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Glossary

allele	A gene variant with a specific sequence and phenotype.
centrality	A network metric which identifies important vertices.
driver mutation	A mutation which promotes cancer growth.
E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by <i>CDH1</i> .
edge or link	A relationship connecting a pair of elements of a graph structure or network, may be weighted or directional.
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.
hereditary	A trait or disease which has a genetic cause and is inherited from family members.
information centrality	A network centrality metric which uses the impact of removing a vertex or node on connections in the network.
intrinsic subtype	Distinguishing cancer by molecular and genetic features.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.

microarray	A high-throughput technique to measure presence or abundance of nucleic acid sequences from binding to probes.
mutant	A variant or dysfunctional phenotype arising from a mutation in a gene.
mutation	A change in DNA sequence that disrupts gene function.
oncogene	A gene that potentially causes cancer, typically by over-expression or mutant gene variants.
PageRank centrality	A network centrality metric which uses eigenvectors with a scaling factor (Brin and Page, 1998).
pathway	A series of biomolecules that produces a particular product or biological function.
recurrent mutation	The repeated occurrence of mutations in a particular gene across cancers.
RNA-Seq	The generation of transcriptome data from sequencing RNA.
shortest path	A path with the fewest possible edges which connects two particular vertices.
somatic mutation	A mutation that occurs in somatic cells, during a patient's lifespan.
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.
tumour suppressor	A gene potentially causes cancer, typically by disruption of functions which protect the cell from cancer.
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.
PR	Progesterone Receptor.
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

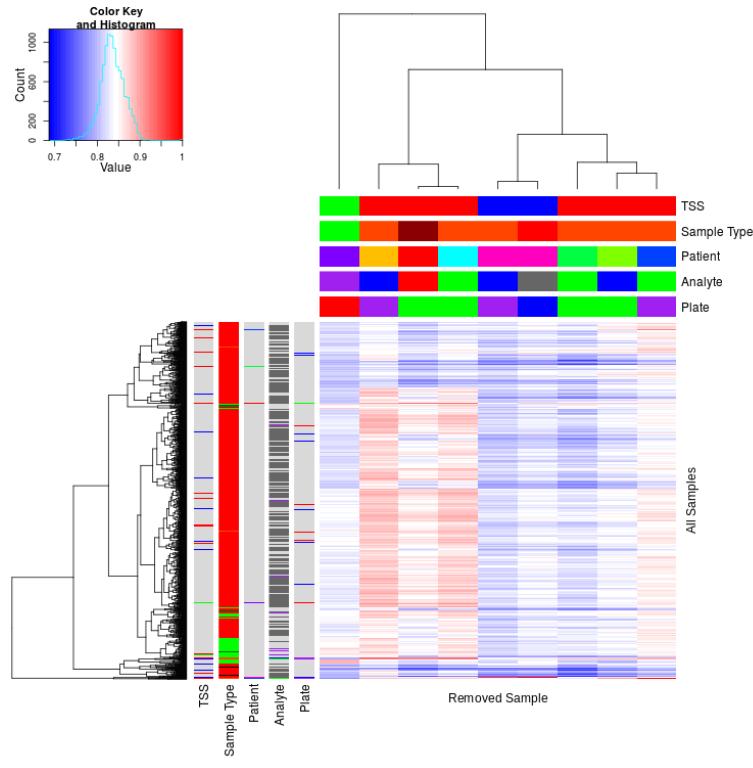


Figure A.1: Correlation profiles of removed samples. Heatmap (Euclidean distance) of samples in The Cancer Genome Atlas (TCGA) breast cancer dataset (left) clustered for all samples against removed samples (top): tissue source site (TSS), sample type with reds for tumour and greens for normal, patient (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.

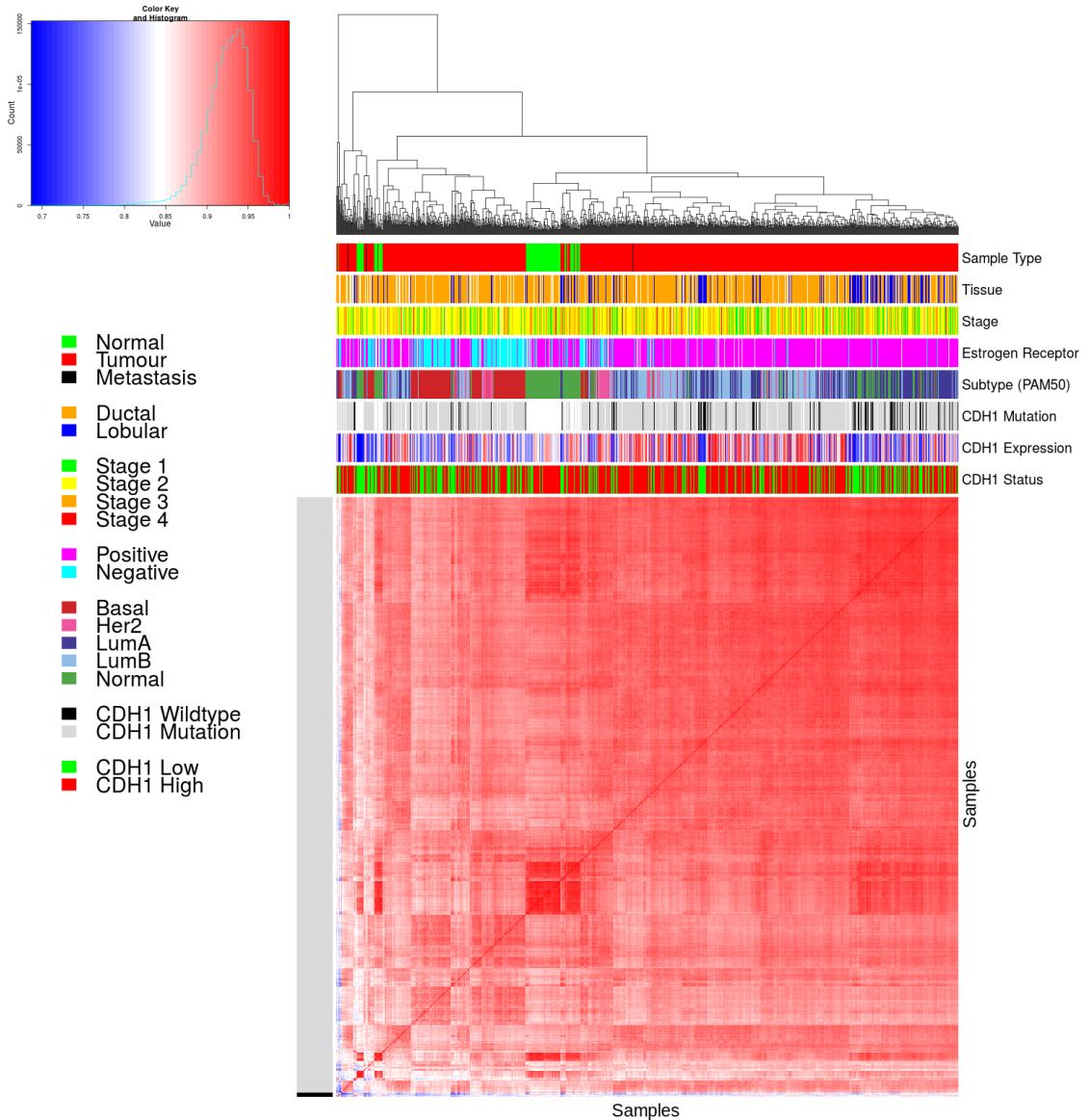


Figure A.2: Correlation analysis and sample removal. Correlation matrix heatmap (Euclidean distance) of all samples in TCGA breast cancer dataset against each other annotated for sample clinical data: sample type, tissue type, tumour stage, Estrogen receptor (ER) and intrinsic subtype (from the PAM50 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 Cancer Data

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.

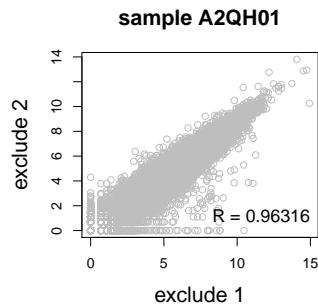


Figure A.3: **Replicate excluded samples.** Both tumour samples of patient A2QH were excluded as they were poorly correlated with other samples, although they were highly similar to each other as shown by Pearson correlation of log-raw counts.

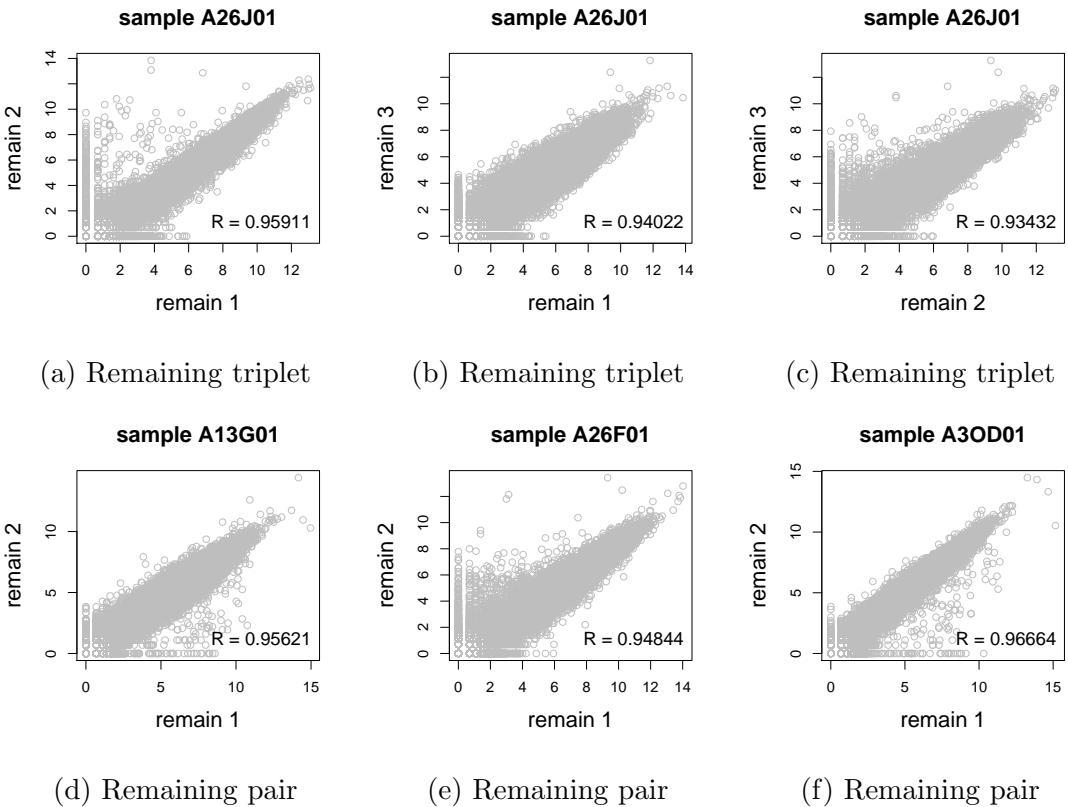


Figure A.4: **Replicate samples with all remaining.** Patient A26J was sampled 3 times and compared pairwise. Pairs of samples were also compared for other patients with replicate samples. In all cases, replicate samples remaining in the dataset were highly concordant, as shown by Pearson correlation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

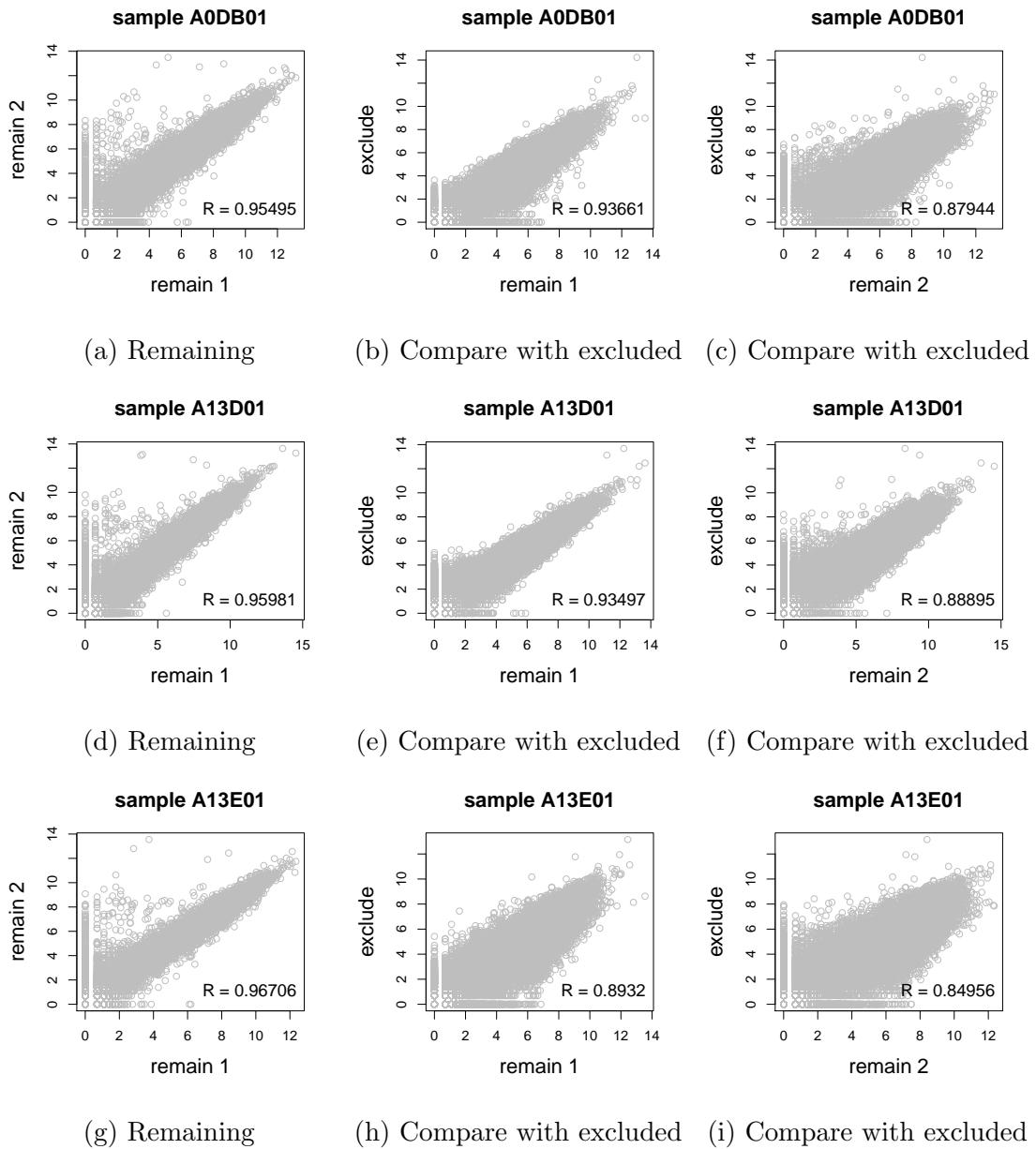


Figure A.5: **Replicate samples with some excluded.** (continued on next page)

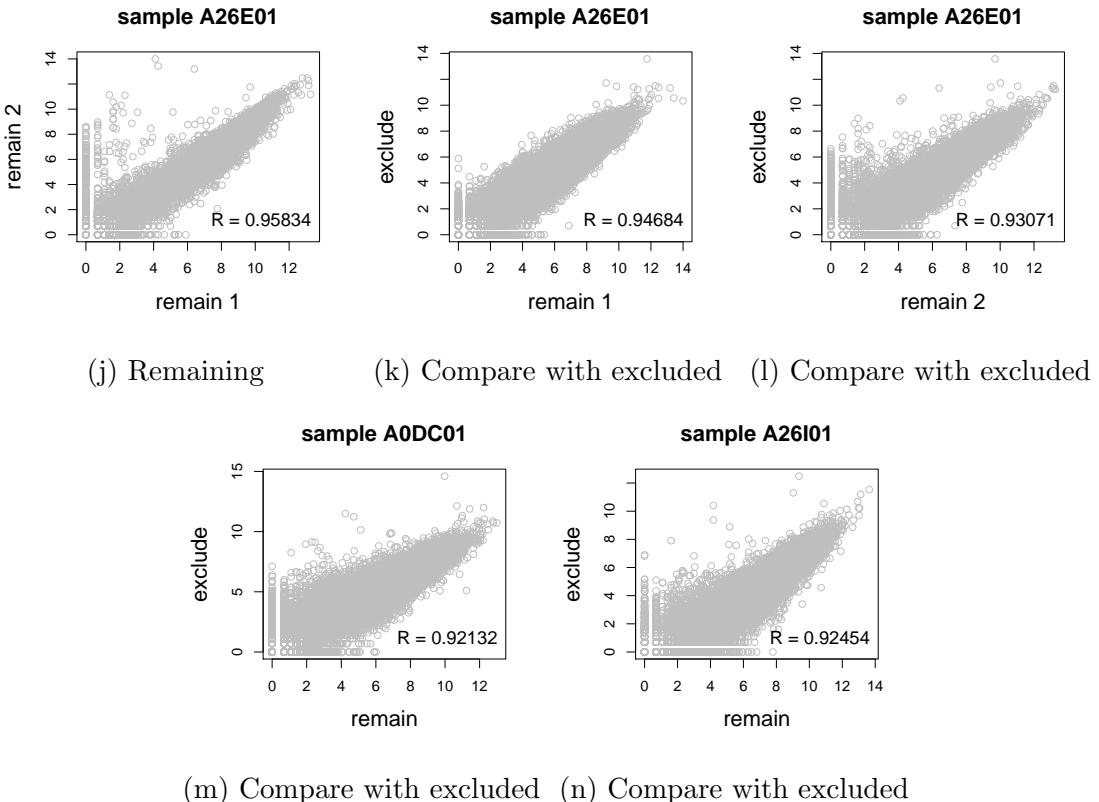


Figure A.5: **Replicate samples with some excluded.** Patients A0DB, A13D, A13E, and A26E were each sampled 3 times and compared pairwise. Pairs of samples were also compared for other patients with replicate samples. In all cases, the replicate samples remaining in the dataset more were highly concordant 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
	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*	χ^2 value	p-value	p-value (False discovery rate (FDR))
<i>TFAP2B</i>	8	36.7	89.5	3.60×10^{-20}	8.37×10^{-17}
<i>ZNF423</i>	15	36.7	78.8	7.89×10^{-18}	1.22×10^{-14}
<i>CALCOCO1</i>	11	36.7	76.8	2.09×10^{-17}	2.59×10^{-14}
<i>RBM5</i>	13	36.7	75.7	3.65×10^{-17}	4.00×10^{-14}
<i>BTG2</i>	7	36.7	71.7	2.72×10^{-16}	1.81×10^{-13}
<i>RXRA</i>	6	36.7	70.5	5.00×10^{-16}	2.97×10^{-13}
<i>SLC27A1</i>	11	36.7	70.3	5.42×10^{-16}	2.97×10^{-13}
<i>MEF2D</i>	12	36.7	69.6	7.86×10^{-16}	3.95×10^{-13}
<i>NISCH</i>	12	36.7	69.6	7.86×10^{-16}	3.95×10^{-13}
<i>AVPR2</i>	9	36.7	69.2	9.36×10^{-16}	4.58×10^{-13}
<i>CRY2</i>	13	36.7	68.9	1.07×10^{-15}	4.98×10^{-13}
<i>RAPGEF3</i>	13	36.7	68.9	1.07×10^{-15}	4.98×10^{-13}
<i>NRIP2</i>	10	36.7	68.2	1.58×10^{-15}	7.18×10^{-13}
<i>DARC</i>	12	36.7	66.4	3.76×10^{-15}	1.54×10^{-12}
<i>SFRS5</i>	12	36.7	66.4	3.76×10^{-15}	1.54×10^{-12}
<i>NOSTRIN</i>	5	36.7	65.1	7.40×10^{-15}	2.70×10^{-12}
<i>KIF13B</i>	12	36.7	63.4	1.69×10^{-14}	5.16×10^{-12}
<i>TENC1</i>	10	36.7	62.5	2.67×10^{-14}	7.40×10^{-12}
<i>MFAP4</i>	12	36.7	60.5	7.17×10^{-14}	1.67×10^{-11}
<i>ELN</i>	13	36.7	59.7	1.07×10^{-13}	2.32×10^{-11}
<i>SGK223</i>	14	36.7	59	1.51×10^{-13}	3.05×10^{-11}
<i>KIF12</i>	11	36.7	58.8	1.74×10^{-13}	3.34×10^{-11}
<i>SELP</i>	11	36.7	58.8	1.74×10^{-13}	3.34×10^{-11}
<i>CIRBP</i>	9	36.7	58.7	1.83×10^{-13}	3.41×10^{-11}
<i>CTDSP1</i>	9	36.7	58.7	1.83×10^{-13}	3.41×10^{-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	2.0×10^{-128}
Peptide chain elongation	83	59	2.0×10^{-128}
Eukaryotic Translation Termination	83	58	2.3×10^{-125}
Viral mRNA Translation	81	57	2.5×10^{-124}
Nonsense Mediated Decay independent of the Exon Junction Complex	88	59	8.6×10^{-124}
Nonsense-Mediated Decay	103	61	5.2×10^{-117}
Nonsense Mediated Decay enhanced by the Exon Junction Complex	103	61	5.2×10^{-117}
Formation of a pool of free 40S subunits	93	58	1.6×10^{-116}
L13a-mediated translational silencing of Ceruloplasmin expression	103	59	1.3×10^{-111}
3' -UTR-mediated translational regulation	103	59	1.3×10^{-111}
GTP hydrolysis and joining of the 60S ribosomal subunit	104	59	6.2×10^{-111}
SRP-dependent cotranslational protein targeting to membrane	104	58	2.9×10^{-108}
Eukaryotic Translation Initiation	111	59	3.0×10^{-106}
Cap-dependent Translation Initiation	111	59	3.0×10^{-106}
Influenza Viral RNA Transcription and Replication	108	57	5.1×10^{-103}
Influenza Infection	117	59	1.5×10^{-102}
Translation	141	64	3.7×10^{-101}
Influenza Life Cycle	112	57	1.4×10^{-100}
GPCR downstream signalling	472	116	1.0×10^{-80}
Hemostasis	422	105	1.4×10^{-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.

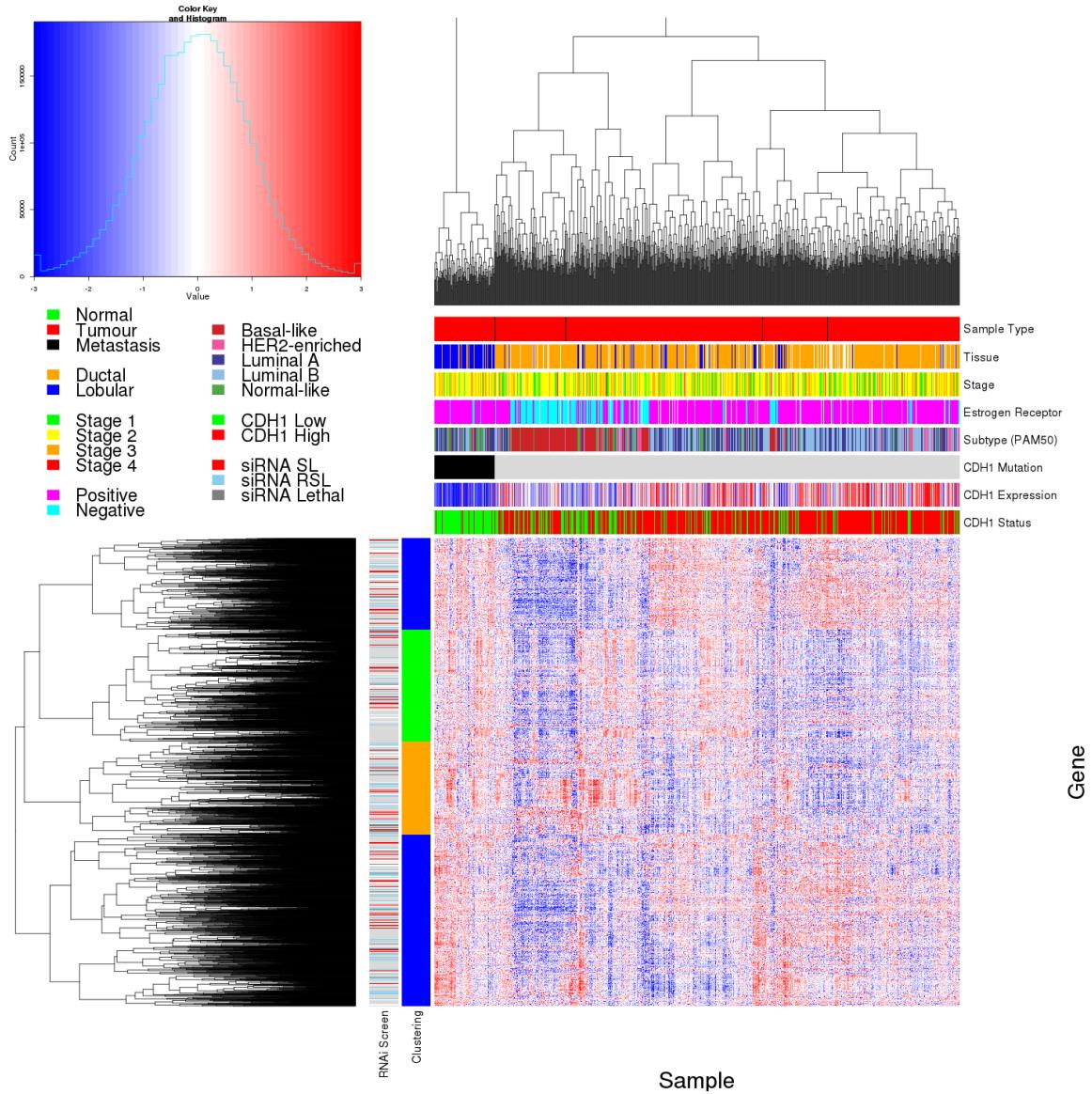


Figure C.1: Synthetic lethal expression profiles of analysed samples. Gene expression profile heatmap (correlation distance) of all samples (separated by *CDH1* somatic mutation status) analysed in TCGA breast cancer dataset for gene expression of 3743 candidate partners of E-cadherin (*CDH1*) from mtSLIPT 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	7.1×10^{-9}
Assembly of the primary cilium		149	14	8.0×10^{-9}
Sphingolipid metabolism		62	8	9.6×10^{-9}
Signalling by ERBB4		133	12	5.1×10^{-8}
PI3K Cascade		65	7	4.9×10^{-7}
Circadian Clock		33	5	4.9×10^{-7}
Nuclear signalling by ERBB4		34	5	4.9×10^{-7}
Intraflagellar transport		35	5	4.9×10^{-7}
PI3K events in ERBB4 signalling		87	8	4.9×10^{-7}
PIP3 activates AKT signalling		87	8	4.9×10^{-7}
PI3K events in ERBB2 signalling		87	8	4.9×10^{-7}
PI-3K cascade:FGFR1		87	8	4.9×10^{-7}
PI-3K cascade:FGFR2		87	8	4.9×10^{-7}
PI-3K cascade:FGFR3		87	8	4.9×10^{-7}
PI-3K cascade:FGFR4		87	8	4.9×10^{-7}
Deadenylation of mRNA		22	4	5.6×10^{-7}
PI3K/AKT activation		90	8	5.6×10^{-7}
Cargo trafficking to the periciliary membrane		38	5	5.6×10^{-7}
Pathways Over-represented in Cluster 2	Pathway	Size	Cluster Genes	p-value (FDR)
G _{αs} signalling events		83	19	5.1×10^{-25}
Extracellular matrix organization		238	30	1.4×10^{-18}
Hemostasis		422	46	2.7×10^{-16}
Aquaporin-mediated transport		32	9	2.7×10^{-16}
Transcriptional regulation of white adipocyte differentiation		56	11	1.7×10^{-15}
Degradation of the extracellular matrix		102	15	1.7×10^{-15}
Integration of energy metabolism		84	13	8.8×10^{-15}
GPCR downstream signalling		472	48	2.8×10^{-14}
G _{αz} signalling events		15	6	5.0×10^{-14}
Molecules associated with elastic fibres		33	8	5.4×10^{-14}
Phase 1 - Functionalization of compounds		67	11	5.6×10^{-14}
Platelet activation, signalling and aggregation		179	20	5.6×10^{-14}
Vasopressin regulates renal water homeostasis via Aquaporins		24	7	6.1×10^{-14}
Elastic fibre formation		37	8	$.03 \times 10^{-13}$
Calmodulin induced events		27	7	3.3×10^{-13}
CaM pathway		27	7	3.3×10^{-13}
cGMP effects		18	6	3.6×10^{-13}
G _{αi} signalling events		167	18	6.3×10^{-13}
Pathways Over-represented in Cluster 3	Pathway	Size	Cluster Genes	p-value (FDR)
Eukaryotic Translation Elongation		86	55	1.1×10^{-112}
Peptide chain elongation		83	54	1.3×10^{-112}
Viral mRNA Translation		81	53	1.6×10^{-111}
Eukaryotic Translation Termination		83	53	7.1×10^{-110}
Nonsense Mediated Decay independent of the Exon Junction Complex		88	54	1.0×10^{-108}
Formation of a pool of free 40S subunits		93	53	4.1×10^{-102}
Nonsense-Mediated Decay		103	54	3.9×10^{-98}
Nonsense Mediated Decay enhanced by the Exon Junction Complex		103	54	3.9×10^{-98}
L13a-mediated translational silencing of Ceruloplasmin expression		103	53	1.2×10^{-95}
3' -UTR-mediated translational regulation		103	53	1.2×10^{-95}
SRP-dependent cotranslational protein targeting to membrane		104	53	4.3×10^{-95}
GTP hydrolysis and joining of the 60S ribosomal subunit		104	53	4.3×10^{-95}
Influenza Viral RNA Transcription and Replication		108	53	9.6×10^{-93}
Eukaryotic Translation Initiation		111	53	4.2×10^{-91}
Cap-dependent Translation Initiation		111	53	4.2×10^{-91}
Influenza Life Cycle		112	53	1.4×10^{-90}
Influenza Infection		117	53	6.2×10^{-88}
Translation		141	55	3×10^{-81}
Pathways Over-represented in Cluster 4	Pathway	Size	Cluster Genes	p-value (FDR)
ECM proteoglycans		66	10	2.9×10^{-11}
deactivation of the beta-catenin transactivating complex		38	7	5.1×10^{-10}
Arachidonic acid metabolism		41	7	1.1×10^{-9}
G _{αq} signalling events		149	14	4.0×10^{-9}
HS-GAG degradation		21	5	4.5×10^{-9}
Uptake and actions of bacterial toxins		22	5	6.1×10^{-9}
Gastrin-CREB signalling pathway via PKC and MAPK		170	15	6.1×10^{-9}
RNA Polymerase I, RNA Polymerase III, and Mitochondrial Transcription		64	8	6.1×10^{-9}
Non-integrin membrane-ECM interactions		53	7	1.5×10^{-8}
Syndecan interactions		25	5	1.5×10^{-8}
NOTCH1 Intracellular Domain Regulates Transcription		40	6	2.3×10^{-8}
Synthesis of Leukotrienes and Eoxins		15	4	3.2×10^{-8}
Signalling by NOTCH1		59	7	5.3×10^{-8}
Regulation of insulin secretion		44	6	6.0×10^{-8}
Metabolism of lipids and lipoproteins		471	37	8.2×10^{-8}
Signalling by NOTCH1		80	8	1.2×10^{-7}
Platelet activation, signalling and aggregation		179	14	1.2×10^{-7}
Recruitment of mitotic centrosome proteins and complexes		64	7	1.2×10^{-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.

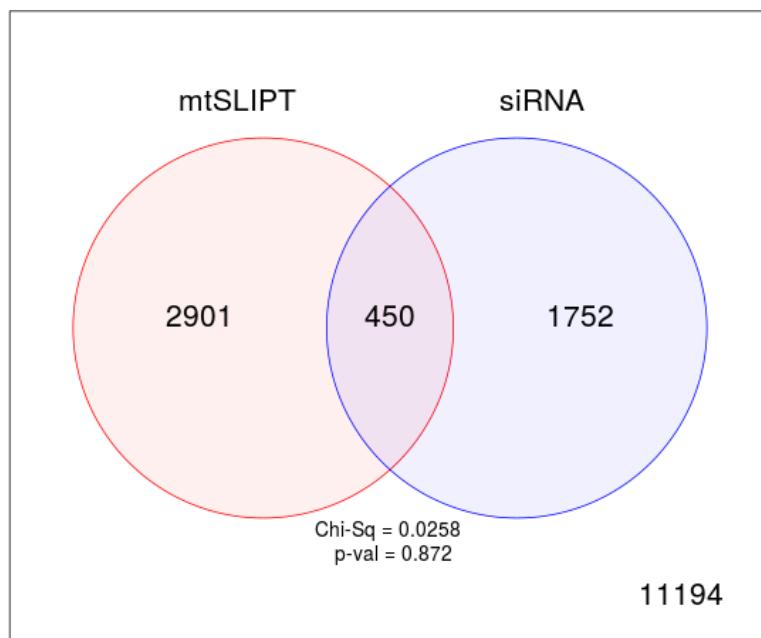


Figure C.2: **Comparison of mtSLIPT to siRNA.** Testing the overlap of gene candidates for E-cadherin synthetic lethal partners between computational (SLIPT) and experimental screening (siRNA) approaches. The χ^2 test suggests that the overlap is no more than would be expected by chance ($p = 0.281$).

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

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

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

C.3.1 Resampling Analysis

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

Reactome Pathway	Over-representation	Permutation
Eukaryotic Translation Elongation	3.2×10^{-128}	$< 7.035 \times 10^{-4}$
Peptide chain elongation	3.2×10^{-128}	$< 7.035 \times 10^{-4}$
Eukaryotic Translation Termination	3.7×10^{-125}	$< 7.035 \times 10^{-4}$
Viral mRNA Translation	4.1×10^{-124}	$< 7.035 \times 10^{-4}$
Nonsense Mediated Decay independent of the Exon Junction Complex	1.4×10^{-123}	$< 7.035 \times 10^{-4}$
Nonsense-Mediated Decay	8.4×10^{-117}	$< 7.035 \times 10^{-4}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex	8.4×10^{-117}	$< 7.035 \times 10^{-4}$
Formation of a pool of free 40S subunits	2.6×10^{-116}	$< 7.035 \times 10^{-4}$
L13a-mediated translational silencing of Ceruloplasmin expression	2.0×10^{-111}	$< 7.035 \times 10^{-4}$
3' -UTR-mediated translational regulation	2.0×10^{-111}	$< 7.035 \times 10^{-4}$
GTP hydrolysis and joining of the 60S ribosomal subunit	9.9×10^{-111}	$< 7.035 \times 10^{-4}$
SRP-dependent cotranslational protein targeting to membrane	4.7×10^{-108}	$< 7.035 \times 10^{-4}$
Eukaryotic Translation Initiation	4.8×10^{-106}	$< 7.035 \times 10^{-4}$
Cap-dependent Translation Initiation	4.8×10^{-106}	$< 7.035 \times 10^{-4}$
Influenza Viral RNA Transcription and Replication	8.1×10^{-103}	$< 7.035 \times 10^{-4}$
Influenza Infection	2.4×10^{-102}	$< 7.035 \times 10^{-4}$
Translation	6.0×10^{-101}	$< 7.035 \times 10^{-4}$
Influenza Life Cycle	2.2×10^{-100}	$< 7.035 \times 10^{-4}$
Disease	2.1×10^{-90}	0.013347
GPCR downstream signalling	1.6×10^{-80}	0.095478
Hemostasis	2.1×10^{-78}	0.2671
Signalling by GPCR	1.2×10^{-73}	0.44939
<i>Extracellular matrix organization</i>	2.2×10^{-67}	0.054008
Metabolism of proteins	1.4×10^{-66}	0.9607
Signal Transduction	2.1×10^{-66}	0.48184
Developmental Biology	2.5×10^{-66}	0.54075
Innate Immune System	5.3×10^{-66}	0.9589
Infectious disease	9.6×10^{-66}	0.21075
Signalling by NGF	1.1×10^{-62}	0.43356
Immune System	2.8×10^{-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	1.2×10^{-9}	0.86279
G_{as} signalling events	2.9×10^{-7}	0.023066
Retinoid metabolism and transport	2.9×10^{-7}	0.299
Acylic chain remodelling of PS	1.1×10^{-5}	0.42584
Transcriptional regulation of white adipocyte differentiation	1.1×10^{-5}	0.53928
Chemokine receptors bind chemokines	1.1×10^{-5}	0.95259
<i>Signalling by NOTCH4</i>	1.2×10^{-5}	0.079229
Defective EXT2 causes exostoses 2	1.2×10^{-5}	0.22292
Defective EXT1 causes exostoses 1, TRPS2 and CHDS	1.2×10^{-5}	0.22292
Platelet activation, signalling and aggregation	1.2×10^{-5}	0.48853
Serotonin receptors	1.4×10^{-5}	0.34596
Nicotinamide salvaging	1.4×10^{-5}	0.70881
Phase 1 - Functionalization of compounds	2×10^{-5}	0.31142
Amine ligand-binding receptors	2.5×10^{-5}	0.34934
Acylic chain remodelling of PE	3.8×10^{-5}	0.42615
Signalling by GPCR	3.8×10^{-5}	0.93888
Molecules associated with elastic fibres	3.9×10^{-5}	0.017982
DAP12 interactions	3.9×10^{-5}	0.71983
Beta defensins	3.9×10^{-5}	0.91458
Cytochrome P ₄₅₀ - arranged by substrate type	4.7×10^{-5}	0.83493
GPCR ligand binding	5.7×10^{-5}	0.95258
Acylic chain remodelling of PC	6.1×10^{-5}	0.42584
Response to elevated platelet cytosolic Ca ²⁺	6.4×10^{-5}	0.54046
Arachidonic acid metabolism	6.7×10^{-5}	0.026696
Defective B4GALT7 causes EDS, progeroid type	7.3×10^{-5}	0.24921
Defective B3GAT3 causes JDSSDHD	7.3×10^{-5}	0.24921
Hydrolysis of LPC	7.3×10^{-5}	0.80663
Elastic fibre formation	7.4×10^{-5}	0.0058768
HS-GAG degradation	9.4×10^{-5}	0.0083179
<i>Bile acid and bile salt metabolism</i>	9.4×10^{-5}	0.079905
Netrin-1 signalling	0.00011	0.92216
Integration of energy metabolism	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.

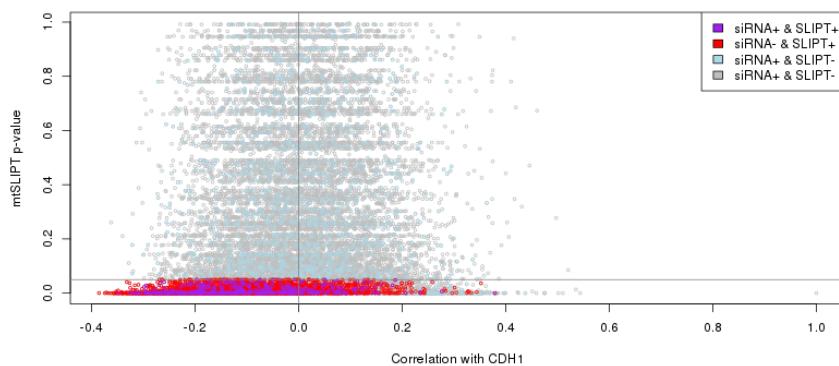


Figure C.3: Compare mtSLIPT and siRNA genes with correlation. The mtSLIPT p-values were compared against Pearson correlation of expression with *CDH1*. Genes detected by SLIPT or siRNA were coloured according to the legend.

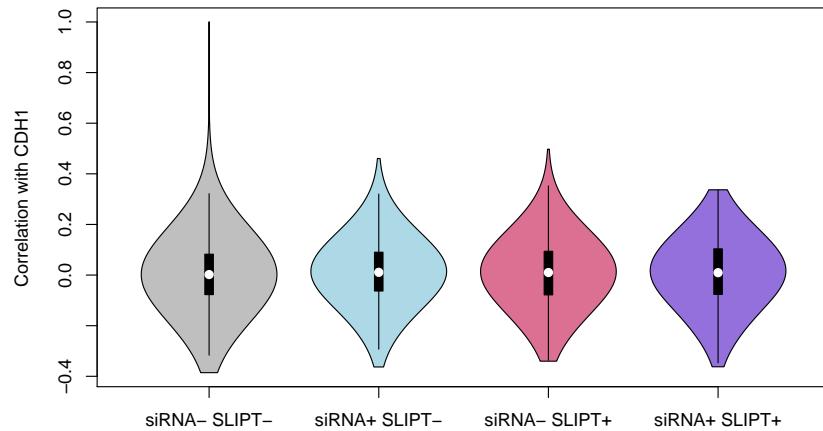


Figure C.4: Compare mtSLIPT and siRNA genes with correlation. Genes detected by mtSLIPT against *CDH1* mutation and siRNA screening were compared against Pearson correlation of expression with *CDH1*. There were no differences in correlation between the gene groups.

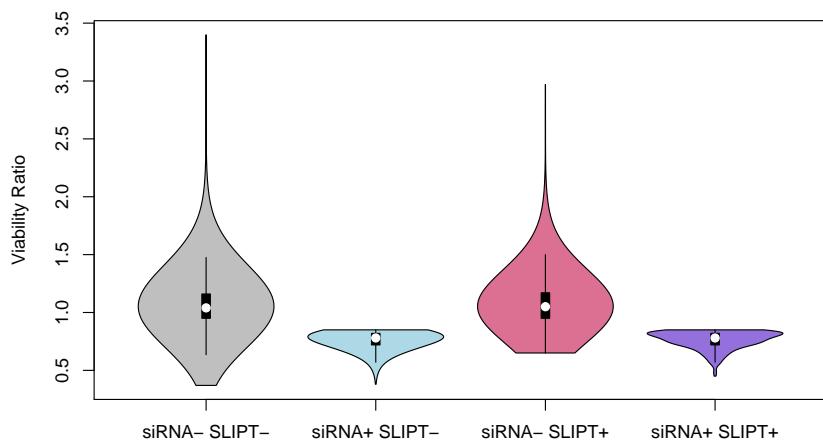


Figure C.5: Compare mtSLIPT and siRNA genes with siRNA viability. Genes detected as candidate synthetic lethal partners by mtSLIPT (in TCGA breast cancer) expression analysis against *CDH1* mutation and experimental screening (with siRNA) were compared against the viability ratio of *CDH1* mutant and 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).

Appendix D

Metagene Analysis

The gene signatures (Gatza *et al.*, 2011, 2014) were used to demonstrate the utility of the metagene approach for use on a wider range of pathways as was performed with the Reactome (Croft *et al.*, 2014) pathways as an alternative approach to identification of synthetic lethal pathways. The direction of metagenes is arbitrary but they have been corrected to ensure the metagene increases in a direction which reflects overall activation of the pathways (as described in Section 2.2.3) which was verified by examining in the following pathway signatures in breast cancer.

Metagenes were derived for well characterised gene signatures in breast cancer (Gatza *et al.*, 2011, 2014). These pathways signatures have expected molecular properties in clinical and molecular subtypes (Parker *et al.*, 2009; Perou *et al.*, 2000). This was performed by examining the pathways expression of these breast cancer gene signatures in TCGA expression data. These metagenes were also compared to somatic mutation to evaluate mutation as a measure of gene activity in comparison to gene and protein expression.

Having established that metagenes generated with this procedure reflect gene activity, the metagene procedure (in Section 2.2.3) was then applied to the Reactome pathways (Croft *et al.*, 2014). These Reactome metagenes were used for synthetic lethal analysis of pathways with SLIPT, directly using pathways activity for identifying synthetic lethal pathways with *CDH1*.

D.1 Pathway Signature Expression

Pathway metagenes (generated as described in Section 2.2.3) for gene signatures of key processes in breast cancer (Gatza *et al.*, 2011) were used to check that metagenes were generated in the correct direction to indicate pathways activation. Some of these

gene signatures are plotted in Figure D.1 for comparison with clinical factors and somatic mutations. The “intrinsic subtypes” was computed by performing the Prediction Analysis of Microarray 50 (PAM50) procedure Parker *et al.* (2009) for RNA-Seq data which was highly concordant ($\chi^2 = 1305.9$, $p = 2.73 \times 10^{-268}$) with the subtypes provided by University of California, Santa Cruz (UCSC) (UCSC, 2012) for TCGA samples (Koboldt *et al.*, 2012) previously analysed by microarrays (as shown in Appendix E). Somatic mutations were reported for gislinkrecurrent mutationrecurrently mutated genes in breast cancer, as reported by TCGA (Koboldt *et al.*, 2012), related genes, and those previously discussed to be important in hereditary breast cancers (*BRCA1*, *BRCA2*, and *CDH1*).

These gene signatures reflect intrinsic subtypes as expected. In particular, the estrogen and progesterone receptor signatures are low in the predominantly ER⁻ and Progesterone receptor (PR)⁻ basal-like subtype tumours. These tumours also had the highest frequency of *TP53* mutations and a corresponding reduction of p53 metagene activity, as expected for loss of a tumour suppressor. The luminal A and luminal B tumour subtypes are the most similar, which is reflected in these metagenes signatures, although they are distinguishable molecular subtypes as shown by elevated phosphoinositide 3-kinase (PI3K), AKT, RAS, and β -catenin signalling in luminal B tumours. However, these pathways were also elevated in basal-like and HER2-enriched subtypes and lowly expressed in the “normal-like” subtype (which contained the normal samples). These intrinsic subtypes specific gene signature profiles were further supported with metagenes for an extended set of signatures (Gatza *et al.*, 2014), as shown in Figure D.4.

TP53 mutations were the most frequent and more common in the basal-like subtype. Similarly, *GATA3* mutations were more common in luminal subtype tumours. PI3K mutations were more frequent across breast tumours, although these were less common in the basal-like subtype despite an elevated metagene (this discrepancy will be discussed further in Section D.2). *CDH1* mutations similarly occurred across molecular subtypes with the exception of the basal-like subtype (as observed in gene expression with Figure 4.1). *CDH1* low samples occurred in all subtypes but were predominantly of the lobular histological subtype. Apart from these genes, mutations did not show clear specificity to a particular subtype and the variation between samples reflects the range of molecular cascades that can result in tumours with similar molecular profiles, supporting the use of gene expression data for cancer diagnostics and identification of molecular targets.

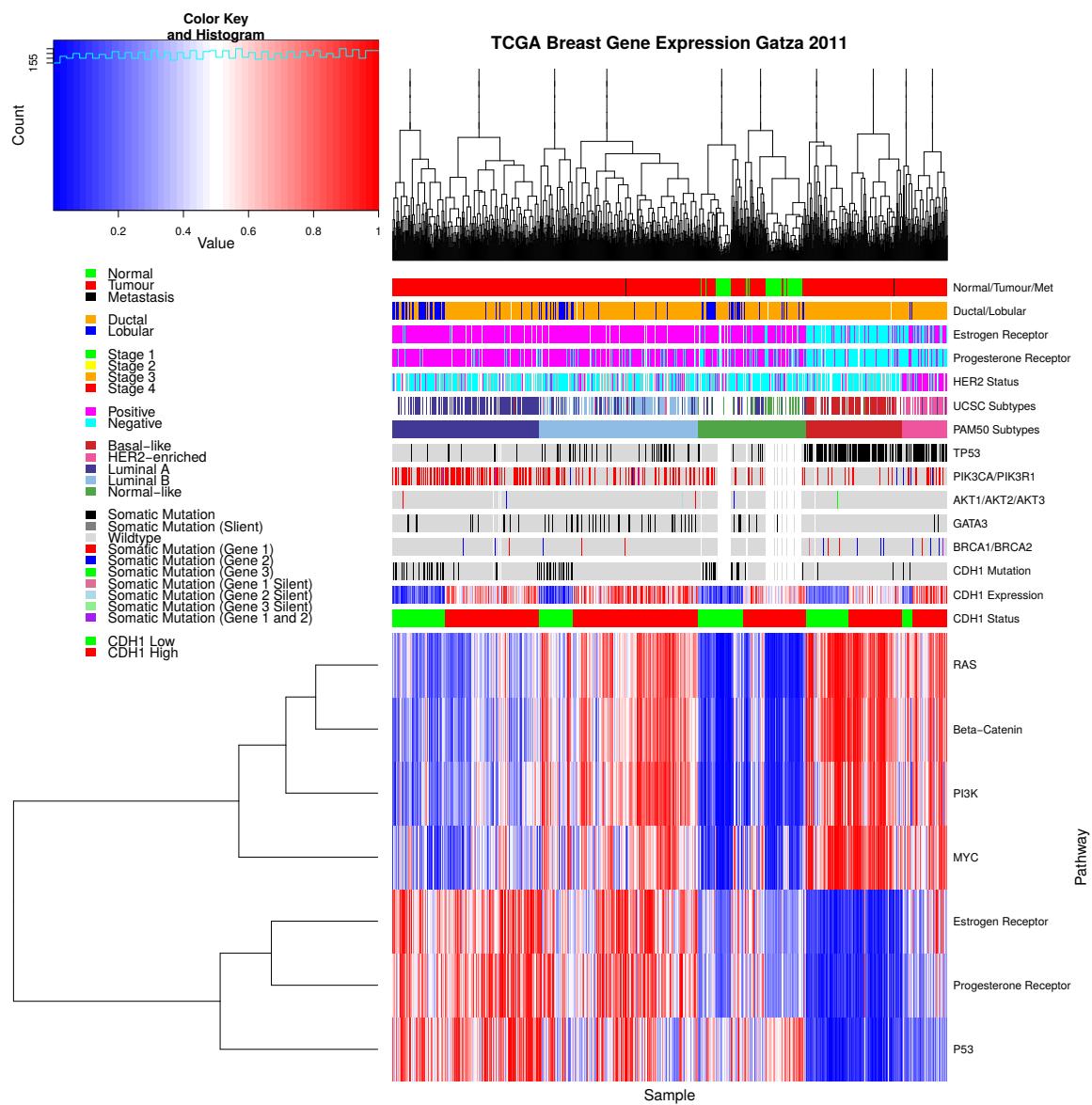


Figure D.1: Pathway metagene expression profiles. Expression profiles for metagene signatures from Gatza *et al.* (2011) in TCGA breast data, annotated for clinical factors (with sample types and histological results coloured according to the legend) and cancer gene mutations (Negative values for mutation are light grey with missing data in white). Intrinsic subtypes are shown as derived from microarray (UCSC) and RNA-Seq (PAM50) data (Koboldt *et al.*, 2012; Parker *et al.*, 2009). Samples were clustered independently for each intrinsic subtypes and by *CDH1* expression status. Pathway expression signatures are consistent with mutations and clinical subgroups.

The direction of each metagene was consistent with the clinical characteristics, which formed a consensus of gene activity as shown for the PI3K and ER signatures (Gatza *et al.*, 2011) in Figures D.2 and D.3, respectively. Supporting data for p53 and BRCA metagenes (Gatza *et al.*, 2011, 2014) are given in the Appendix (Figures D.5 and D.6). In each of the examples for gene signatures, the expression of the majority of the genes were highly concordant with the metagene, being either positively or negatively correlated. These were generally consistent with established clinical and molecular subtypes of breast cancer and the recurrent mutations shown. However, the *PIK3CA* and *PIK3R1* mutant samples did not necessarily have elevated PI3K pathways metagene activity (as shown in Figure D.2).

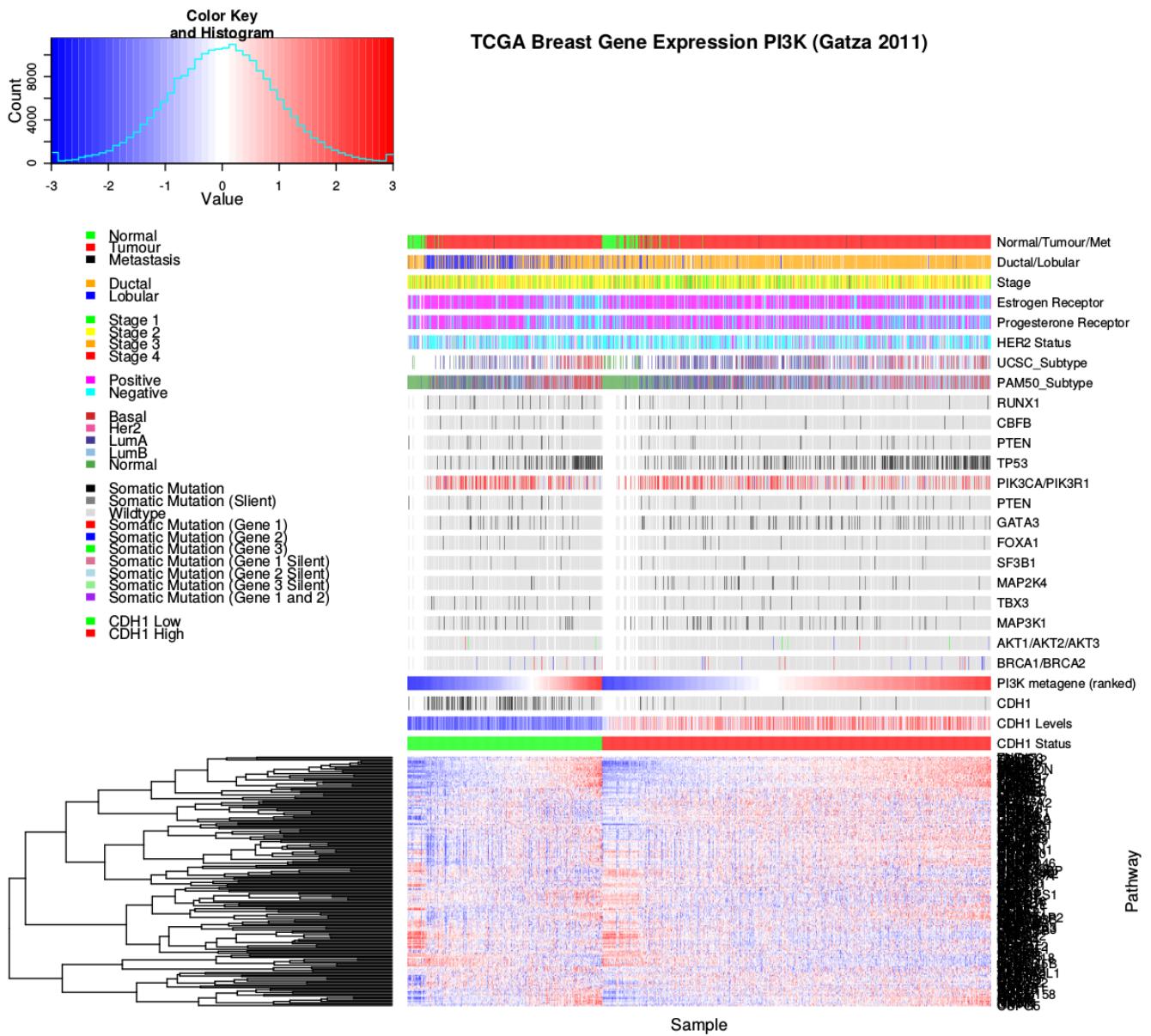


Figure D.2: **Expression profiles for constituent genes of PI3K.** Expression profiles the genes contained in the PI3K gene signature from Gatza *et al.* (2011) in TCGA breast data, annotated for clinical factors and cancer gene mutations. Samples are separated by *CDH1* expression status and sorted by the metagene. In both cases, the majority of genes were consistent with the direction of the PI3K metagene, although considerable proportion were inversely correlated with the metagene. Normal samples had low PI3K metagene expression and *TP53* mutant samples had high PI3K expression. Although, oncogenic *PIK3CA* and tumour suppressor *PIK3R1* mutations across samples including those with low metagene response.

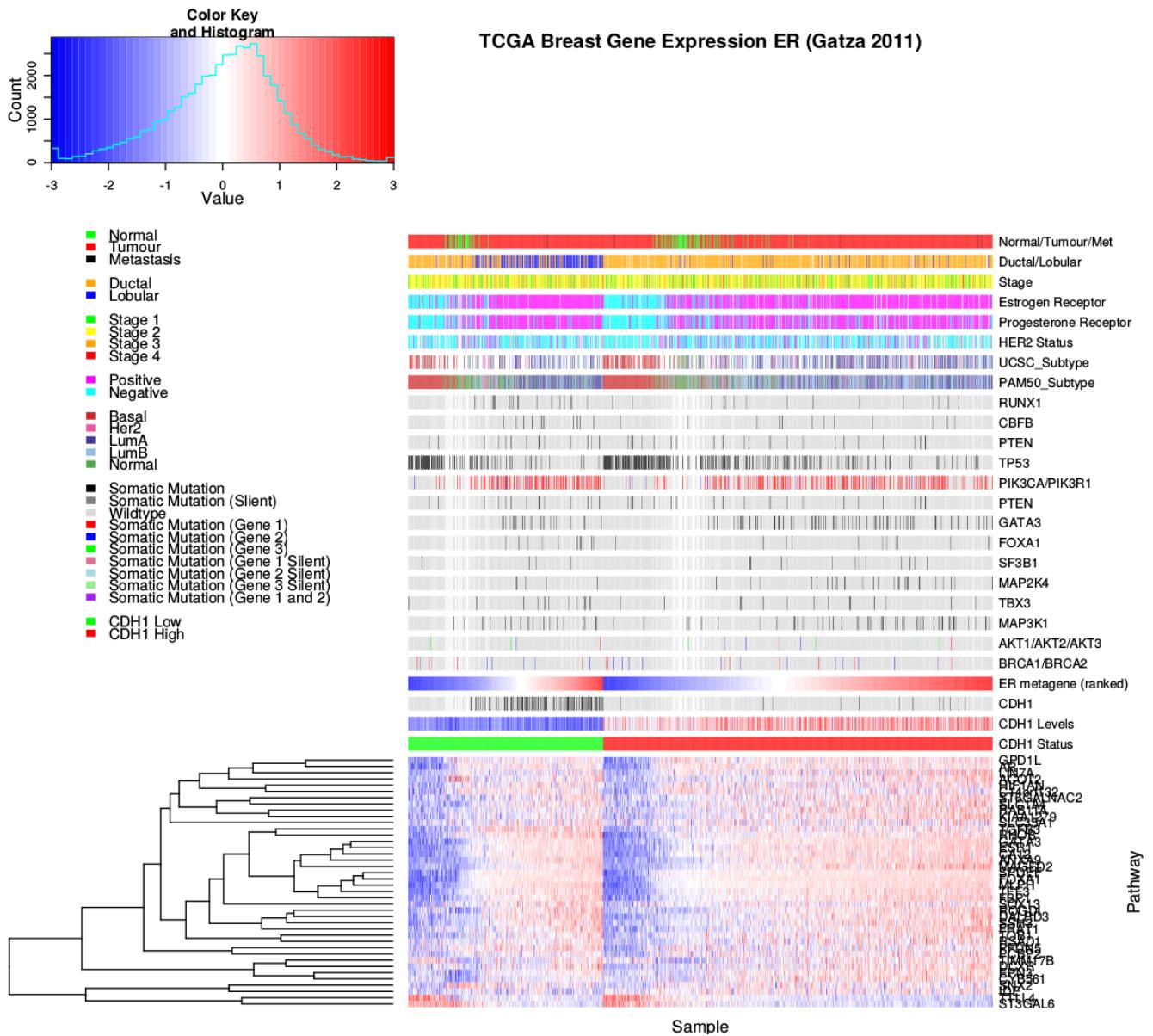


Figure D.3: **Expression profiles for estrogen receptor related genes.** Expression profiles the genes contained in the estrogen receptor (ER) gene signature from Gatza *et al.* (2011) in TCGA breast data, annotated for clinical factors and cancer gene mutations. Samples are separated by *CDH1* expression status and sorted by the metagene. In both cases, the majority of genes were consistent with the direction of the metagene, with very few exceptions being inversely correlated. Estrogen receptor (by antibody staining) negative samples had low metagene expression, as expected. These were more likely to be ductal and basal subtypes, lacking *CDH1* or *PIK3CA* mutations.

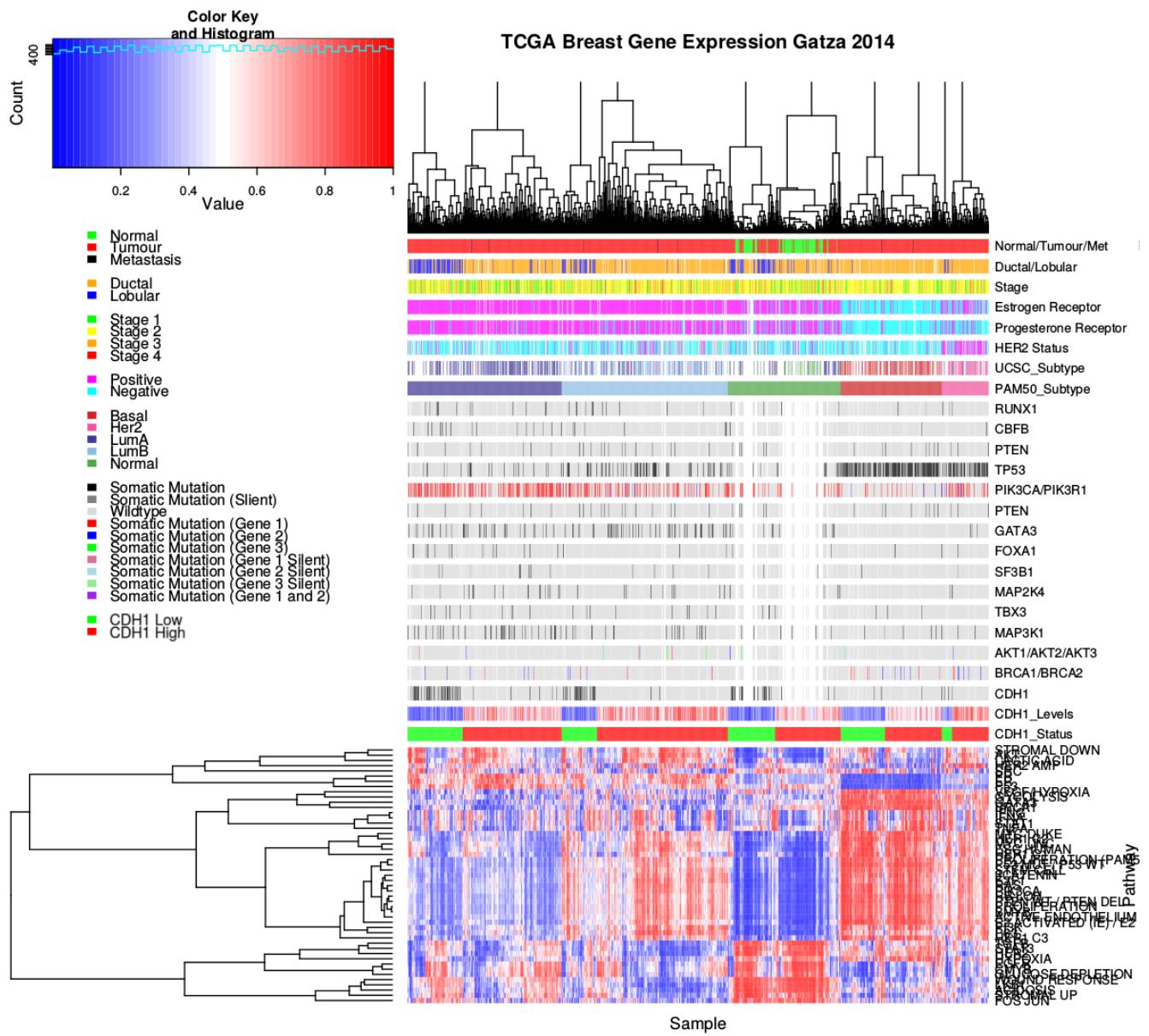


Figure D.4: **Pathway metagene expression profiles.** Expression profiles for metagene signatures from Gatza *et al.* (2014) in TCGA breast data, annotated for clinical factors and cancer gene mutations.

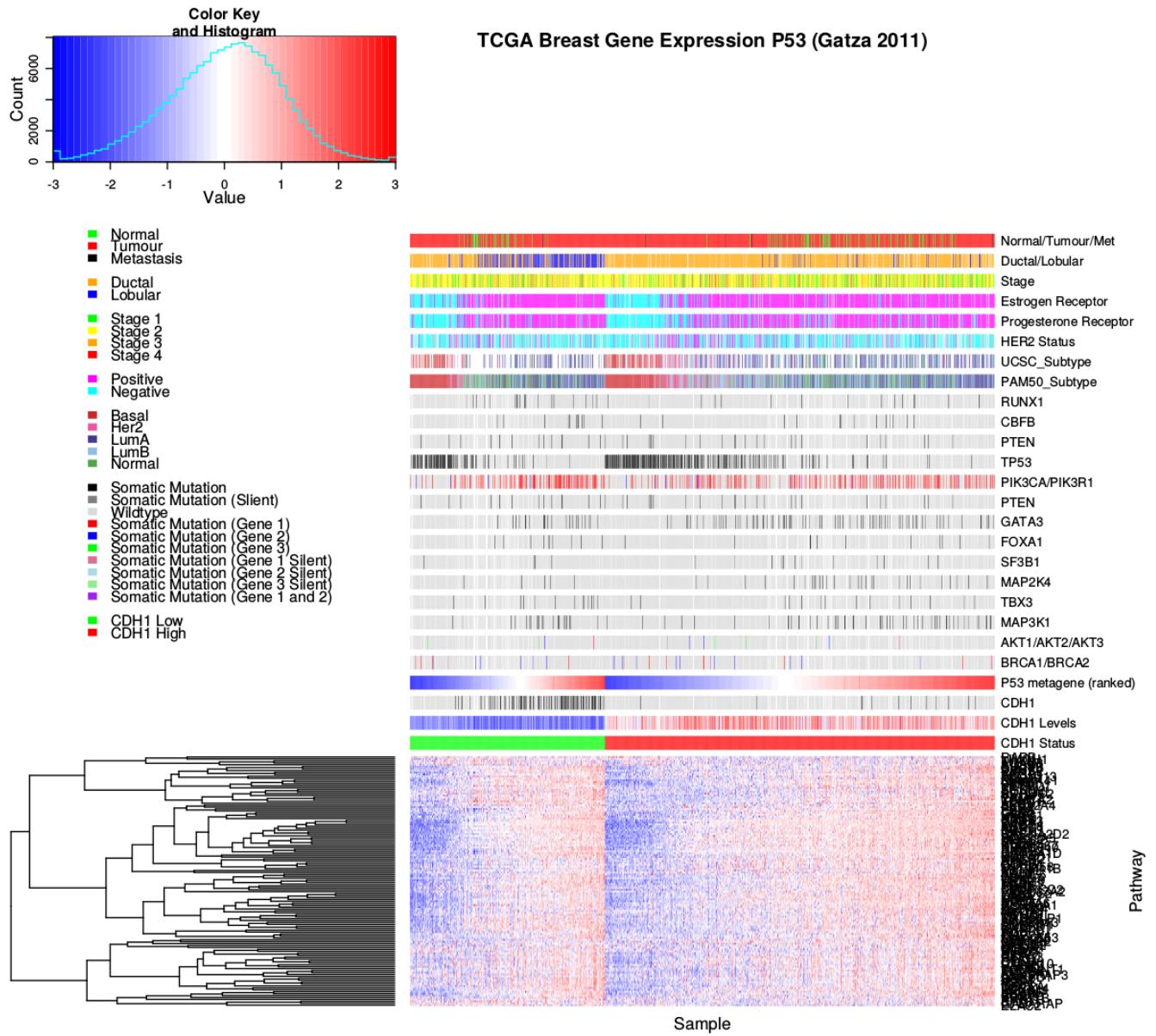


Figure D.5: Expression profiles for p53 related genes. Expression profiles the genes contained in the *TP53* gene signature from Gatza *et al.* (2011) in TCGA breast data, annotated for clinical factors and cancer gene mutations. Samples were separated by *CDH1* expression status and sorted by the metagene. 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.

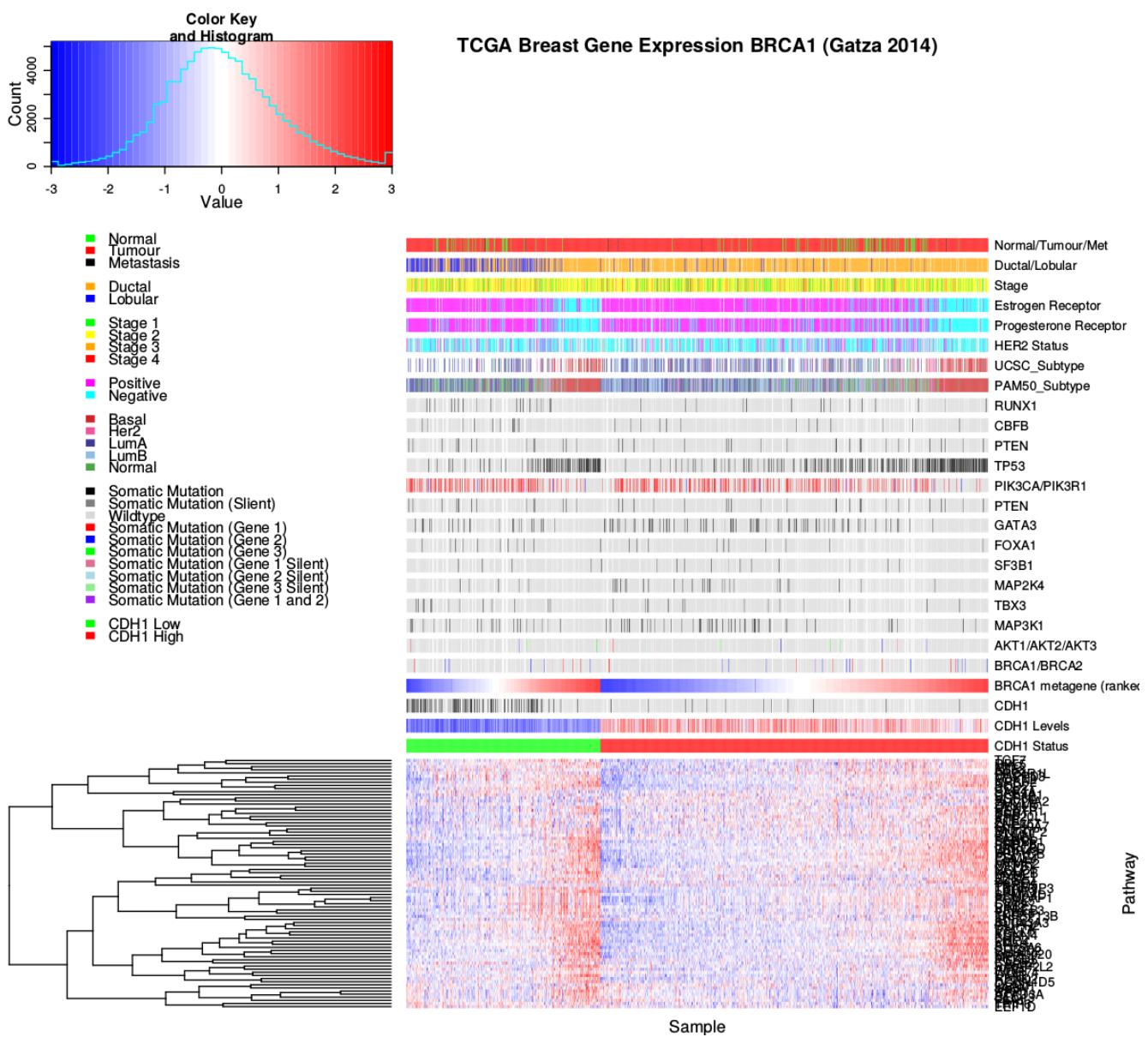


Figure D.6: **Expression profiles for BRCA related genes.** Expression profiles the genes contained in the gene signature related to *BRCA1* and *BRCA2* functions from Gatza *et al.* (2014) in TCGA breast data, annotated for clinical factors and cancer gene mutations. Samples were separated by *CDH1* 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.

D.2 Somatic Mutation

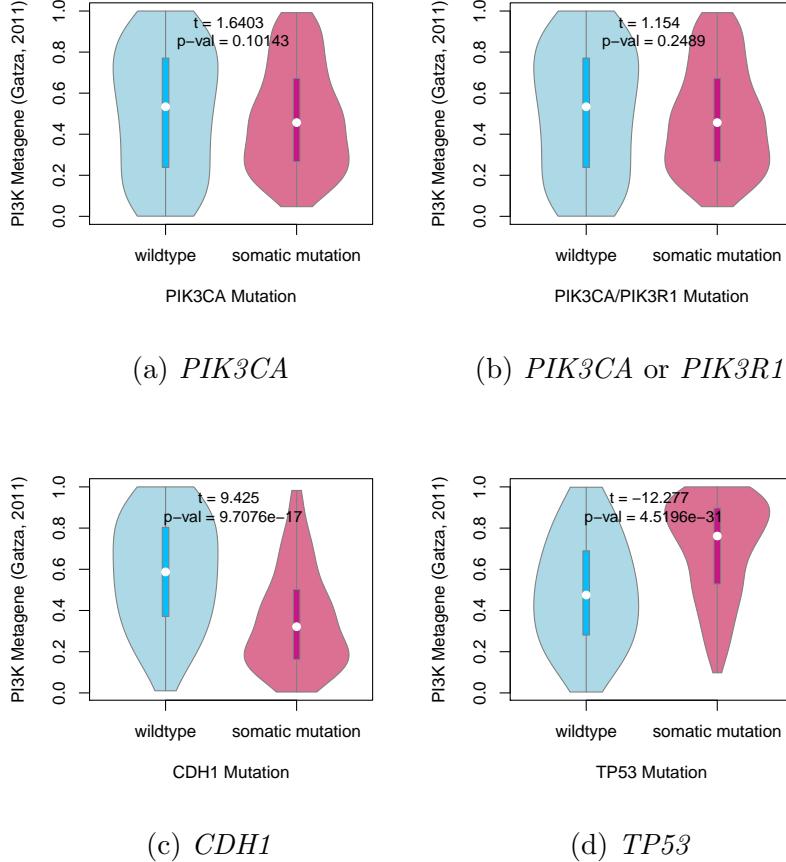


Figure D.7: Somatic mutation against the PI3K metagene. Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their association with the PI3K (Gatza *et al.*, 2011) pathways metagene. The tumour suppressors *CDH1* and *TP53* showed an increase and decrease in the metagene respectively, whereas *PIK3CA* and *PIK3R1* mutations had little effect on the metagene levels.

It should be noted that metagenes, while consistent with the consensus of constituent expressed genes, were not necessarily reflecting the somatic mutation status. The PI3K (Gatza *et al.*, 2011) metagene levels in particular, were not statistically significantly varying between mutant and wild-type *PIK3CA* samples (shown in Figure D.7). However, the PI3K metagene differed across *CDH1* and *TP53* mutations, remarkably in opposite directions considering that PI3K is an oncogenic growth pathways and these are both most frequently tumour suppressors inactivated in cancers. This shows that

CDH1 and *TP53* deficient tumours have distinct molecular growth pathways and that synthetic lethal interventions against loss of *CDH1* function may not be applicable to other cancers with driver mutations such as *TP53*, although these were kept in the analysis for comparison. These differences may be related to these mutations being more frequent in tumours with difference clinical characteristics (as observed in Section D.1). Thus mutations do not necessarily have corresponding changes in pathways expression, particularly for oncogenes which may change in function rather than being upregulated.

While the more specific *PIK3CA* (Gatza *et al.*, 2014) metagene showed significant differences with *PIK3CA* and *PIK3R1* mutations (as shown in Figure D.8), this metagene replicated stronger differences for *CDH1* and *TP53*. These differences were less pronounced in the protein levels of p110 α (enocded by *PIK3CA*) and the downstream AKT gene (shown in Figures D.9 and D.10 respectively). However, this may be due to this regulatory cascade (kinases) being transmitted as a change in protein state (phosphorylation) rather than changes in expression levels. Another consideration is that mutations at different loci have different effects on protein function, particularly for oncogenes.

D.3 Synthetic Lethal Reactome Metagenes

Metagene analysis was performed for synthetic lethal pathways against *CDH1* mutation. These were described and compared to expression analysis in Section 4.3.

Table D.1: Candidate synthetic lethal metagenes against *CDH1* from mtSLIPT

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

D.4 Expression of Somatic Mutations

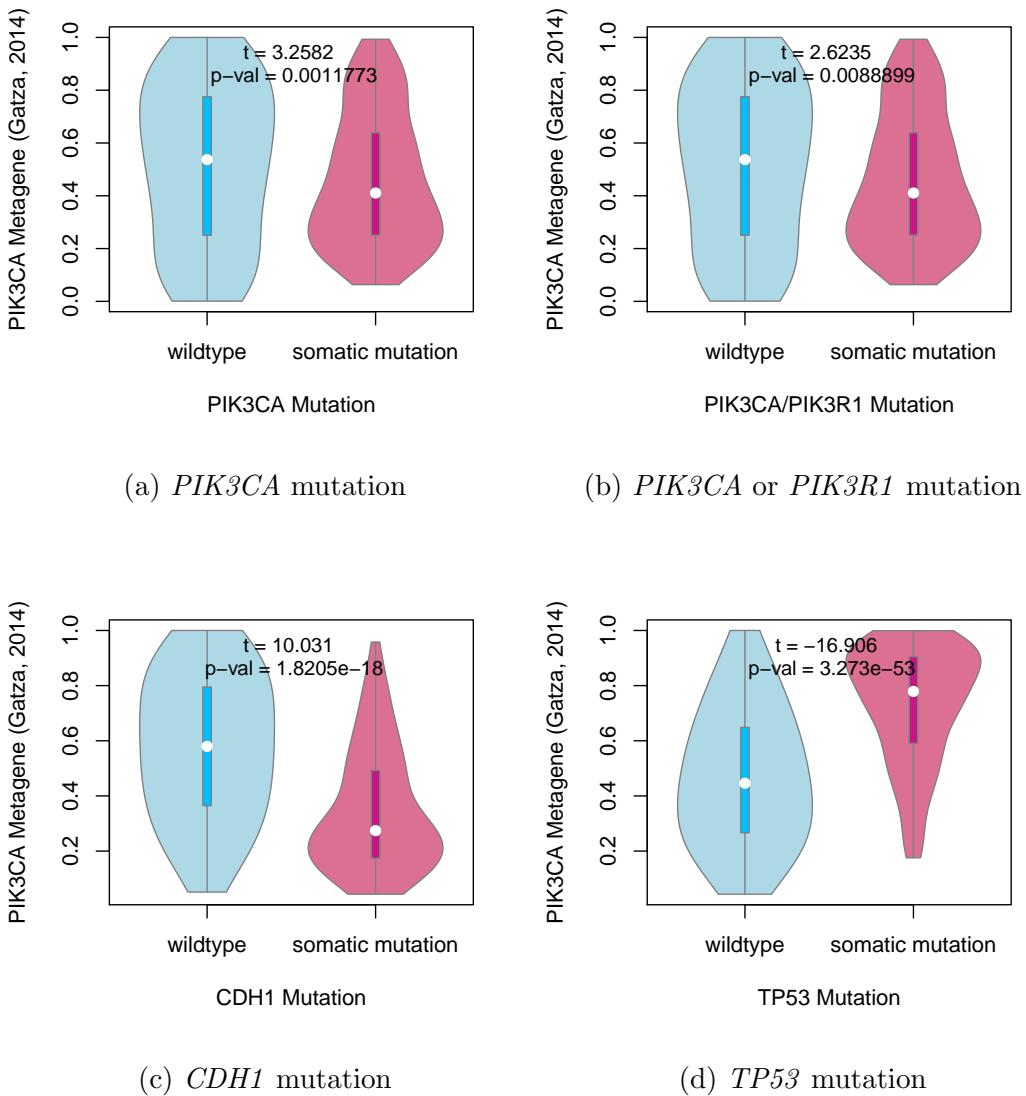


Figure D.8: **Somatic mutation against PIK3CA metagene.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the PIK3CA (Gatza *et al.*, 2014) pathway metagene. The tumour suppressors *CDH1* and *TP53* showed an increase and decrease in the metagene respectively, whereas *PIK3CA* and *PIK3R1* mutations weaker evidence of decrease in metagene levels.

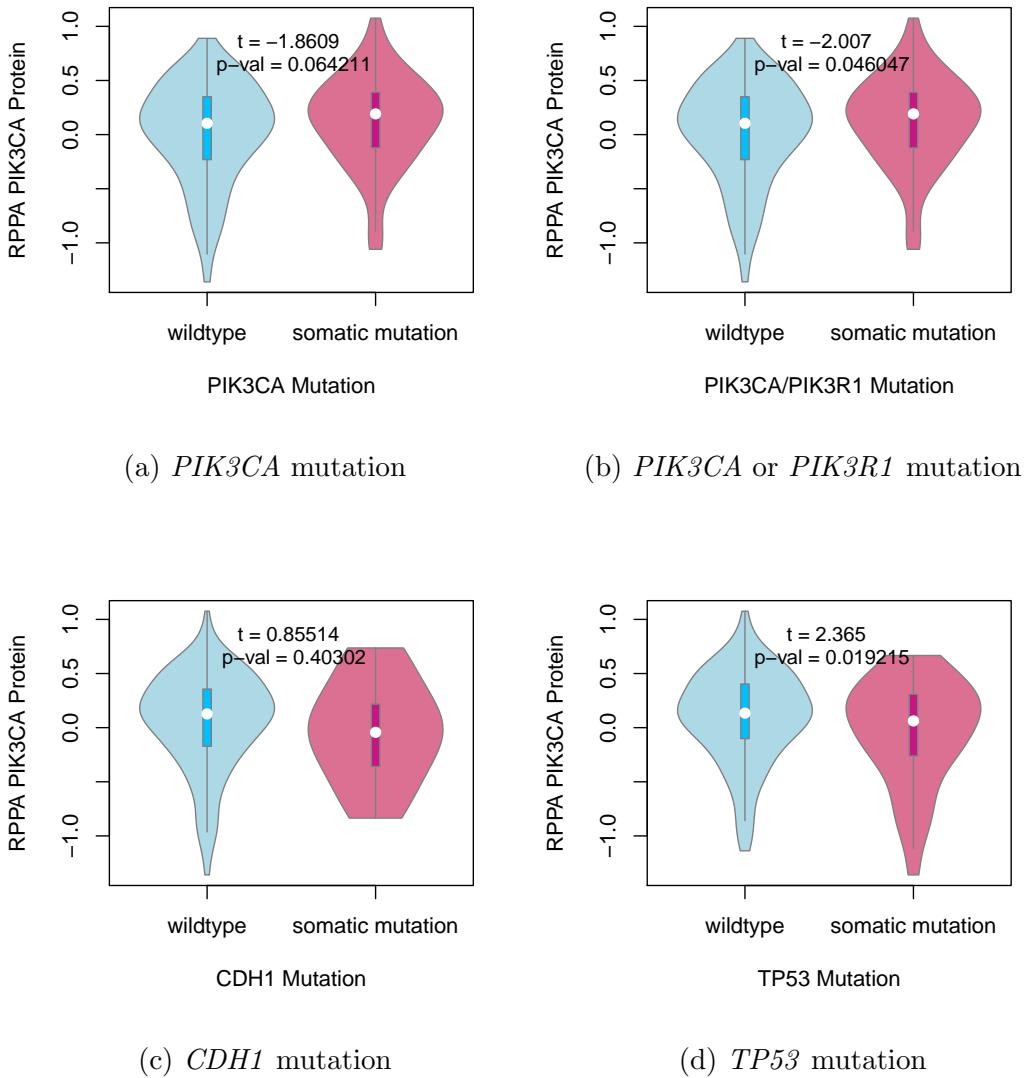


Figure D.9: Somatic mutation against PI3K protein. Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the expression of the p110 α protein (encoded by *PIK3CA*). Protein levels were significantly elevated in samples with *PIK3CA* or *PIK3R1* mutations and lower in samples with *TP53* mutations.

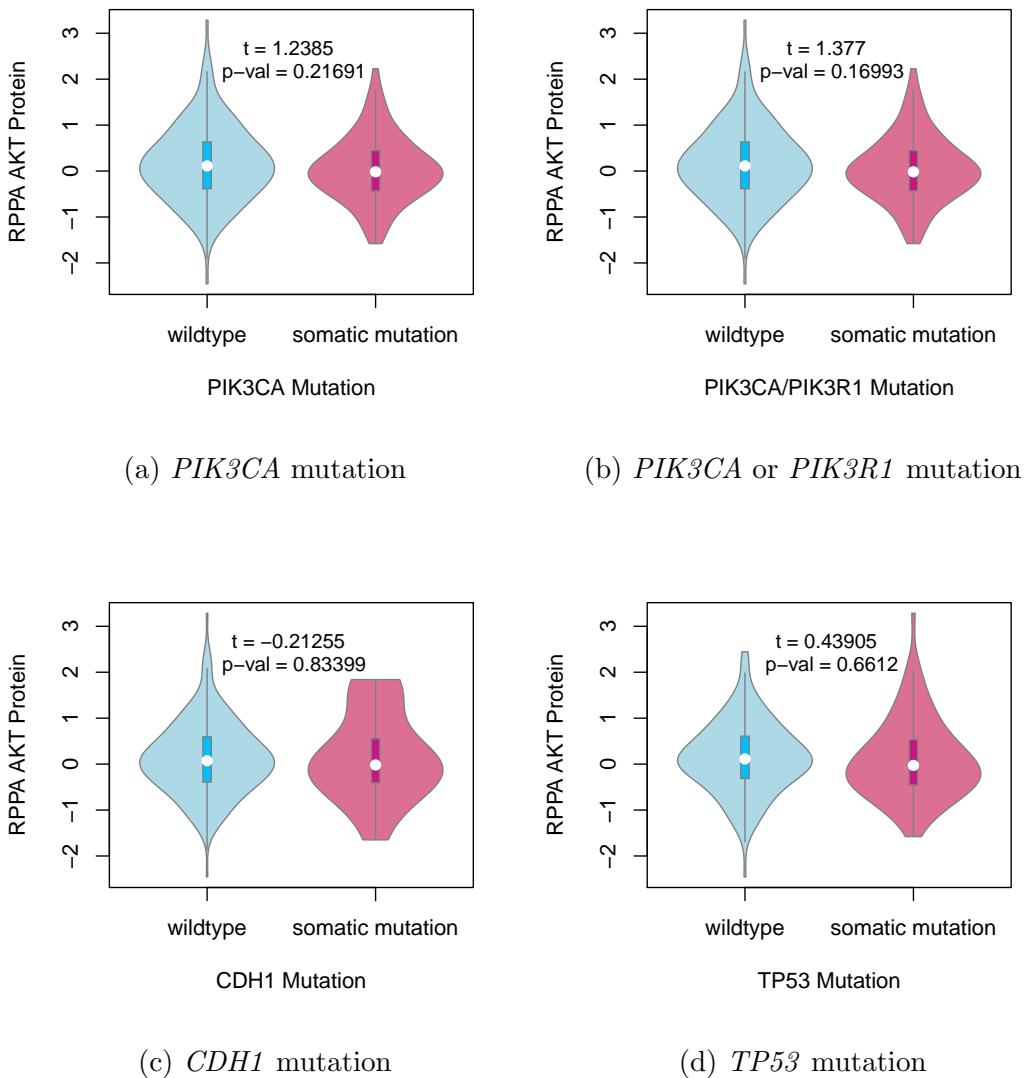


Figure D.10: **Somatic mutation against AKT protein.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the expression of the AKT protein (a downstream target of *PIK3CA*). Protein levels were not significantly different in samples with mutations in any of these cancer genes.

Appendix E

Intrinsic Subtyping

The intrinsic subtypes for TCGA breast cancer samples provided by UCSC (Koboldt *et al.*, 2012; UCSC, 2012) that were derived from microarray analysis have been compared to the PAM50 results for performing subtyping from RNA-Seq data (Parker *et al.*, 2009). As shown in Table E.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 E.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 F

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*.

F.1 Synthetic Lethal Genes and Pathways

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

Gene	Observed*	Expected*	χ^2 value	p-value	p-value (FDR)
<i>PRAF2</i>	17	50.4	121	3.54×10^{-25}	1.45×10^{-21}
<i>EMP3</i>	17	50.4	115	5.06×10^{-24}	1.48×10^{-20}
<i>PLEKHO1</i>	22	50.4	112	2.14×10^{-23}	4.75×10^{-20}
<i>SELM</i>	20	50.4	111	5.13×10^{-23}	8.09×10^{-20}
<i>GYPC</i>	20	50.4	110	5.77×10^{-23}	8.45×10^{-20}
<i>COX7A1</i>	18	50.4	109	1.15×10^{-22}	1.39×10^{-19}
<i>TNFSF12</i>	20	50.4	106	4.06×10^{-22}	4.38×10^{-19}
<i>SEPT4</i>	17	50.4	106	6.58×10^{-22}	5.91×10^{-19}
<i>LGALS1</i>	19	50.4	105	6.64×10^{-22}	5.91×10^{-19}
<i>RARRES2</i>	27	50.4	105	8.02×10^{-22}	6.85×10^{-19}
<i>VEGFB</i>	16	50.4	104	1.19×10^{-21}	9.74×10^{-19}
<i>PRR24</i>	22	50.4	102	2.96×10^{-21}	2.02×10^{-18}
<i>SYNC</i>	19	50.4	102	3.73×10^{-21}	2.39×10^{-18}
<i>MAGEH1</i>	17	50.4	100	9.52×10^{-21}	5.01×10^{-18}
<i>HSPB2</i>	23	50.4	99.6	1.19×10^{-20}	5.82×10^{-18}
<i>SMARCD3</i>	19	50.4	99	1.59×10^{-20}	7.57×10^{-18}
<i>CREM</i>	13	50.4	98.1	2.48×10^{-20}	1.13×10^{-17}
<i>GNG11</i>	20	50.4	97.3	3.68×10^{-20}	1.59×10^{-17}
<i>GNAI2</i>	17	50.4	96.4	5.75×10^{-20}	2.36×10^{-17}
<i>FUNDC2</i>	22	50.4	95.9	7.39×10^{-20}	2.91×10^{-17}
<i>CNRIP1</i>	21	50.4	95.3	1.0×10^{-19}	3.66×10^{-17}
<i>CALHM2</i>	22	50.4	93.1	2.94×10^{-19}	1.06×10^{-16}
<i>ARID5A</i>	18	50.4	92.7	3.47×10^{-19}	1.22×10^{-16}
<i>ST3GAL3</i>	27	50.4	92.2	4.49×10^{-19}	1.56×10^{-16}
<i>LOC339524</i>	21	50.4	92.1	4.8×10^{-19}	1.59×10^{-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 F.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	7.5×10^{-140}
Hemostasis	445	138	1.8×10^{-121}
Developmental Biology	432	125	9.2×10^{-107}
Axon guidance	289	94	1.5×10^{-102}
Eukaryotic Translation Termination	84	49	1.9×10^{-99}
GPCR ligand binding	373	108	3.8×10^{-99}
Viral mRNA Translation	82	48	3.3×10^{-98}
Formation of a pool of free 40S subunits	94	51	3.3×10^{-98}
Eukaryotic Translation Elongation	87	49	1.6×10^{-97}
Peptide chain elongation	84	48	7.2×10^{-97}
Class A/1 (Rhodopsin-like receptors)	289	90	2.7×10^{-96}
Nonsense Mediated Decay independent of the Exon Junction Complex	89	49	3.0×10^{-96}
Infectious disease	349	100	2.6×10^{-94}
GTP hydrolysis and joining of the 60S ribosomal subunit	105	52	3.4×10^{-94}
L13a-mediated translational silencing of Ceruloplasmin expression	104	51	2.8×10^{-92}
3' -UTR-mediated translational regulation	104	51	2.8×10^{-92}
Neuronal System	272	84	8.4×10^{-92}
SRP-dependent cotranslational protein targeting to membrane	105	51	9.5×10^{-92}
Eukaryotic Translation Initiation	112	52	2.0×10^{-90}
Cap-dependent Translation Initiation	112	52	2.0×10^{-90}

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

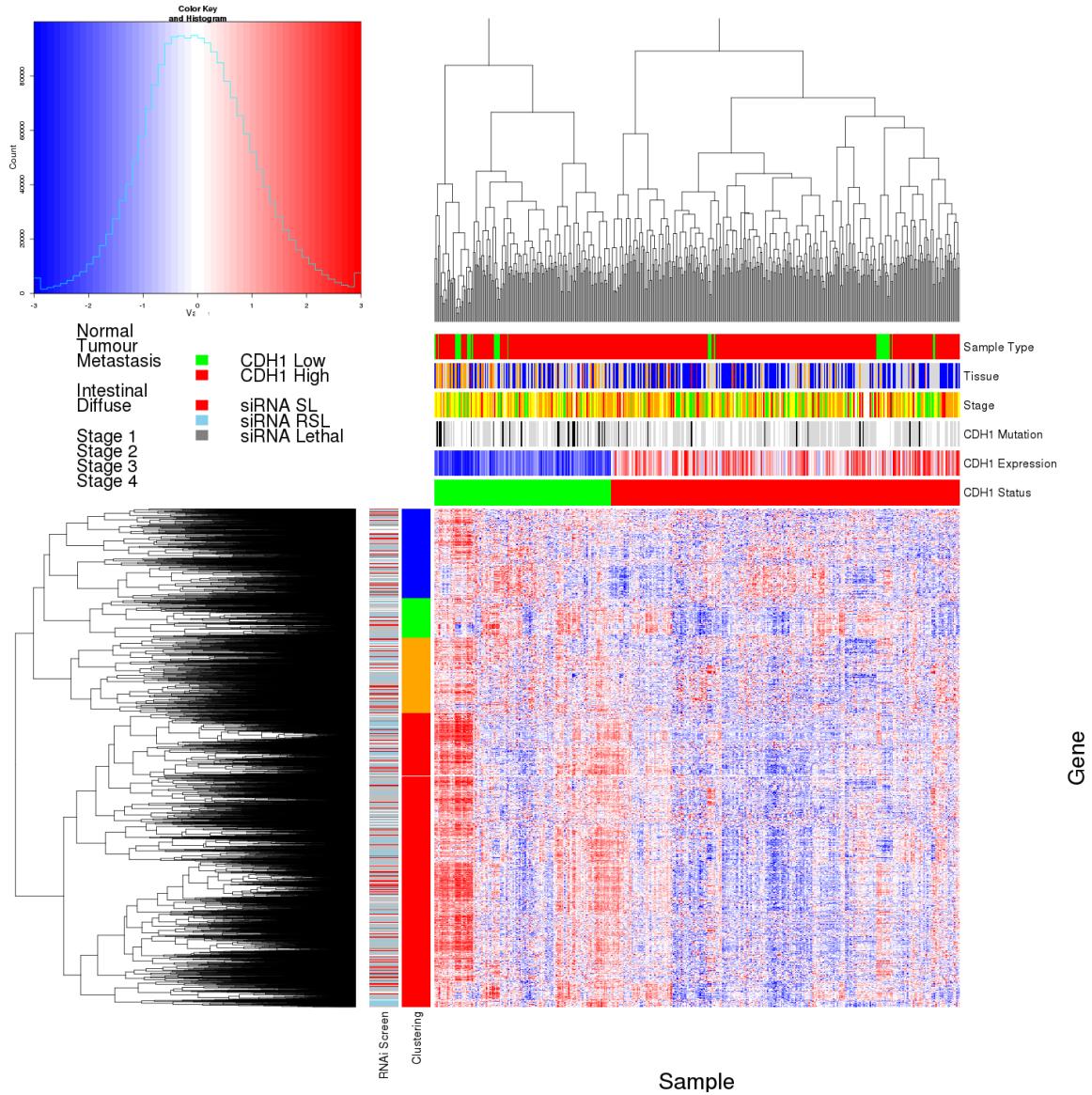


Figure F.1: Synthetic lethal expression profiles of analysed samples. Gene expression profile heatmap (correlation distance) of all samples (separated by the $1/3$ quantile of $CDH1$ expression) analysed in TCGA stomach cancer dataset for gene expression of 4365 candidate partners of E-cadherin ($CDH1$) 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 F.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	1.3×10^{-97}
Formation of a pool of free 40S subunits	94	51	1.3×10^{-97}
Eukaryotic Translation Elongation	87	49	4.8×10^{-97}
Peptide chain elongation	84	48	1.4×10^{-96}
Eukaryotic Translation Termination	84	48	1.4×10^{-96}
GTP hydrolysis and joining of the 60S ribosomal subunit	105	52	7.9×10^{-94}
Nonsense Mediated Decay independent of the Exon Junction Complex	89	48	3.1×10^{-93}
L13a-mediated translational silencing of Ceruloplasmin expression	104	51	5.1×10^{-92}
3' -UTR-mediated translational regulation	104	51	5.1×10^{-92}
SRP-dependent cotranslational protein targeting to membrane	105	51	1.7×10^{-91}
Eukaryotic Translation Initiation	112	52	3.3×10^{-90}
Cap-dependent Translation Initiation	112	52	3.3×10^{-90}
Translation	142	56	3.6×10^{-85}
Nonsense-Mediated Decay	104	48	1.2×10^{-84}
Nonsense Mediated Decay enhanced by the Exon Junction Complex	104	48	1.2×10^{-84}
Influenza Viral RNA Transcription and Replication	109	48	4.1×10^{-82}
Influenza Life Cycle	113	48	3.4×10^{-80}
Influenza Infection	118	48	6.4×10^{-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	1.3×10^{-15}
Phosphorylation of CD3 and TCR zeta chains	18	6	1.7×10^{-12}
Generation of second messenger molecules	29	7	2.7×10^{-12}
PD-1 signalling	21	6	7.4×10^{-12}
TCR signalling	62	9	4.3×10^{-11}
Translocation of ZAP-70 to Immunological synapse	16	5	1.1×10^{-10}
Interferon alpha/beta signalling	68	9	1.6×10^{-10}
Initial triggering of complement	17	5	1.6×10^{-10}
IKK complex recruitment mediated by RIP1	19	5	5.1×10^{-10}
TRIF-mediated programmed cell death	10	4	6.2×10^{-10}
Creation of C4 and C2 activators	11	4	1.3×10^{-9}
RHO GTPases Activate NADPH Oxidases	11	4	1.3×10^{-9}
Interferon Signalling	175	15	2.3×10^{-9}
Chemokine receptors bind chemokines	52	7	4.0×10^{-9}
Interferon gamma signalling	74	8	1.6×10^{-8}
TRAF6 mediated induction of TAK1 complex	15	4	1.6×10^{-8}
Activation of IRF3/IRF7 mediated by TBK1/IKK epsilon	16	4	2.7×10^{-8}
Downstream TCR signalling	45	6	3.5×10^{-8}
Pathways Over-represented in Cluster 3	Pathway Size	Cluster Genes	p-value (FDR)
Uptake and actions of bacterial toxins	22	4	3.5×10^{-6}
Neurotoxicity of clostridium toxins	10	3	3.5×10^{-6}
Activation of PPARGC1A (PGC-1alpha) by phosphorylation	10	3	3.5×10^{-6}
SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	28	4	1.4×10^{-5}
Assembly of the primary cilium	149	10	2.5×10^{-5}
Serotonin Neurotransmitter Release Cycle	15	3	2.5×10^{-5}
Glycosaminoglycan metabolism	114	8	3.3×10^{-5}
Platelet homeostasis	54	5	3.3×10^{-5}
Norepinephrine Neurotransmitter Release Cycle	17	3	3.3×10^{-5}
Acetylcholine Neurotransmitter Release Cycle	17	3	3.3×10^{-5}
G _{αs} signalling events	100	7	5.5×10^{-5}
GABA synthesis, release, reuptake and degradation	19	3	5.6×10^{-5}
deactivation of the beta-catenin transactivating complex	39	4	6.7×10^{-5}
Dopamine Neurotransmitter Release Cycle	20	3	6.7×10^{-5}
IRS-related events triggered by IGF1R	83	6	7.1×10^{-5}
Generic Transcription Pathway	186	11	7.1×10^{-5}
Termination of O-glycan biosynthesis	21	3	7.4×10^{-5}
Kinesins	22	3	8.5×10^{-5}
Pathways Over-represented in Cluster 4	Pathway Size	Cluster Genes	p-value (FDR)
Extracellular matrix organization	241	97	8.8×10^{-126}
Axon guidance	289	75	8.3×10^{-72}
Hemostasis	445	101	8.3×10^{-72}
Developmental Biology	432	95	3.0×10^{-67}
Response to elevated platelet cytosolic Ca ²⁺	84	37	5.8×10^{-67}
Platelet degranulation	79	36	5.8×10^{-67}
Degradation of the extracellular matrix	104	39	6.7×10^{-63}
Platelet activation, signalling and aggregation	186	52	6.6×10^{-62}
ECM proteoglycans	66	31	8.1×10^{-61}
Neuronal System	272	64	5.1×10^{-60}
Signalling by PDGF	173	47	9.7×10^{-57}
Integrin cell surface interactions	82	31	1.9×10^{-53}
Collagen biosynthesis and modifying enzymes	56	26	1.1×10^{-52}
Collagen formation	67	28	1.4×10^{-52}
Class A/1 (Rhodopsin-like receptors)	289	61	2.3×10^{-52}
GPCR ligand binding	373	73	2.8×10^{-52}
Elastic fibre formation	38	22	4.7×10^{-52}
Non-integrin membrane-ECM interactions	53	24	7.0×10^{-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.

F.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 F.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.

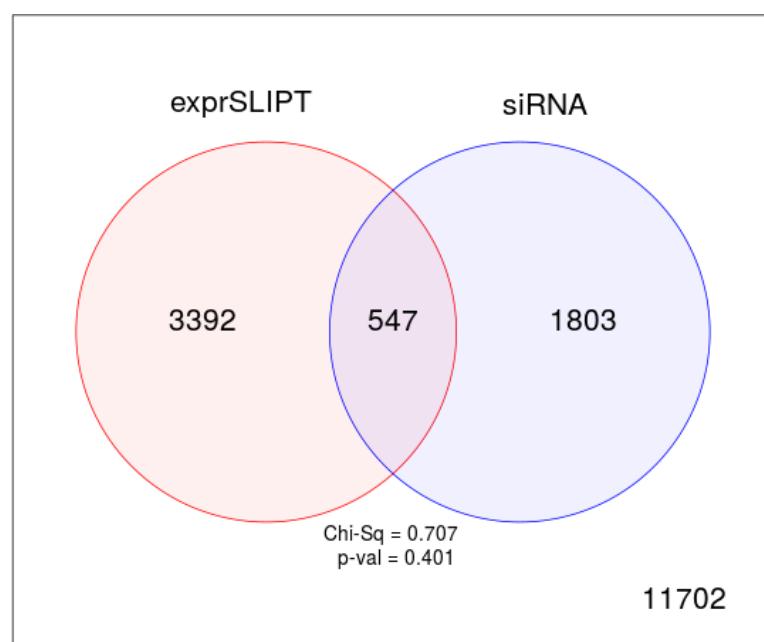


Figure F.2: **Comparison of SLIPT in stomach to siRNA.** The overlap of gene candidates for E-cadherin synthetic lethal partners between computational (SLIPT) and experimental screening (siRNA) approaches. The χ^2 test suggests that the overlap is no more than would be expected by chance ($p = 0.281$).

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

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

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

F.2.1 Resampling Analysis

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

Reactome Pathway	Over-representation	Permutation
<i>Extracellular matrix organization</i>	7.5×10^{-140}	0.070215
Hemostasis	1.8×10^{-121}	0.25804
Developmental Biology	9.2×10^{-107}	0.53032
Axon guidance	1.5×10^{-102}	0.6704
Eukaryotic Translation Termination	1.9×10^{-99}	$> 1.031 \times 10^{-5}$
GPCR ligand binding	3.8×10^{-99}	0.54914
Viral mRNA Translation	3.3×10^{-98}	$> 1.031 \times 10^{-5}$
Formation of a pool of free 40S subunits	3.3×10^{-98}	$> 1.031 \times 10^{-5}$
Eukaryotic Translation Elongation	1.6×10^{-97}	$> 1.031 \times 10^{-5}$
Peptide chain elongation	7.2×10^{-97}	$> 1.031 \times 10^{-5}$
Class A/1 (Rhodopsin-like receptors)	2.7×10^{-96}	0.58174
Nonsense Mediated Decay independent of the Exon Junction Complex	3×10^{-96}	$> 1.031 \times 10^{-5}$
Infectious disease	2.6×10^{-94}	0.25484
GTP hydrolysis and joining of the 60S ribosomal subunit	3.4×10^{-94}	$> 1.031 \times 10^{-5}$
L13a-mediated translational silencing of Ceruloplasmin expression	2.8×10^{-92}	$> 1.031 \times 10^{-5}$
3' -UTR-mediated translational regulation	2.8×10^{-92}	$> 1.031 \times 10^{-5}$
Neuronal System	8.4×10^{-92}	0.53433
SRP-dependent cotranslational protein targeting to membrane	9.5×10^{-92}	$> 1.031 \times 10^{-5}$
Eukaryotic Translation Initiation	2.0×10^{-90}	$> 1.031 \times 10^{-5}$
Cap-dependent Translation Initiation	2.0×10^{-90}	$> 1.031 \times 10^{-5}$
Nonsense-Mediated Decay	7.4×10^{-90}	$> 1.031 \times 10^{-5}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex	7.4×10^{-90}	$> 1.031 \times 10^{-5}$
Adaptive Immune System	8.1×10^{-88}	0.14116
Translation	1.3×10^{-87}	$> 1.031 \times 10^{-5}$
Platelet activation, signalling and aggregation	1.3×10^{-86}	0.28959
Influenza Infection	1×10^{-82}	$> 1.031 \times 10^{-5}$
Influenza Viral RNA Transcription and Replication	2.4×10^{-82}	$> 1.031 \times 10^{-5}$
Influenza Life Cycle	2×10^{-80}	$> 1.031 \times 10^{-5}$
Response to elevated platelet cytosolic Ca ²⁺	4.9×10^{-78}	0.50817
Signalling by NGF	1.6×10^{-75}	0.38518
Rho GTPase cycle	5.1×10^{-75}	0.14864
Signalling by PDGF	7.4×10^{-74}	0.40493
<i>Signalling by Rho GTPases</i>	5.1×10^{-73}	0.077217
Glycosaminoglycan metabolism	1.4×10^{-68}	0.52984
G _{αi} signalling events	1.8×10^{-66}	0.9254
Metabolism of carbohydrates	1.1×10^{-65}	0.39501
G_{αs} signalling events	2.7×10^{-65}	0.0050293
Potassium Channels	2.7×10^{-65}	0.53359
Transmission across Chemical Synapses	1.8×10^{-64}	0.81833
ECM proteoglycans	3.4×10^{-64}	0.083482
Peptide ligand-binding receptors	4.8×10^{-64}	0.62817
Degradation of the extracellular matrix	1.1×10^{-63}	0.80879
Platelet homeostasis	5.3×10^{-63}	0.53134
NGF signalling via TRKA from the plasma membrane	6.1×10^{-63}	0.57117
Integration of energy metabolism	4.5×10^{-61}	0.10889
Collagen formation	5.4×10^{-61}	0.29896
Integrin cell surface interactions	7×10^{-59}	0.18167
Collagen biosynthesis and modifying enzymes	7×10^{-59}	0.30208
Neurotransmitter Receptor Binding And Downstream Transmission	8.7×10^{-57}	0.82522
In The Postsynaptic Cell		
Signalling by Wnt	8.7×10^{-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 F.6: Pathways for *CDH1* partners from SLIPT in stomach and siRNA

Reactome Pathway	Over-representation	Permutation
Platelet activation, signalling and aggregation	3.9×10^{-9}	0.49557
Class A/1 (Rhodopsin-like receptors)	3.9×10^{-9}	0.98432
Response to elevated platelet cytosolic Ca ²⁺	5.5×10^{-8}	0.54349
Platelet homeostasis	5.7×10^{-8}	0.45017
Nucleotide-like (purinergic) receptors	1.8×10^{-7}	0.36966
Peptide ligand-binding receptors	3.8×10^{-7}	0.91294
Molecules associated with elastic fibres	7.1×10^{-7}	0.0025868
Amine ligand-binding receptors	8.6×10^{-7}	0.43303
G _{ai} signalling events	9.8×10^{-7}	0.99626
GPCR ligand binding	1.1×10^{-6}	0.97733
Elastic fibre formation	1.5×10^{-6}	0.0025868
G _{aq} signalling events	1.9×10^{-6}	0.86089
P2Y receptors	3.8×10^{-6}	0.18795
Serotonin receptors	3.8×10^{-6}	0.37853
Signal amplification	2.3×10^{-5}	0.47856
Gastrin-CREB signalling pathway via PKC and MAPK	2.3×10^{-5}	0.98567
Complement cascade	2.4×10^{-5}	$> 3.4628 \times 10^{-6}$
Glycosaminoglycan metabolism	2.5×10^{-5}	0.38953
Glycogen breakdown (glycogenolysis)	2.7×10^{-5}	0.83772
Defective B4GALT7 causes EDS, progeroid type	4.9×10^{-5}	0.10792
Defective B3GAT3 causes JDSSDHD	4.9×10^{-5}	0.10792
Role of LAT2/NTAL/LAB on calcium mobilization	5.6×10^{-5}	0.35373
Cell surface interactions at the vascular wall	5.6×10^{-5}	0.47642
G_{as} signalling events	6×10^{-5}	0.019858
Signalling by NOTCH	6×10^{-5}	0.19008
A tetrasaccharide linker sequence is required for GAG synthesis	0.00017	0.47642
Extracellular matrix organization	0.00018	0.0047308
Collagen formation	0.00018	0.19245
Effects of PIP2 hydrolysis	0.0002	0.37779
Syndecan interactions	0.0002	0.37779
Diseases associated with glycosaminoglycan metabolism	0.00023	0.01028
Diseases of glycosylation	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-kB 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
SEMA3A-Plexin repulsion signalling by inhibiting Integrin adhesion	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).

F.3 Metagene Analysis

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

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

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

Synthetic Lethal Genes in Pathways

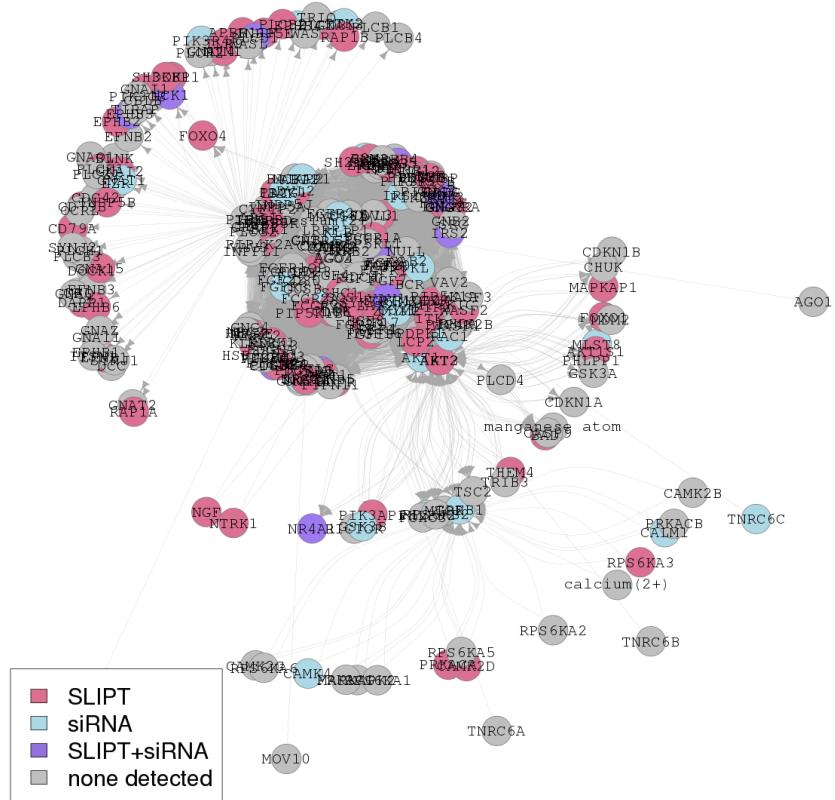


Figure G.1: Synthetic lethality in the PI3K/AKT pathway. The Reactome PI3K/AKT pathway with synthetic lethal candidates, coloured as shown in the legend.

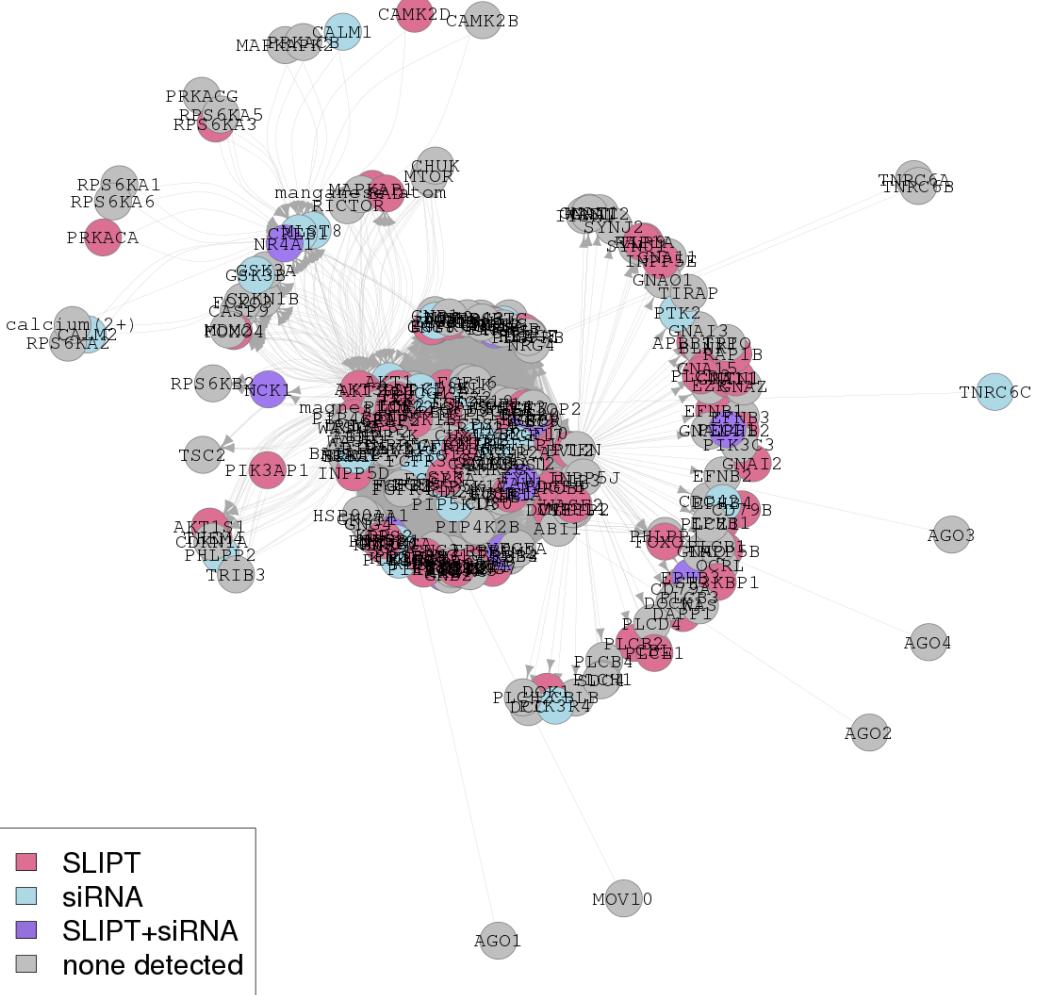


Figure G.2: Synthetic lethality in the PI3K/AKT pathway in cancer. The Reactome PI3K/AKT in cancer pathway with synthetic lethal candidates, coloured as shown in the legend.

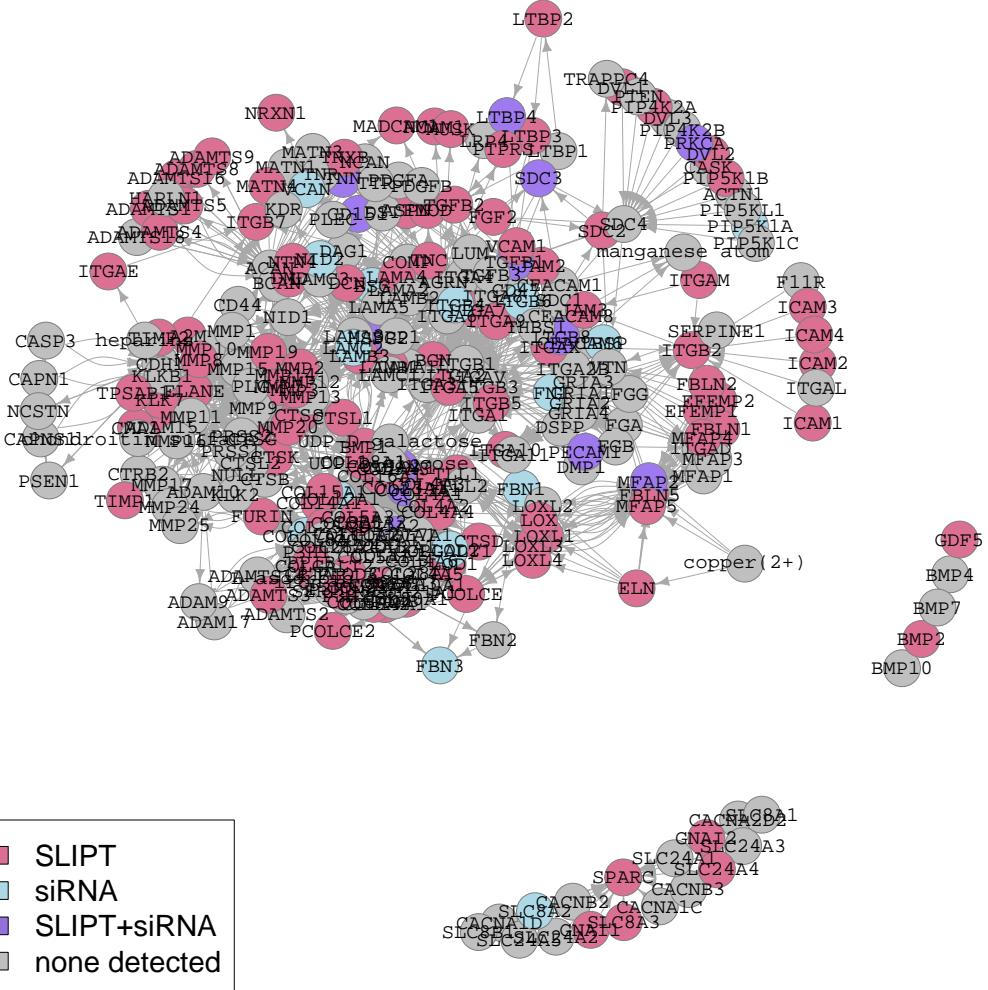


Figure G.3: **Synthetic lethality in the Extracellular Matrix.** The Reactome Extracellular Matrix pathway with synthetic lethal candidates, coloured as shown in the legend.

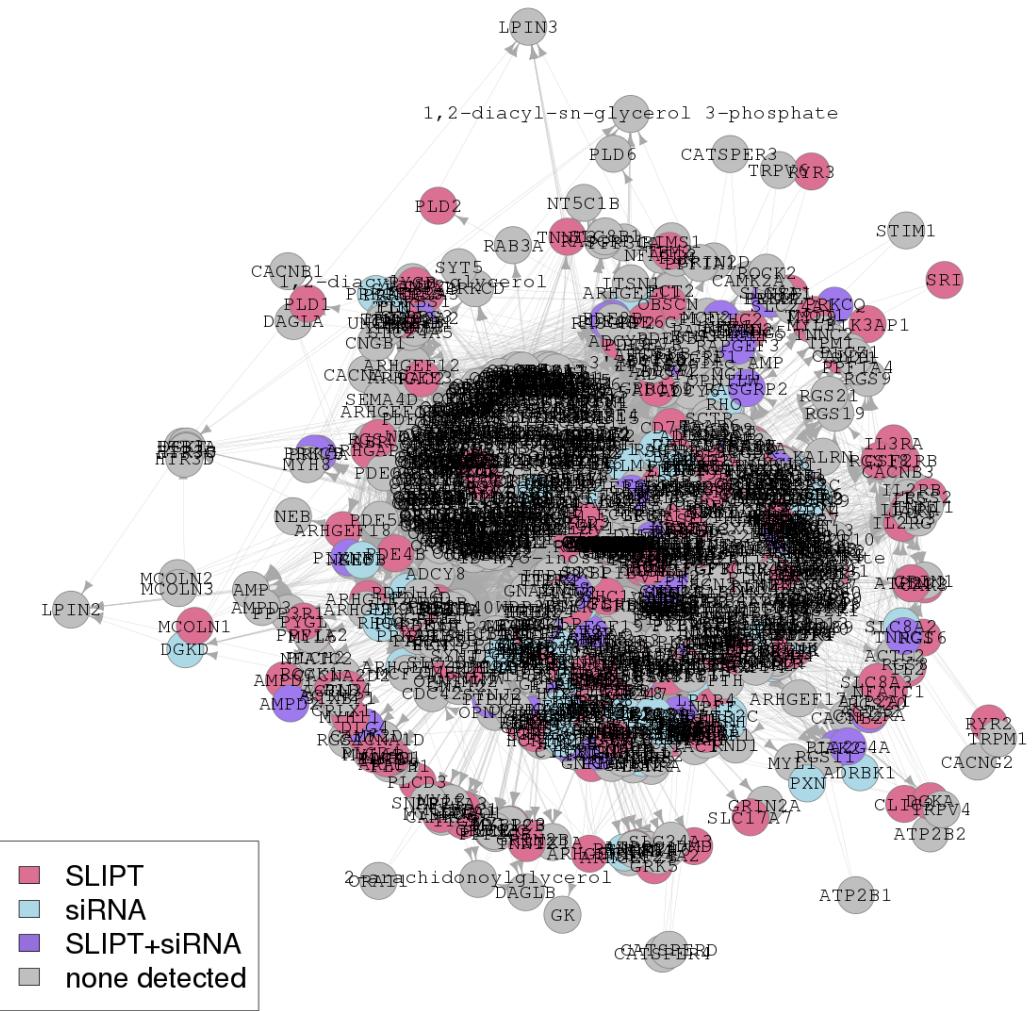


Figure G.4: **Synthetic lethality in the GPCR Downstream.** The Reactome G protein coupled receptor (GPCR) Downstream pathway with synthetic lethal candidates, coloured as shown in the legend.

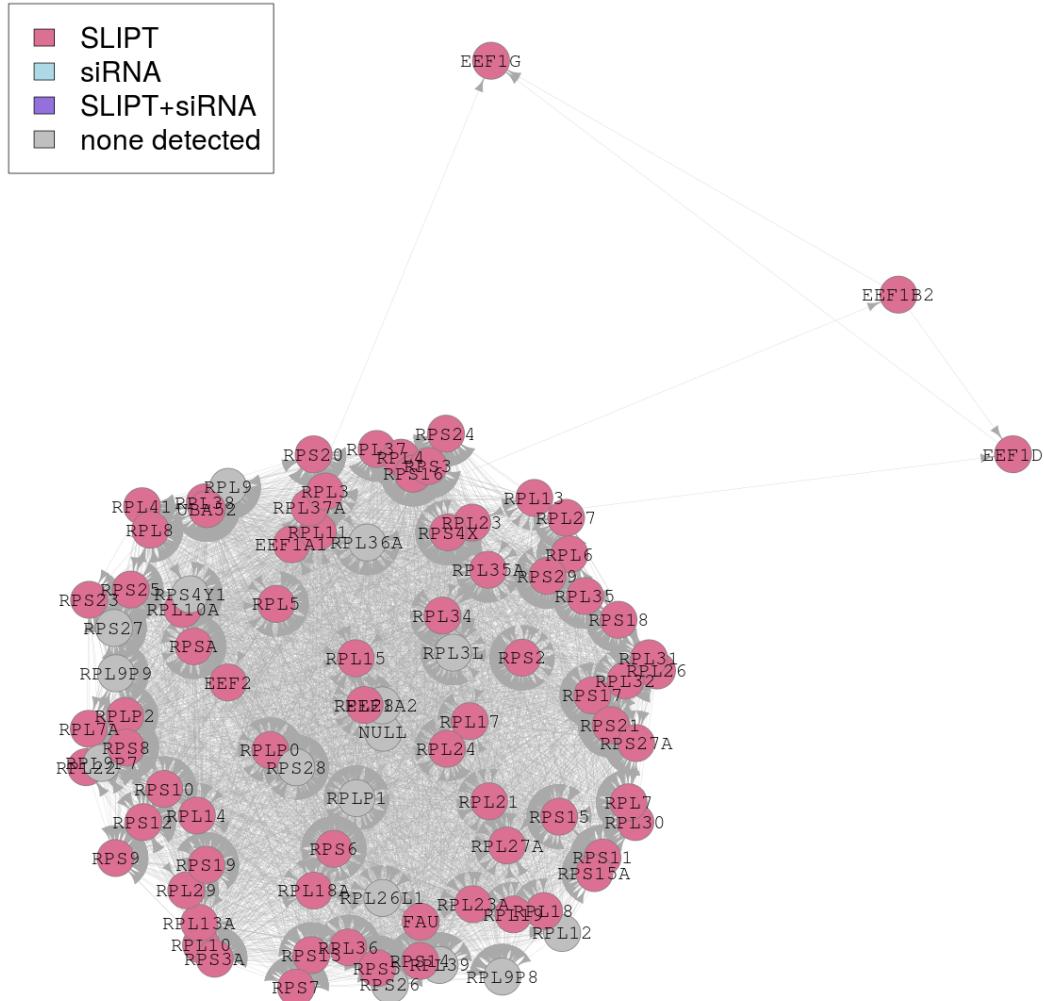


Figure G.5: Synthetic lethality in the Translation Elongation. The Reactome Translation Elongation pathway with synthetic lethal candidates, coloured as shown in the legend.

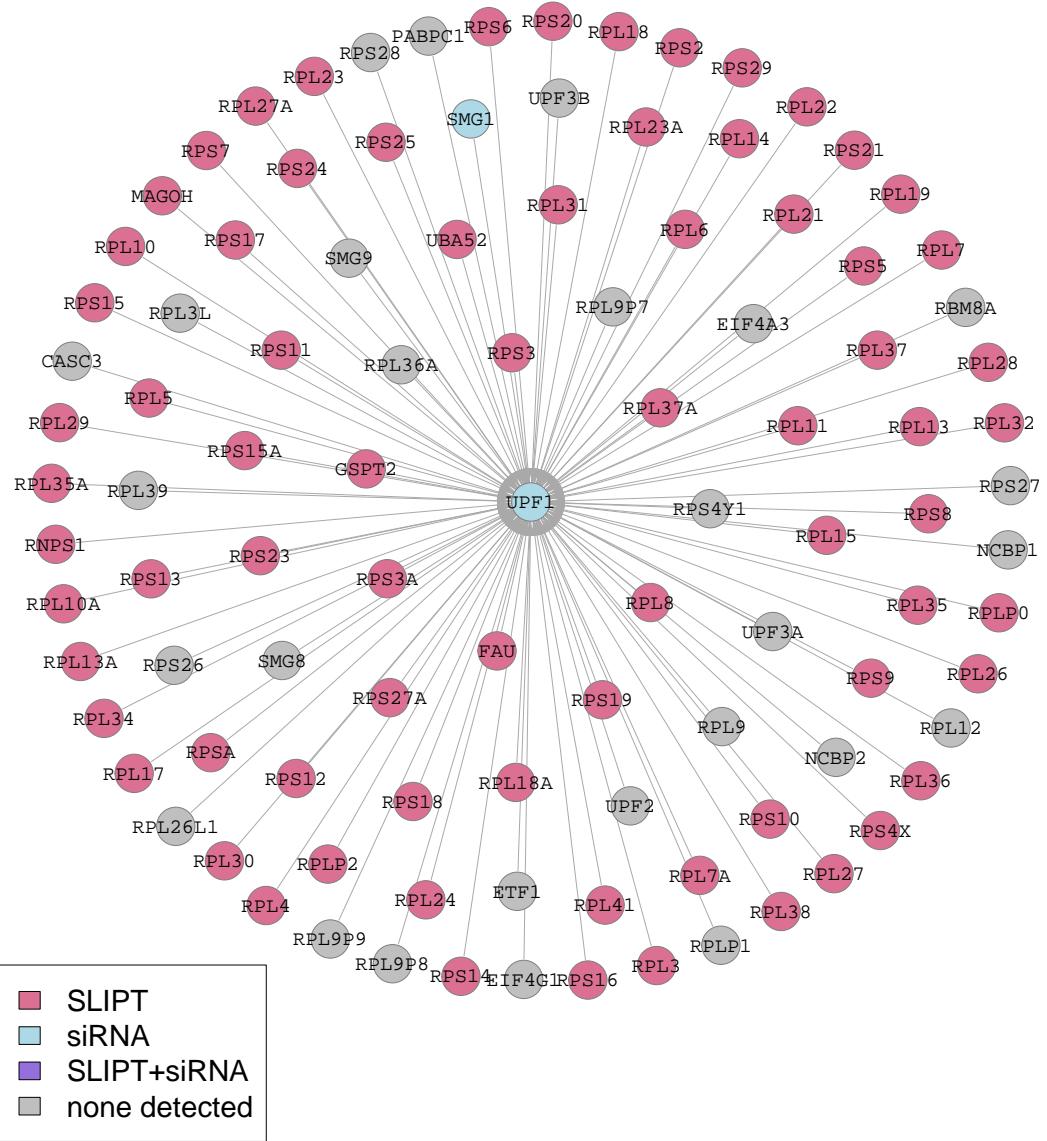


Figure G.6: **Synthetic lethality in the Nonsense-mediated Decay.** The Reactome nonsense-mediated decay (NMD) pathway with synthetic lethal candidates, coloured as shown in the legend.

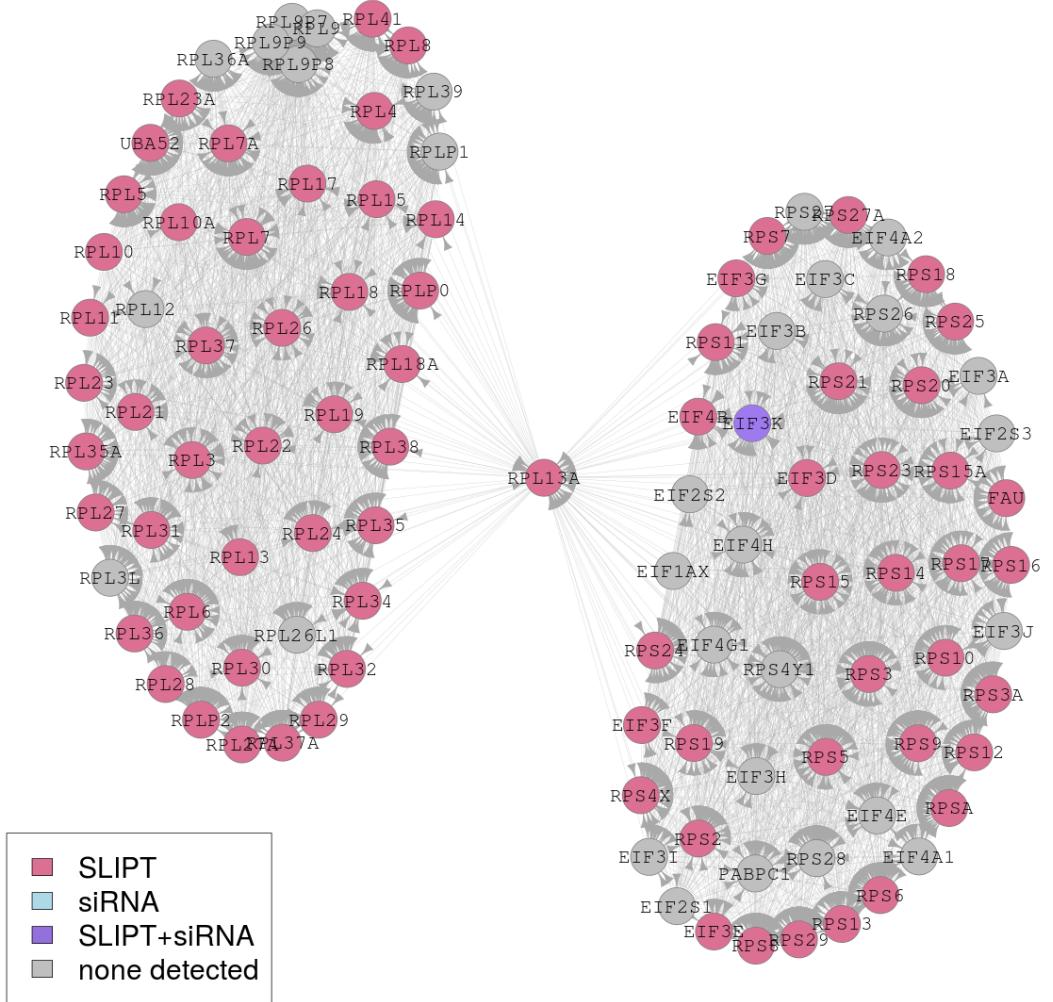


Figure G.7: Synthetic lethality in the 3' UTR. The Reactome 3' untranslated region (UTR) pathway with synthetic lethal candidates, coloured as shown in the legend.

Appendix H

Network Analysis for Mutation SLIPT

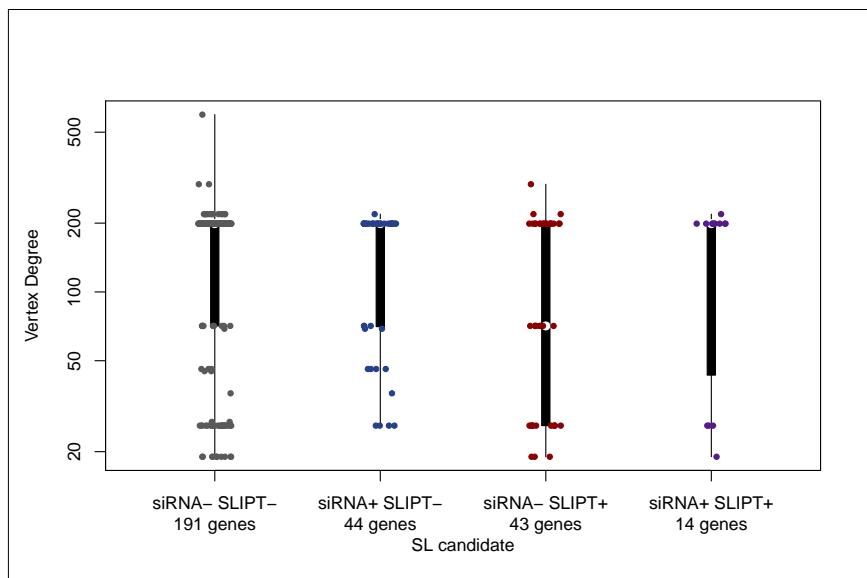


Figure H.1: **Synthetic lethality and vertex degree.** The number of connected genes (vertex degree) was compared (on a log-scale) across genes detected by mtSLIPT and siRNA screening in the Reactome G_{αi} pathway. There were no differences in vertex degree between the groups (shown in Table 5.1), although genes detected by siRNA included those with the fewest connections.

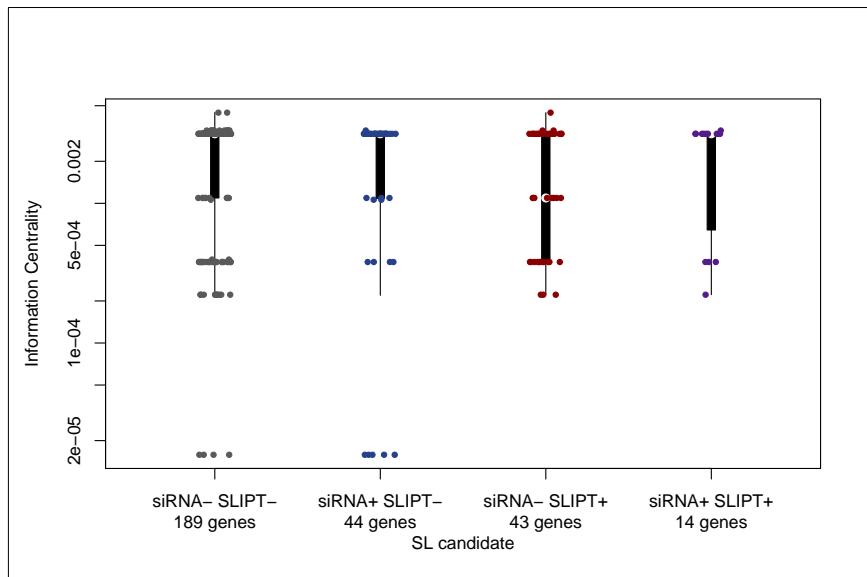


Figure H.2: Synthetic lethality and centrality. The information centrality was compared (on a log-scale) across genes detected by SLIPT and siRNA screening in the Reactome $G_{\alpha i}$ pathway. Genes detected by SLIPT or siRNA did not have higher centrality than other genes (shown in Table H.2). Genes detected by SLIPT spanned the range of centrality values.

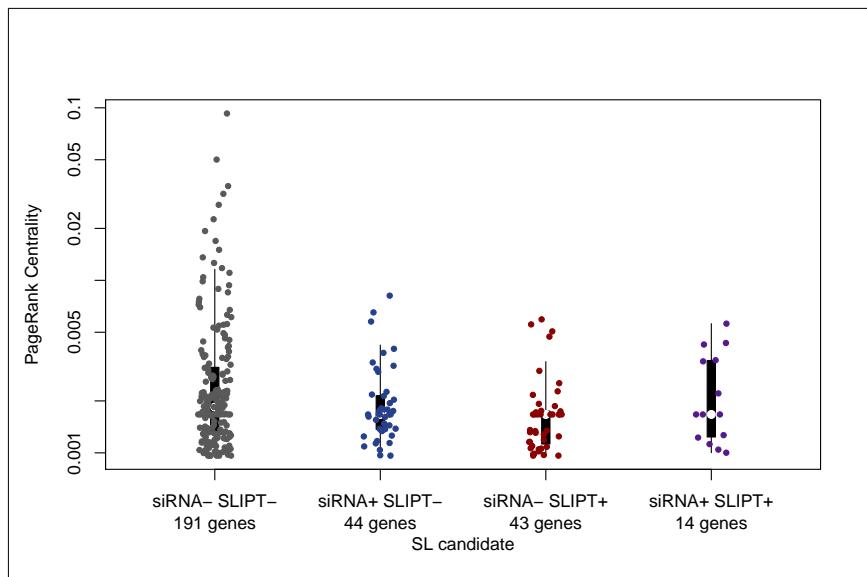


Figure H.3: Synthetic lethality and PageRank. The PageRank centrality was compared (on a log-scale) across genes detected by mtSLIPT and siRNA screening in the Reactome $G_{\alpha i}$ pathway. Genes detected by either synthetic lethal detection approach had a more restricted range of centrality values neither of these had a significant association with centrality (shown in Table H.3).

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

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

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

Appendix I

Pathway Structure for Mutation SLIPT

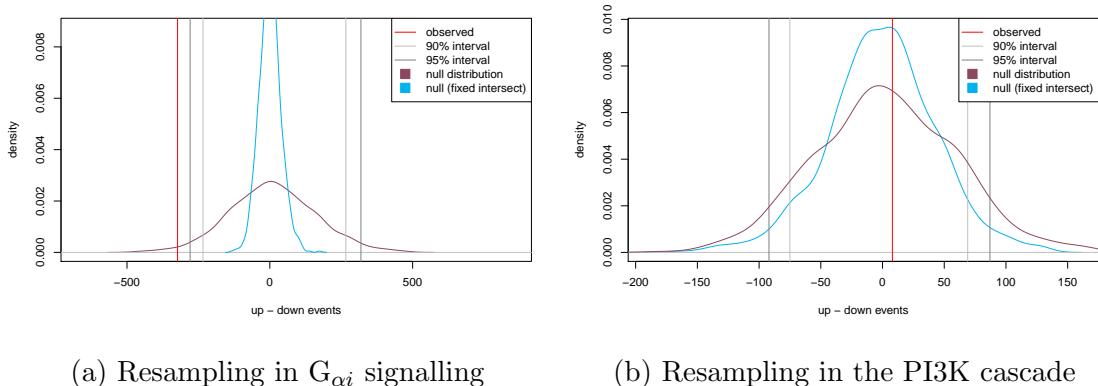


Figure I.1: **Structure of synthetic lethality resampling.** A null distribution with 10,000 iterations of the number of siRNA genes upstream or downstream of mtSLIPT genes (depicted as the difference of these) in each pathway. To assess significance, the observed events (with shortest paths) were compared to the 90% and 95% intervals for the null distribution (shown in blue). Genes detected by both methods were not fixed to the same number as observed for the alternative null distribution (shown in violet), although the significance of the observed number of events (red) was changed in either case. The genes detected by both approaches were included in computing the number of shortest paths (in either direction) between SLIPT and siRNA genes. The permutations show (a) a significant pathway relationship for $G_{\alpha i}$ signalling and (b) a non-significant relationship for the PI3K cascade.

Table I.1: Resampling for pathway structure of synthetic lethal detection methods

Pathway	Graph		States		Observed				Permutation p-value		p-value (FDR)
	Nodes	Edges	mtSL	siRNA	Up	Down	Up–Down	Up/Down	Up–Down	Down–Up	Down–Up
PI3K Cascade	138	1495	42	25	131	123	8	1.065	0.4473	0.5466	0.7263
PI3K/AKT Signalling in Cancer	275	12882	56	44	478	440	38	1.086	0.4163	0.5810	0.7263
G_{ai} Signalling	292	22003	57	58	543	866	-323	0.627	0.9507	0.0488	0.488
GPCR downstream	1270	142071	218	160	7632	6500	1132	1.174	0.1707	0.8291	0.8751
Elastic fibre formation	42	175	16	7	6	7	-1	0.857	0.5512	0.3681	0.7263
Extracellular matrix	299	3677	81	29	313	347	-34	0.902	0.5762	0.4215	0.7263
Formation of Fibrin	52	243	11	5	8	19	-11	0.421	0.7993	0.1800	0.6000
Nonsense-Mediated Decay	103	102	56	2	0	0	0		0.197	0.1373	0.6000
3'-UTR-mediated translational regulation	107	2860	56	1	52	1	51	52	0.1210	0.8751	0.8751
Eukaryotic Translation Elongation	92	3746	57	0	0	0	0		0.4952	0.4892	0.7263

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 χ^2

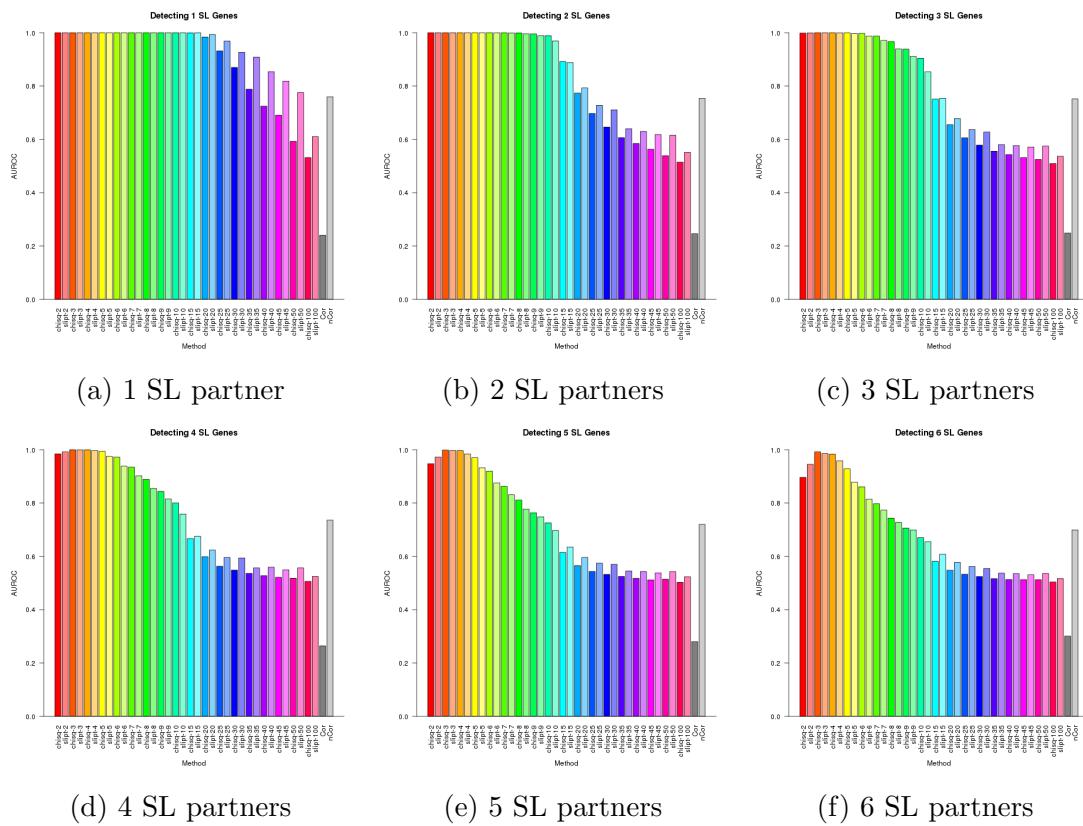


Figure J.1: Performance of χ^2 and SLIPT across quantiles. (continued on next page)

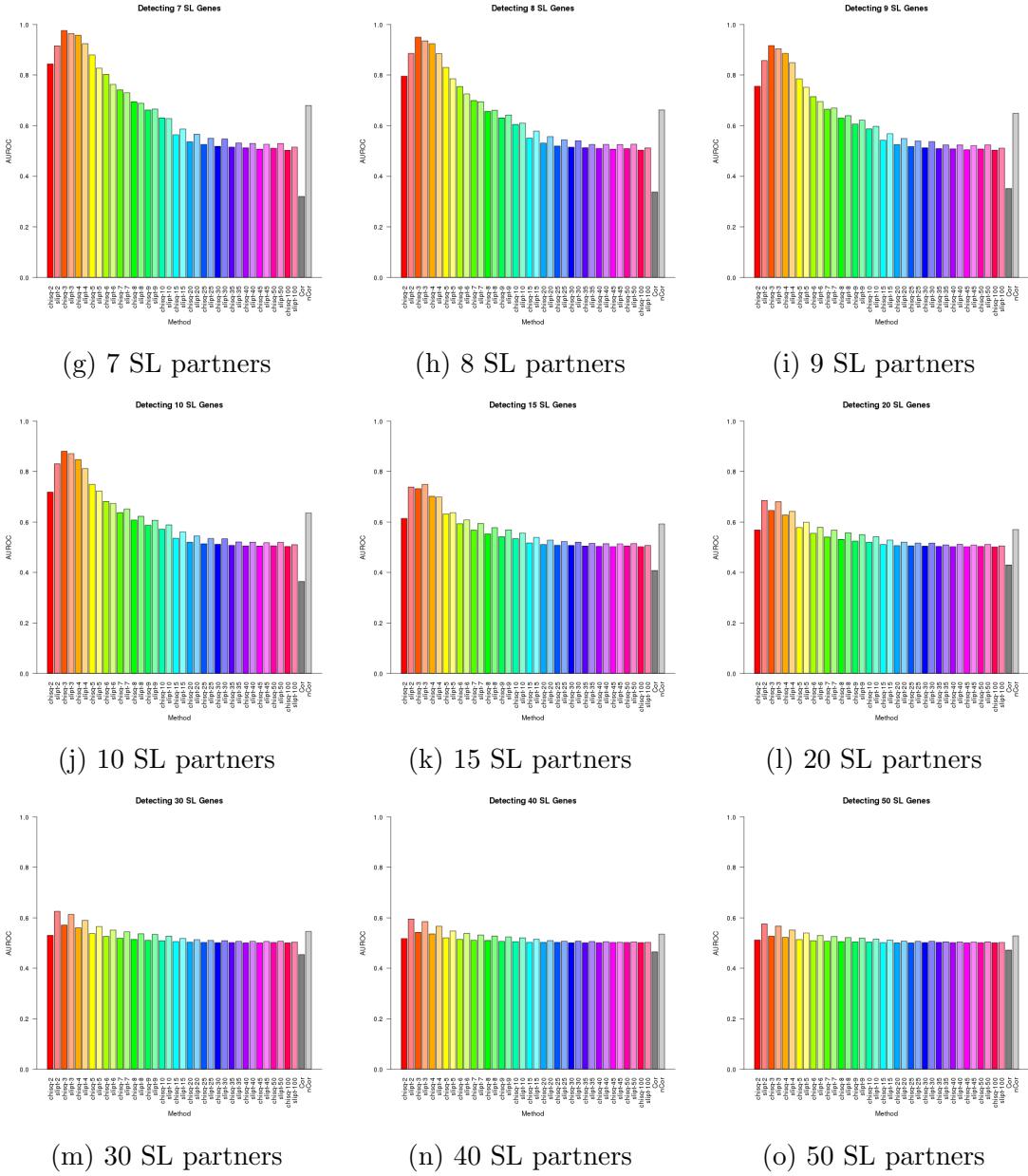


Figure J.1: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^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 χ^2 for higher numbers of synthetic lethal genes and finer quantiles.

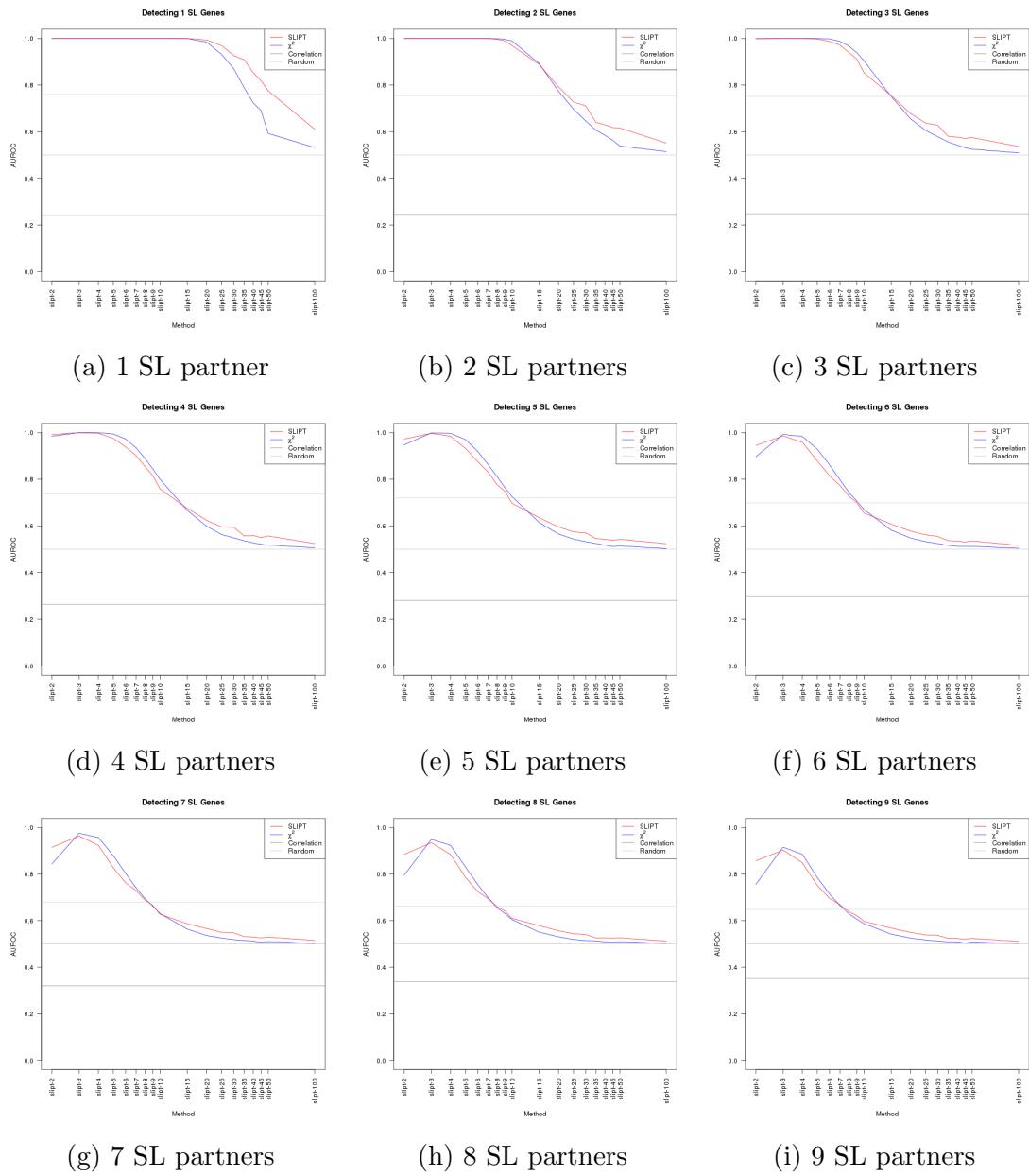


Figure J.2: **Performance of χ^2 and SLIPT across quantiles.** (continued on next page)

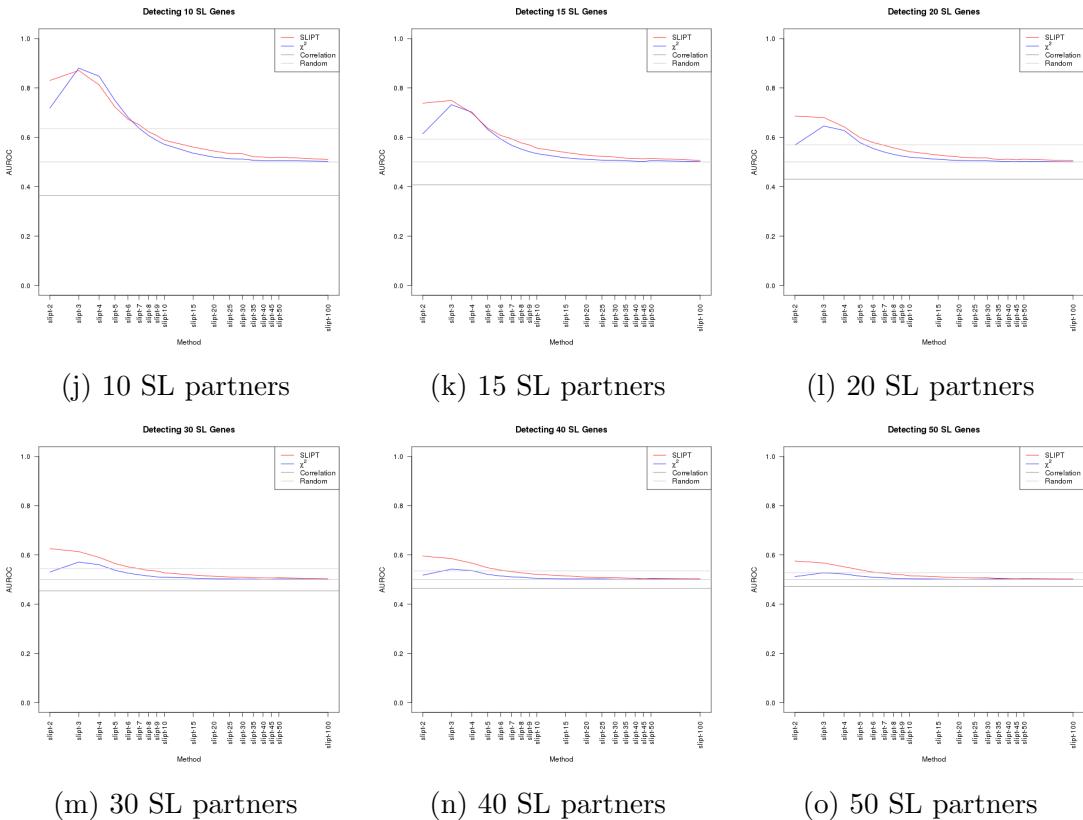


Figure J.2: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^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 χ^2 for higher numbers of synthetic lethal genes and finer quantiles.

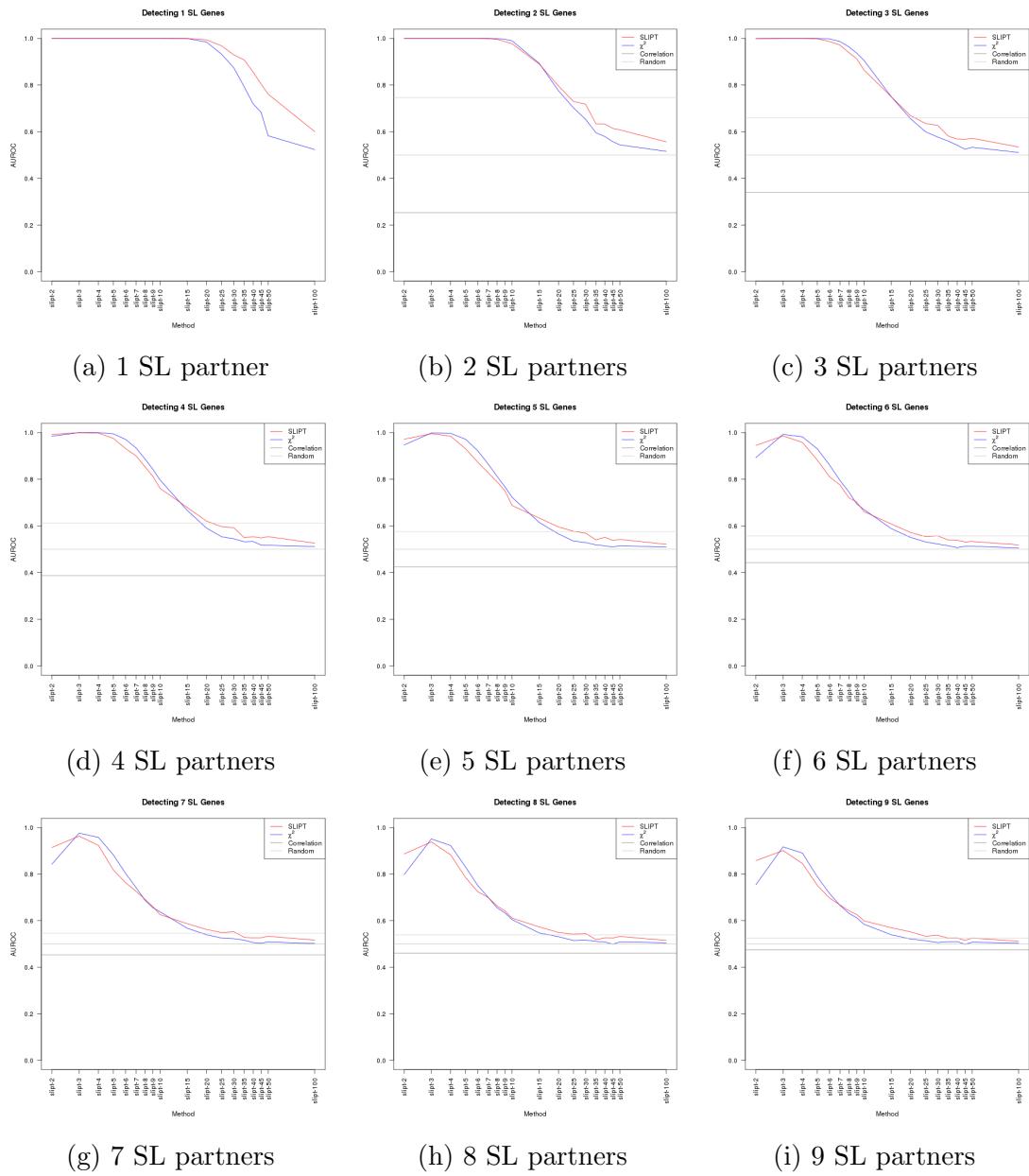


Figure J.3: **Performance of χ^2 and SLIPT across quantiles with more genes.**
 (continued on next page)

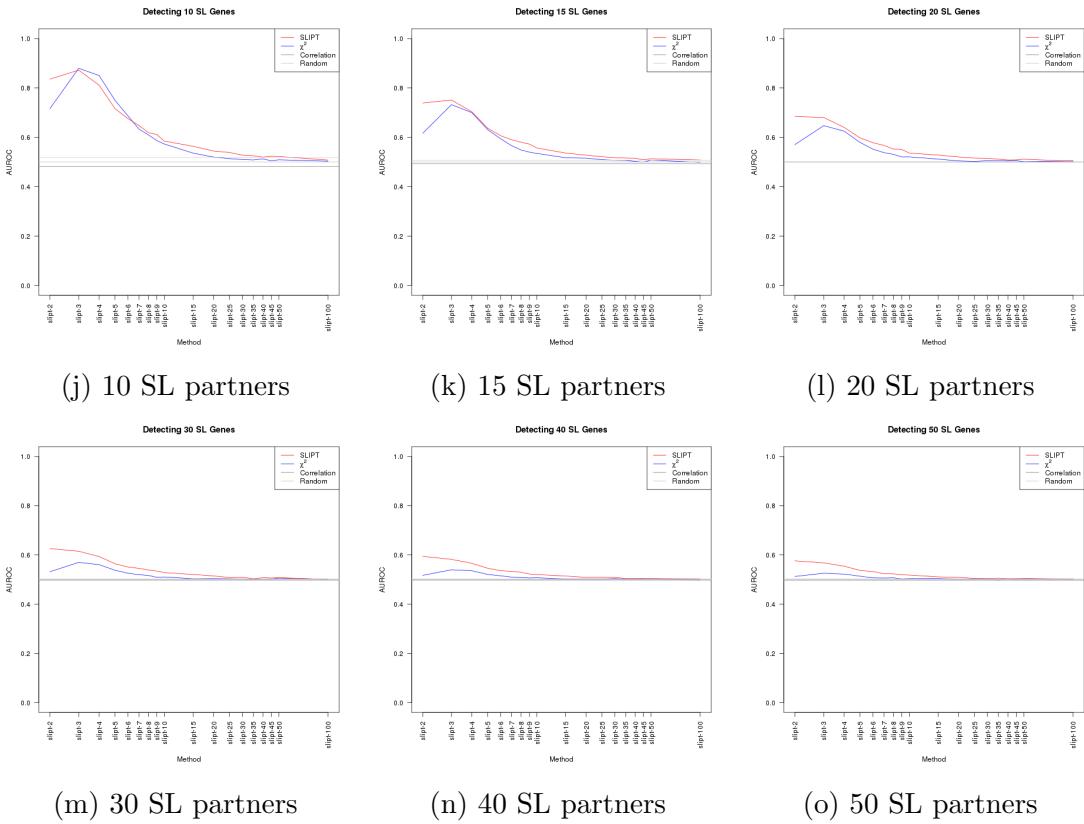


Figure J.3: Performance of χ^2 and SLIPT across quantiles with more genes.
 Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^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 χ^2 for higher numbers of synthetic lethal genes and finer quantiles.

J.1 Correlated Query Genes affects Specificity

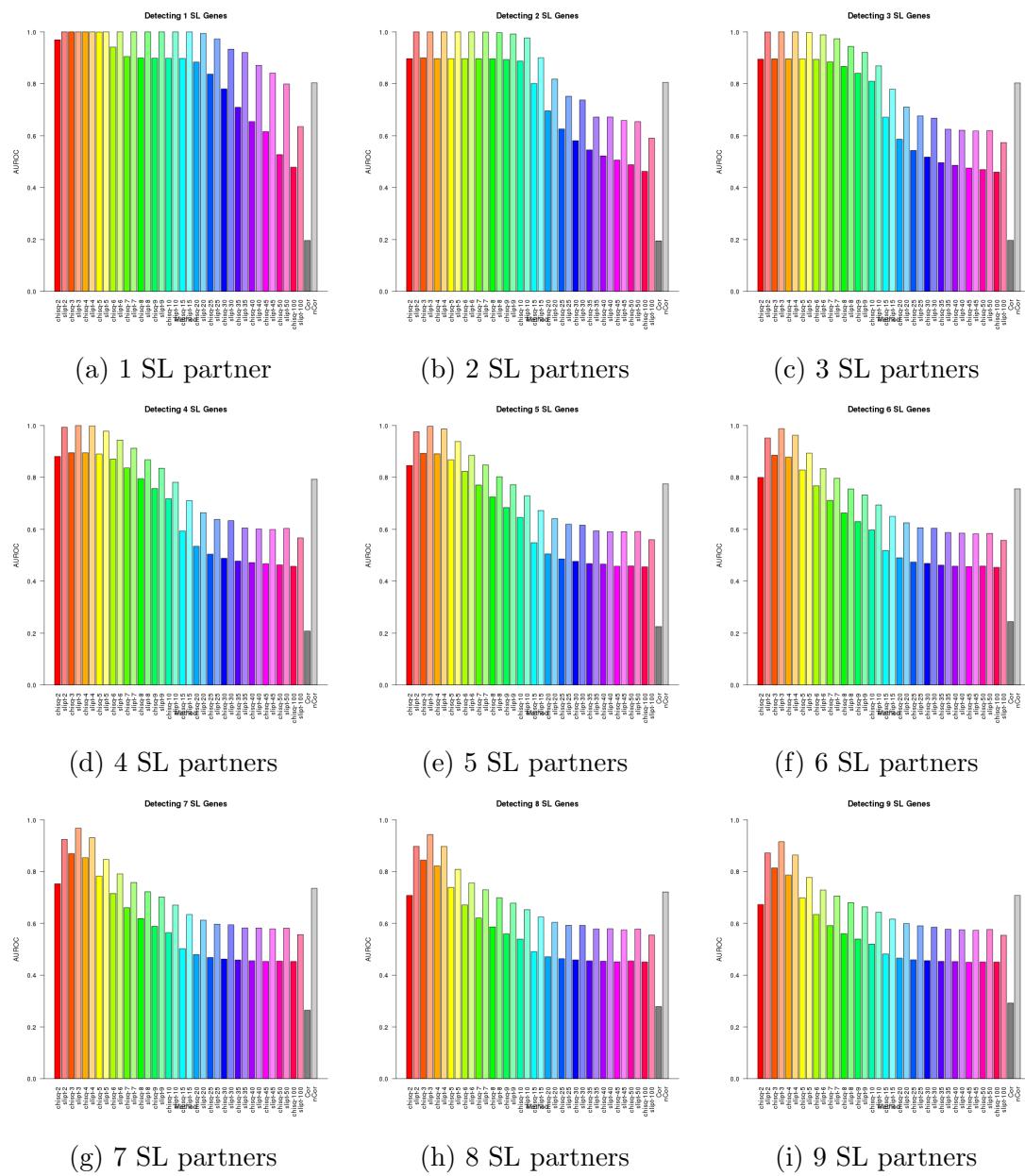


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. (continued on next page)

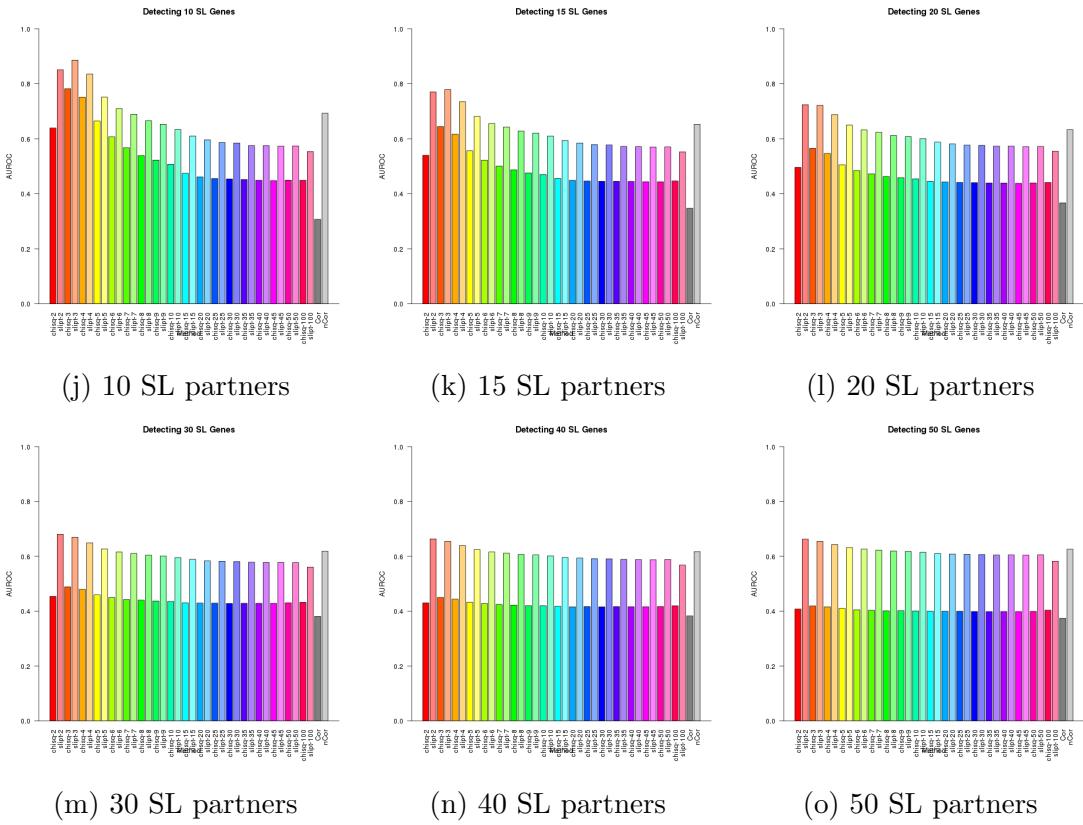


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^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 χ^2 with positively correlated genes.

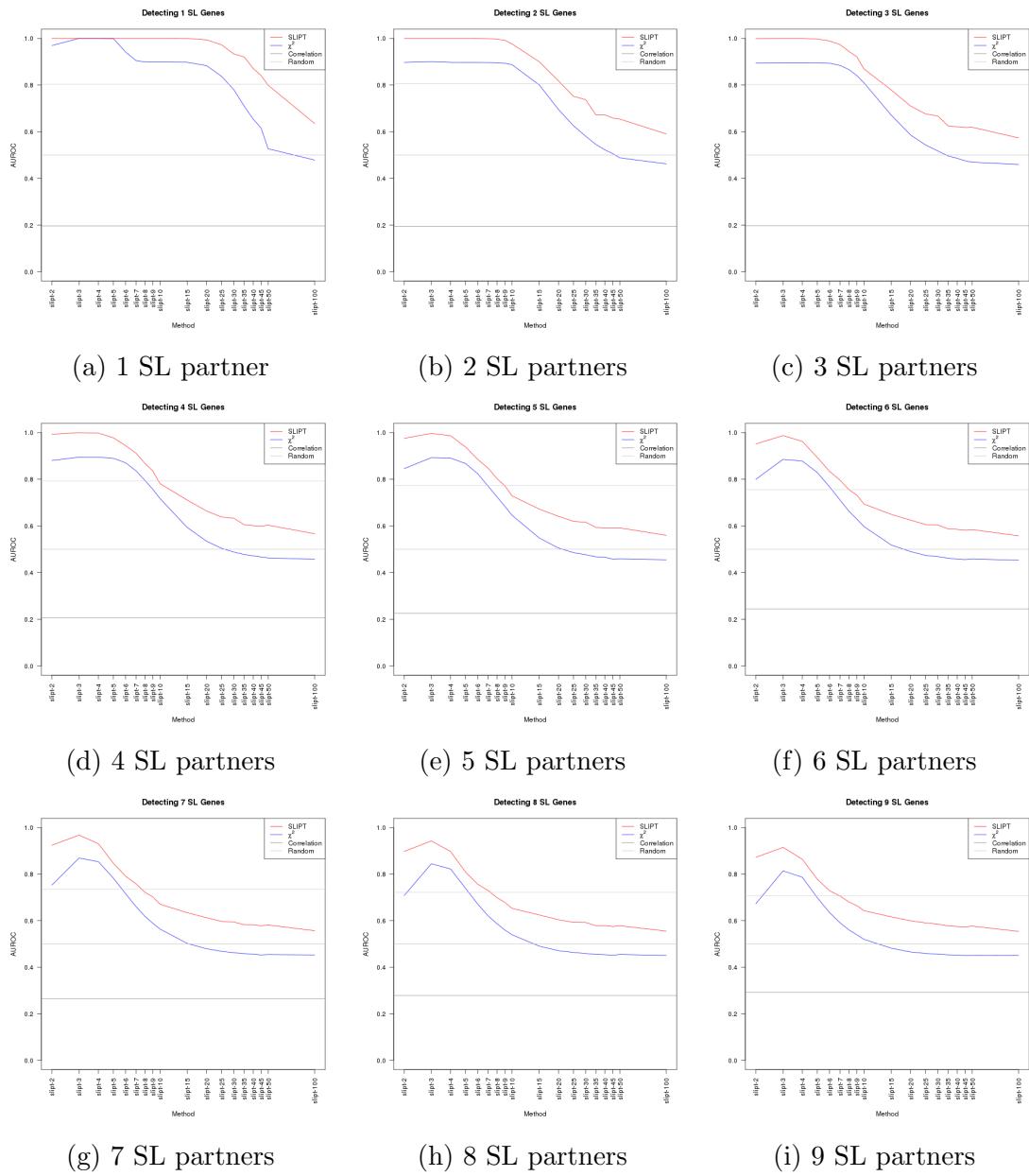


Figure J.5: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

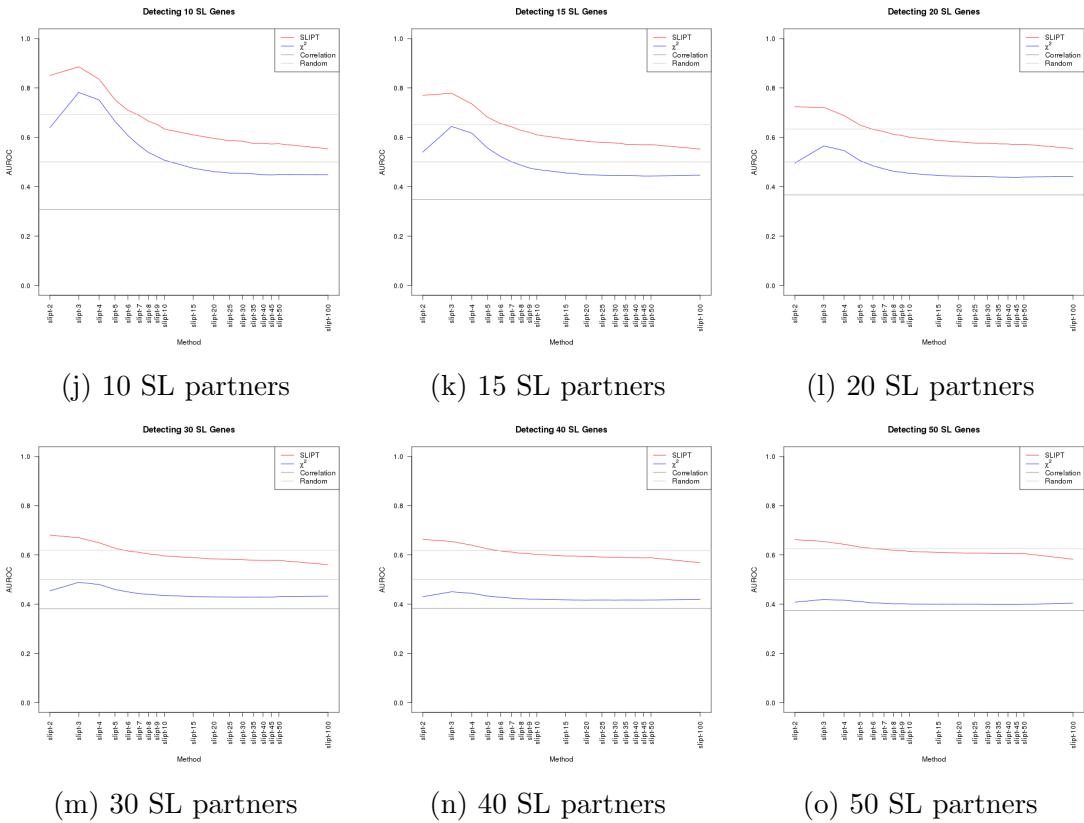


Figure J.5: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^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 χ^2 with positively correlated genes.

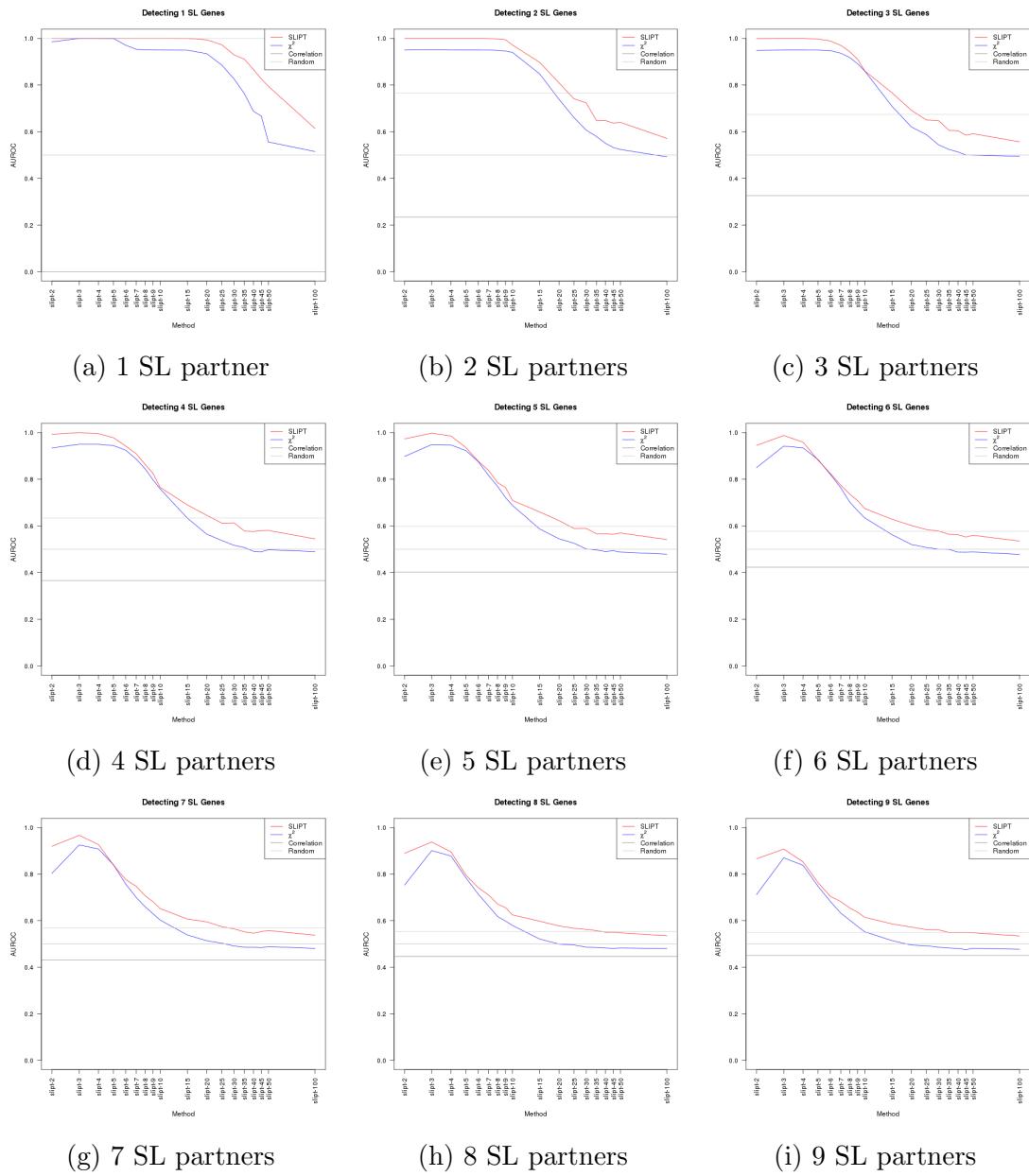


Figure J.6: **Performance of χ^2 and SLIPT across quantiles with query correlation and more genes.** (continued on next page)

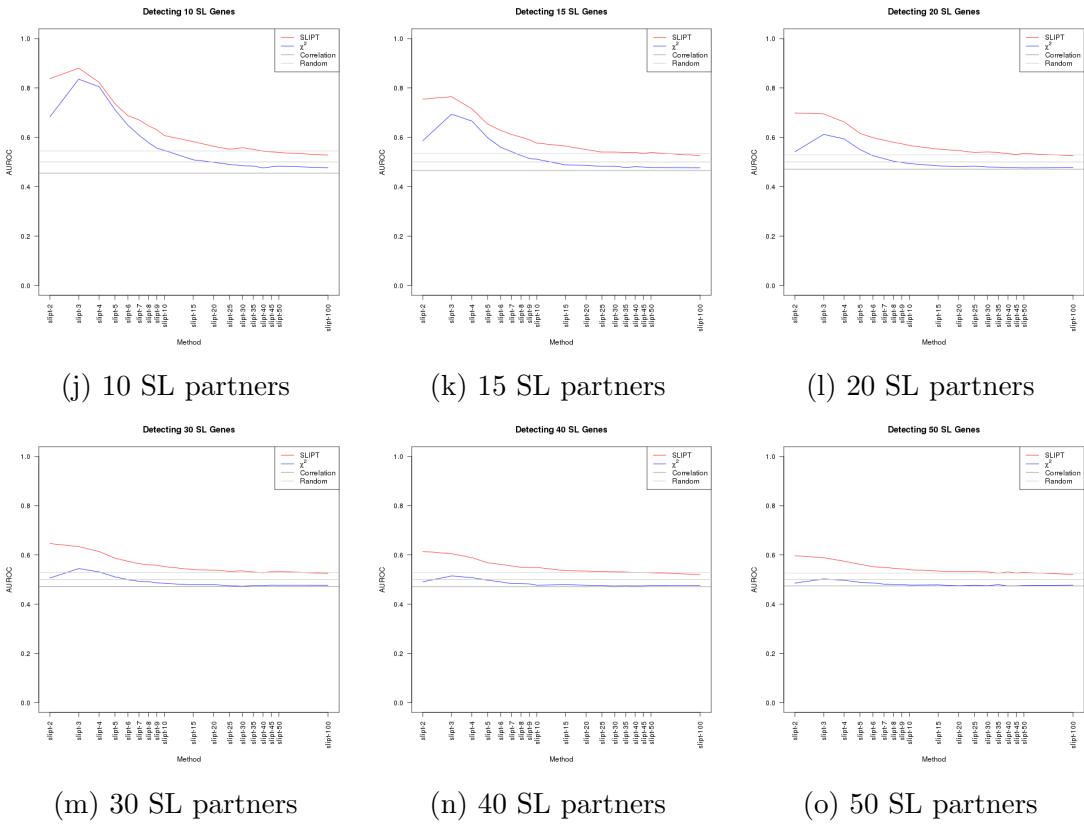


Figure J.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^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 χ^2 with positively correlated genes.

Appendix K

Simulations on Graph Structures

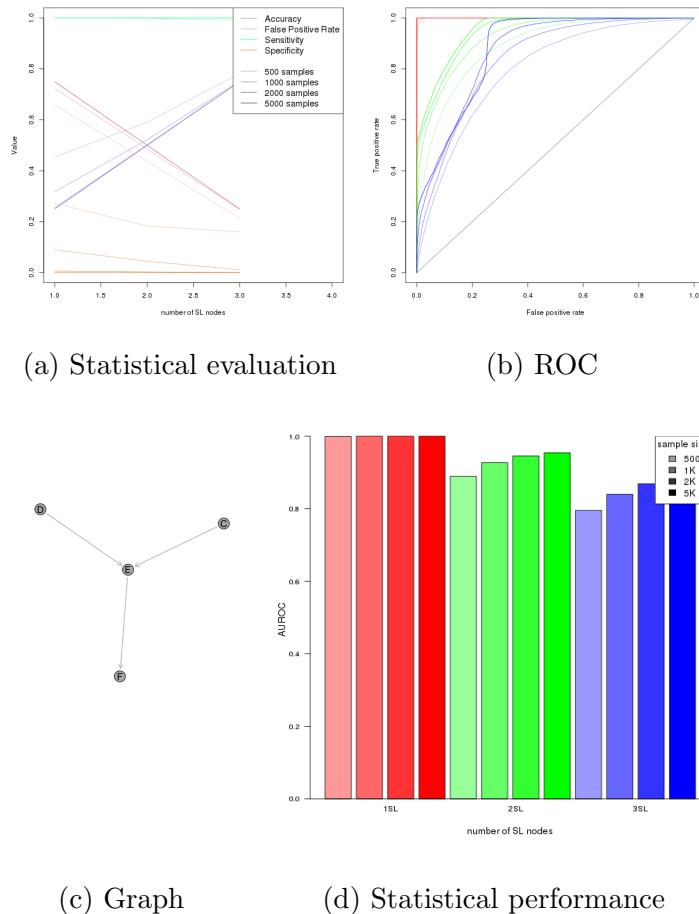


Figure K.1: **Performance of simulations on a simple graph.** Simulation of synthetic lethality was performed using a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.1b match Figure K.1d.

K.0.1 Simulations from Inhibiting Graph Structures

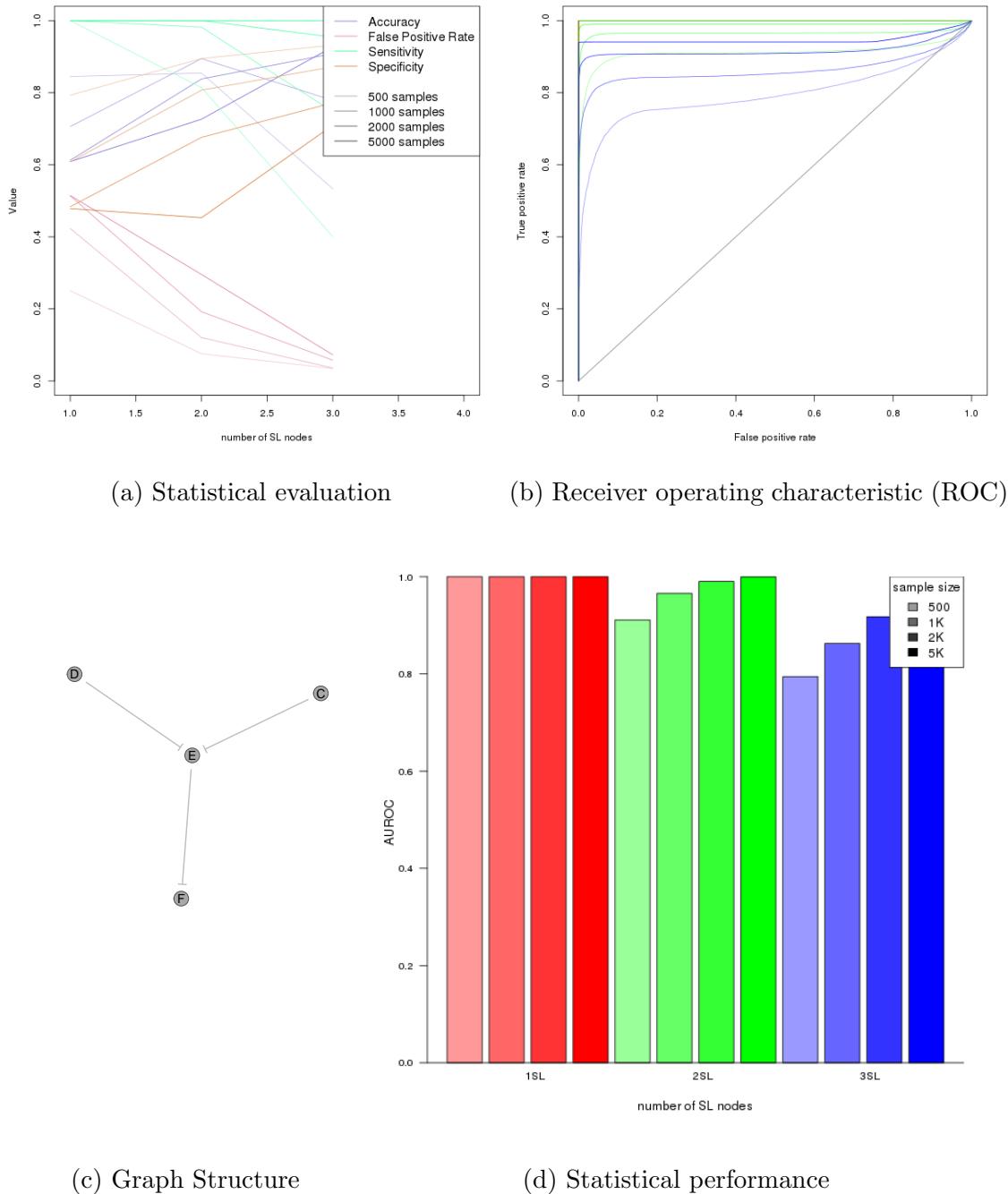
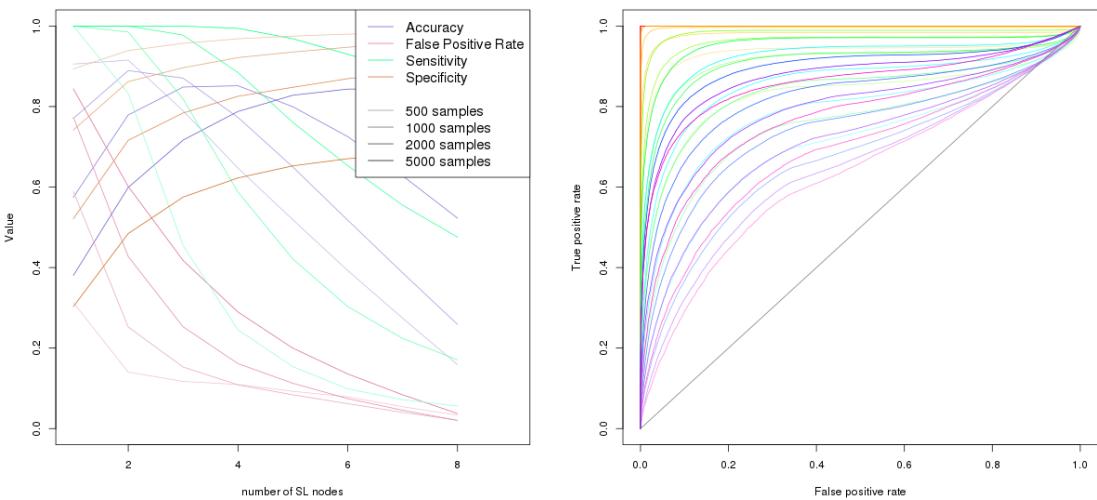
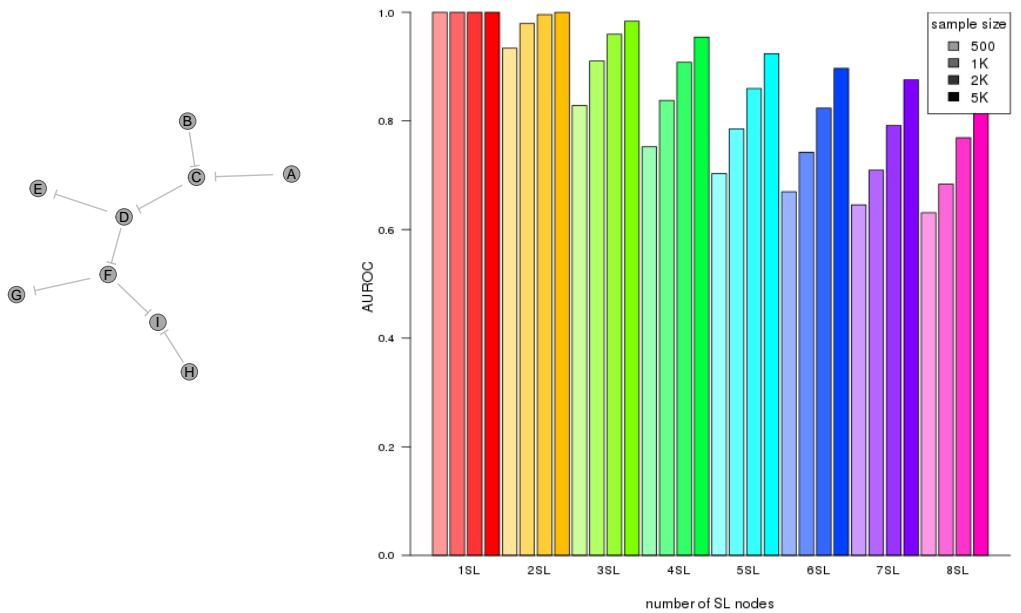


Figure K.2: Performance of simulations on an inhibiting graph. Simulation of synthetic lethality used a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.2b match Figure K.2d.



(a) Statistical evaluation

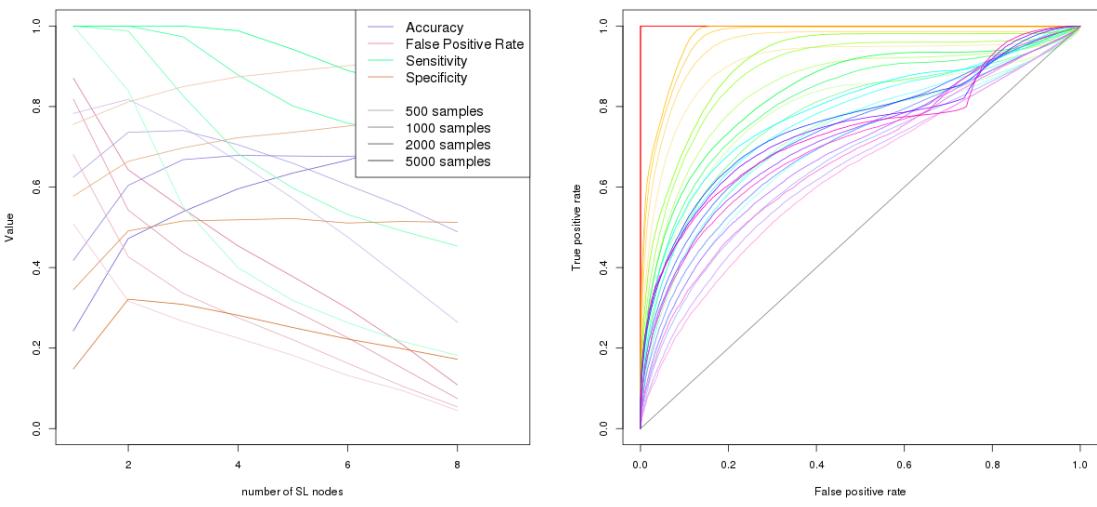
(b) ROC



(c) Graph Structure

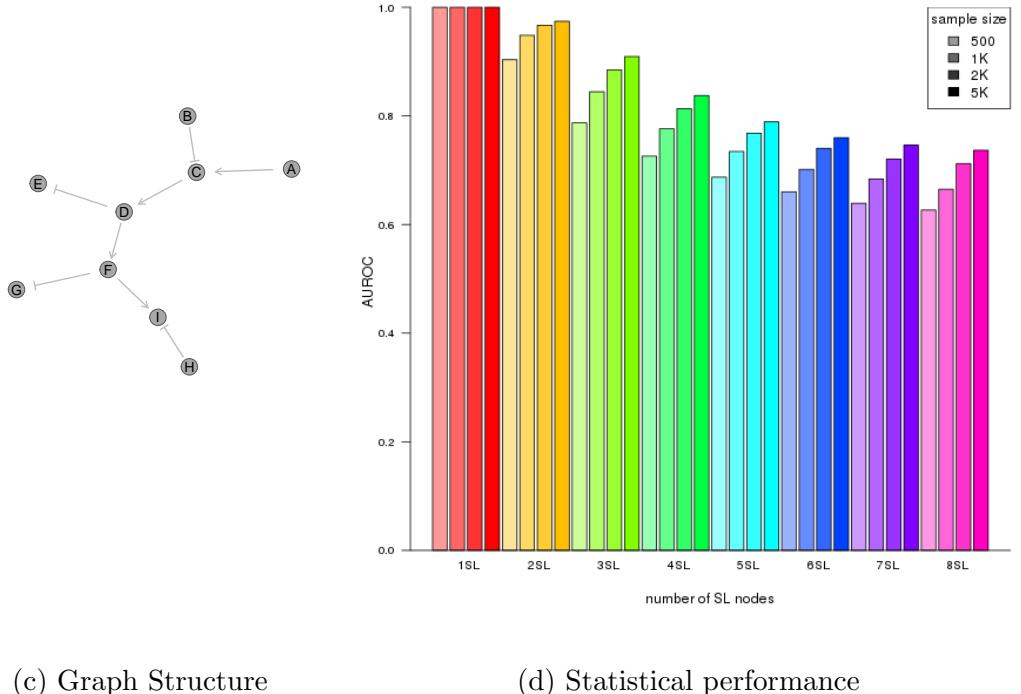
(d) Statistical performance

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

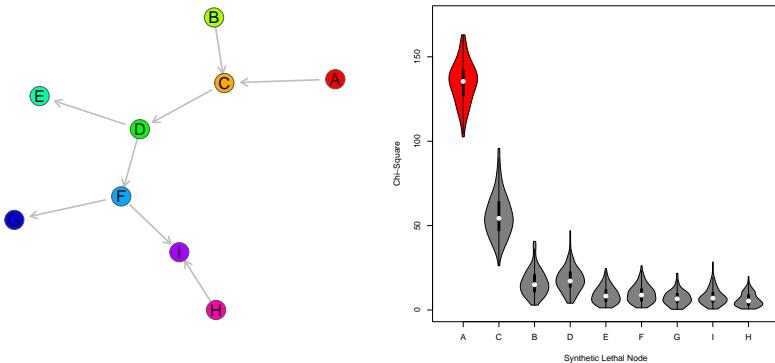


(c) Graph Structure

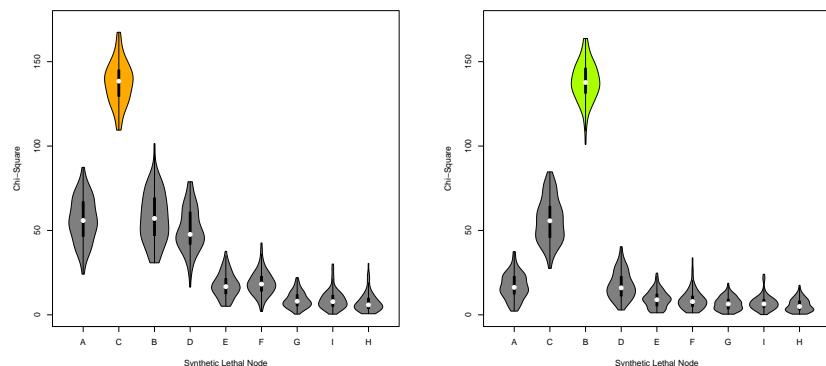
(d) Statistical performance

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.

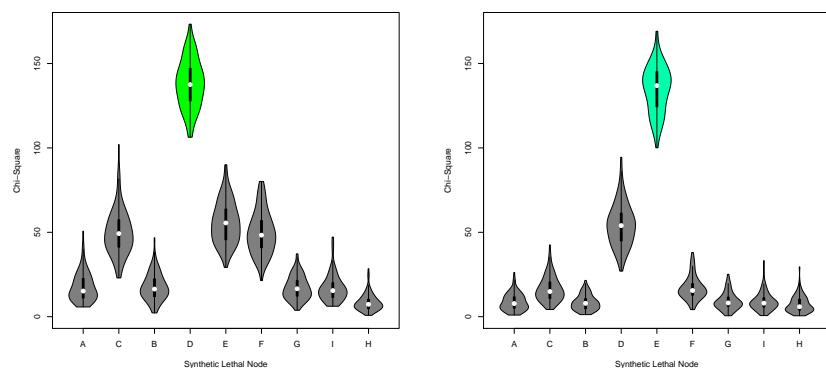
K.1 Simulation across Graph Structures



(a) Activating Graph Structure (b) χ^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)

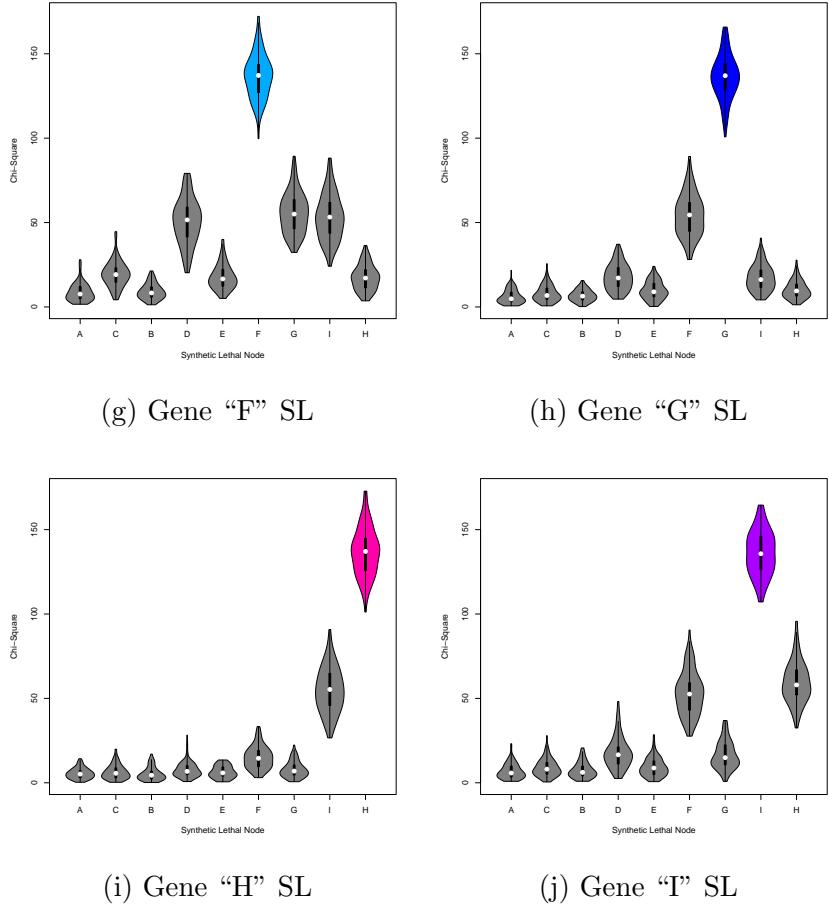
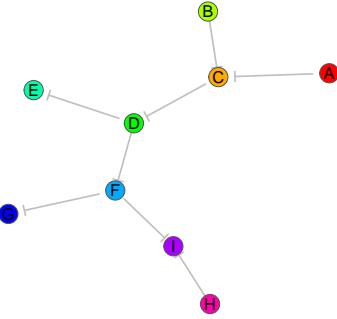
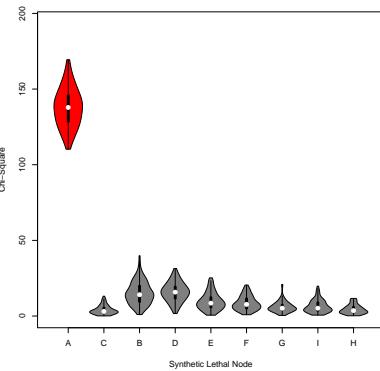


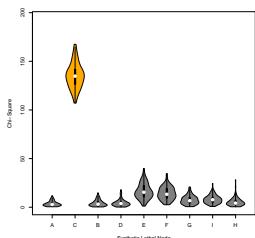
Figure K.5: Detection of synthetic lethality within a graph structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from SLIPT was computed for each gene across the graph. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were computed 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.



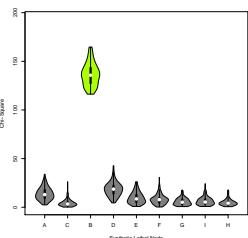
(a) Inhibiting Graph Structure



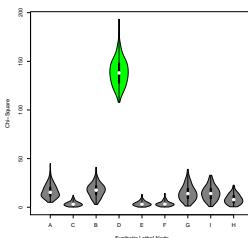
(b) χ^2 distribution for "A" SL



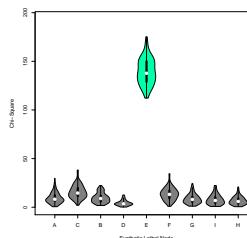
(c) Gene "B" SL



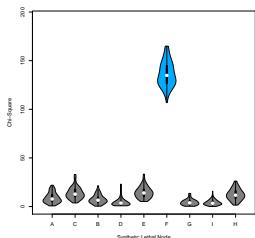
(d) Gene "C" SL



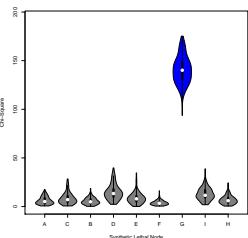
(e) Gene "D" SL



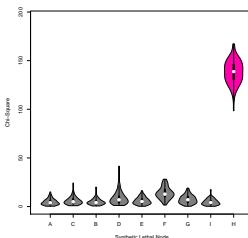
(f) Gene "E" SL



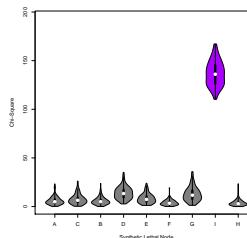
(g) Gene "F" SL



(h) Gene "G" SL

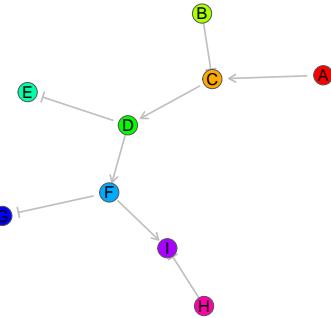


(i) Gene "H" SL

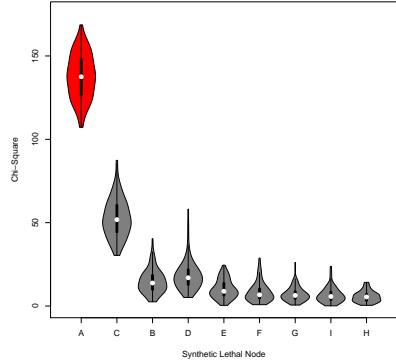


(j) Gene "I" SL

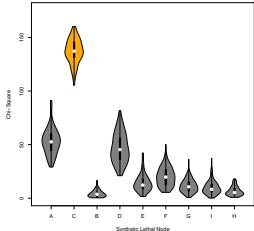
Figure K.6: Detection of synthetic lethality within an inhibiting graph. Each gene was designated to be synthetic lethal separately and the χ^2 value from SLIPT was computed for each gene across the graph structure with inhibiting relationships. For each synthetic lethal gene (highlighted in the respective colours), the χ^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 χ^2 values with inhibiting relationships.



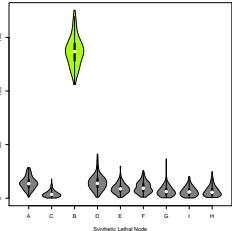
(a) Inhibiting Graph Structure



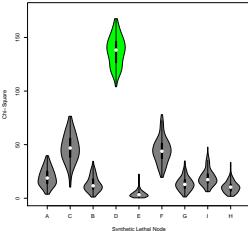
(b) χ^2 distribution for "A" SL



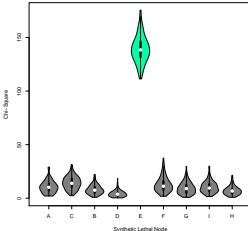
(c) Gene "B" SL



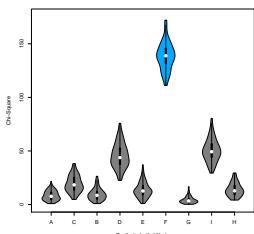
(d) Gene "C" SL



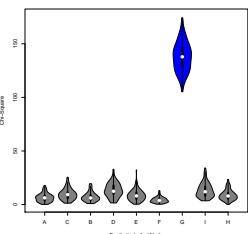
(e) Gene "D" SL



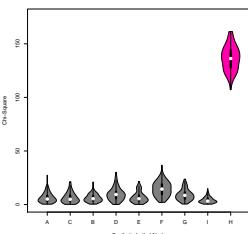
(f) Gene "E" SL



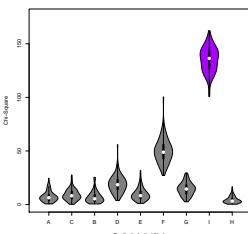
(g) Gene "F" SL



(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 χ^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 χ^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

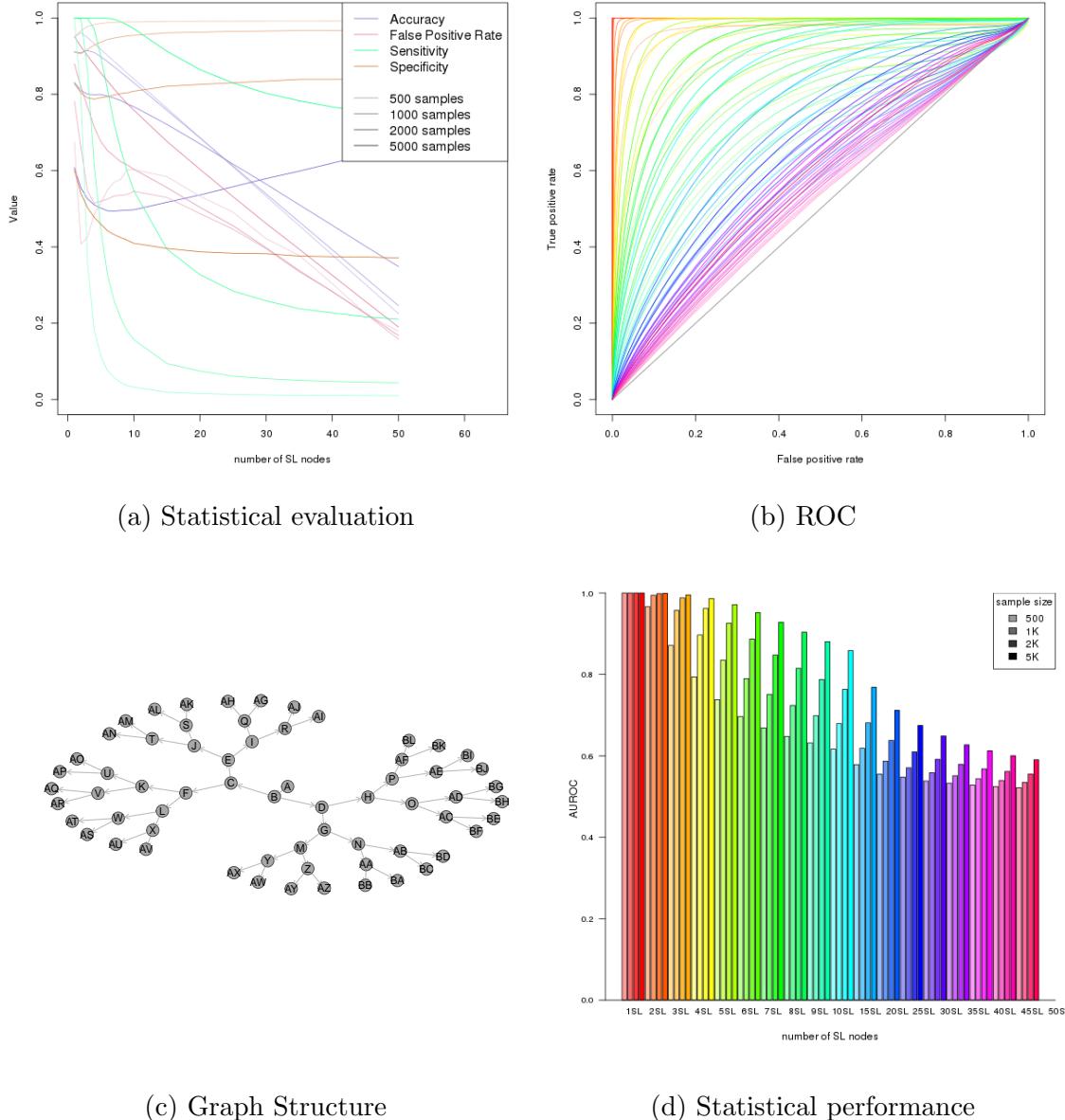
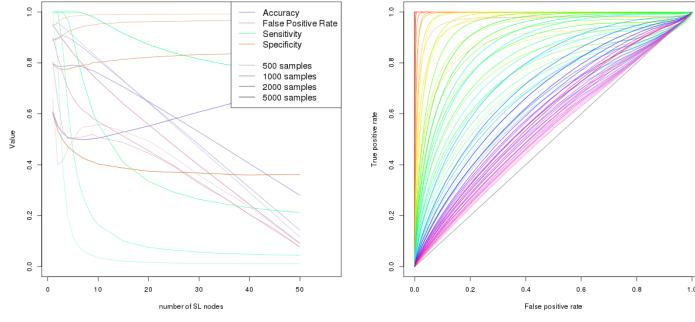
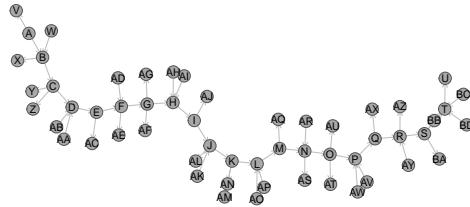


Figure K.8: **Performance of simulations on a branching graph.** Simulation of synthetic lethality used a multivariate normal distribution from a branching graph. For each parameter, 10,000 simulations were used. Colours in Figure K.8b match Figure K.8d.

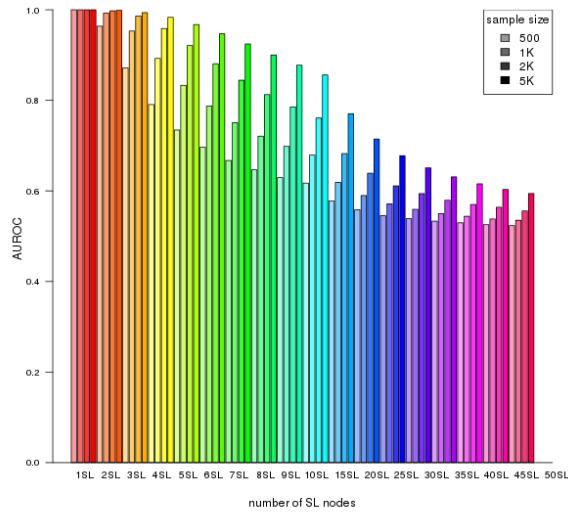


(a) Statistical evaluation

(b) ROC

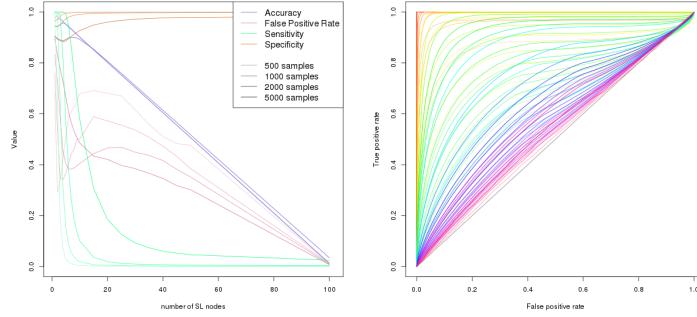


(c) Graph Structure



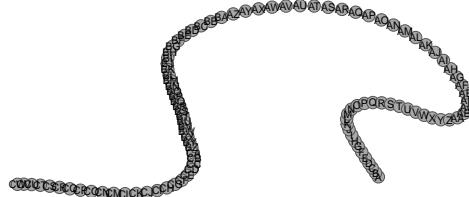
(d) Statistical performance

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.

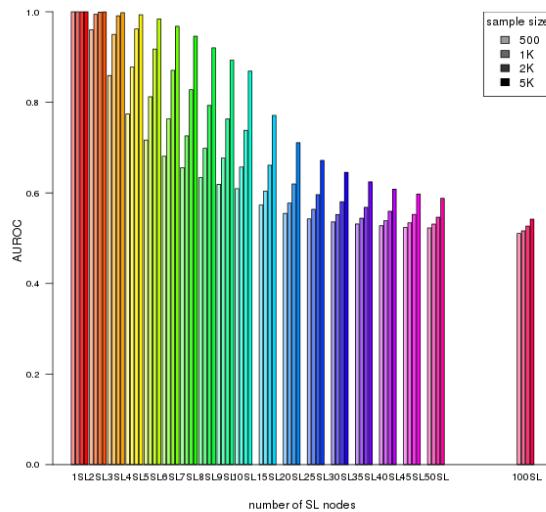


(a) Statistical evaluation

(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

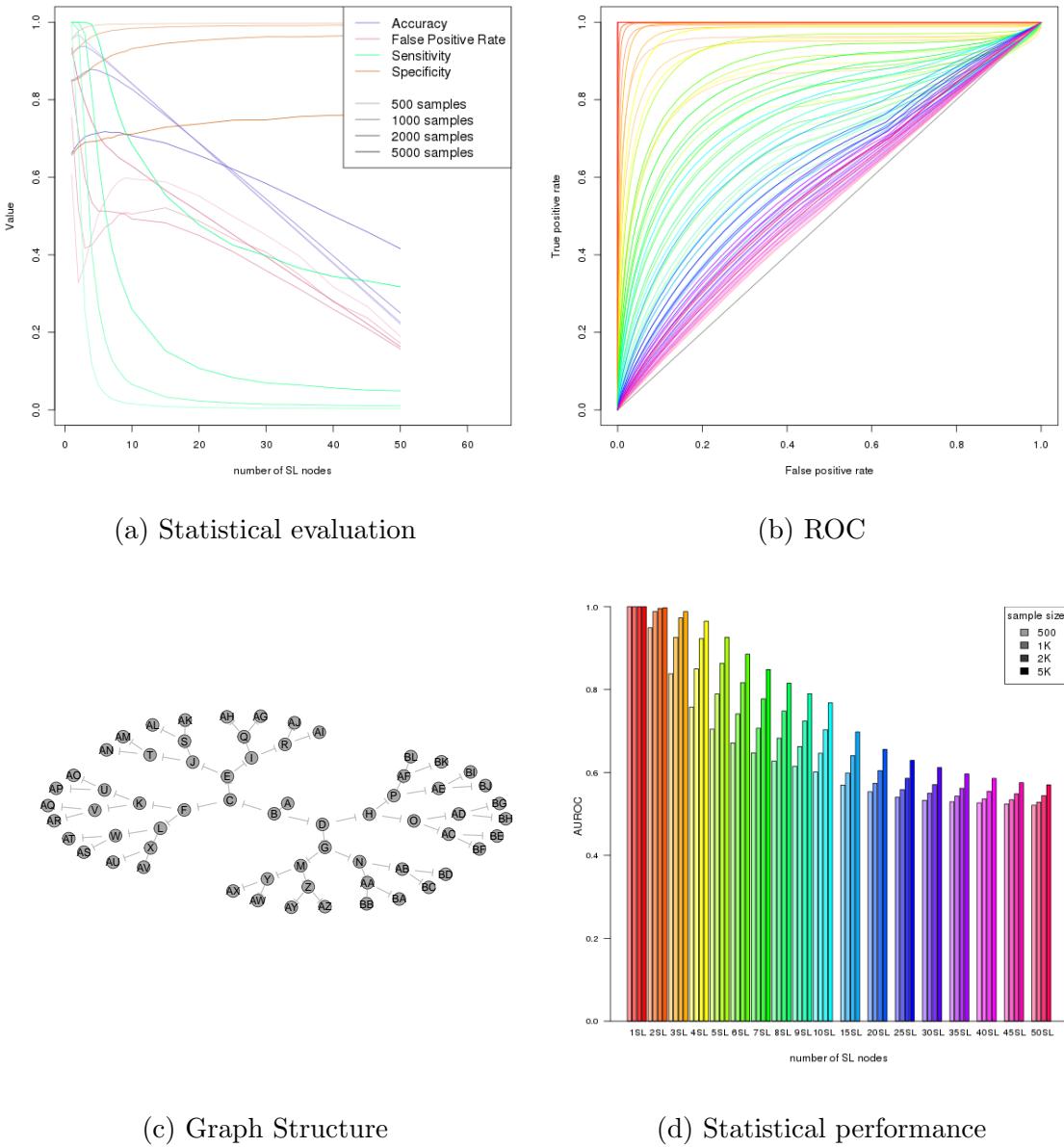
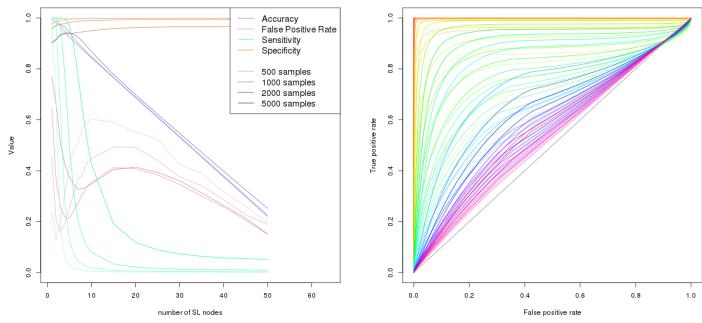
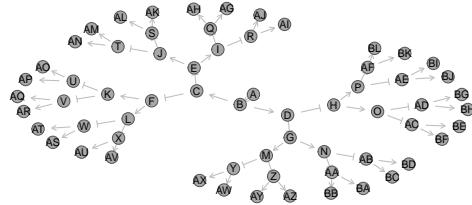


Figure K.11: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a branching graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.11b match Figure K.11d.

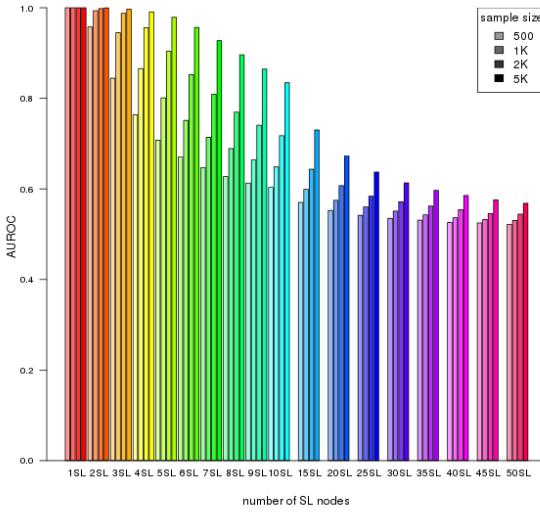


(a) Statistical evaluation

(b) ROC

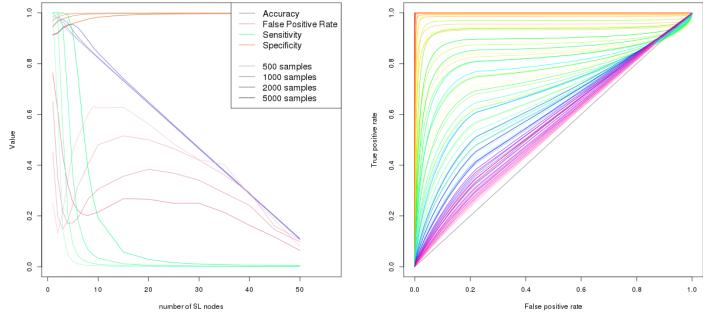


(c) Graph Structure



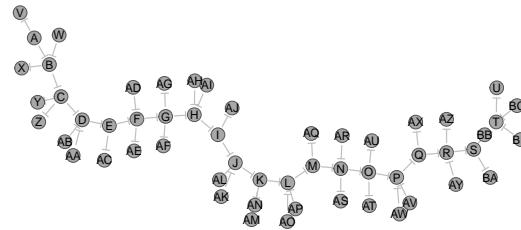
(d) Statistical performance

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.

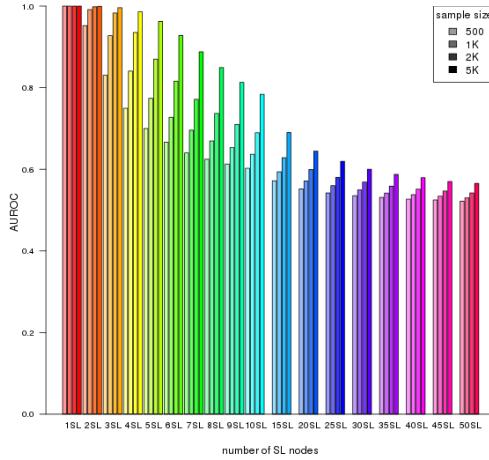


(a) Statistical evaluation

(b) ROC

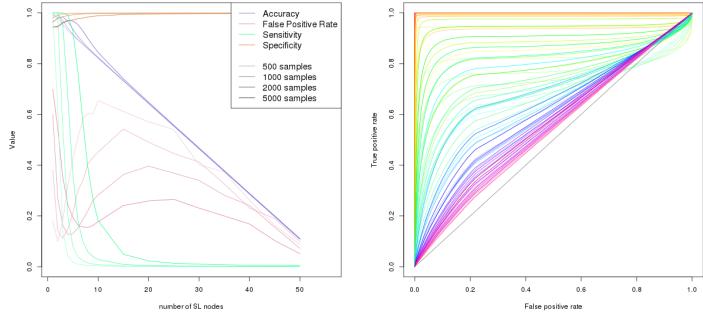


(c) Graph Structure



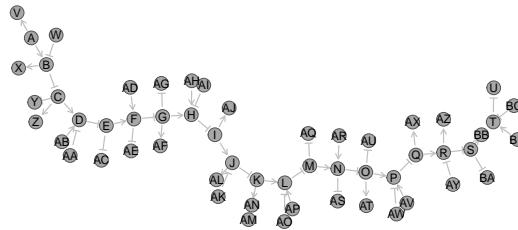
(d) Statistical performance

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.

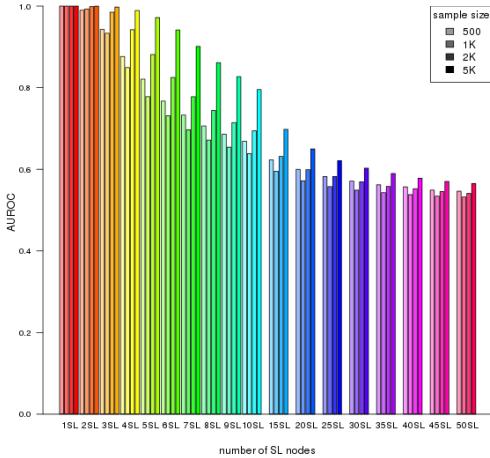


(a) Statistical evaluation

(b) ROC

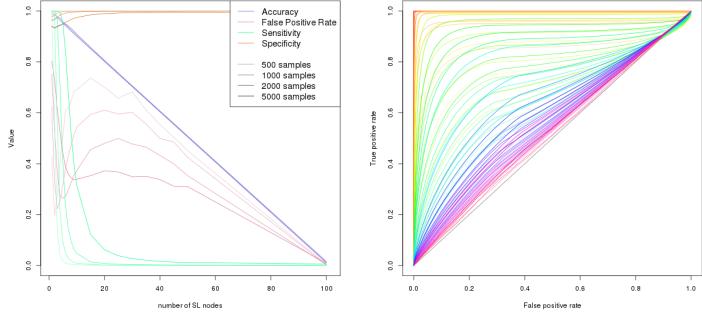


(c) Graph Structure



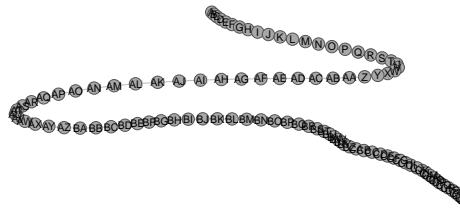
(d) Statistical performance

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.

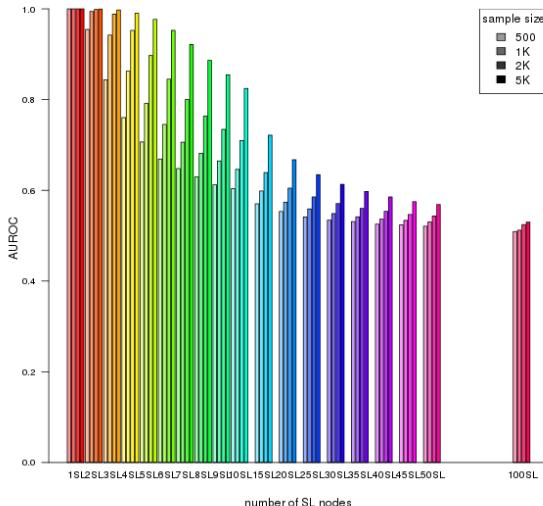


(a) Statistical evaluation

(b) ROC

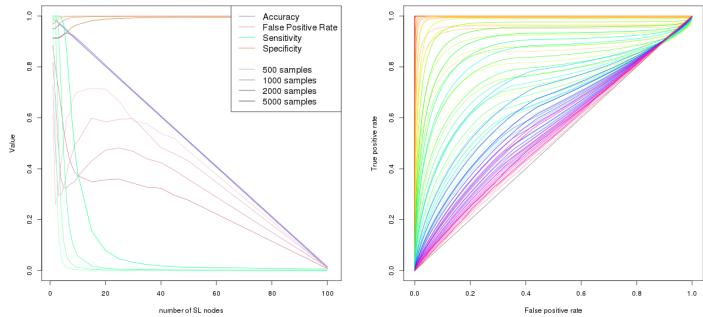


(c) Graph Structure

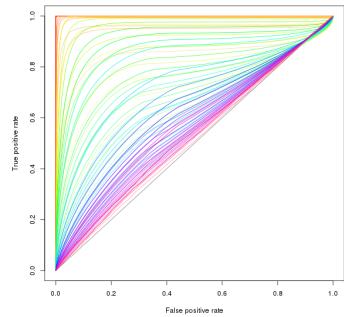


(d) Statistical performance

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.



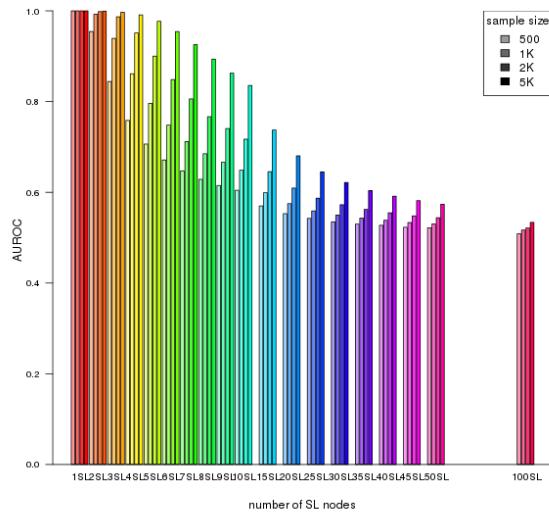
(a) Statistical evaluation



(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

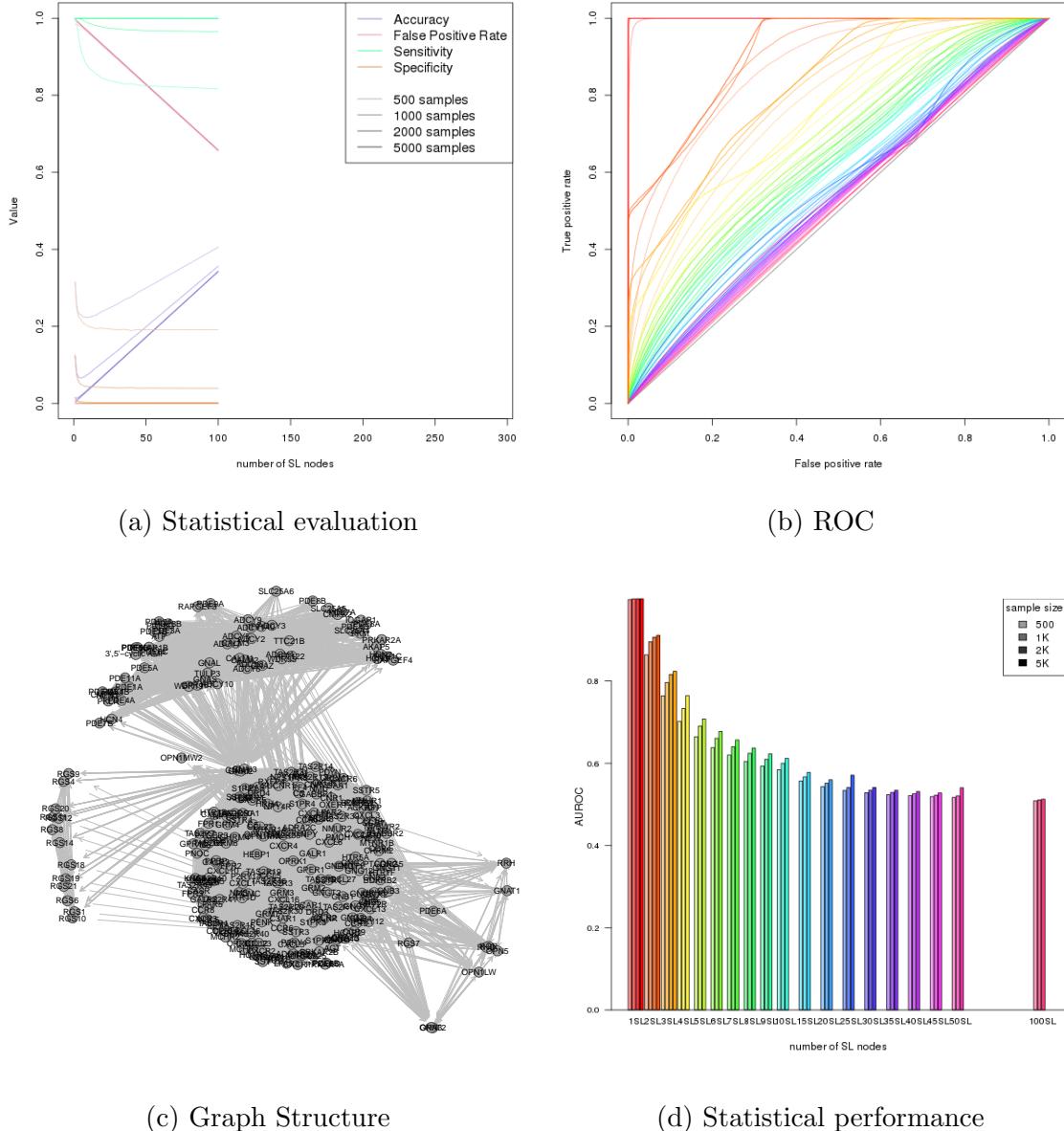


Figure K.17: Performance of simulations on the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution based on the Reactome $G_{\alpha i}$ signalling pathway. Performance of SLIPT was high across parameters for detecting synthetic lethality in the 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.

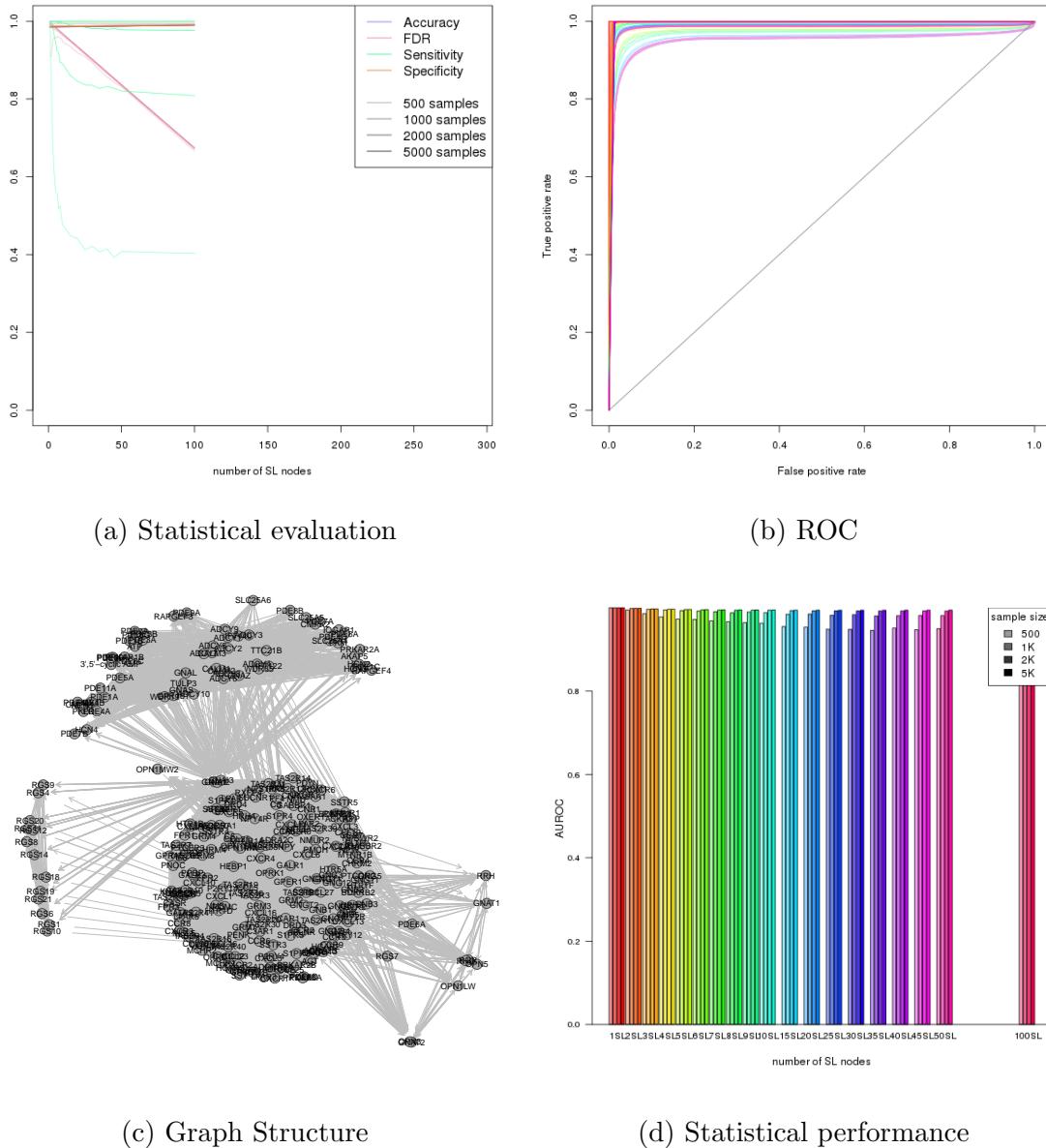


Figure K.18: Performance of simulations including the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution (without correlation structure apart from the Reactome $G_{\alpha i}$ signalling pathway. Performance of SLIPT was high across parameters 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.