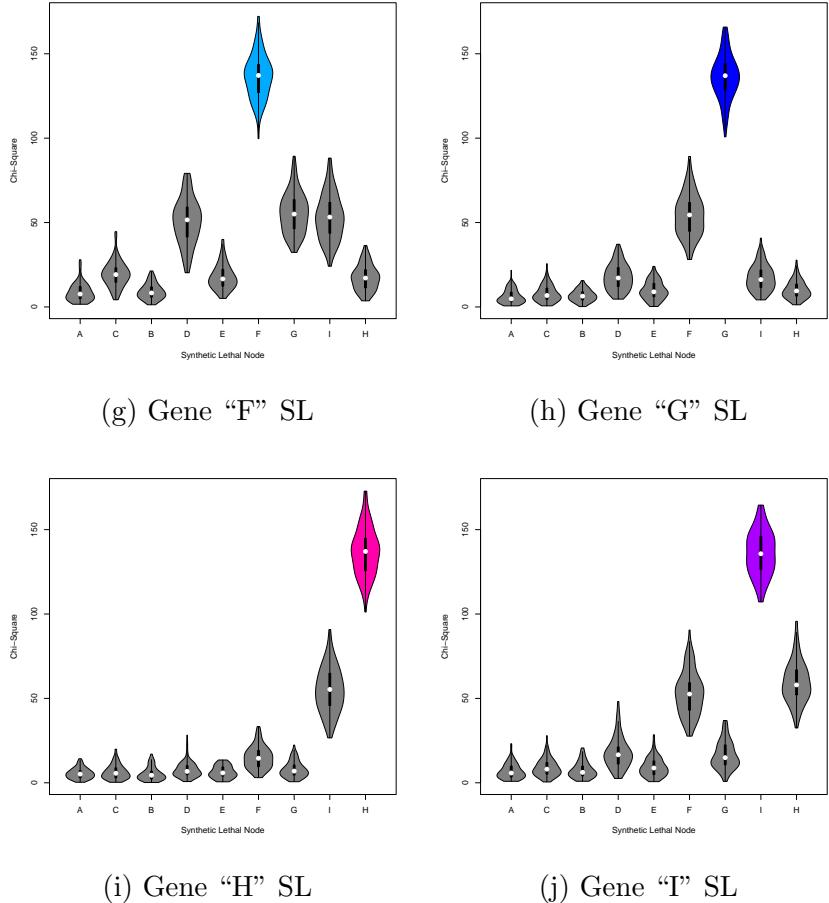


(c) Gene “B” SL      (d) Gene “C” SL

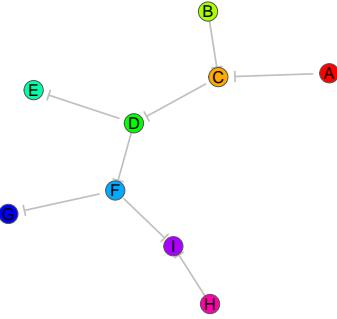


(e) Gene “D” SL      (f) Gene “E” SL

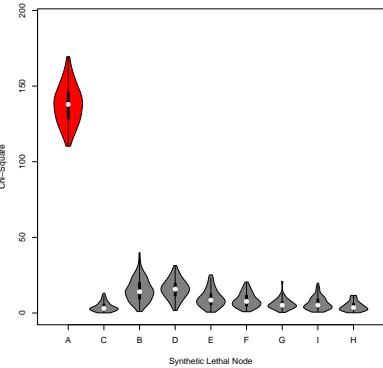
Figure K.5: **Detection of synthetic lethality within a graph Structure.** (continued on next page)



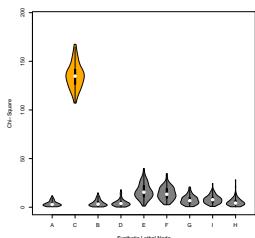
**Figure K.5: Detection of synthetic lethality within a graph structure.** Each gene was designated to be synthetic lethal separately and the  $\chi^2$  value from SLIPT was computed for each gene across the graph. For each synthetic lethal gene (highlighted in the respective colours), the  $\chi^2$  values were computed in 100 simulations of datasets of 20,000 genes including the graph structure and 1000 samples. For each synthetic lethal gene, the adjacent genes in the network also had elevated test statistics.



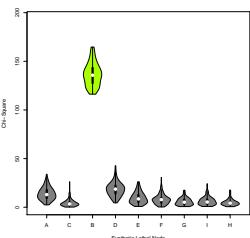
(a) Inhibiting Graph Structure



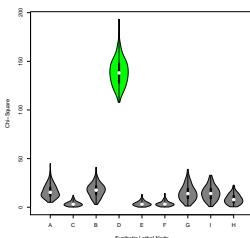
(b)  $\chi^2$  distribution for "A" SL



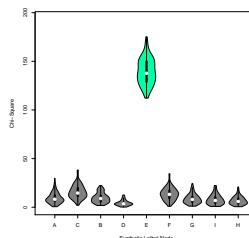
(c) Gene "B" SL



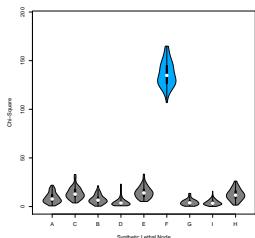
(d) Gene "C" SL



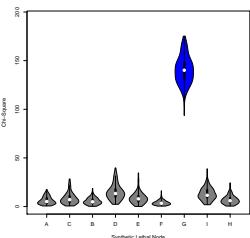
(e) Gene "D" SL



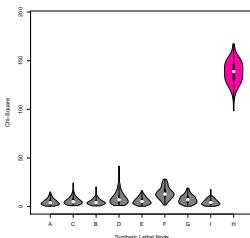
(f) Gene "E" SL



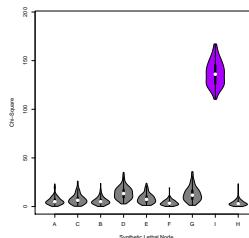
(g) Gene "F" SL



(h) Gene "G" SL

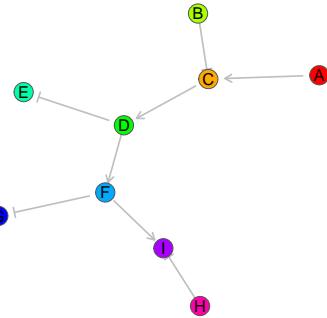


(i) Gene "H" SL

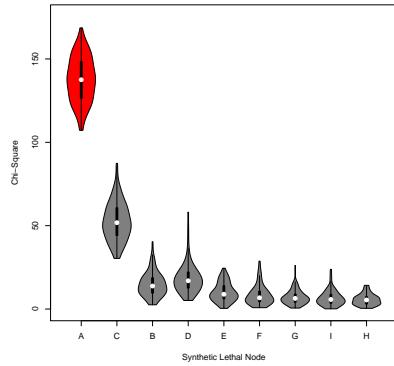


(j) Gene "I" SL

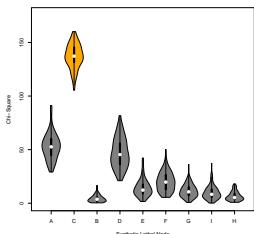
**Figure K.6: Detection of synthetic lethality within an inhibiting graph.** Each gene was designated to be synthetic lethal separately and the  $\chi^2$  value from SLIPT was computed for each gene across the graph structure with inhibiting relationships. For each synthetic lethal gene (highlighted in the respective colours), the  $\chi^2$  values were computed in 100 simulations of datasets of 20,000 genes including the graph structure and 1000 samples. For each synthetic lethal gene, the adjacent genes exhibited lower  $\chi^2$  values with inhibiting relationships.



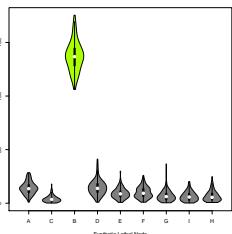
(a) Inhibiting Graph Structure



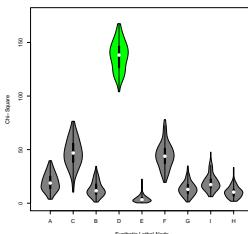
(b)  $\chi^2$  distribution for "A" SL



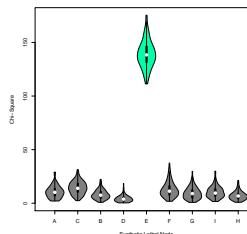
(c) Gene "B" SL



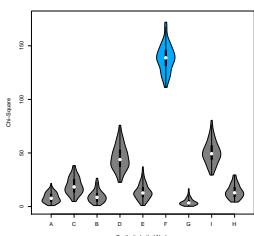
(d) Gene "C" SL



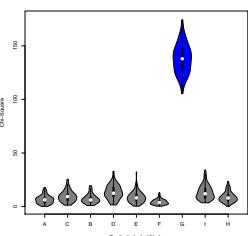
(e) Gene "D" SL



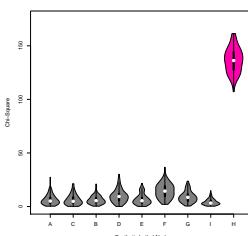
(f) Gene "E" SL



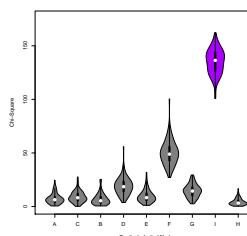
(g) Gene "F" SL



(h) Gene "G" SL



(i) Gene "H" SL



(j) Gene "I" SL

**Figure K.7: Detection of synthetic lethality within an inhibiting graph.** Each gene was designated to be synthetic lethal separately and the  $\chi^2$  value from SLIPT was computed for each gene across the graph structure with inhibiting and relationships. For each synthetic lethal gene (highlighted in the respective colours), the  $\chi^2$  values were computed in 100 simulations of datasets of 20,000 genes including the graph structure and 1000 samples.

## K.2 Simulations from Complex Graph Structures

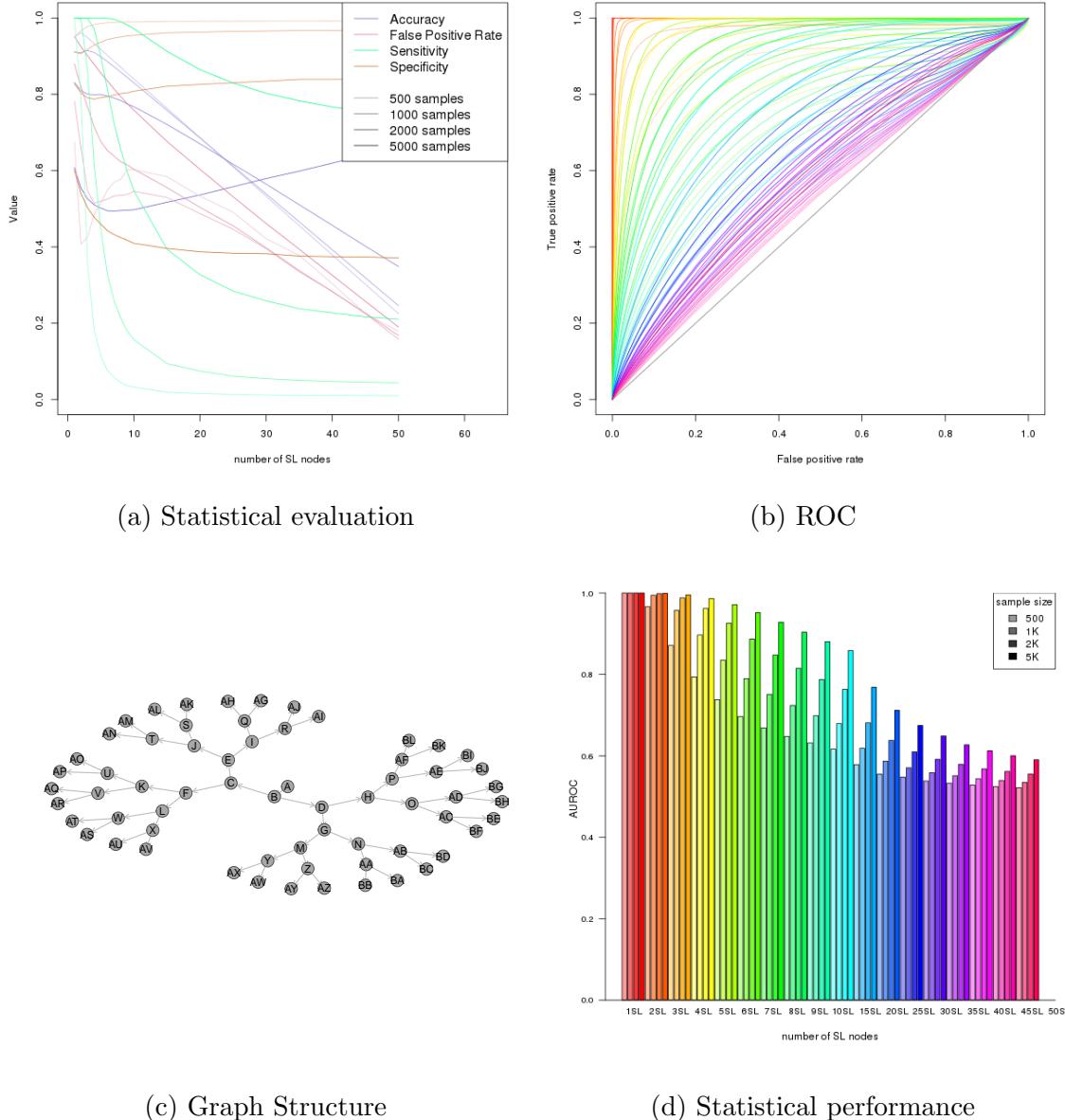
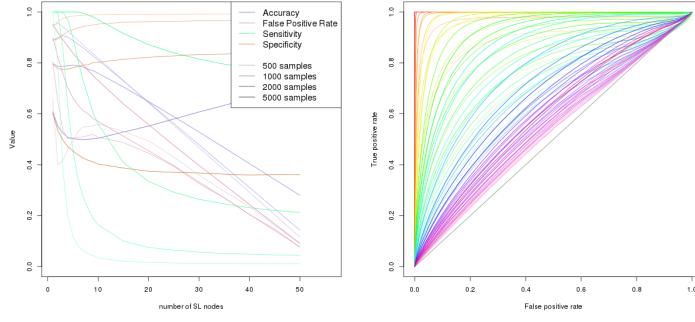
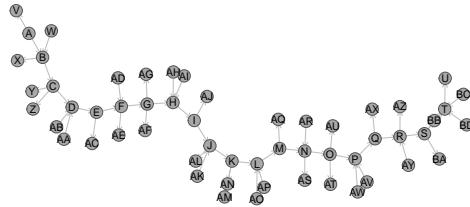


Figure K.8: **Performance of simulations on a branching graph.** Simulation of synthetic lethality used a multivariate normal distribution from a branching graph. For each parameter, 10,000 simulations were used. Colours in Figure K.8b match Figure K.8d.

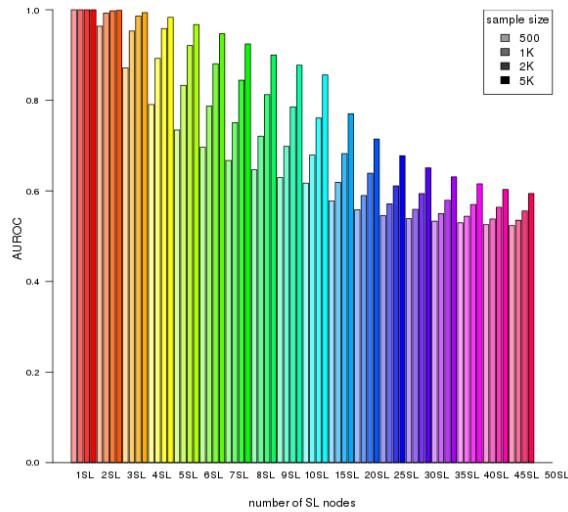


(a) Statistical evaluation

(b) ROC

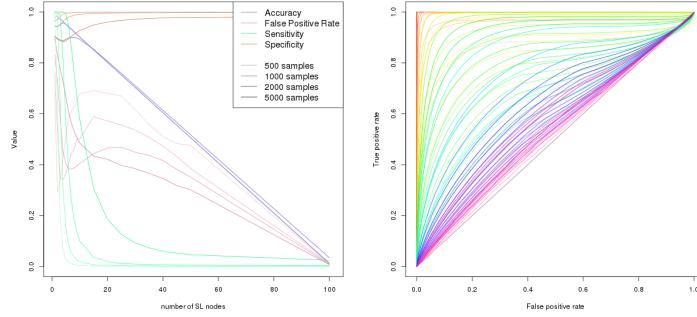


(c) Graph Structure



(d) Statistical performance

Figure K.9: **Performance of simulations on a complex graph.** Simulation of synthetic lethality used a multivariate normal distribution from a complex graph. For each parameter, 10,000 simulations were used. Colours in Figure K.9b match Figure K.9d.

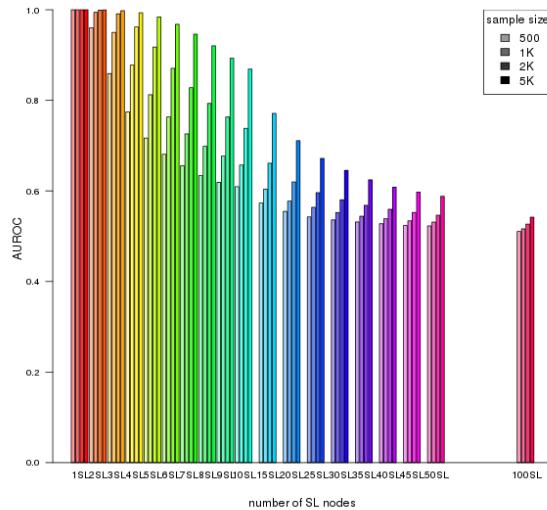


(a) Statistical evaluation

(b) ROC



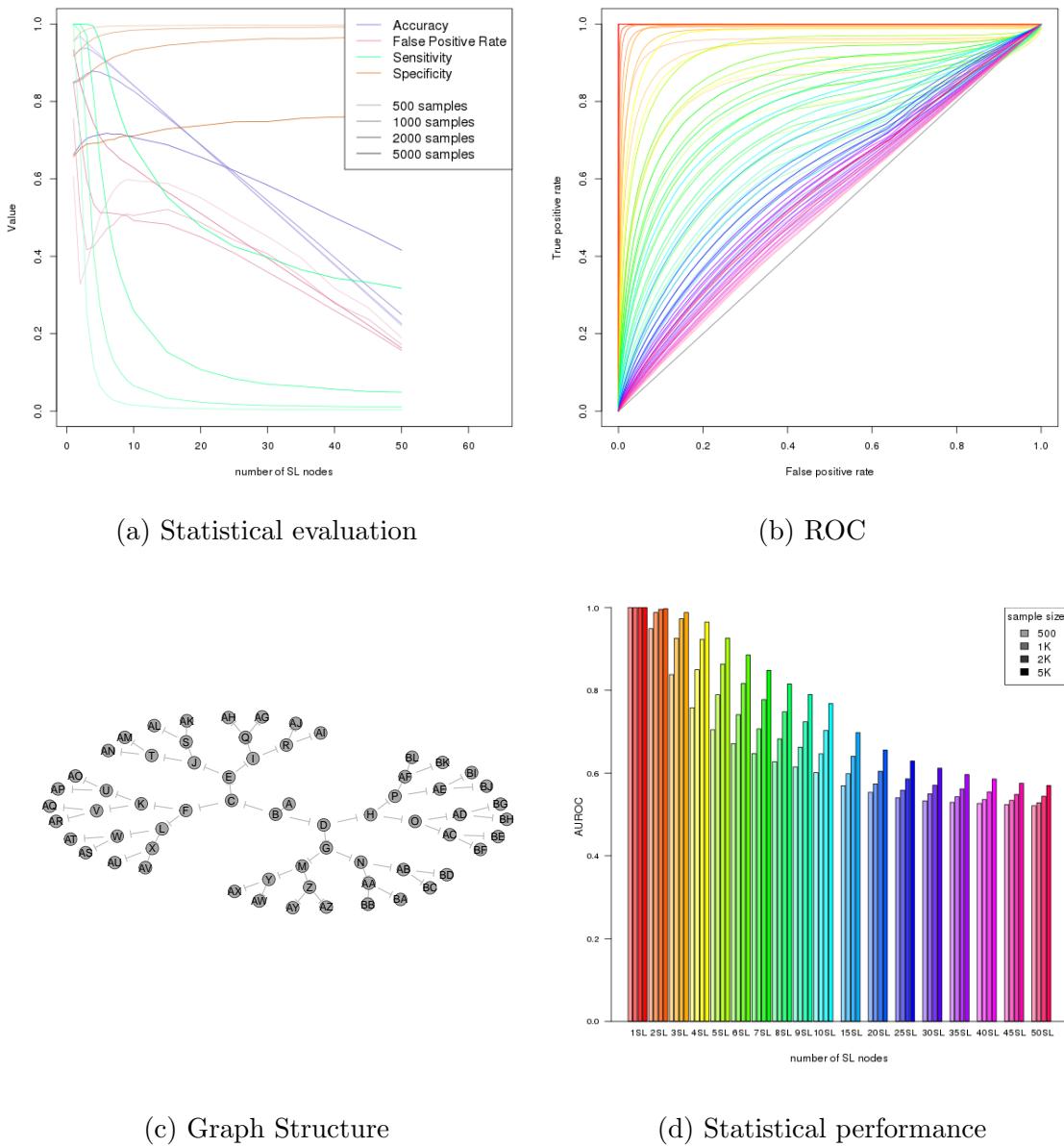
(c) Graph Structure



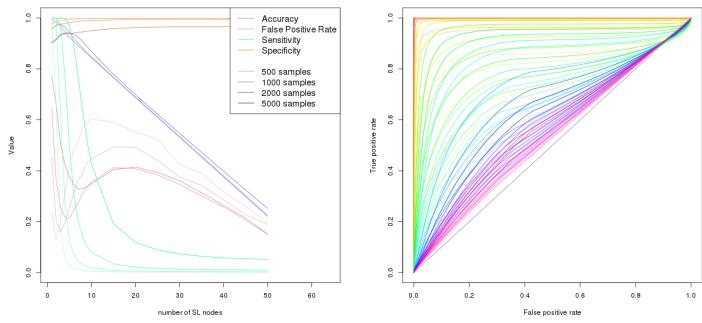
(d) Statistical performance

Figure K.10: **Performance of simulations on a large graph.** Simulation of synthetic lethality used a multivariate normal distribution from a large graph. For each parameter, 10,000 simulations were used. Colours in Figure K.10b match Figure K.10d.

### K.2.1 Simulations from Complex Inhibiting Graphs

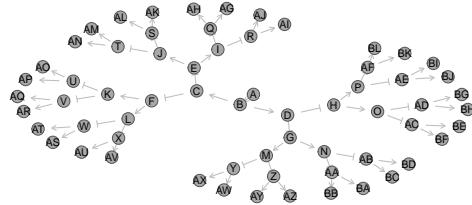


**Figure K.11: Performance of simulations on a branching graph with inhibition.**  
 Simulation of synthetic lethality used a multivariate normal distribution from a branching graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.11b match Figure K.11d.

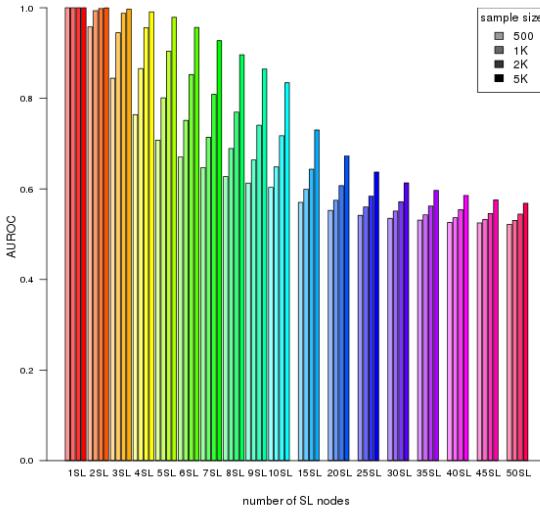


(a) Statistical evaluation

(b) ROC

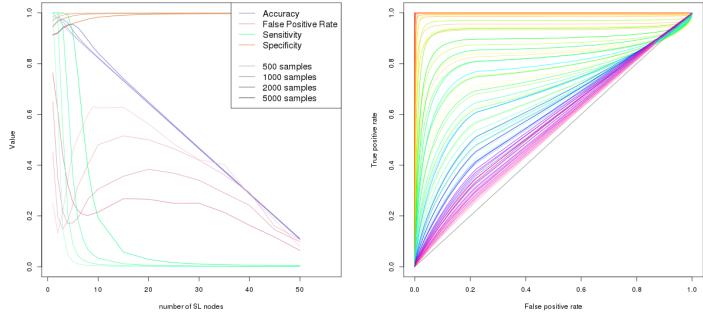


(c) Graph Structure



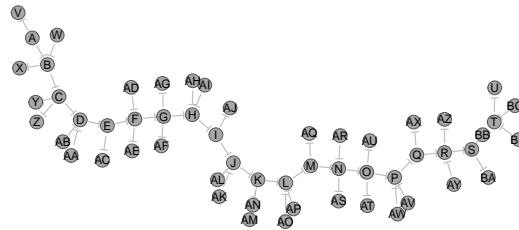
(d) Statistical performance

**Figure K.12: Performance of simulations on a branching graph with inhibition.**  
 Simulation of synthetic lethality used a multivariate normal distribution from a branching graph with alternating inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.12b match Figure K.12d.

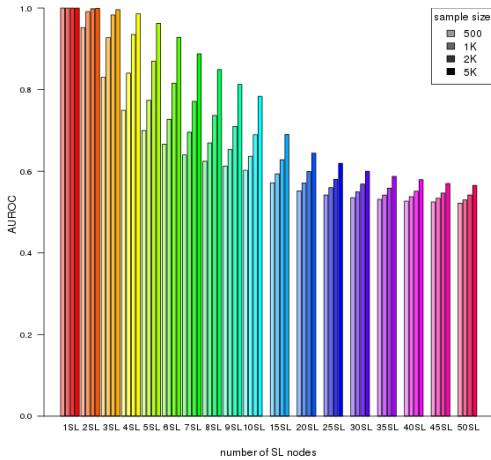


(a) Statistical evaluation

(b) ROC

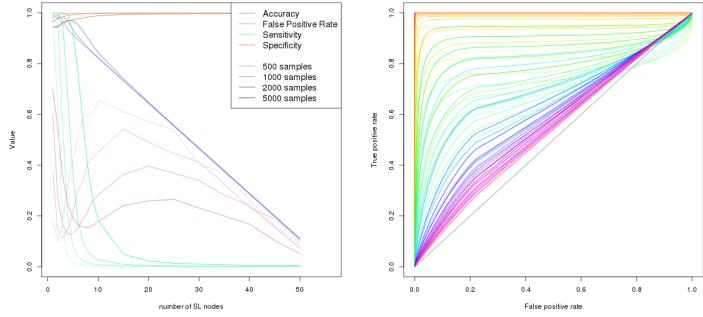


(c) Graph Structure



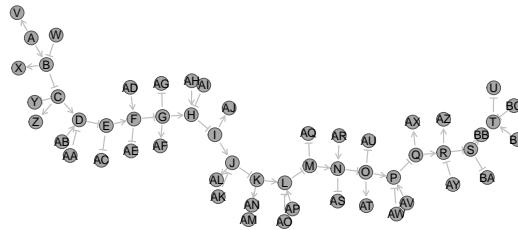
(d) Statistical performance

**Figure K.13: Performance of simulations on a complex graph with inhibition.**  
 Simulation of synthetic lethality used a multivariate normal distribution from a complex graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.13b match Figure K.13d.

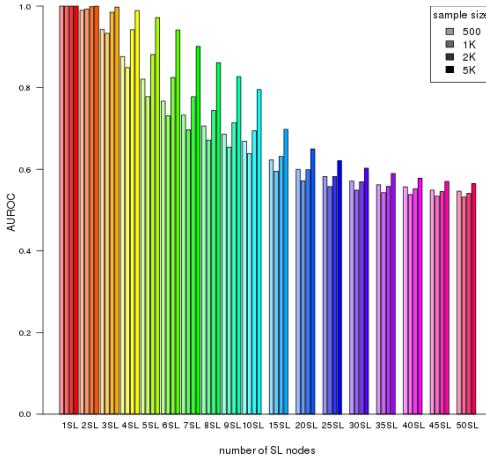


(a) Statistical evaluation

(b) ROC

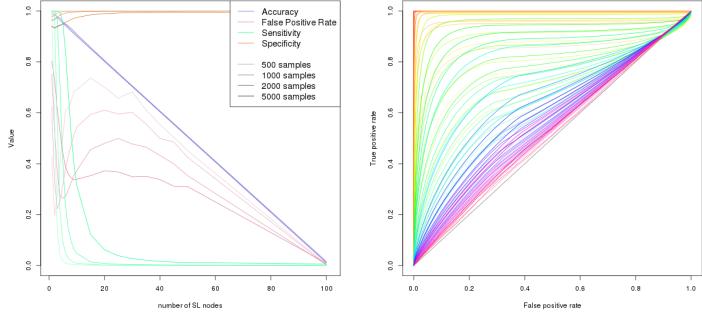


(c) Graph Structure



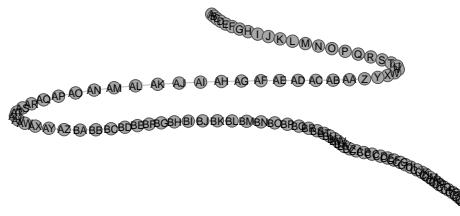
(d) Statistical performance

Figure K.14: **Performance of simulations on a complex graph with inhibition.** Simulation of synthetic lethality used a multivariate normal distribution from a complex graph with a combination of relationships. For each parameter, 10,000 simulations were used. Colours in Figure K.14b match Figure K.14d.

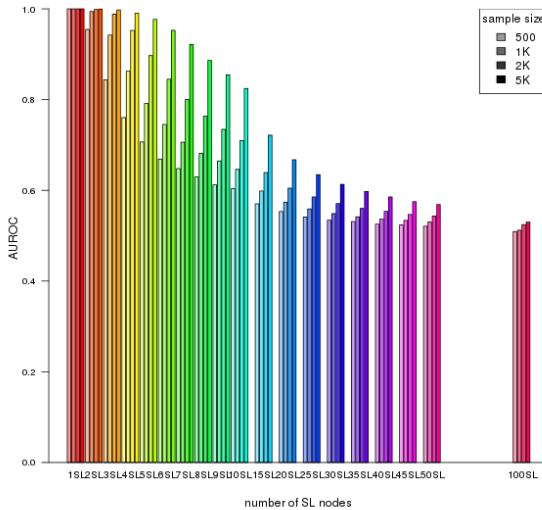


(a) Statistical evaluation

(b) ROC

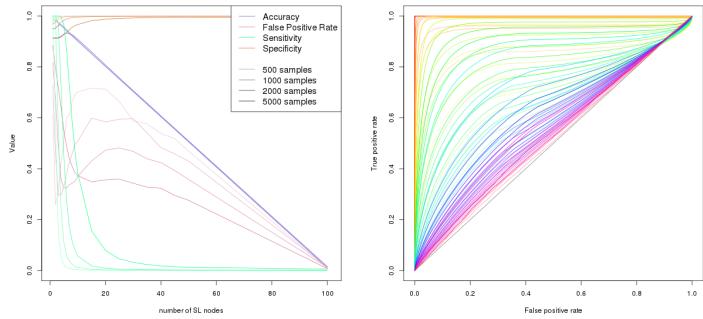


(c) Graph Structure

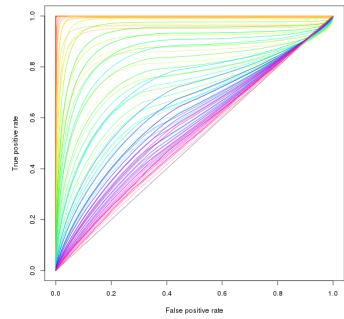


(d) Statistical performance

**Figure K.15: Performance of simulations on a large constructed graph with inhibition.** Simulation of synthetic lethality used a multivariate normal distribution from a large graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.15b match Figure K.15d.



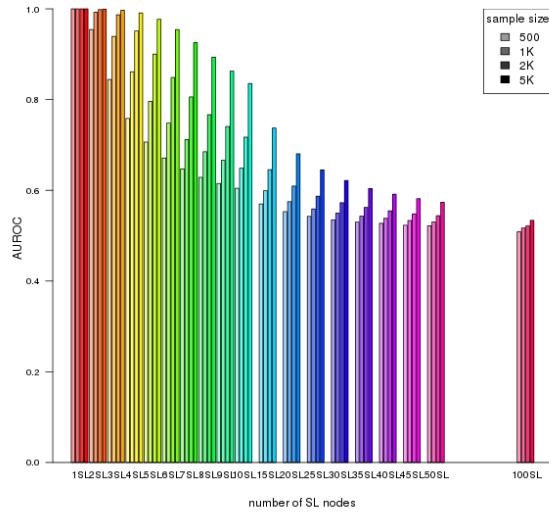
(a) Statistical evaluation



(b) ROC



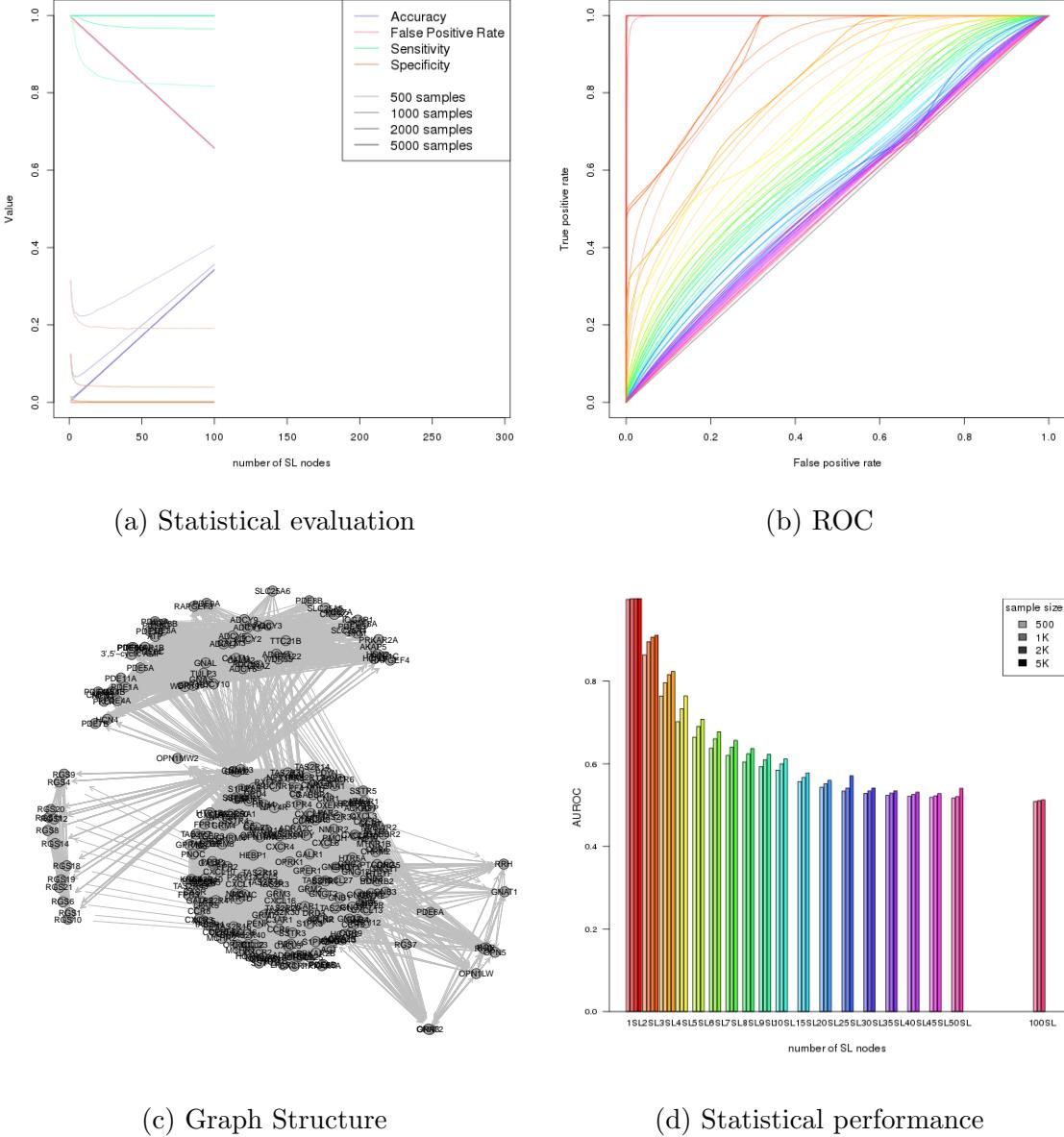
(c) Graph Structure



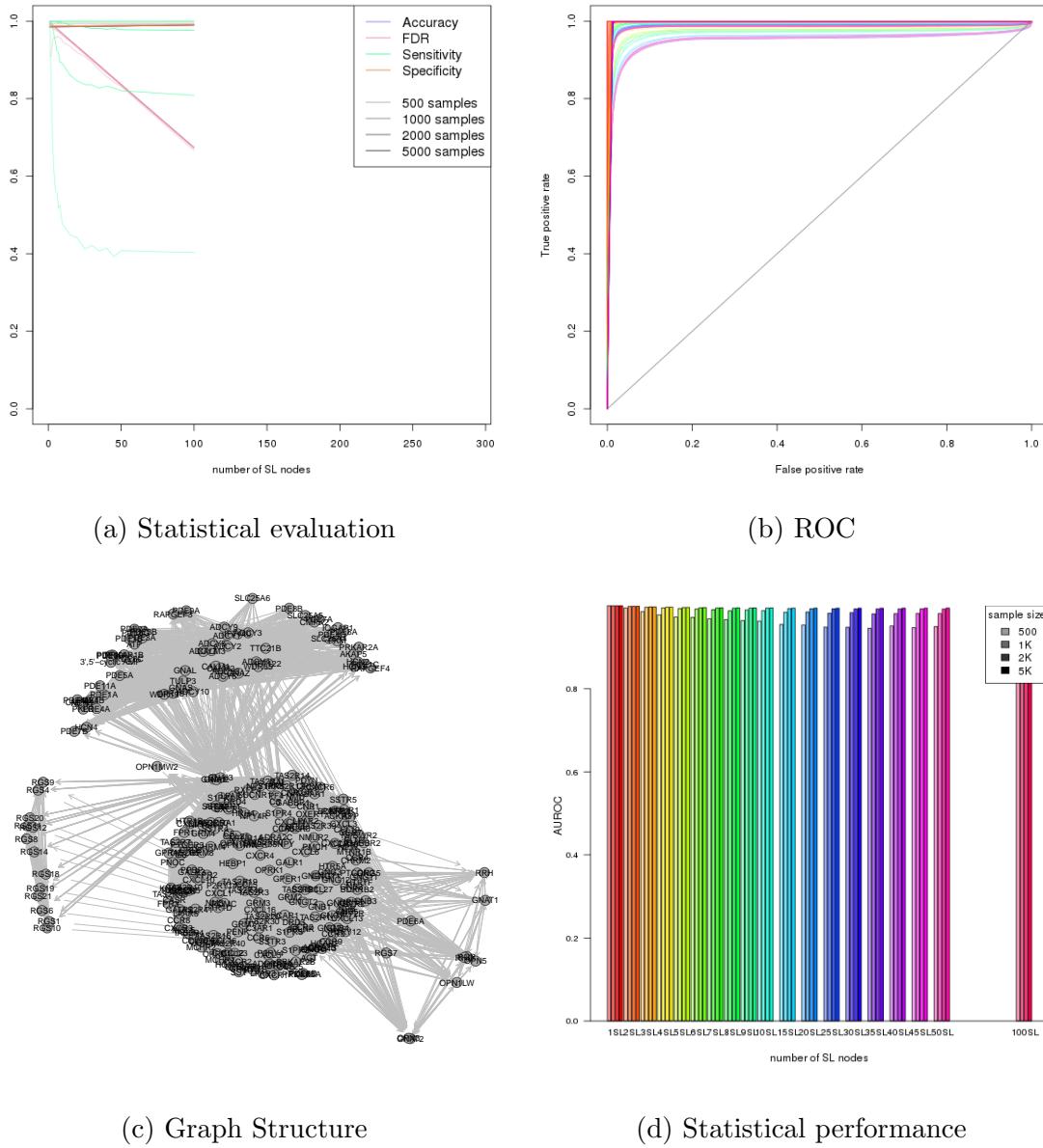
(d) Statistical performance

**Figure K.16: Performance of simulations on a large constructed graph with inhibition.** Simulation of synthetic lethality used a multivariate normal distribution from a large graph with alternating inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.16b match Figure K.16d.

### K.3 Simulations from Pathway Graph Structures



**Figure K.17: Performance of simulations on the  $G_{\alpha i}$  signalling pathway.** Simulation of synthetic lethality used a multivariate normal distribution based on the Reactome  $G_{\alpha i}$  signalling pathway. Performance of SLIPT was high across parameters for detecting synthetic lethality in the graph structure within a larger dataset. The performance decreased for a greater number of true positives to detect but the accuracy increased with a low false positive rate.



**Figure K.18: Performance of simulations including the  $G_{\alpha i}$  signalling pathway.** Simulation of synthetic lethality used a multivariate normal distribution (without correlation structure apart from the Reactome  $G_{\alpha i}$  signalling pathway. Performance of SLIPT was high across parameters for detecting synthetic lethality in the graph structure within a larger dataset. The sensitivity decreased for a greater number of true positives to detect but the specificity remained high with a low false positive rate.