

Contents

Glossary	xiii
Acronyms	xv
1 Introduction and Literature Review	1
1.1 Cancer Research in the Post-Genomic Era	1
1.1.1 Cancer is a Global Health Issue	2
1.1.1.1 The Genetics and Molecular Biology of Cancers	3
1.1.2 The Genomics Revolution in Cancer Research	3
1.1.2.1 High-Throughput Technologies	4
1.1.2.2 Bioinformatics and Genomic Data	5
1.1.3 Genomics Projects	5
1.1.3.1 The Cancer Genome Project	6
1.1.3.2 The Cancer Genome Atlas Project	6
1.1.4 Genomic Cancer Medicine	8
1.1.4.1 Cancer Genes and Driver Mutations	8
1.1.4.2 Precision Cancer Medicine	9
1.1.4.3 Molecular Diagnostics and Pan-Cancer Medicine	9
1.1.4.4 Targeted Therapeutics and Pharmacogenomics	10
1.1.5 Systems and Network Biology	11
1.2 Synthetic Lethal Cancer Medicine	12
1.2.1 Synthetic Lethal Genetic Interactions	12
1.2.2 Synthetic Lethal Concepts in Genetics	14
1.2.3 Synthetic Lethality in Model Systems	14
1.2.3.1 Synthetic Lethal Pathways and Networks	15
1.2.3.2 Evolution of Synthetic Lethality	15
1.2.4 Synthetic Lethality in Cancer	16
1.2.5 Clinical Impact of Synthetic Lethality in Cancer	18
1.2.6 High-throughput Screening for Synthetic Lethality	19
1.2.6.1 Synthetic Lethal Screens	21
1.2.7 Computational Prediction of Synthetic Lethality	22
1.2.7.1 Bioinformatics Approaches to Genetic Interactions	22
1.2.7.2 Comparative Genomics	23
1.2.7.3 Analysis and Modelling of Protein Data	26
1.2.7.4 Differential Gene Expression	27
1.2.7.5 Data Mining and Machine Learning	28

1.2.7.6	Mutually Exclusive Bimodality	31
1.2.7.7	Rationale for Further Development	32
1.3	E-cadherin as a Synthetic Lethal Target	32
1.3.1	The <i>CDH1</i> gene and its Biological Functions	33
1.3.1.1	Cytoskeleton	33
1.3.1.2	Extracellular and Tumour Micro-environment	33
1.3.1.3	Cell-Cell Adhesion and Signalling	34
1.3.2	<i>CDH1</i> as a Tumour (and Invasion) Suppressor	34
1.3.2.1	Breast Cancers and Invasion	34
1.3.3	Hereditary Diffuse Gastric (and Lobular Breast) Cancer	35
1.3.4	Cell Line Models of <i>CDH1</i> Null Mutations	36
1.4	Summary and Research Direction of Thesis	37
1.4.1	Thesis Aims	38
2	Methods and Resources	40
2.1	Bioinformatics Resources for Genomics Research	40
2.1.1	Public Data and Software Packages	40
2.1.1.1	Cancer Genome Atlas Data	41
2.1.1.2	Reactome and Annotation Data	42
2.2	Data Handling	42
2.2.1	Normalisation	42
2.2.2	Sample Triage	43
2.2.3	Metagenes and the Singular Value Decomposition	43
2.2.4	Candidate Triage and Integration with Screen Data	45
2.3	Techniques	46
2.3.1	Statistical Procedures and Tests	46
2.3.2	Gene Set Over-representation Analysis	47
2.3.3	Clustering	47
2.3.4	Heatmap	47
2.3.5	Modelling and Simulations	48
2.3.5.1	Receiver Operating Characteristic Curves	49
2.3.6	Resampling Analysis	49
2.4	Pathway Structure Methods	50
2.4.1	Network and Graph Analysis	50
2.4.2	Sourcing Graph Structure Data	51
2.4.3	Constructing Pathway Subgraphs	51
2.4.4	Network Analysis Metrics	52
2.5	Implementation	53
2.5.1	Computational Resources and Linux Utilities	53
2.5.2	R Language and Packages	54
2.5.3	High Performance and Parallel Computing	57
3	Methods Developed During Thesis	59
3.1	A Synthetic Lethal Detection Methodology	59
3.2	Synthetic Lethal Simulation and Modelling	61
3.2.1	A Model of Synthetic Lethality in Expression Data	62

3.2.2	Simulation Procedure	66
3.3	Detecting Simulated Synthetic Lethal Partners	69
3.3.1	Binomial Simulation of Synthetic Lethality	69
3.3.2	Multivariate Normal Simulation of Synthetic Lethality	71
3.3.2.1	Multivariate Normal Simulation with Correlated Genes	73
3.3.2.2	Specificity with Query-Correlated Pathways	81
3.4	Graph Structure Methods	83
3.4.1	Upstream and Downstream Gene Detection	83
3.4.1.1	Permutation Analysis for Statistical Significance	84
3.4.1.2	Hierarchy Based on Biological Context	84
3.4.2	Simulating Gene Expression from Graph Structures	85
3.5	Customised Functions and Packages Developed	90
3.5.1	Synthetic Lethal Interaction Prediction Tool	90
3.5.2	Data Visualisation	91
3.5.3	Extensions to the iGraph Package	93
3.5.3.1	Sampling Simulated Data from Graph Structures	93
3.5.3.2	Plotting Directed Graph Structures	93
3.5.3.3	Computing Information Centrality	94
3.5.3.4	Testing Pathway Structure with Permutation Testing .	94
3.5.3.5	Metapackage to Install iGraph Functions	95
4	Synthetic Lethal Analysis of Gene Expression Data	96
4.1	Synthetic Lethal Genes in Breast Cancer	97
4.1.1	Synthetic Lethal Pathways in Breast Cancer	98
4.1.2	Expression Profiles of Synthetic Lethal Partners	100
4.1.2.1	Subgroup Pathway Analysis	103
4.2	Comparing Synthetic Lethal Gene Candidates	105
4.2.1	Primary siRNA Screen Candidates	105
4.2.2	Comparison with Correlation	105
4.2.3	Comparison with Primary Screen Viability	108
4.2.4	Comparison with Secondary siRNA Screen Validation	110
4.2.5	Comparison to Primary Screen at Pathway Level	111
4.2.5.1	Resampling Genes for Pathway Enrichment	113
4.2.6	Integrating Synthetic Lethal Pathways and Screens	118
4.3	Synthetic Lethal Pathway Metagenes	119
4.4	Replication in Stomach Cancer	120
4.5	Discussion	121
4.5.1	Strengths of the SLIPT Methodology	121
4.5.2	Synthetic Lethal Pathways for E-cadherin	123
4.5.3	Replication and Validation	125
4.5.3.1	Integration with siRNA Screening	125
4.5.3.2	Replication across Tissues	125
4.6	Summary	126

5 Synthetic Lethal Pathway Structure	128
5.1 Synthetic Lethal Genes in Reactome Pathways	128
5.1.1 The PI3K/AKT Pathway	129
5.1.2 The Extracellular Matrix	131
5.1.3 G Protein Coupled Receptors	134
5.1.4 Gene Regulation and Translation	134
5.2 Network Analysis of Synthetic Lethal Genes	135
5.2.1 Gene Connectivity and Vertex Degree	136
5.2.2 Gene Importance and Centrality	137
5.2.2.1 Information Centrality	137
5.2.2.2 PageRank Centrality	139
5.3 Relationships between Synthetic Lethal Genes	141
5.3.1 Hierarchical Pathway Structure	141
5.3.1.1 Contextual Hierarchy of PI3K	141
5.3.1.2 Testing Contextual Hierarchy of Synthetic Lethal Genes	141
5.3.2 Upstream or Downstream Synthetic Lethality	145
5.3.2.1 Measuring Structure of Candidates within PI3K . .	145
5.3.2.2 Resampling for Synthetic Lethal Pathway Structure .	147
5.4 Discussion	149
5.5 Summary	151
6 Simulation and Modelling of Synthetic Lethal Pathways	152
6.1 Synthetic Lethal Detection Methods	153
6.1.1 Performance of SLIPT and χ^2 across Quantiles	154
6.1.1.1 Correlated Query Genes affects Specificity	157
6.1.2 Alternative Synthetic Lethal Detection Strategies	159
6.1.2.1 Correlation for Synthetic Lethal Detection	160
6.1.2.2 Testing for Bimodality with BiSEp	161
6.2 Simulations with Graph Structures	162
6.2.1 Performance over Graph Structures	163
6.2.1.1 Simple Graph Structures	163
6.2.1.2 Constructed Graph Structures	166
6.2.2 Performance with Inhibitions	168
6.2.3 Synthetic Lethality across Graph Structures	174
6.2.4 Performance within a Simulated Human Genome	177
6.3 Simulations in More Complex Graph Structures	182
6.3.1 Simulations over Pathway-based Graphs	183
6.3.2 Pathway Structures in a Simulated Human Genome	185
6.4 Discussion	188
6.4.1 Simulation Procedure	188
6.4.2 Comparing Methods with Simulated Data	189
6.4.3 Design and Performance of SLIPT	190
6.4.4 Simulations from Graph Structures	192
6.5 Summary	193

7 Discussion	195
7.1 Synthetic Lethality and <i>CDH1</i> Biology	195
7.1.1 Established Functions of <i>CDH1</i>	196
7.1.2 The Molecular Role of <i>CDH1</i> in Cancer	196
7.2 Significance	197
7.2.1 Synthetic Lethality in the Genomic Era	197
7.2.2 Clinical Interventions based on Synthetic Lethality	199
7.3 Future Directions	200
7.4 Conclusions	202
Bibliography	204
A Sample Quality	228
A.1 Sample Correlation	228
A.2 Replicate Samples in The Cancer Genome Atlas (TCGA) Breast	230
B Software Used for Thesis	234
C Mutation Analysis in Breast Cancer	243
C.1 Synthetic Lethal Genes and Pathways	243
C.2 Synthetic Lethal Expression Profiles	244
C.3 Comparison to Primary Screen	247
C.3.1 Resampling Analysis	249
C.4 Compare SLIPT genes	251
D Metagene Analysis	253
D.1 Pathway Signature Expression	253
D.2 Somatic Mutation	262
D.3 Synthetic Lethal Reactome Metagenes	263
D.4 Expression of Somatic Mutations	265
E Intrinsic Subtyping	268
F Stomach Expression Analysis	270
F.1 Synthetic Lethal Genes and Pathways	270
F.2 Comparison to Primary Screen	273
F.2.1 Resampling Analysis	275
F.3 Metagene Analysis	277
G Synthetic Lethal Genes in Pathways	279
H Pathway Connectivity for Mutation SLIPT	287
I Information Centrality for Gene Essentiality	291
J Pathway Structure for Mutation SLIPT	294

K Performance of SLIPT and χ^2	297
K.1 Correlated Query Genes affects Specificity	303
L Simulations on Graph Structures	309
L.0.1 Simulations from Inhibiting Graph Structures	310
L.1 Simulation across Graph Structures	313
L.2 Simulations from Complex Graph Structures	317
L.2.1 Simulations from Complex Inhibiting Graphs	320
L.3 Simulations from Pathway Graph Structures	326

List of Figures

1.1	Synthetic genetic interactions	13
1.2	Synthetic lethality in cancer	17
2.1	Read count density	44
2.2	Read count sample mean	44
3.1	Framework for synthetic lethal prediction	60
3.2	Synthetic lethal prediction adapted for mutation	61
3.3	A model of synthetic lethal gene expression	63
3.4	Modelling synthetic lethal gene expression	64
3.5	Synthetic lethality with multiple genes	65
3.6	Simulating gene function	67
3.7	Simulating synthetic lethal gene function	67
3.8	Simulating synthetic lethal gene expression	68
3.9	Performance of binomial simulations	70
3.10	Comparison of statistical performance	70
3.11	Performance of multivariate normal simulations	72
3.12	Simulating expression with correlated gene blocks	74
3.13	Simulating expression with correlated gene blocks	75
3.14	Synthetic lethal prediction across simulations	77
3.15	Performance with correlations	78
3.16	Comparison of statistical performance with correlation structure	79
3.17	Performance with query correlations	80
3.18	Statistical evaluation of directional criteria	81
3.19	Performance of directional criteria	82
3.20	Simulated graph structures	86
3.21	Simulating expression from a graph structure	87
3.22	Simulating expression from graph structure with inhibitions	88
3.23	Demonstration of violin plots with custom features	92
3.24	Demonstration of annotated heatmap	92
3.25	Simulating graph structures	94
4.1	Synthetic lethal expression profiles of analysed samples	101
4.2	Comparison of SLIPT with siRNA	106
4.3	Comparison of SLIPT and siRNA genes with correlation	106
4.4	Comparison of SLIPT and siRNA genes with correlation	108
4.5	Comparison of SLIPT and siRNA genes with screen viability	109

4.6	Comparison of SLIPT genes with siRNA screen viability	109
4.7	Resampled intersection of SLIPT and siRNA candidate genes	114
5.1	synthetic lethality in the PI3K cascade	130
5.2	synthetic lethality in Elastic Fibre Formation	132
5.3	Synthetic lethality in Fibrin Clot Formation	133
5.4	Synthetic lethality and vertex degree	136
5.5	Synthetic lethality and centrality	139
5.6	Synthetic lethality and PageRank	140
5.7	Hierarchical structure of PI3K	142
5.8	Hierarchy score in PI3K against synthetic lethality in PI3K	143
5.9	Structure of synthetic lethality in PI3K	144
5.10	Structure of synthetic lethality resampling in PI3K	146
6.1	Performance of χ^2 and SLIPT across quantiles	155
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	156
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation .	157
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	158
6.5	Performance of negative correlation and SLIPT	161
6.6	Simple graph structures	164
6.7	Performance of simulations on a simple graph	165
6.8	Performance of simulations is similar in simple graphs	166
6.9	Performance of simulations on a pathway	167
6.10	Performance of simulations on a simple graph with inhibition	169
6.11	Performance is higher on a simple inhibiting graph	171
6.12	Performance of simulations on a constructed graph with inhibition . .	172
6.13	Performance is affected by inhibition in graphs	173
6.14	Detection of synthetic lethality within a graph structure	175
6.15	Performance of simulations including a simple graph	179
6.16	Performance on a simple graph improves with more genes	180
6.17	Performance on an inhibiting graph improves with more genes	181
6.18	Performance of simulations on the PI3K cascade	184
6.19	Performance of simulations including the PI3K cascade	186
6.20	Performance on pathways improves with more genes	187
A.1	Correlation profiles of removed samples	228
A.2	Correlation analysis and sample removal	229
A.3	Replicate excluded samples	230
A.4	Replicate samples with all remaining	231
A.5	Replicate samples with some excluded	232
C.1	Synthetic lethal expression profiles of analysed samples	245
C.2	Comparison of mtSLIPT to short interfering RNA (siRNA)	247
C.3	Compare mtSLIPT and siRNA genes with correlation	251
C.4	Compare mtSLIPT and siRNA genes with correlation	251
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	252

D.1	Pathway metagene expression profiles	255
D.2	Expression profiles for constituent genes of PI3K	257
D.3	Expression profiles for estrogen receptor related genes	258
D.4	Pathway metagene expression profiles	259
D.5	Expression profiles for p53 related genes	260
D.6	Expression profiles for BRCA related genes	261
D.7	Somatic mutation against the PI3K metagene	262
D.8	Somatic mutation against PIK3CA metagene	265
D.9	Somatic mutation against PI3K protein	266
D.10	Somatic mutation against AKT protein	267
F.1	Synthetic lethal expression profiles of stomach samples	272
F.2	Comparison of SLIPT in stomach to siRNA	273
G.1	Synthetic lethality in the PI3K/AKT pathway	279
G.2	Synthetic lethality in the PI3K/AKT pathway in cancer	280
G.3	Synthetic lethality in the Extracellular Matrix	281
G.4	Synthetic lethality in the GPCRs	282
G.5	Synthetic lethality in the GPCR Downstream	283
G.6	Synthetic lethality in the Translation Elongation	284
G.7	Synthetic lethality in the Nonsense-mediated Decay	285
G.8	Synthetic lethality in the 3' UTR	286
H.1	Synthetic lethality and vertex degree	287
H.2	Synthetic lethality and centrality	288
H.3	Synthetic lethality and PageRank	289
I.1	Information centrality distribution	293
J.1	Synthetic lethality and heirarchy score in PI3K	294
J.2	Heirarchy score in PI3K against synthetic lethality in PI3K	295
J.3	Structure of synthetic lethality in PI3K	295
J.4	Structure of synthetic lethality resampling	296
K.1	Performance of χ^2 and SLIPT across quantiles	297
K.2	Performance of χ^2 and SLIPT across quantiles	299
K.3	Performance of χ^2 and SLIPT across quantiles with more genes	301
K.4	Performance of χ^2 and SLIPT across quantiles with query correlation	303
K.5	Performance of χ^2 and SLIPT across quantiles with query correlation	305
K.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	307
L.1	Performance of simulations on a simple graph	309
L.2	Performance of simulations on an inhibiting graph	310
L.3	Performance of simulations on a constructed graph with inhibition	311
L.4	Performance of simulations on a constructed graph with inhibition	312
L.5	Detection of synthetic lethality within a graph structure	313
L.6	Detection of synthetic lethality within an inhibiting graph	315

L.7	Detection of synthetic lethality within an inhibiting graph	316
L.8	Performance of simulations on a branching graph	317
L.9	Performance of simulations on a complex graph	318
L.10	Performance of simulations on a large graph	319
L.11	Performance of simulations on a branching graph with inhibition	320
L.12	Performance of simulations on a branching graph with inhibition	321
L.13	Performance of simulations on a complex graph with inhibition	322
L.14	Performance of simulations on a complex graph with inhibition	323
L.15	Performance of simulations on a large constructed graph with inhibition	324
L.16	Performance of simulations on a large constructed graph with inhibition	325
L.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	326
L.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	327

List of Tables

1.1	Methods for predicting genetic interactions	22
1.2	Methods for predicting synthetic lethality in cancer	23
1.3	Methods used by Wu <i>et al.</i> (2014)	25
2.1	Excluded samples by batch and clinical characteristics.	43
2.2	Computers used during thesis	53
2.3	Linux utilities and applications used during thesis	54
2.4	R installations used during thesis	55
2.5	R Packages used during thesis	55
2.6	R packages developed during thesis	57
4.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT	98
4.2	Pathways for <i>CDH1</i> partners from SLIPT	99
4.3	Pathways for clusters of <i>CDH1</i> partners from SLIPT	104
4.4	ANOVA for synthetic lethality and correlation with <i>CDH1</i>	107
4.5	Comparison of Synthetic Lethal Interaction Prediction Tool (SLIPT) genes against secondary siRNA screen	111
4.6	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	112
4.7	Pathways for <i>CDH1</i> partners from SLIPT	115
4.8	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen .	116
4.9	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT	119
5.1	ANOVA for synthetic lethality and vertex degree	137
5.2	ANOVA for synthetic lethality and information centrality	139
5.3	ANOVA for synthetic lethality and PageRank centrality	141
5.4	ANOVA for synthetic lethality and PI3K hierarchy	144
5.5	Resampling for pathway structure of synthetic lethal detection methods	148
B.1	Complete list of R packages used during this thesis	234
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT	243
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	244
C.3	Pathways for clusters of <i>CDH1</i> partners from mtSLIPT	246
C.4	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA	248
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	249
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	250
D.1	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT	264

E.1	Comparison of intrinsic subtypes	268
F.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	270
F.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	271
F.4	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	274
F.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	275
F.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA	276
F.7	Synthetic lethal metagenes against <i>CDH1</i> in stomach cancer	277
H.1	ANOVA for synthetic lethality and vertex degree	290
H.2	ANOVA for synthetic lethality and information centrality	290
H.3	ANOVA for synthetic lethality and PageRank centrality	290
I.1	Information centrality for genes and molecules in the Reactome network	292
J.1	ANOVA for synthetic lethality and PI3K hierarchy	294
J.2	Resampling for pathway structure of synthetic lethal detection methods	296

Glossary

allele	A gene variant with a specific sequence and phenotype.
driver mutation	A mutation which promotes cancer growth.
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.
hereditary	A trait or disease which has a genetic cause and is inherited from family members.
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.

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.
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.
wild-type	A natural phenotype of a trait or the normally functional allele which encodes it.

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.
PI3K	Phosphoinositide 3-kinase.
PR	Progesterone Receptor.
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*	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.

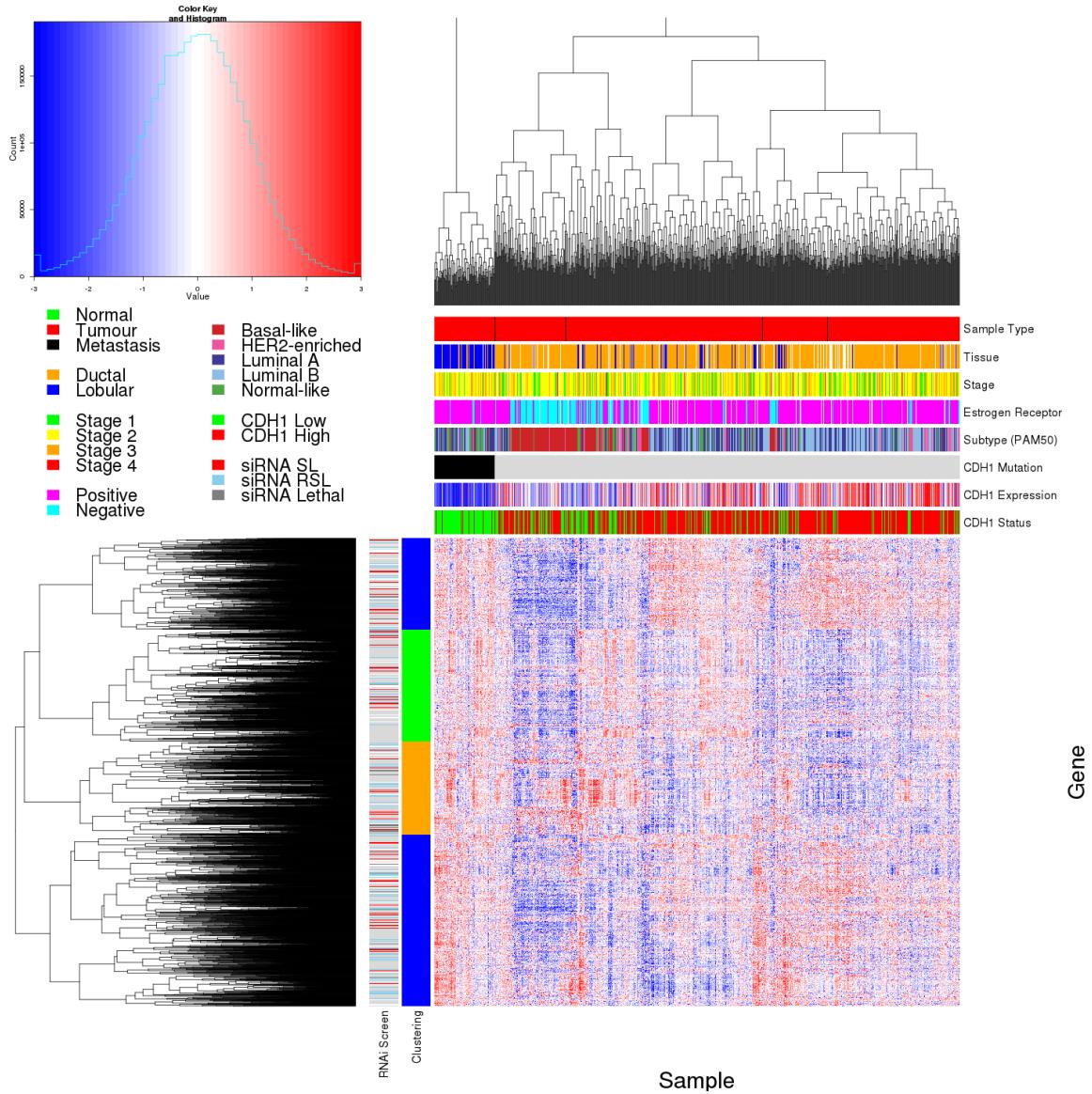


Figure C.1: Synthetic lethal expression profiles of analysed samples. Gene expression profile heatmap (correlation distance) of all samples (separated by *CDH1* somatic mutation status) analysed in **TCGA** breast cancer dataset for gene expression of 3743 candidate partners of **E-cadherin** (*CDH1*) 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.

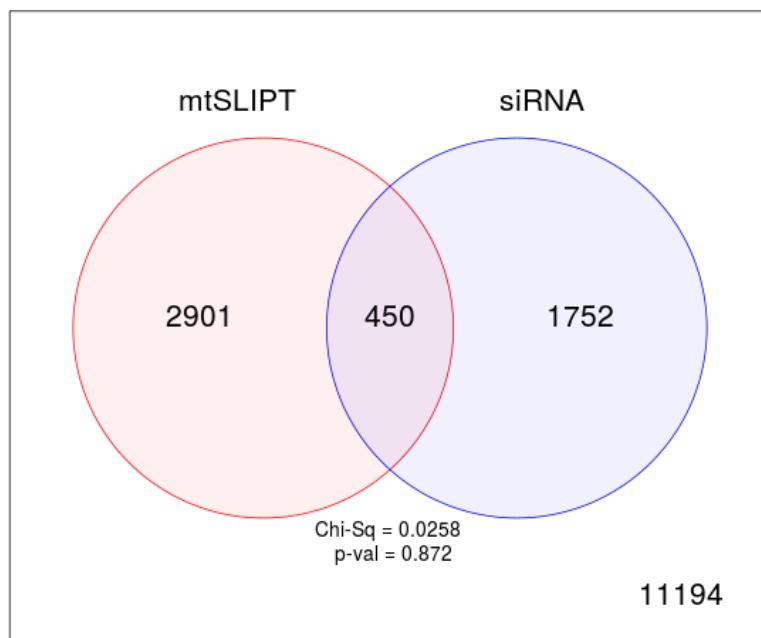


Figure C.2: **Comparison of mtSLIPT to siRNA.** Testing the overlap of gene candidates for [E-cadherin](#) synthetic lethal partners between computational (SLIPT) and experimental screening (siRNA) approaches. The χ^2 test suggests that the overlap is no more than would be expected by chance ($p = 0.281$).

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.

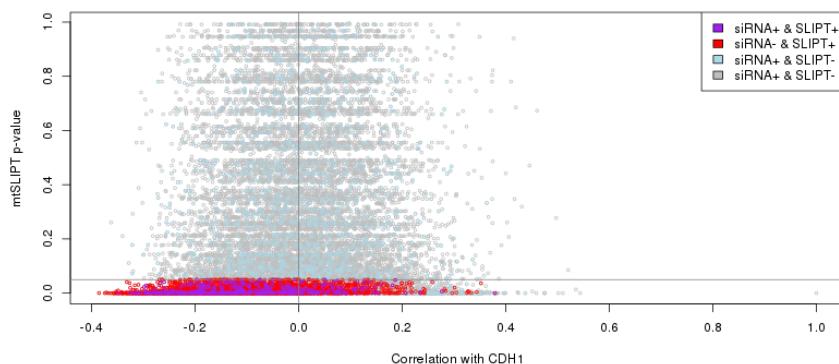


Figure C.3: **Compare mtSLIPT and siRNA genes with correlation.** The mtSLIPT p-values were compared against Pearson correlation of expression with *CDH1*. Genes detected by SLIPT or siRNA were coloured according to the legend.

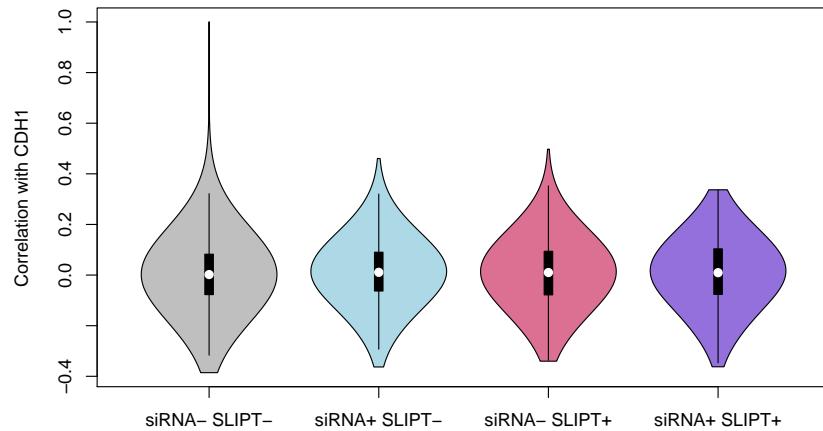


Figure C.4: **Compare mtSLIPT and siRNA genes with correlation.** Genes detected by mtSLIPT against *CDH1* mutation and siRNA screening were compared against Pearson correlation of expression with *CDH1*. There were no differences in correlation between the gene groups.

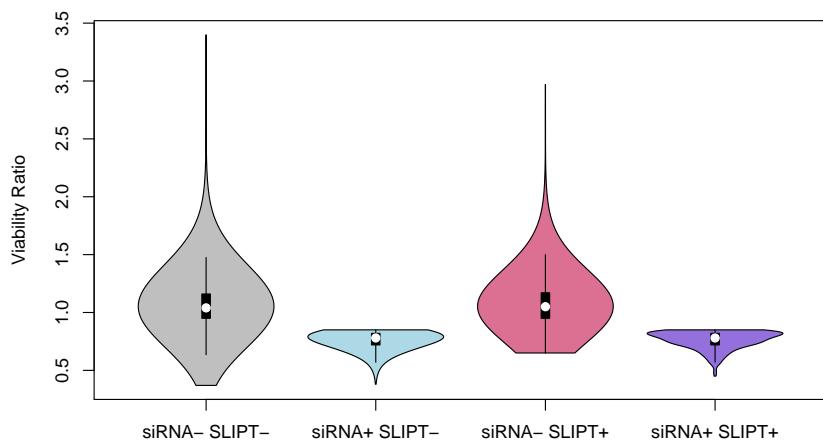


Figure C.5: Compare mtSLIPT and siRNA genes with siRNA viability. Genes detected as candidate synthetic lethal partners by mtSLIPT (in TCGA breast cancer) expression analysis against *CDH1* mutation and experimental screening (with siRNA) were compared against the viability ratio of *CDH1* mutant and 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**. Metagenes serve as a summary of activity for each **pathways**. The direction of **metagenes** (derived by the singular value matrix decomposition) is generally arbitrary but care has been taken to ensure that these occur in a direction which reflect overall activation of the **pathways** (as described in Section 2.2.3). **Metagenes** were derived for well characterised gene signatures in breast cancer (Gatza *et al.*, 2011, 2014) to verify that these **pathways** signatures are consistent with expected molecular properties of each molecular subtype (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 Estrogen receptor (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.

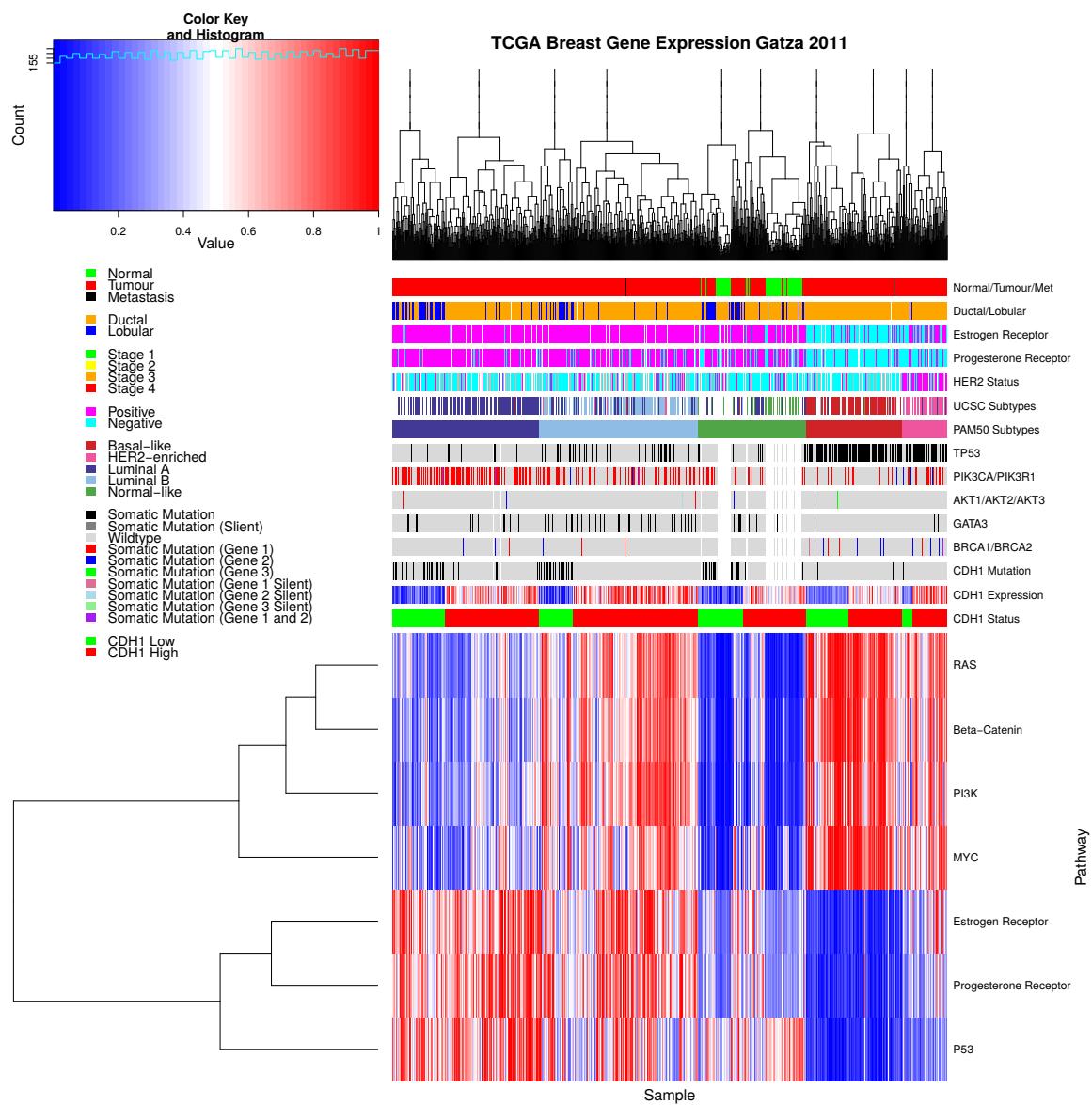


Figure D.1: **Pathway metagene expression profiles.** Expression profiles for metagene signatures from [Gatza et al. \(2011\)](#) in TCGA breast data, annotated for clinical factors (with sample types and histological results coloured according to the legend) and cancer gene mutations (Negative values 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).

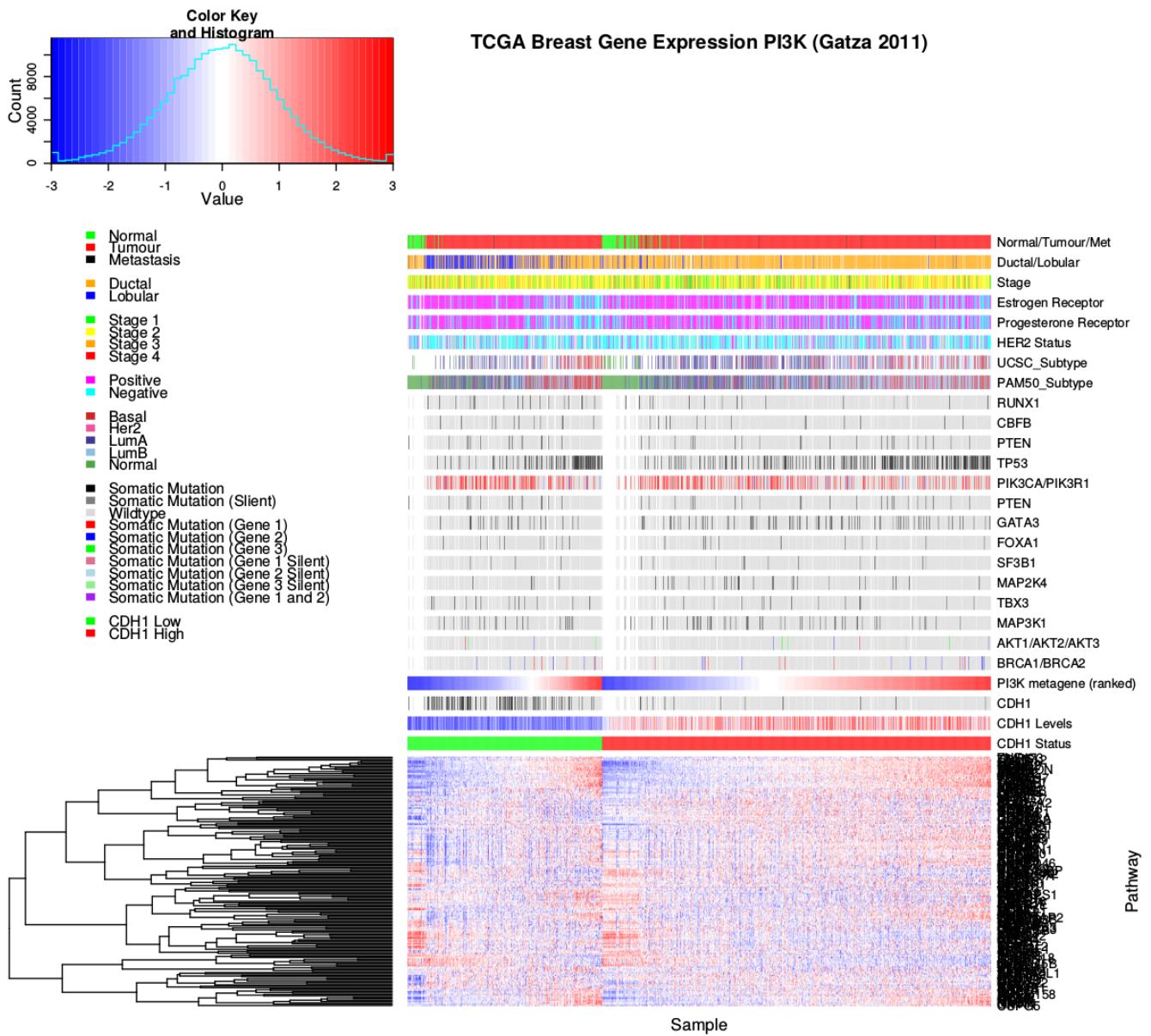


Figure D.2: **Expression profiles for constituent genes of PI3K.** Expression profiles the genes contained in the PI3K gene signature from Gatza *et al.* (2011) in TCGA breast data, annotated for clinical factors and cancer gene mutations. Samples are separated by *CDH1* expression status and sorted 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.

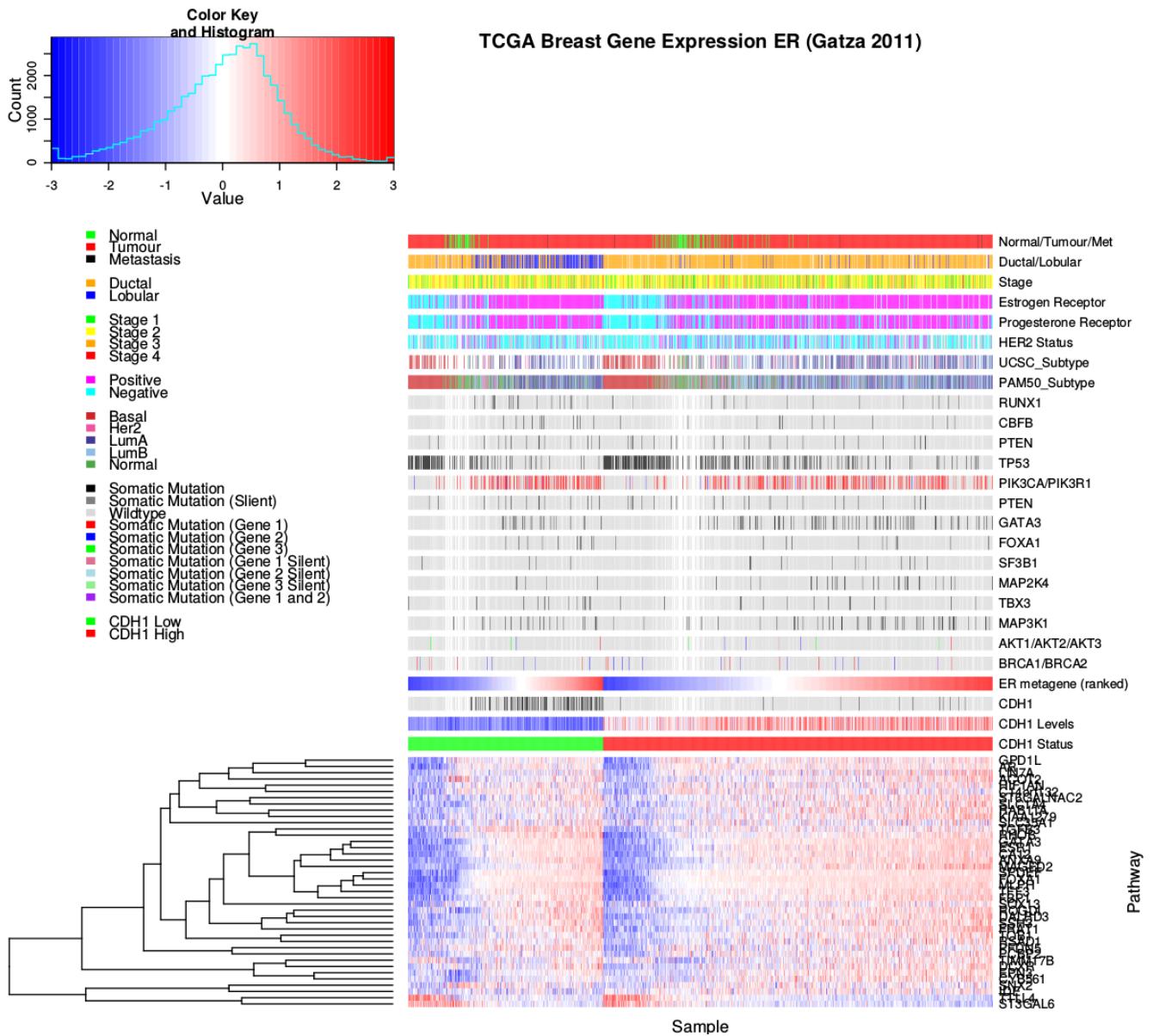


Figure D.3: **Expression profiles for estrogen receptor related genes.** Expression profiles the genes contained in the estrogen receptor (ER) gene signature from [Gatza *et al.* \(2011\)](#) in TCGA breast data, annotated for clinical factors and cancer gene [mutations](#). Samples are separated by *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.

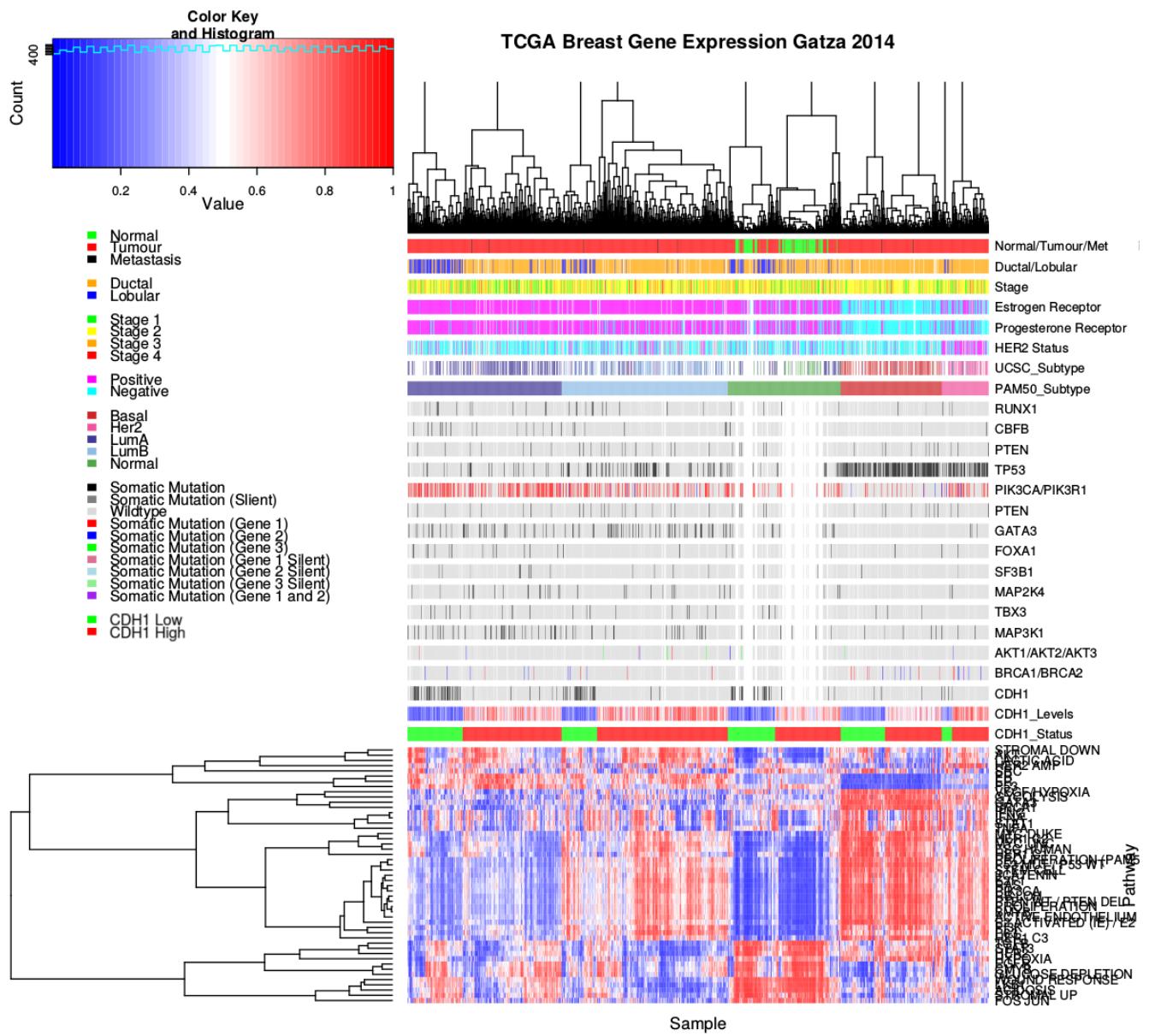


Figure D.4: **Pathway metagene expression profiles.** Expression profiles for metagene signatures from Gatza *et al.* (2014) in TCGA breast data, annotated for clinical factors and cancer gene mutations.

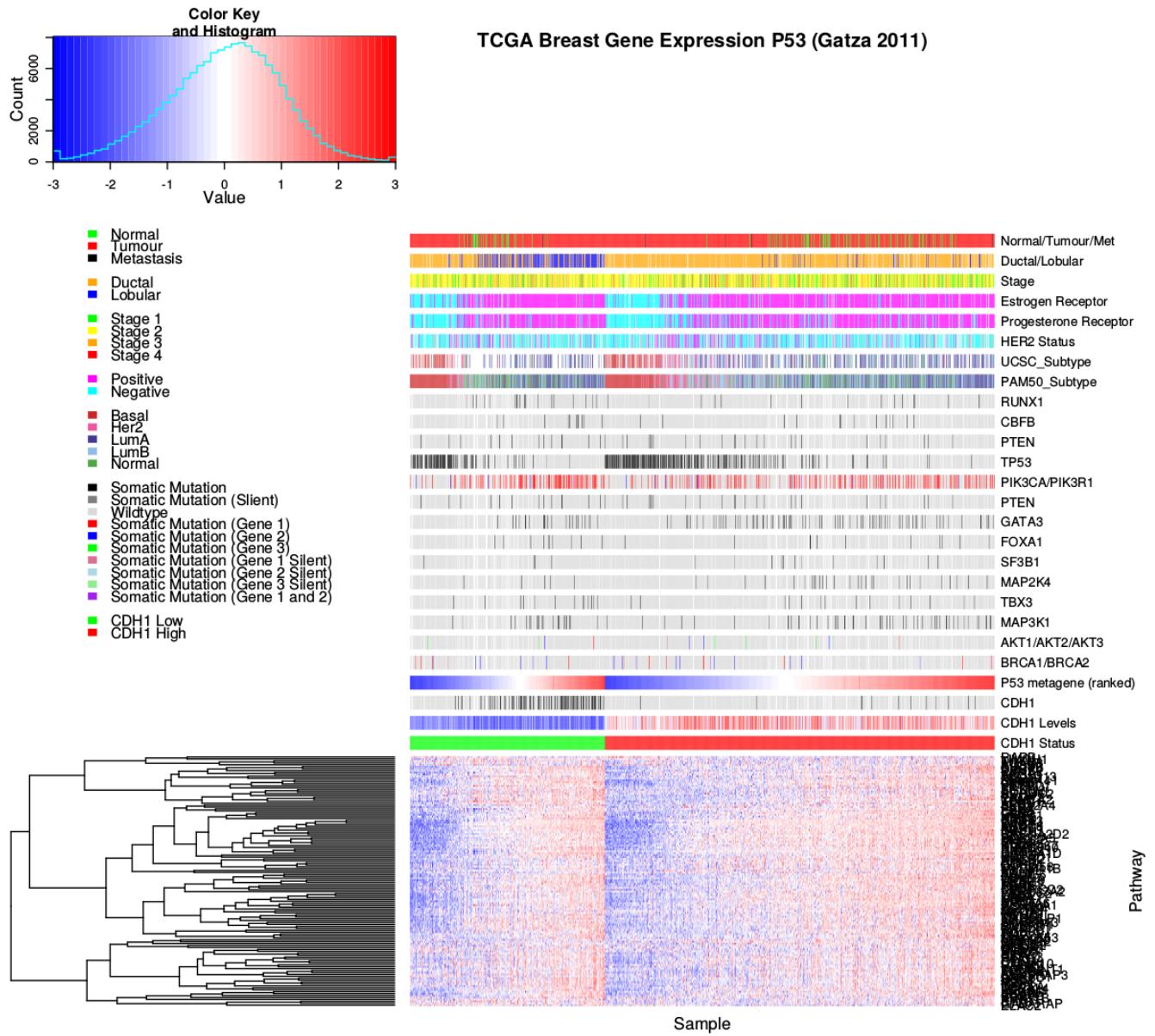


Figure D.5: Expression profiles for p53 related genes. Expression profiles the genes contained in the *TP53* gene signature from [Gatza et al. \(2011\)](#) in [TCGA](#) breast data, annotated for clinical factors and cancer gene mutations. Samples were separated by *CDH1* expression status and sorted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

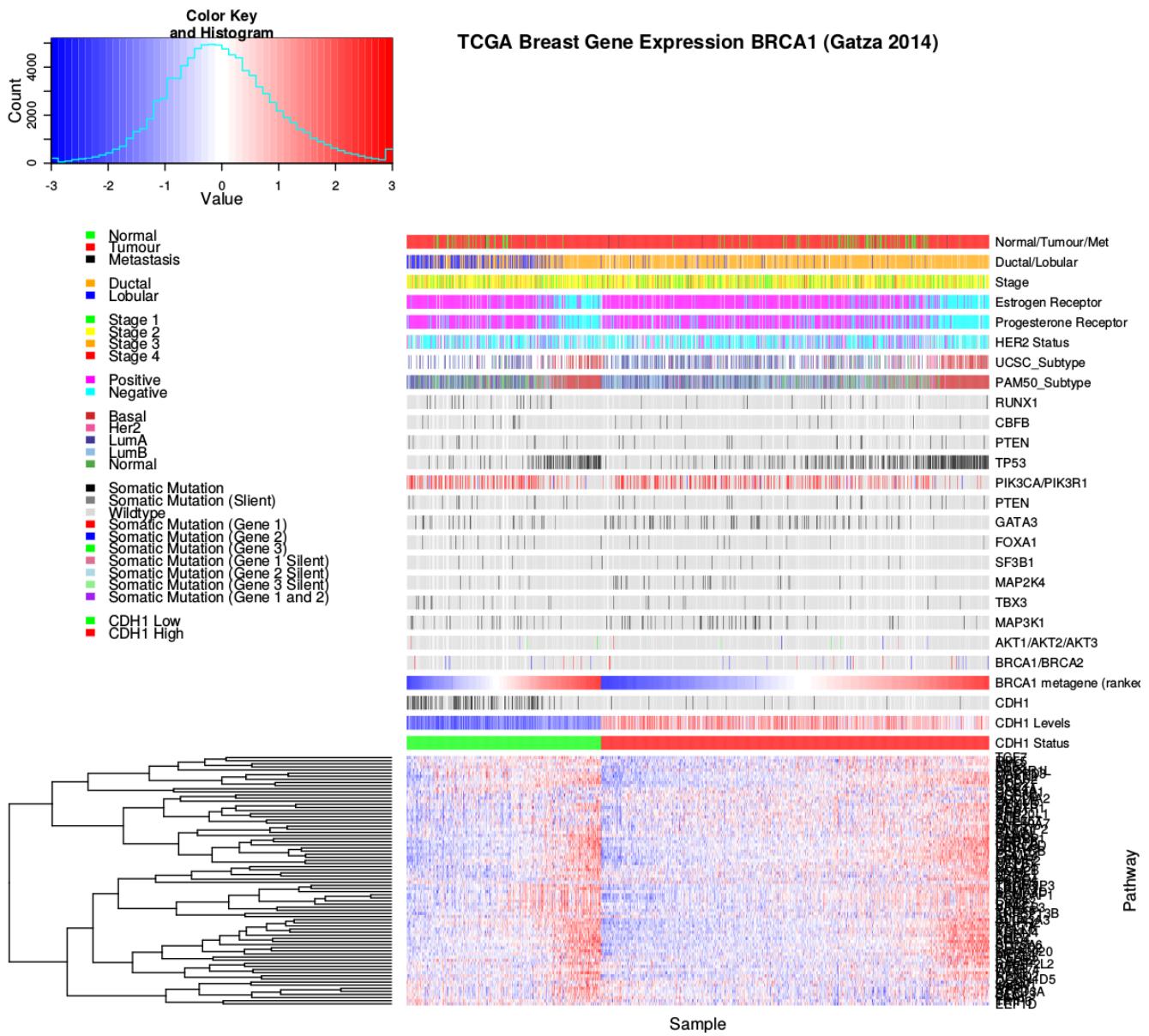


Figure D.6: Expression profiles for BRCA related genes. Expression profiles the genes contained in the gene signature related to *BRCA1* and *BRCA2* functions from [Gatza et al. \(2014\)](#) in **TCGA** breast data, annotated for clinical factors and cancer gene mutations. Samples were separated by *CDH1*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

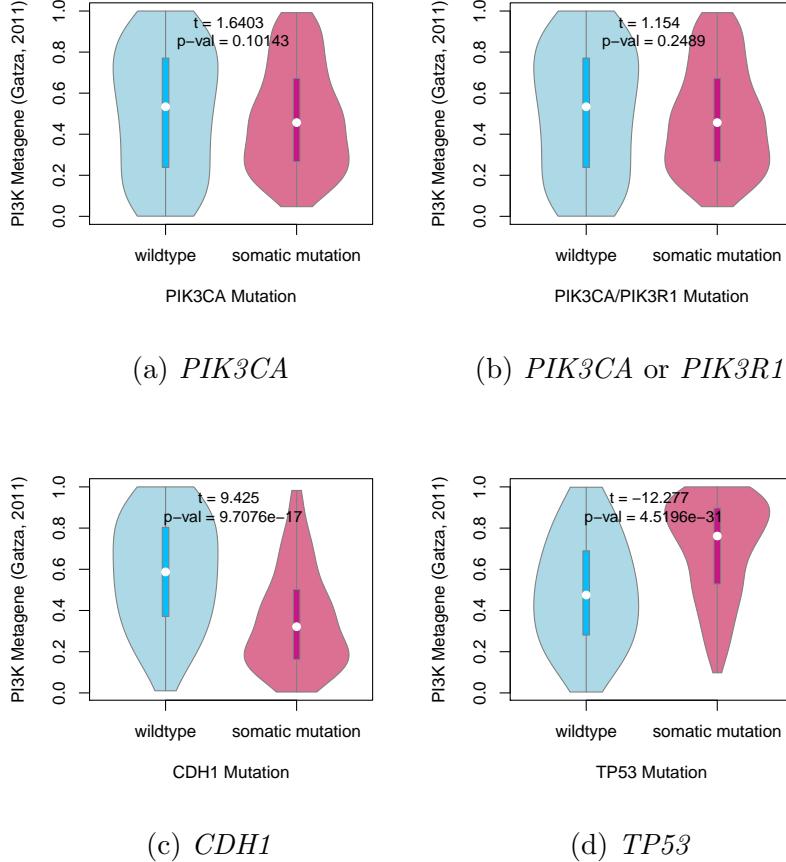


Figure D.7: **Somatic mutation against the PI3K metagene.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their association with the PI3K (Gatza *et al.*, 2011) pathways metagene. The tumour suppressors *CDH1* and *TP53* showed an increase and decrease in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

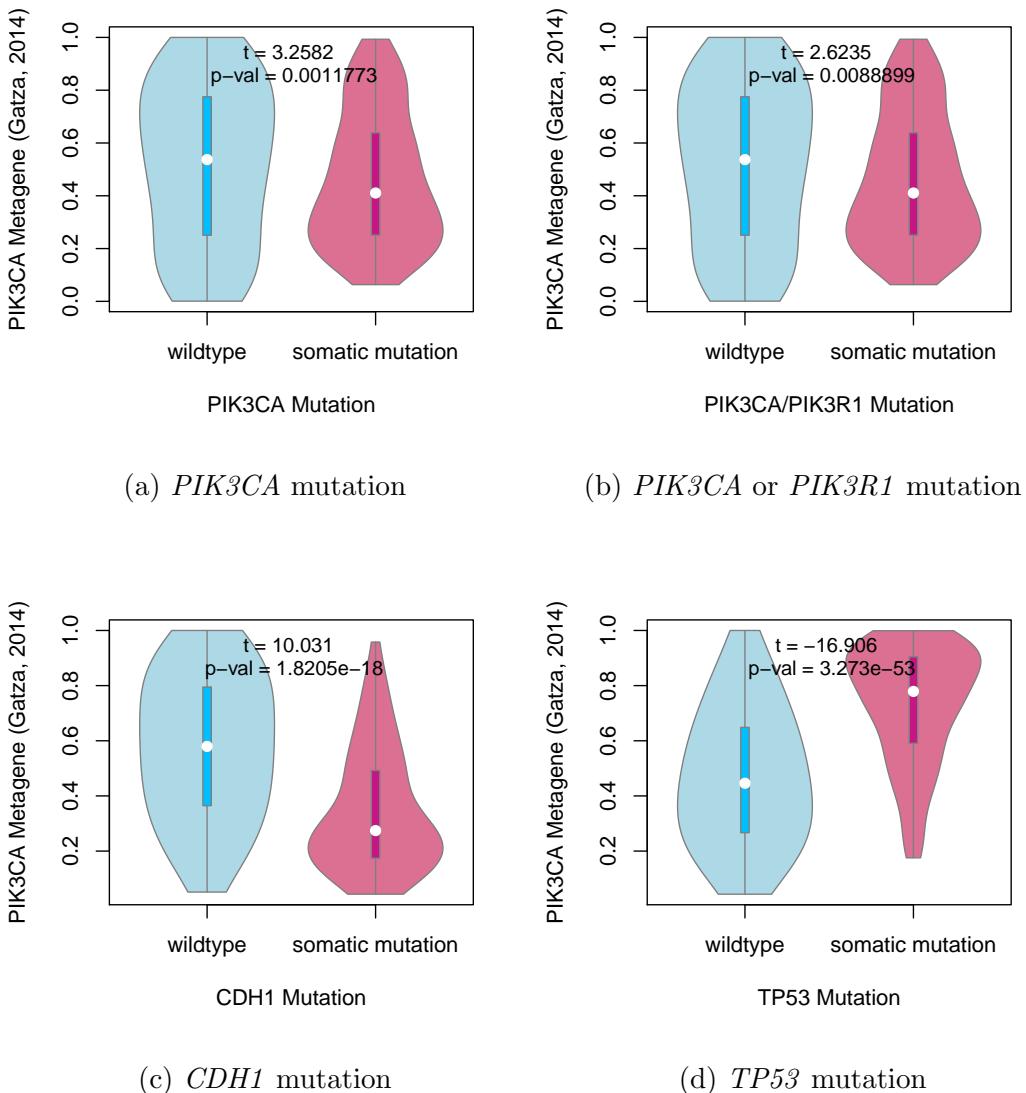


Figure D.8: **Somatic mutation against PIK3CA metagene.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in [TCGA](#) breast cancer for their effect on the PIK3CA (Gatza *et al.*, 2014) pathway metagene. The tumour suppressors *CDH1* and *TP53* showed an increase and decrease in the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

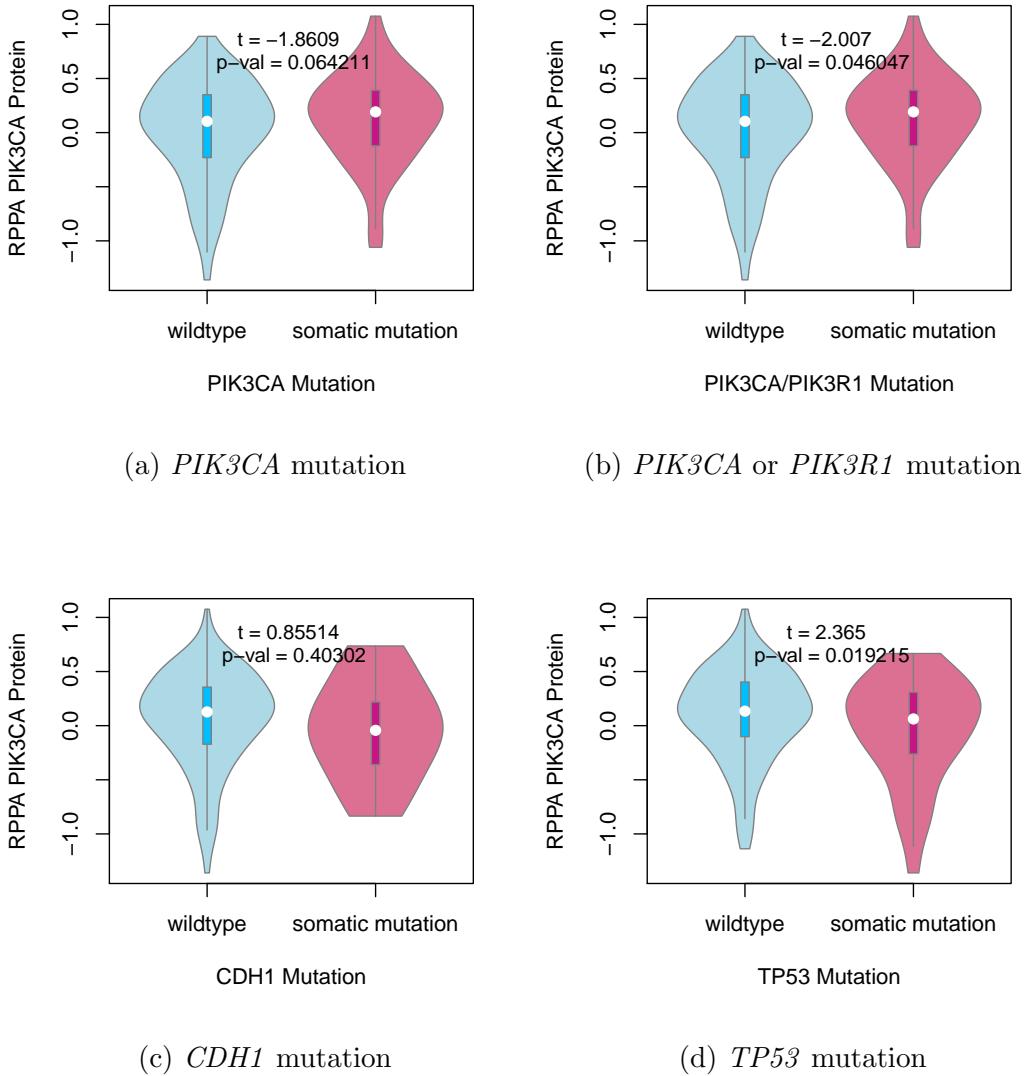


Figure D.9: Somatic mutation against PI3K protein. Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the expression of the p110 α protein (encoded by *PIK3CA*). Protein levels were significantly elevated in samples with *PIK3CA* or *PIK3R1* mutations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

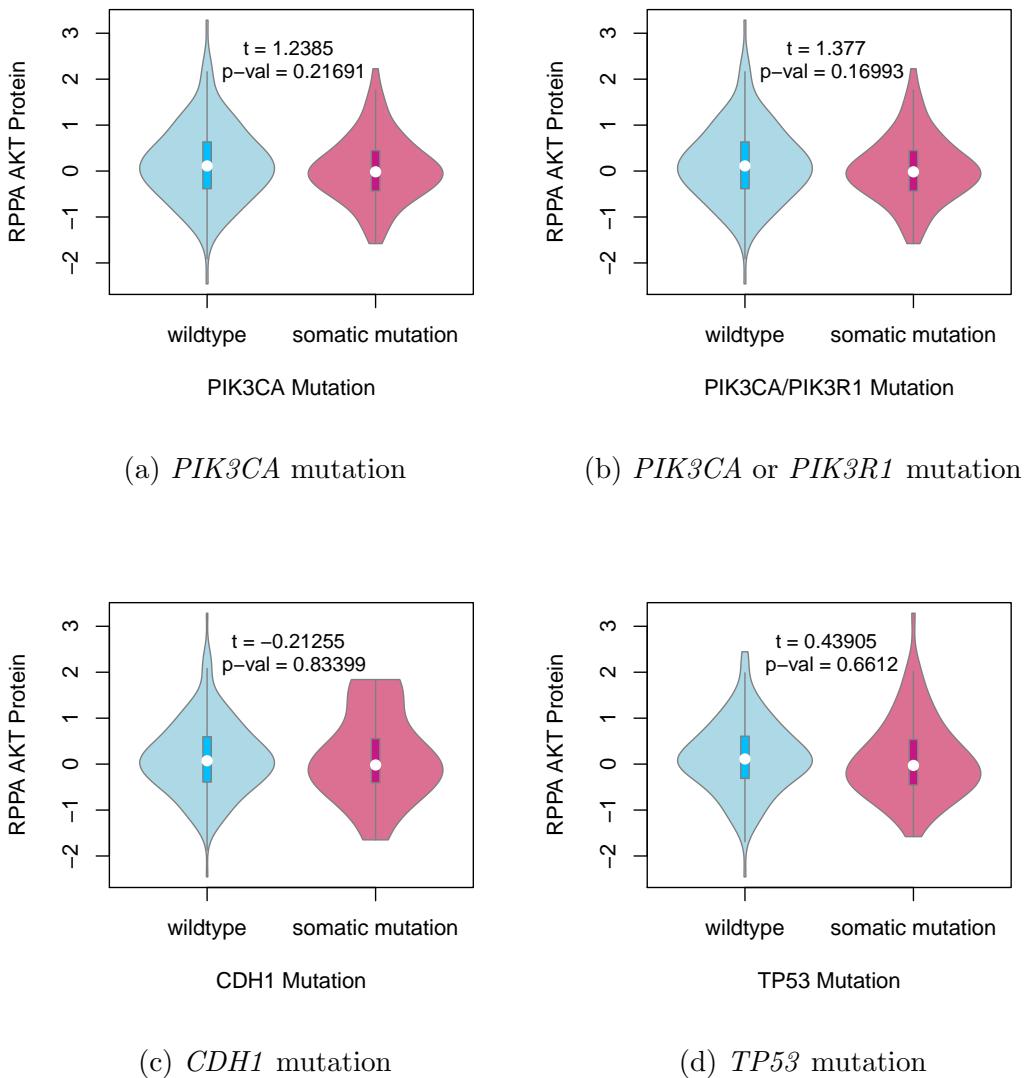


Figure D.10: **Somatic mutation against AKT protein.** Mutations in *PIK3CA*, *PIK3R1*, *CDH1*, and *TP53* were examined in TCGA breast cancer for their effect on the expression of the AKT protein (a downstream target of *PIK3CA*). Protein levels were not significantly different in samples with mutations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

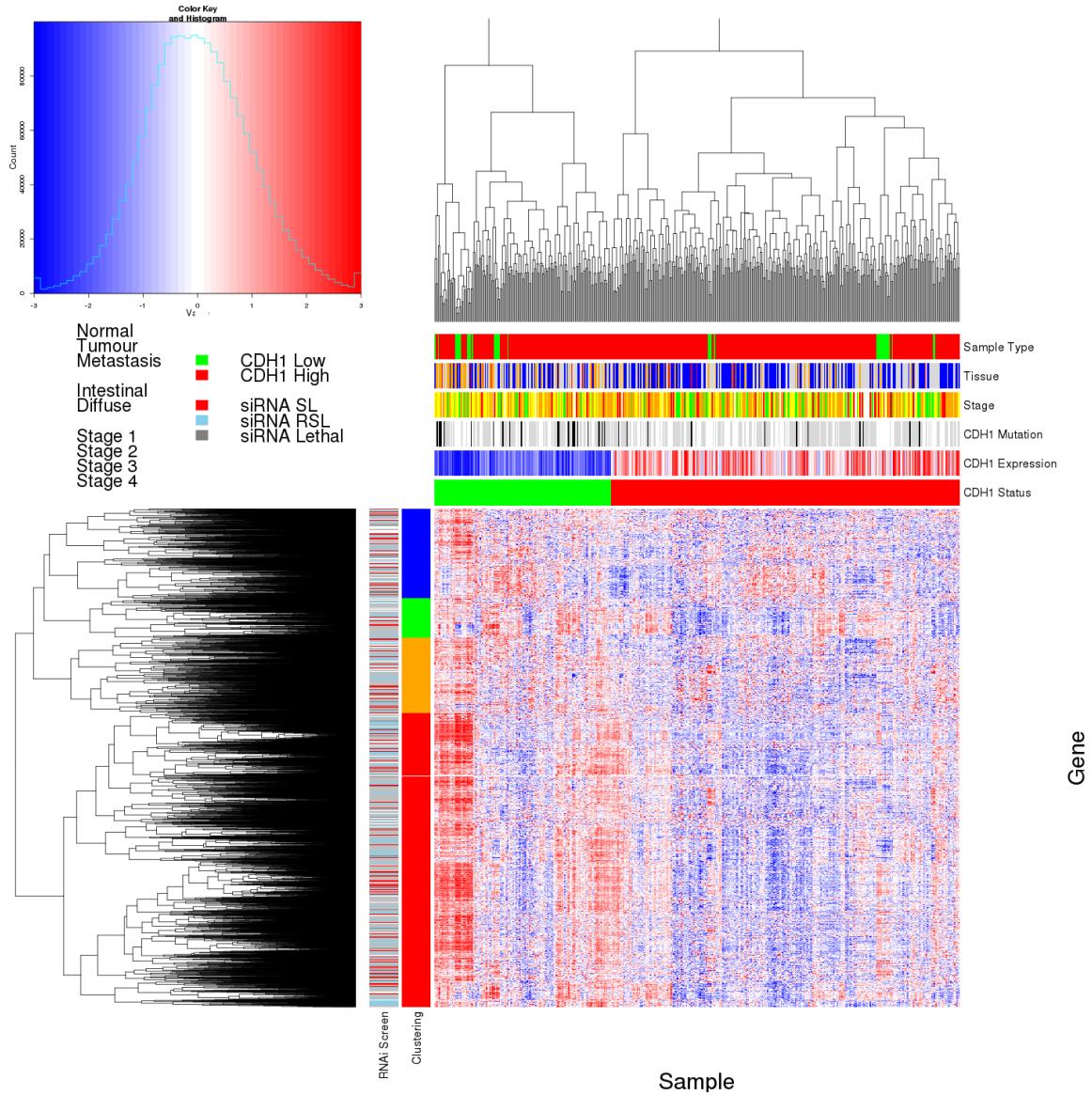


Figure F.1: Synthetic lethal expression profiles of analysed samples. Gene expression profile heatmap (correlation distance) of all samples (separated by the $1/3$ quantile of *CDH1* expression) analysed in [TCGA](#) stomach cancer dataset for gene expression of 4365 candidate partners of **E-cadherin** (*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.

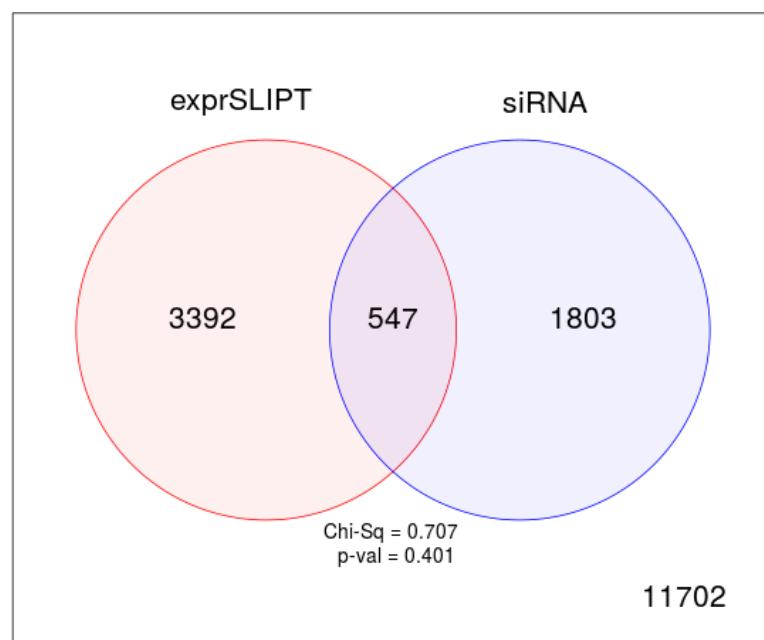


Figure F.2: **Comparison of SLIPT in stomach to siRNA.** The overlap of gene candidates for [E-cadherin](#) synthetic lethal partners between computational (SLIPT) and experimental screening (siRNA) approaches. The χ^2 test suggests that the overlap is no more than would be expected by chance ($p = 0.281$).

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 Ca2+	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
<i>G_{ai} signalling events</i>	1.8×10^{-66}	0.9254
Metabolism of carbohydrates	1.1×10^{-65}	0.39501
G_{as} 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.