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# Glossary

E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by <i>CDH1</i> .
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.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.
mutation	A change in DNA sequence that disrupts gene function.
RNA-Seq	The generation of transcriptome data from sequencing RNA.
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.

# Acronyms

ANOVA	Analysis of Variance.
ER	Estrogen Receptor.
FDR	False Discovery Rate.
mRNA	Messenger RNA.
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (against mutation).
PAM50	Prediction Analysis of Microarray 50.
RNA	Ribonucleic Acid.
siRNA	Short Interfering RNA.
SLIPT	Synthetic Lethal Interaction Prediction Tool.
TCGA	The Cancer Genome Atlas (genomics project).
UCSC	University of California, Santa Cruz.

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# Appendix C

## Mutation Analysis in Breast Cancer

### C.1 Synthetic Lethal Genes and Pathways

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

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

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

Strongest candidate SL partners for *CDH1* by mtSLIPT with observed and expected numbers of *CDH1* mutant TCGA breast tumours with low expression of partner genes.

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

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

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

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

## C.2 Synthetic Lethal Expression Profiles

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



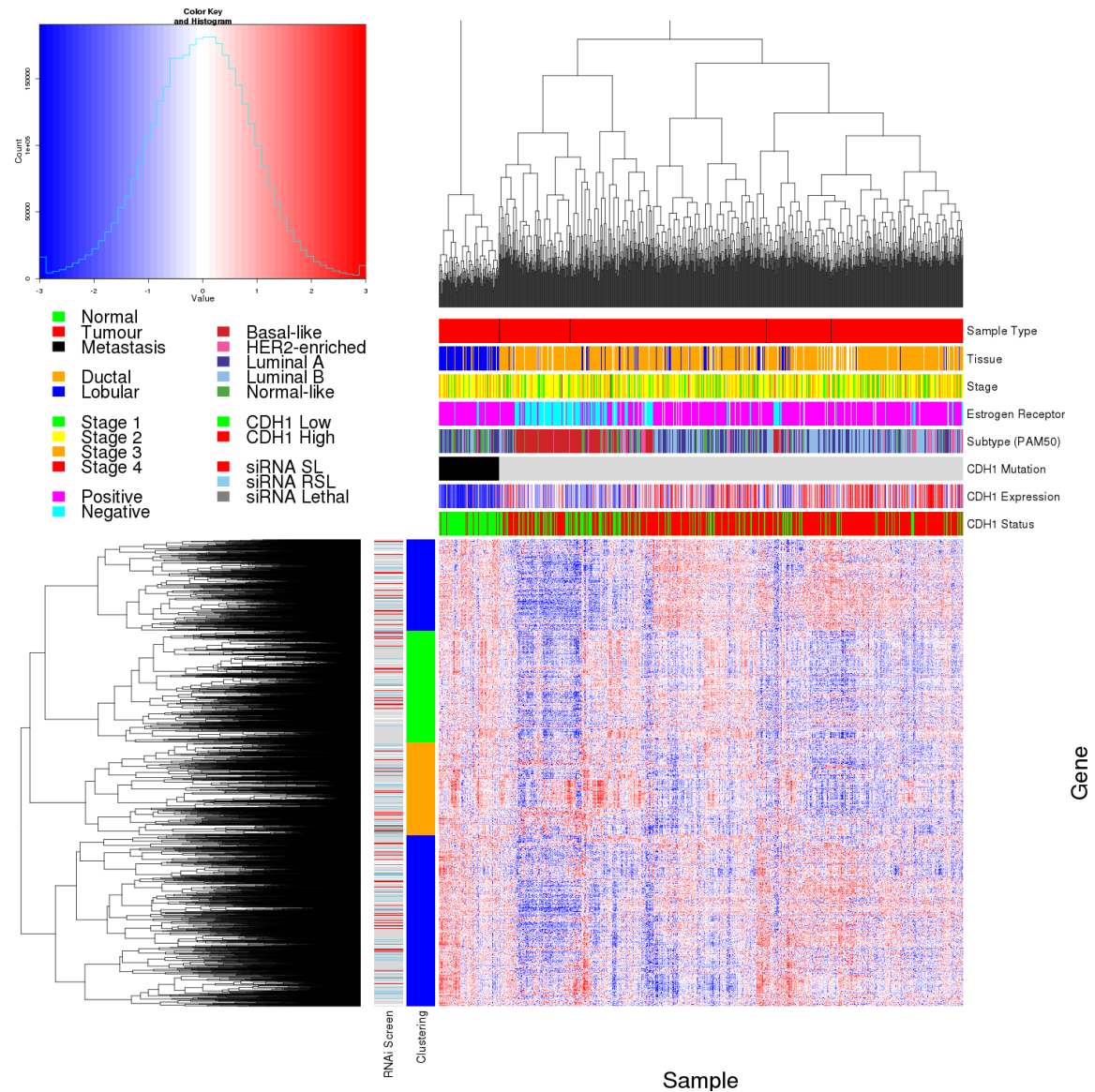


Figure C.1: **Synthetic lethal expression profiles of analysed samples.** Gene expression profile heatmap (correlation distance) of all samples (separated by *CDH1* somatic mutation status) analysed in TCGA breast cancer dataset for gene expression of 3743 candidate partners of E-cadherin (*CDH1*) from mtSLIPT prediction (with significant FDR adjusted  $p < 0.05$ ). Deeply clustered, inter-correlated genes form several main groups, each containing genes that were SL candidates or toxic in an siRNA screen Telford *et al.* (2015). Clusters had different sample groups highly expressing the synthetic lethal candidates in *CDH1* mutant samples and often lowly expressing *CDH1* wildtype 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* wildtype) basal subtype and ER negative samples have depleted expression among most candidate synthetic lethal partners.

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

Pathways Over-represented in Cluster 1	Pathway Size	Cluster Genes	p-value (FDR)
Olfactory Signalling Pathway	57	8	$7.1 \times 10^{-9}$
Assembly of the primary cilium	149	14	$8.0 \times 10^{-9}$
Sphingolipid metabolism	62	8	$9.6 \times 10^{-9}$
Signalling by ERBB4	133	12	$5.1 \times 10^{-8}$
PI3K Cascade	65	7	$4.9 \times 10^{-7}$
Circadian Clock	33	5	$4.9 \times 10^{-7}$
Nuclear signalling by ERBB4	34	5	$4.9 \times 10^{-7}$
Intraflagellar transport	35	5	$4.9 \times 10^{-7}$
PI3K events in ERBB4 signalling	87	8	$4.9 \times 10^{-7}$
PIP3 activates AKT signalling	87	8	$4.9 \times 10^{-7}$
PI3K events in ERBB2 signalling	87	8	$4.9 \times 10^{-7}$
PI-3K cascade:FGFR1	87	8	$4.9 \times 10^{-7}$
PI-3K cascade:FGFR2	87	8	$4.9 \times 10^{-7}$
PI-3K cascade:FGFR3	87	8	$4.9 \times 10^{-7}$
PI-3K cascade:FGFR4	87	8	$4.9 \times 10^{-7}$
Deadenylation of mRNA	22	4	$5.6 \times 10^{-7}$
PI3K/AKT activation	90	8	$5.6 \times 10^{-7}$
Cargo trafficking to the periciliary membrane	38	5	$5.6 \times 10^{-7}$
Pathways Over-represented in Cluster 2	Pathway Size	Cluster Genes	p-value (FDR)
G <sub>αs</sub> signalling events	83	19	$5.1 \times 10^{-25}$
Extracellular matrix organization	238	30	$1.4 \times 10^{-18}$
Hemostasis	422	46	$2.7 \times 10^{-16}$
Aquaporin-mediated transport	32	9	$2.7 \times 10^{-16}$
Transcriptional regulation of white adipocyte differentiation	56	11	$1.7 \times 10^{-15}$
Degradation of the extracellular matrix	102	15	$1.7 \times 10^{-15}$
Integration of energy metabolism	84	13	$8.8 \times 10^{-15}$
GPCR downstream signalling	472	48	$2.8 \times 10^{-14}$
G <sub>αz</sub> signalling events	15	6	$5.0 \times 10^{-14}$
Molecules associated with elastic fibres	33	8	$5.4 \times 10^{-14}$
Phase 1 - Functionalization of compounds	67	11	$5.6 \times 10^{-14}$
Platelet activation, signalling and aggregation	179	20	$5.6 \times 10^{-14}$
Vasopressin regulates renal water homeostasis via Aquaporins	24	7	$6.1 \times 10^{-14}$
Elastic fibre formation	37	8	$.03 \times 10^{-13}$
Calmodulin induced events	27	7	$3.3 \times 10^{-13}$
CaM pathway	27	7	$3.3 \times 10^{-13}$
cGMP effects	18	6	$3.6 \times 10^{-13}$
G <sub>αi</sub> signalling events	167	18	$6.3 \times 10^{-13}$
Pathways Over-represented in Cluster 3	Pathway Size	Cluster Genes	p-value (FDR)
Eukaryotic Translation Elongation	86	55	$1.1 \times 10^{-112}$
Peptide chain elongation	83	54	$1.3 \times 10^{-112}$
Viral mRNA Translation	81	53	$1.6 \times 10^{-111}$
Eukaryotic Translation Termination	83	53	$7.1 \times 10^{-110}$
Nonsense Mediated Decay independent of the Exon Junction Complex	88	54	$1.0 \times 10^{-108}$
Formation of a pool of free 40S subunits	93	53	$4.1 \times 10^{-102}$
Nonsense-Mediated Decay	103	54	$3.9 \times 10^{-98}$
Nonsense Mediated Decay enhanced by the Exon Junction Complex	103	54	$3.9 \times 10^{-98}$
LI3a-mediated translational silencing of Ceruloplasmin expression	103	53	$1.2 \times 10^{-95}$
3' -UTR-mediated translational regulation	103	53	$1.2 \times 10^{-95}$
SRP-dependent cotranslational protein targeting to membrane	104	53	$4.3 \times 10^{-95}$
GTP hydrolysis and joining of the 60S ribosomal subunit	104	53	$4.3 \times 10^{-95}$
Influenza Viral RNA Transcription and Replication	108	53	$9.6 \times 10^{-93}$
Eukaryotic Translation Initiation	111	53	$4.2 \times 10^{-91}$
Cap-dependent Translation Initiation	111	53	$4.2 \times 10^{-91}$
Influenza Life Cycle	112	53	$1.4 \times 10^{-90}$
Influenza Infection	117	53	$6.2 \times 10^{-88}$
Translation	141	55	$3 \times 10^{-81}$
Pathways Over-represented in Cluster 4	Pathway Size	Cluster Genes	p-value (FDR)
ECM proteoglycans	66	10	$2.9 \times 10^{-11}$
deactivation of the beta-catenin transactivating complex	38	7	$5.1 \times 10^{-10}$
Arachidonic acid metabolism	41	7	$1.1 \times 10^{-9}$
G <sub>αq</sub> signalling events	149	14	$4.0 \times 10^{-9}$
HS-GAG degradation	21	5	$4.5 \times 10^{-9}$
Uptake and actions of bacterial toxins	22	5	$6.1 \times 10^{-9}$
Gastrin-CREB signalling pathway via PKC and MAPK	170	15	$6.1 \times 10^{-9}$
RNA Polymerase I, RNA Polymerase III, and Mitochondrial Transcription	64	8	$6.1 \times 10^{-9}$
Non-integrin membrane-ECM interactions	53	7	$1.5 \times 10^{-8}$
Syndecan interactions	25	5	$1.5 \times 10^{-8}$
NOTCH1 Intracellular Domain Regulates Transcription	40	6	$2.3 \times 10^{-8}$
Synthesis of Leukotrienes and Eoxins	15	4	$3.2 \times 10^{-8}$
Signalling by NOTCH1	59	7	$5.3 \times 10^{-8}$
Regulation of insulin secretion	44	6	$6.0 \times 10^{-8}$
Metabolism of lipids and lipoproteins	471	37	$8.2 \times 10^{-8}$
Signalling by NOTCH	80	8	$1.2 \times 10^{-7}$
Platelet activation, signalling and aggregation	179	14	$1.2 \times 10^{-7}$
Recruitment of mitotic centrosome proteins and complexes	64	7	$1.2 \times 10^{-7}$

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

### C.3 Comparison to Primary Screen

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

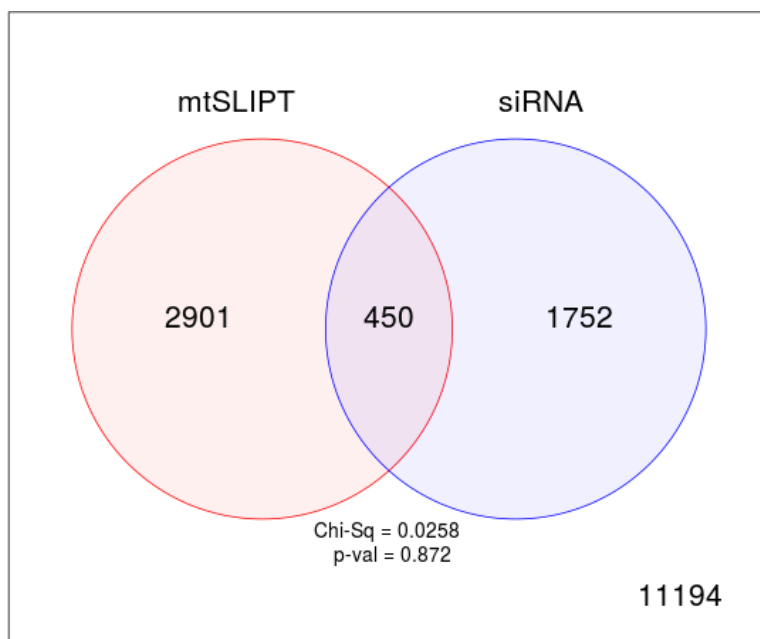


Figure C.2: **Comparison of mtSLIPT to siRNA.** Testing the overlap of gene candidates for *E-cadherin* synthetic lethal partners between computational (SLIPT) and experimental screening (siRNA) approaches. The  $\chi^2$  test suggests that the overlap is no more than would be expected by chance ( $p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

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

Table C.4: Pathways for *CDH1* partners from mtSLIPT and siRNA

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

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

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

### C.3.1 Resampling Analysis

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

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

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

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

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

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

## C.4 Compare SLIPT genes

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

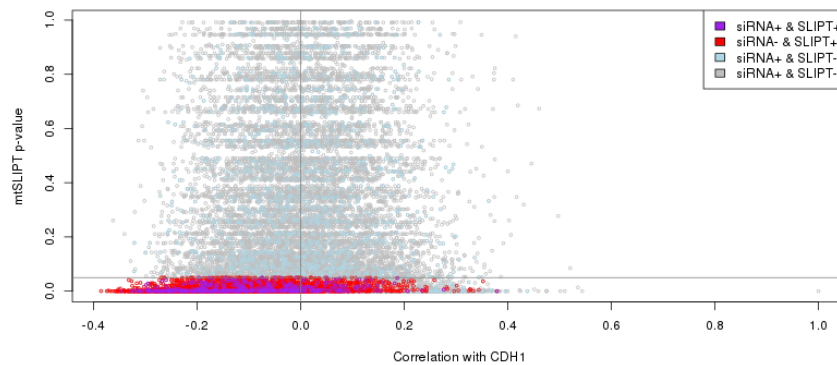


Figure C.3: **Compare mtSLIPT and siRNA genes with correlation.** The mtSLIPT p-values were compared against Pearson's correlation of expression with *CDH1*. Genes detected by SLIPT or siRNA were coloured according to the legend.

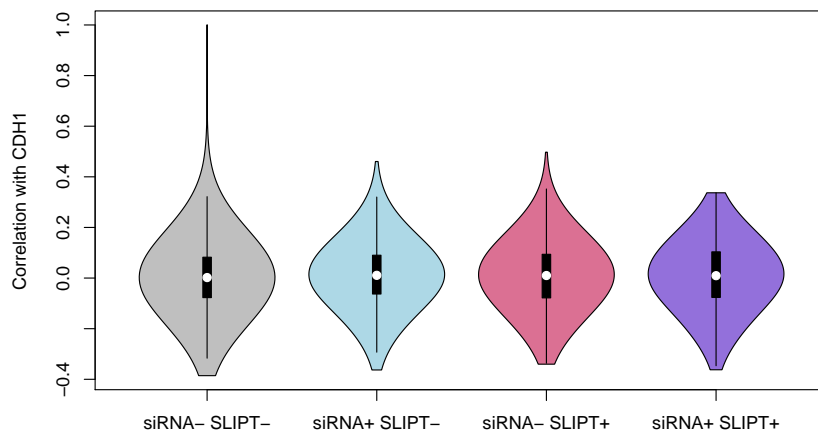


Figure C.4: **Compare mtSLIPT and siRNA genes with correlation.** Genes detected by mtSLIPT against *CDH1* mutation and siRNA screening were compared against Pearson's correlation of expression with *CDH1*. There were no differences in correlation between the gene groups.

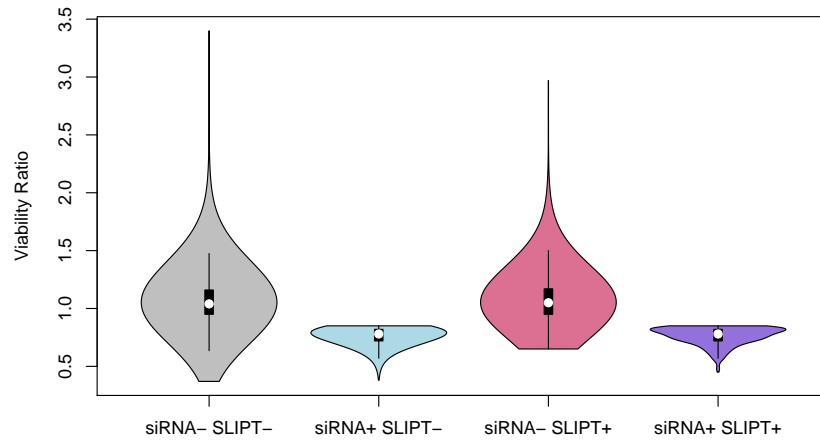


Figure C.5: **Compare *mtSLIPT* and *siRNA* genes with *siRNA* viability.** Genes detected as candidate synthetic lethal partners by *mtSLIPT* (in TCGA breast cancer) expression analysis against *CDH1* mutation and experimental screening (with *siRNA*) were compared against the viability ratio of *CDH1*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



## C.5 Metagene Analysis

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

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

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

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

## C.6 Expression of Somatic Mutations

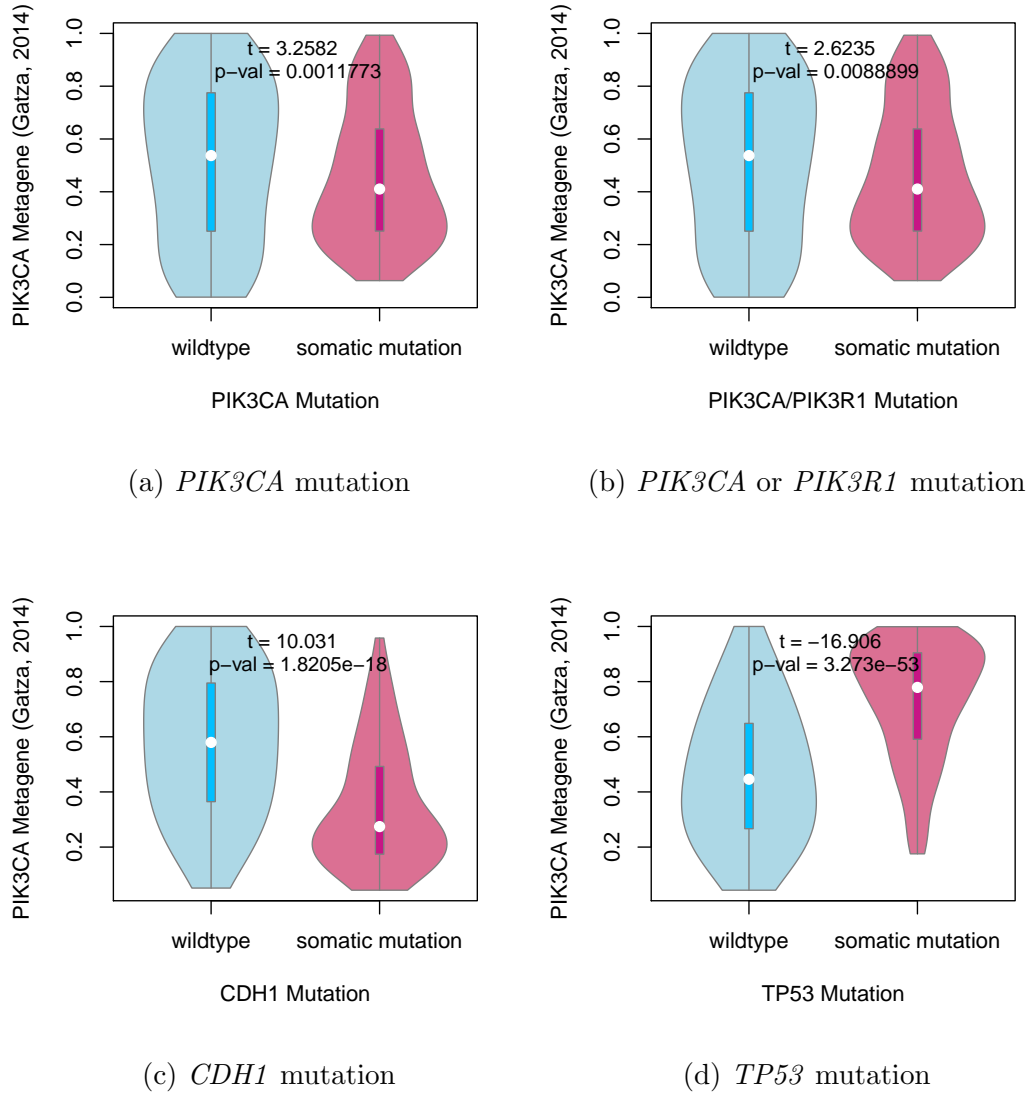
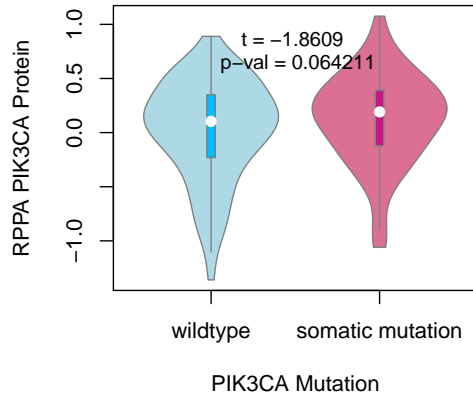
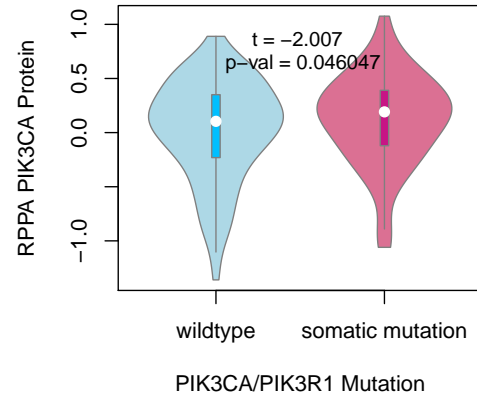


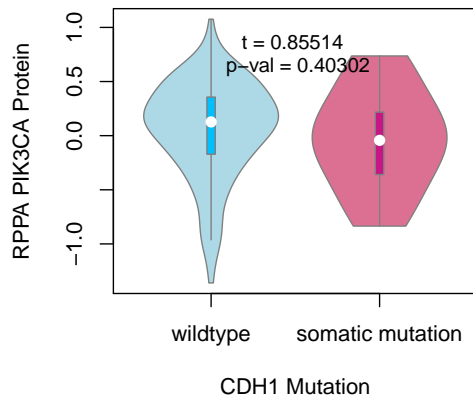
Figure C.6: **Somatic mutation against PIK3CA metagene.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the PIK3CA (Gatza *et al.*, 2014) pathway metagene. The tumour suppressors *CDH1* and *TP53* showed an increase and decrease in the metagene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



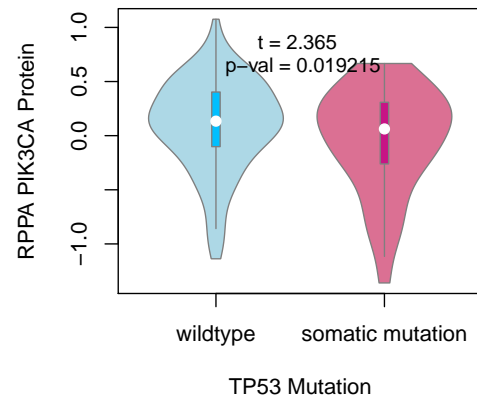
(a) *PIK3CA* mutation



(b) *PIK3CA* or *PIK3R1* mutation

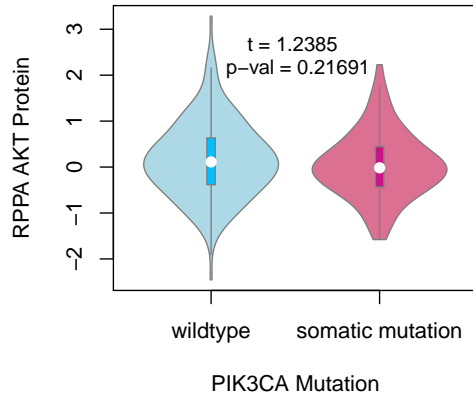


(c) *CDH1* mutation

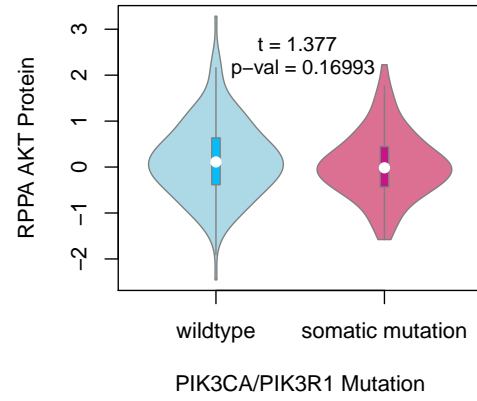


(d) *TP53* mutation

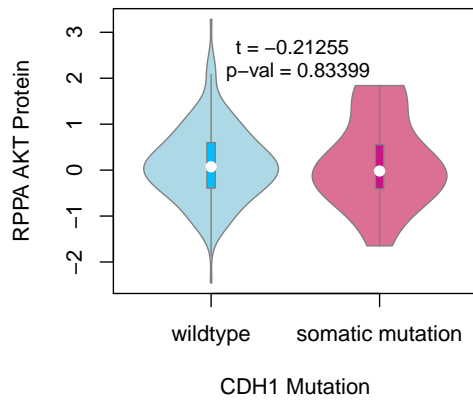
Figure C.7: **Somatic mutation against PI3K protein.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the expression of the p110 $\alpha$  protein (encoded by *PIK3CA*). Protein levels were significantly elevated in samples with *PIK3CA* or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



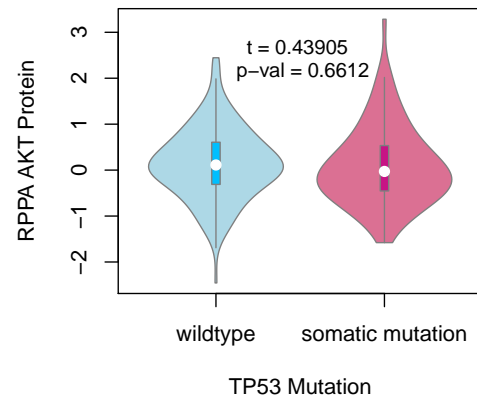
(a) *PIK3CA* mutation



(b) *PIK3CA* or *PIK3R1* mutation



(c) *CDH1* mutation



(d) *TP53* mutation

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

## C.7 Metagene Expression Profiles

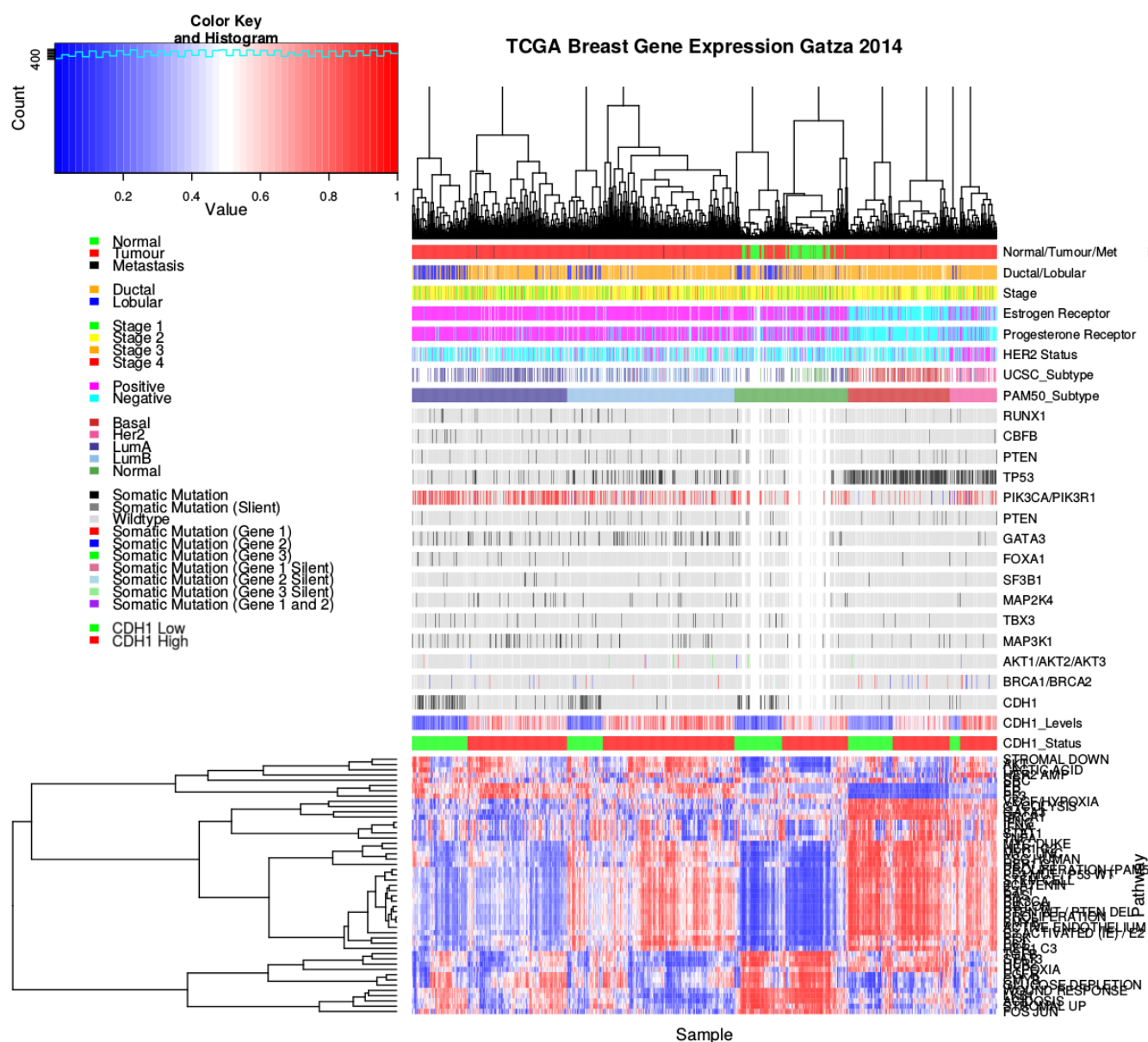


Figure C.9: **Pathway metagene expression profiles.** Expression profiles for metagene signatures from Gatzka *et al.* (2014) in TCGA breast data, annotated for clinical factors and cancer gene mutations.

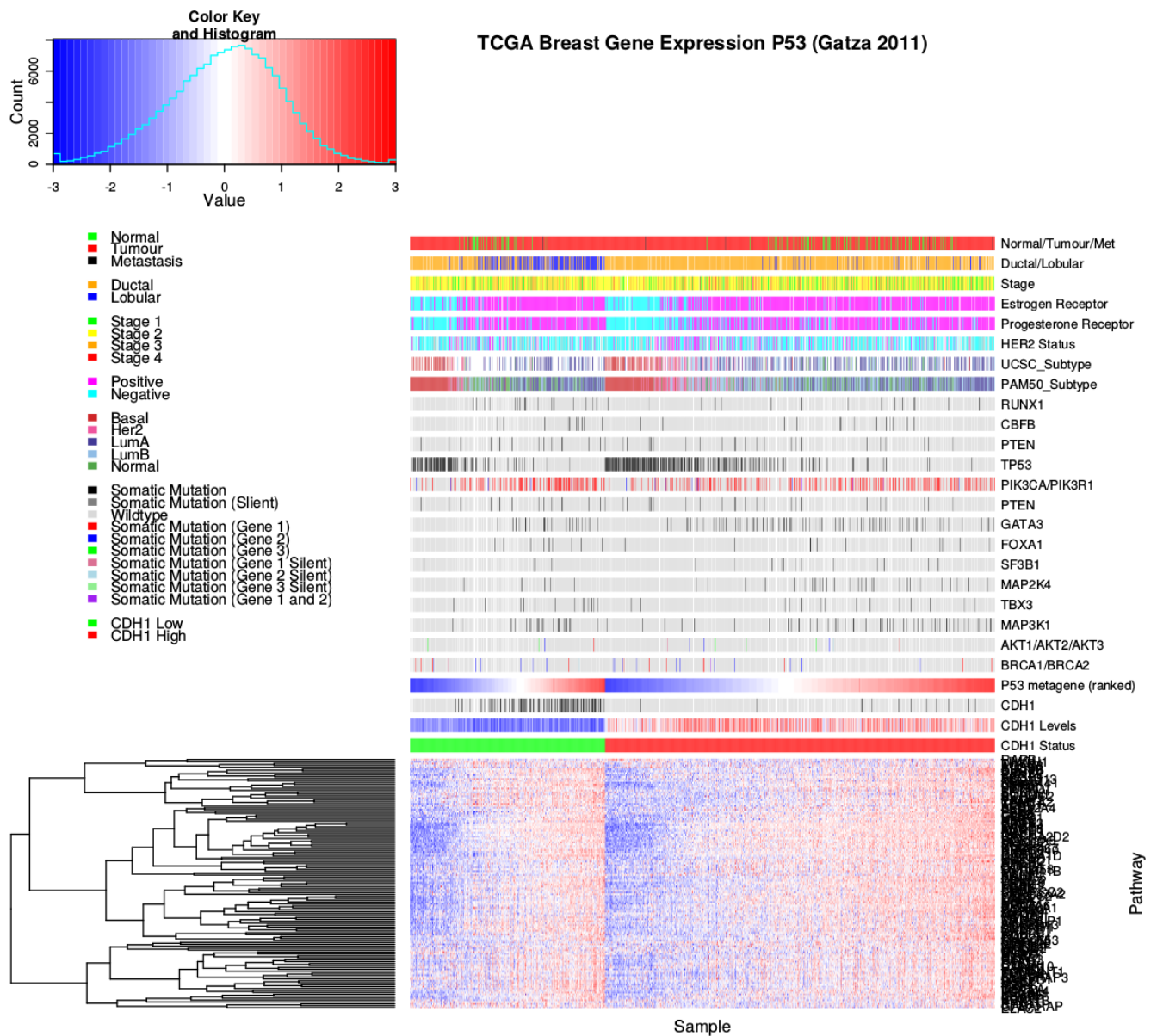


Figure C.10: **Expression profiles for p53 related genes.** Expression profiles the genes contained in the *TP53* gene signature from Gatza *et al.* (2011) in TCGA breast data, annotated for clinical factors and cancer gene mutations. Samples were separated by *CDH1* expression status and sorted by the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



# Appendix D

## Intrinsic Subtyping

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

Table D.1: Comparison of intrinsic subtypes

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

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

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

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



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

# Appendix E

## Stomach Expression Analysis

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

### E.1 Synthetic Lethal Genes and Pathways

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

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

SLIPT partners of *CDH1* with observed and expected numbers of [TCGA](#) stomach cancer samples with low expression of both genes.

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

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

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

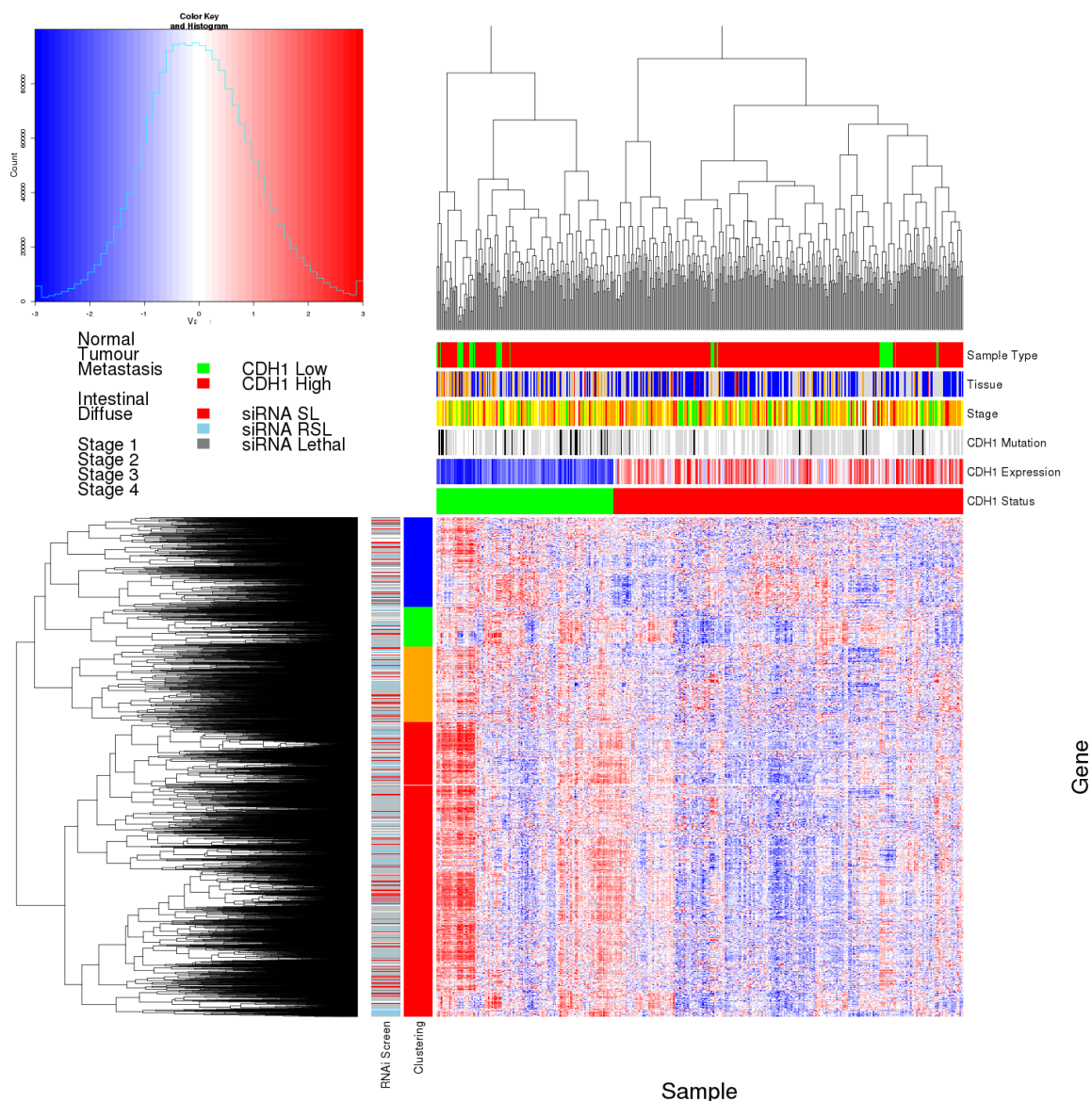


Figure E.1: **Synthetic lethal expression profiles of analysed samples.** Gene expression profile heatmap (correlation distance) of all samples (separated by the  $1/3$  quantile of *CDH1* expression) analysed in TCGA stomach cancer dataset for gene expression of 4365 candidate partners of E-cadherin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

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

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

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

## E.2 Comparison to Primary Screen

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

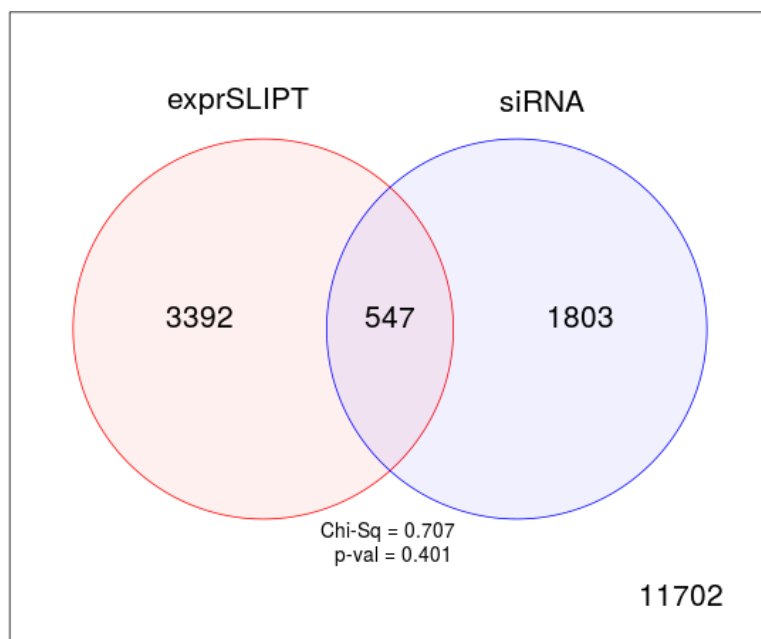


Figure E.2: **Comparison of SLIPT in stomach to siRNA.** The overlap of gene candidates for *E-cadherin* synthetic lethal partners between computational (SLIPT) and experimental screening (siRNA) approaches. The  $\chi^2$  test suggests that the overlap is no more than would be expected by chance ( $p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

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

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

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

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

## E.2.1 Resampling Analysis

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

Reactome Pathway	Over-representation	Permutation
<i>Extracellular matrix organization</i>	$7.5 \times 10^{-140}$	0.070215
Hemostasis	$1.8 \times 10^{-121}$	0.25804
Developmental Biology	$9.2 \times 10^{-107}$	0.53032
Axon guidance	$1.5 \times 10^{-102}$	0.6704
<b>Eukaryotic Translation Termination</b>	$1.9 \times 10^{-99}$	$> 1.031 \times 10^{-5}$
GPCR ligand binding	$3.8 \times 10^{-99}$	0.54914
<b>Viral mRNA Translation</b>	$3.3 \times 10^{-98}$	$> 1.031 \times 10^{-5}$
<b>Formation of a pool of free 40S subunits</b>	$3.3 \times 10^{-98}$	$> 1.031 \times 10^{-5}$
<b>Eukaryotic Translation Elongation</b>	$1.6 \times 10^{-97}$	$> 1.031 \times 10^{-5}$
<b>Peptide chain elongation</b>	$7.2 \times 10^{-97}$	$> 1.031 \times 10^{-5}$
Class A/1 (Rhodopsin-like receptors)	$2.7 \times 10^{-96}$	0.58174
<b>Nonsense Mediated Decay independent of the Exon Junction Complex</b>	$3 \times 10^{-96}$	$> 1.031 \times 10^{-5}$
Infectious disease	$2.6 \times 10^{-94}$	0.25484
<b>GTP hydrolysis and joining of the 60S ribosomal subunit</b>	$3.4 \times 10^{-94}$	$> 1.031 \times 10^{-5}$
<b>L13a-mediated translational silencing of Ceruloplasmin expression</b>	$2.8 \times 10^{-92}$	$> 1.031 \times 10^{-5}$
<b>3' -UTR-mediated translational regulation</b>	$2.8 \times 10^{-92}$	$> 1.031 \times 10^{-5}$
Neuronal System	$8.4 \times 10^{-92}$	0.53433
<b>SRP-dependent cotranslational protein targeting to membrane</b>	$9.5 \times 10^{-92}$	$> 1.031 \times 10^{-5}$
<b>Eukaryotic Translation Initiation</b>	$2.0 \times 10^{-90}$	$> 1.031 \times 10^{-5}$
<b>Cap-dependent Translation Initiation</b>	$2.0 \times 10^{-90}$	$> 1.031 \times 10^{-5}$
<b>Nonsense-Mediated Decay</b>	$7.4 \times 10^{-90}$	$> 1.031 \times 10^{-5}$
<b>Nonsense Mediated Decay enhanced by the Exon Junction Complex</b>	$7.4 \times 10^{-90}$	$> 1.031 \times 10^{-5}$
Adaptive Immune System	$8.1 \times 10^{-88}$	0.14116
<b>Translation</b>	$1.3 \times 10^{-87}$	$> 1.031 \times 10^{-5}$
Platelet activation, signalling and aggregation	$1.3 \times 10^{-86}$	0.28959
<b>Influenza Infection</b>	$1 \times 10^{-82}$	$> 1.031 \times 10^{-5}$
<b>Influenza Viral RNA Transcription and Replication</b>	$2.4 \times 10^{-82}$	$> 1.031 \times 10^{-5}$
<b>Influenza Life Cycle</b>	$2 \times 10^{-80}$	$> 1.031 \times 10^{-5}$
Response to elevated platelet cytosolic $\text{Ca}^{2+}$	$4.9 \times 10^{-78}$	0.50817
Signalling by NGF	$1.6 \times 10^{-75}$	0.38518
Rho GTPase cycle	$5.1 \times 10^{-75}$	0.14864
Signalling by PDGF	$7.4 \times 10^{-74}$	0.40493
<i>Signalling by Rho GTPases</i>	$5.1 \times 10^{-73}$	0.077217
Glycosaminoglycan metabolism	$1.4 \times 10^{-68}$	0.52984
$\text{G}_{\alpha i}$ signalling events	$1.8 \times 10^{-66}$	0.9254
Metabolism of carbohydrates	$1.1 \times 10^{-65}$	0.39501
<b><math>\text{G}_{\alpha s}</math> signalling events</b>	$2.7 \times 10^{-65}$	0.0050293
Potassium Channels	$2.7 \times 10^{-65}$	0.53359
Transmission across Chemical Synapses	$1.8 \times 10^{-64}$	0.81833
ECM proteoglycans	$3.4 \times 10^{-64}$	0.083482
Peptide ligand-binding receptors	$4.8 \times 10^{-64}$	0.62817
Degradation of the extracellular matrix	$1.1 \times 10^{-63}$	0.80879
Platelet homeostasis	$5.3 \times 10^{-63}$	0.53134
NGF signalling via TRKA from the plasma membrane	$6.1 \times 10^{-63}$	0.5717
Integration of energy metabolism	$4.5 \times 10^{-61}$	0.10889
Collagen formation	$5.4 \times 10^{-61}$	0.29896
Integrin cell surface interactions	$7 \times 10^{-59}$	0.18167
Collagen biosynthesis and modifying enzymes	$7 \times 10^{-59}$	0.30208
Neurotransmitter Receptor Binding And Downstream Transmission	$8.7 \times 10^{-57}$	0.82522
In The Postsynaptic Cell	$8.7 \times 10^{-57}$	0.25468
Signalling by Wnt	$8.7 \times 10^{-57}$	0.25468

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



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

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

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

## E.3 Metagene Analysis

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

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

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

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