

Contents

Glossary	xiii
Acronyms	xiv
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	4
1.1.2.1 High-Throughput Technologies	4
1.1.2.2 Bioinformatics and Genomics Data	6
1.1.3 Genomics Projects	6
1.1.3.1 The Cancer Genome Project	7
1.1.3.2 The Cancer Genome Atlas Project	7
1.1.4 Genomic Cancer Medicine	9
1.1.4.1 Cancer Genes and Driver Mutations	10
1.1.4.2 Precision Cancer Medicine	11
1.1.4.3 Molecular Diagnostics and Pan-Cancer Medicine	11
1.1.4.4 Targeted Therapeutics and Pharmacogenomics	11
1.1.5 Systems and Network Biology	12
1.1.5.1 Network Medicine and Polypharmacology	14
1.2 A Synthetic Lethal Approach to Cancer Medicine	15
1.2.1 Synthetic Lethal Genetic Interactions	15
1.2.2 Synthetic Lethal Concepts in Genetics	16
1.2.3 Synthetic Lethality in Model Systems	17
1.2.3.1 Synthetic Lethal Pathways and Networks	17
1.2.3.2 Evolution of Synthetic Lethality	18
1.2.4 Synthetic Lethality in Cancer	19
1.2.5 Clinical Impact of Synthetic Lethality in Cancer	20
1.2.6 High-throughput Screening for Synthetic Lethality	22
1.2.6.1 Synthetic Lethal Screens	23
1.2.7 Computational Prediction of Synthetic Lethality	26
1.2.7.1 Bioinformatics Approaches to Genetic Interactions	26
1.2.7.2 Comparative Genomics	27
1.2.7.3 Analysis and Modelling of Protein Data	30
1.2.7.4 Differential Gene Expression	32

1.2.7.5	Data Mining and Machine Learning	33
1.2.7.6	Mutually Exclusive Bimodality	36
1.2.7.7	Rationale for Further Development	36
1.3	E-cadherin as a Synthetic Lethal Target	37
1.3.1	The <i>CDH1</i> gene and its Biological Functions	37
1.3.1.1	Cytoskeleton	37
1.3.1.2	Extracellular and Tumour Micro-environment	38
1.3.1.3	Cell-Cell Adhesion and Signalling	38
1.3.2	<i>CDH1</i> as a Tumour (and Invasion) Suppressor	38
1.3.2.1	Breast Cancers and Invasion	39
1.3.3	Hereditary Diffuse Gastric Cancer and Lobular Breast Cancer .	39
1.3.4	Cell Line Models of <i>CDH1</i> Null Mutations	40
1.4	Summary and Research Direction of Thesis	41
1.4.1	Thesis Aims	43
2	Methods and Resources	44
2.1	Bioinformatics Resources for Genomics Research	44
2.1.1	Public Data and Software Packages	44
2.1.1.1	Cancer Genome Atlas Data	45
2.1.1.2	Reactome and Annotation Data	46
2.2	Data Handling	46
2.2.1	Normalisation	46
2.2.2	Sample Triage	47
2.2.3	Metagenes and the Singular Value Decomposition	47
2.2.3.1	Candidate Triage and Integration with Screen Data .	49
2.3	Techniques	50
2.3.1	Statistical Procedures and Tests	50
2.3.2	Gene Set Over-representation Analysis	51
2.3.3	Clustering	51
2.3.4	Heatmap	51
2.3.5	Modeling and Simulations	52
2.3.5.1	Receiver Operating Characteristic (Performance) . .	53
2.3.6	Resampling Analysis	53
2.4	Pathway Structure Methods	54
2.4.1	Network and Graph Analysis	54
2.4.2	Sourcing Graph Structure Data	55
2.4.3	Constructing Pathway Subgraphs	55
2.4.4	Network Analysis Metrics	56
2.5	Implementation	57
2.5.1	Computational Resources and Linux Utilities	57
2.5.2	R Language and Packages	58
2.5.3	High Performance and Parallel Computing	61

3 Methods Developed During Thesis	63
3.1 A Synthetic Lethal Detection Methodology	63
3.2 Synthetic Lethal Simulation and Modelling	66
3.2.1 A Model of Synthetic Lethality in Expression Data	66
3.2.2 Simulation Procedure	70
3.3 Detecting Simulated Synthetic Lethal Partners	73
3.3.1 Binomial Simulation of Synthetic lethality	73
3.3.2 Multivariate Normal Simulation of Synthetic lethality	75
3.3.2.1 Multivariate Normal Simulation with Correlated Genes	78
3.3.2.2 Specificity with Query-Correlated Pathways	85
3.3.2.3 Importance of Directional Testing	85
3.4 Graph Structure Methods	87
3.4.1 Upstream and Downstream Gene Detection	87
3.4.1.1 Permutation Analysis for Statistical Significance	88
3.4.1.2 Hierarchy Based on Biological Context	89
3.4.2 Simulating Gene Expression from Graph Structures	90
3.5 Customised Functions and Packages Developed	94
3.5.1 Synthetic Lethal Interaction Prediction Tool	94
3.5.2 Data Visualisation	95
3.5.3 Extensions to the iGraph Package	98
3.5.3.1 Sampling Simulated Data from Graph Structures	98
3.5.3.2 Plotting Directed Graph Structures	98
3.5.3.3 Computing Information Centrality	99
3.5.3.4 Testing Pathway Structure with Permutation Testing .	99
3.5.3.5 Metapackage to Install iGraph Functions	100
4 Synthetic Lethal Analysis of Gene Expression Data	101
4.1 Synthetic Lethal Genes in Breast Cancer	102
4.1.1 Synthetic Lethal Pathways in Breast Cancer	104
4.1.2 Expression Profiles of Synthetic Lethal Partners	105
4.1.2.1 Subgroup Pathway Analysis	108
4.2 Comparing Synthetic Lethal Gene Candidates	111
4.2.1 Primary short interfering RNA (siRNA) Screen Candidates . .	111
4.2.2 Comparison with Correlation	111
4.2.3 Comparison with Primary Screen Viability	113
4.2.4 Comparison with Secondary siRNA Screen Validation	115
4.2.5 Comparison to Primary Screen at Pathway Level	117
4.2.5.1 Resampling Genes for Pathway Enrichment	119
4.2.6 Integrating Synthetic Lethal Pathways and Screens	122
4.3 Metagene Analysis	124
4.3.1 Pathway Expression	125
4.3.2 Somatic Mutation	127
4.3.3 Synthetic Lethal Pathway Metagenes	131
4.3.4 Synthetic Lethality in Breast Cancer	132
4.4 Replication in Stomach Cancer	133
4.5 Discussion	134

4.5.1	Strengths of the SLIPT Methodology	134
4.5.2	Synthetic Lethal Pathways for E-cadherin	135
4.5.3	Replication and Validation	137
4.5.3.1	Integration with siRNA Screening	137
4.5.3.2	Replication across Tissues	138
4.6	Summary	138
5	Synthetic Lethal Pathway Structure	140
5.1	Synthetic Lethal Genes in Reactome Pathways	140
5.1.1	The PI3K/AKT Pathway	141
5.1.2	The Extracellular Matrix	143
5.1.3	G Protein Coupled Receptors	146
5.1.4	Gene Regulation and Translation	146
5.2	Network Analysis of Synthetic Lethal Genes	147
5.2.1	Gene Connectivity and Vertex Degree	148
5.2.2	Gene Importance and Centrality	149
5.2.2.1	Information Centrality	149
5.2.2.2	PageRank Centrality	151
5.3	Relationships between Synthetic Lethal Genes	153
5.3.1	Hierarchical Pathway Structure	153
5.3.1.1	Contextual Hierarchy of PI3K	153
5.3.1.2	Testing Contextual Hierarchy of Synthetic Lethal Genes	153
5.3.2	Upstream or Downstream Synthetic Lethality	157
5.3.2.1	Measuring Structure of Candidates within PI3K . . .	157
5.3.2.2	Resampling for Synthetic Lethal Pathway Structure .	159
5.4	Discussion	161
5.5	Summary	163
6	Simulation and Modeling of Synthetic Lethal Pathways	165
6.1	Synthetic Lethal Detection Methods	166
6.1.1	Performance of SLIPT and χ^2 across Quantiles	166
6.1.1.1	Correlated Query Genes affects Specificity	170
6.1.2	Alternative Synthetic Lethal Detection Strategies	172
6.1.2.1	Correlation for Synthetic Lethal Detection	172
6.1.2.2	Testing for Bimodality with BiSEp	174
6.2	Simulations with Graph Structures	175
6.2.1	Performance over a Graph Structure	176
6.2.1.1	Simple Graph Structures	176
6.2.1.2	Constructed Graph Structures	178
6.2.2	Performance with Inhibitions	181
6.2.3	Synthetic Lethality across Graph Structures	186
6.2.4	Performance within a Simulated Human Genome	190
6.3	Simulations in More Complex Graph Structures	194
6.3.1	Simulations over Pathway-based Graphs	195
6.3.2	Pathway Structures in a Simulated Human Genome	198
6.4	Discussion	201

6.4.1	Simulation Procedure	201
6.4.2	Comparing Methods with Simulated Data	202
6.4.3	Design and Performance of SLIPT	203
6.4.4	Simulations from Graph Structures	205
6.5	Summary	206
7	Discussion	208
7.1	Synthetic Lethality and <i>CDH1</i> Biology	208
7.1.1	Established Functions of <i>CDH1</i>	209
7.1.2	The Molecular Role of <i>CDH1</i> in Cancer	209
7.2	Significance	210
7.2.1	Synthetic Lethality in the Genomic Era	210
7.2.2	Clinical Interventions based on Synthetic Lethality	212
7.3	Future Directions	213
7.4	Conclusions	215
References		217
A	Sample Quality	240
A.1	Sample Correlation	240
A.2	Replicate Samples in The Cancer Genome Atlas (TCGA) Breast	243
B	Software Used for Thesis	247
C	Mutation Analysis in Breast Cancer	256
C.1	Synthetic Lethal Genes and Pathways	256
C.2	Synthetic Lethal Expression Profiles	259
C.3	Comparison to Primary Screen	262
C.3.1	Resampling Analysis	264
C.4	Compare Synthetic Lethal Interaction Prediction Tool (SLIPT) genes .	266
C.5	Metagene Analysis	268
C.6	Expression of Somatic Mutations	269
C.7	Metagene Expression Profiles	272
D	Intrinsic Subtyping	275
E	Stomach Expression Analysis	277
E.1	Synthetic Lethal Genes and Pathways	277
E.2	Comparison to Primary Screen	281
E.2.1	Resampling Analysis	283
E.3	Metagene Analysis	285
F	Synthetic Lethal Genes in Pathways	286
G	Pathway Connectivity for Mutation SLIPT	294
H	Information Centrality for Gene Essentiality	298

I Pathway Structure for Mutation SLIPT	301
J Performance of SLIPT and χ^2	304
J.1 Correlated Query Genes affects Specificity	310
K Graph Structures	316
K.1 Simulations from Simple Graph Structures	316
K.1.1 Simulations from Inhibiting Graph Structures	318
K.2 Simulation across Graph Structures	321
K.3 Simulations from Complex Graph Structures	325
K.3.1 Simulations from Complex Inhibiting Graphs	328
K.4 Simulations from Pathway Graph Structures	334

List of Figures

1.1	Synthetic genetic interactions	16
1.2	Synthetic lethality in cancer	20
2.1	Read count density	48
2.2	Read count sample mean	48
3.1	Framework for synthetic lethal prediction	64
3.2	Synthetic lethal prediction adapted for mutation	65
3.3	A model of synthetic lethal gene expression	67
3.4	Modeling synthetic lethal gene expression	68
3.5	Synthetic lethality with multiple genes	69
3.6	Simulating gene function	71
3.7	Simulating synthetic lethal gene function	71
3.8	Simulating synthetic lethal gene expression	72
3.9	Performance of binomial simulations	74
3.10	Comparison of statistical performance	74
3.11	Performance of multivariate normal simulations	76
3.12	Simulating expression with correlated gene blocks	79
3.13	Simulating expression with correlated gene blocks	80
3.14	Synthetic lethal prediction across simulations	81
3.15	Performance with correlations	82
3.16	Comparison of statistical performance with correlation structure	83
3.17	Performance with query correlations	84
3.18	Statistical evaluation of directional criteria	85
3.19	Performance of directional criteria	86
3.20	Simulated graph structures	90
3.21	Simulating expression from a graph structure	92
3.22	Simulating expression from graph structure with inhibitions	93
3.23	Demonstration of violin plots with custom features	96
3.24	Demonstration of annotated heatmap	96
3.25	Simulating graph structures	99
4.1	Synthetic lethal expression profiles of analysed samples	107
4.2	Comparison of SLIPT to siRNA	111
4.3	Compare SLIPT and siRNA genes with correlation	112
4.4	Compare SLIPT and siRNA genes with correlation	113
4.5	Compare SLIPT and siRNA genes with viability	114

4.6	Compare SLIPT genes with siRNA viability	115
4.7	Resampled intersection of SLIPT and siRNA candidates	119
4.8	Pathway metagene expression profiles	126
4.9	Expression profiles for constituent genes of PI3K	128
4.10	Expression profiles for estrogen receptor related genes	129
4.11	Somatic mutation against the PI3K metagene	130
5.1	Synthetic Lethality in the PI3K Cascade	142
5.2	Synthetic Lethality in the Elastic Fibre Formation Pathway	144
5.3	Synthetic Lethality in the Fibrin Clot Formation	145
5.4	Synthetic Lethality and Vertex Degree	148
5.5	Synthetic Lethality and Centrality	151
5.6	Synthetic Lethality and PageRank	152
5.7	Hierarchical Structure of PI3K	154
5.8	Hierarchy Score in PI3K against Synthetic Lethality in PI3K	155
5.9	Structure of Synthetic Lethality in PI3K	157
5.10	Structure of Synthetic Lethality Resampling in PI3K	158
6.1	Performance of χ^2 and SLIPT across quantiles	168
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	169
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation .	170
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	171
6.5	Performance of negative correlation and SLIPT	173
6.6	Simple graph structures	176
6.7	Performance of simulations on a simple graph	177
6.8	Performance of simulations is similar in simple graphs	179
6.9	Performance of simulations on a pathway	180
6.10	Performance of simulations on a simple graph with inhibition	182
6.11	Performance is higher on a simple inhibiting graph	183
6.12	Performance of simulations on a constructed graph with inhibition . . .	184
6.13	Performance is affected by inhibition in graphs	186
6.14	Detection of Synthetic Lethality within a Graph Structure with Inhibitions	188
6.15	Performance of simulations including a simple graph	191
6.16	Performance on a simple graph improves with more genes	192
6.17	Performance on an inhibiting graph improves with more genes	194
6.18	Performance of simulations on the PI3K cascade	197
6.19	Performance of simulations including the PI3K cascade	199
6.20	Performance on pathways improves with more genes	200
A.1	Correlation profiles of removed samples	241
A.2	Correlation analysis and sample removal	242
A.3	Replicate excluded samples	243
A.4	Replicate samples with all remaining	244
A.5	Replicate samples with some excluded	245
C.1	Synthetic lethal expression profiles of analysed samples	260

C.2	Comparison of mtSLIPT to siRNA	262
C.3	Compare mtSLIPT and siRNA genes with correlation	266
C.4	Compare mtSLIPT and siRNA genes with correlation	266
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	267
C.6	Somatic mutation against PIK3CA metagene	269
C.7	Somatic mutation against PI3K protein	270
C.8	Somatic mutation against AKT protein	271
C.9	Pathway metagene expression profiles	272
C.10	Expression profiles for p53 related genes	273
C.11	Expression profiles for BRCA related genes	274
E.1	Synthetic lethal expression profiles of stomach samples	279
E.2	Comparison of SLIPT in stomach to siRNA	281
F.1	Synthetic Lethality in the PI3K/AKT Pathway	286
F.2	Synthetic Lethality in the PI3K/AKT Pathway in Cancer	287
F.3	Synthetic Lethality in the Extracellular Matrix	288
F.4	Synthetic Lethality in the GPCRs	289
F.5	Synthetic Lethality in the GPCR Downstream	290
F.6	Synthetic Lethality in the Translation Elongation	291
F.7	Synthetic Lethality in the Nonsense-mediated Decay	292
F.8	Synthetic Lethality in the 3' UTR	293
G.1	Synthetic Lethality and Vertex Degree	294
G.2	Synthetic Lethality and Centrality	295
G.3	Synthetic Lethality and PageRank	296
H.1	Information centrality distribution	300
I.1	Synthetic Lethality and Heirarchy Score in PI3K	301
I.2	Heirarchy Score in PI3K against Synthetic Lethality in PI3K	302
I.3	Structure of Synthetic Lethality in PI3K	302
I.4	Structure of Synthetic Lethality Resampling	303
J.1	Performance of χ^2 and SLIPT across quantiles	304
J.2	Performance of χ^2 and SLIPT across quantiles	306
J.3	Performance of χ^2 and SLIPT across quantiles with more genes	308
J.4	Performance of χ^2 and SLIPT across quantiles with query correlation .	310
J.5	Performance of χ^2 and SLIPT across quantiles with query correlation .	312
J.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	314
K.1	Performance of simulations on a simple graph	317
K.2	Performance of simulations on an inhibiting graph	318
K.3	Performance of simulations on a constructed graph with inhibition	319
K.4	Performance of simulations on a constructed graph with inhibition	320
K.5	Detection of Synthetic Lethality within a Graph Structure	321
K.6	Detection of Synthetic Lethality within an Inhibiting Graph Structure .	323

K.7	Detection of Synthetic Lethality within an Inhibiting Graph Structure	324
K.8	Performance of simulations on a branching graph	325
K.9	Performance of simulations on a complex graph	326
K.10	Performance of simulations on a large graph	327
K.11	Performance of simulations on a branching graph with inhibition	328
K.12	Performance of simulations on a branching graph with inhibition	329
K.13	Performance of simulations on a complex graph with inhibition	330
K.14	Performance of simulations on a complex graph with inhibition	331
K.15	Performance of simulations on a large constructed graph with inhibition	332
K.16	Performance of simulations on a large constructed graph with inhibition	333
K.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	334
K.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	335

List of Tables

1.1	Methods for Predicting Genetic Interactions	27
1.2	Methods for Predicting Synthetic Lethality in Cancer	28
1.3	Methods used by Wu <i>et al.</i> (2014)	29
2.1	Excluded Samples by Batch and Clinical Characteristics	47
2.2	Computers used during Thesis	57
2.3	Linux Utilities and Applications used during Thesis	58
2.4	R Installations used during Thesis	59
2.5	R Packages used during Thesis	59
2.6	R Packages Developed during Thesis	61
4.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT	103
4.2	Pathways for <i>CDH1</i> partners from SLIPT	105
4.3	Pathway composition for clusters of <i>CDH1</i> partners from SLIPT	109
4.4	Analysis of variance (ANOVA) for Synthetic Lethality and Correlation with <i>CDH1</i>	113
4.5	Comparing SLIPT genes against secondary siRNA screen in breast cancer	116
4.6	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	118
4.7	Pathways for <i>CDH1</i> partners from SLIPT	121
4.8	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen	123
4.9	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT	132
5.1	ANOVA for Synthetic Lethality and Vertex Degree	149
5.2	ANOVA for Synthetic Lethality and Information Centrality	151
5.3	ANOVA for Synthetic Lethality and PageRank Centrality	153
5.4	ANOVA for Synthetic Lethality and PI3K Hierarchy	156
5.5	Resampling for pathway structure of synthetic lethal detection methods	160
B.1	R Packages used during Thesis	247
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT	257
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	258
C.3	Pathway composition for clusters of <i>CDH1</i> partners from mtSLIPT	261
C.4	Pathway composition for <i>CDH1</i> partners from mtSLIPT and siRNA	263
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	264
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	265
C.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT	268

D.1	Comparison of Intrinsic Subtypes	275
E.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	277
E.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	278
E.3	Pathway composition for clusters of <i>CDH1</i> partners in stomach SLIPT	280
E.4	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	282
E.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	283
E.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA screen	284
E.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT in stomach cancer	285
G.1	ANOVA for Synthetic Lethality and Vertex Degree	297
G.2	ANOVA for Synthetic Lethality and Information Centrality	297
G.3	ANOVA for Synthetic Lethality and PageRank Centrality	297
H.1	Information centrality for genes and molecules in the Reactome network	299
I.1	ANOVA for Synthetic Lethality and PI3K Hierarchy	301
I.2	Resampling for pathway structure of synthetic lethal detection methods	303

Glossary

synthetic lethal Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.

Acronyms

ANOVA	Analysis of Variance.
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (with respect to mutation).
siRNA	Short interfering ribonucleic acid.
SLIPT	Synthetic lethal interaction prediction tool.
TCGA	The Cancer Genome Atlas (genomics project).

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Appendix F

Synthetic Lethal Genes in Pathways

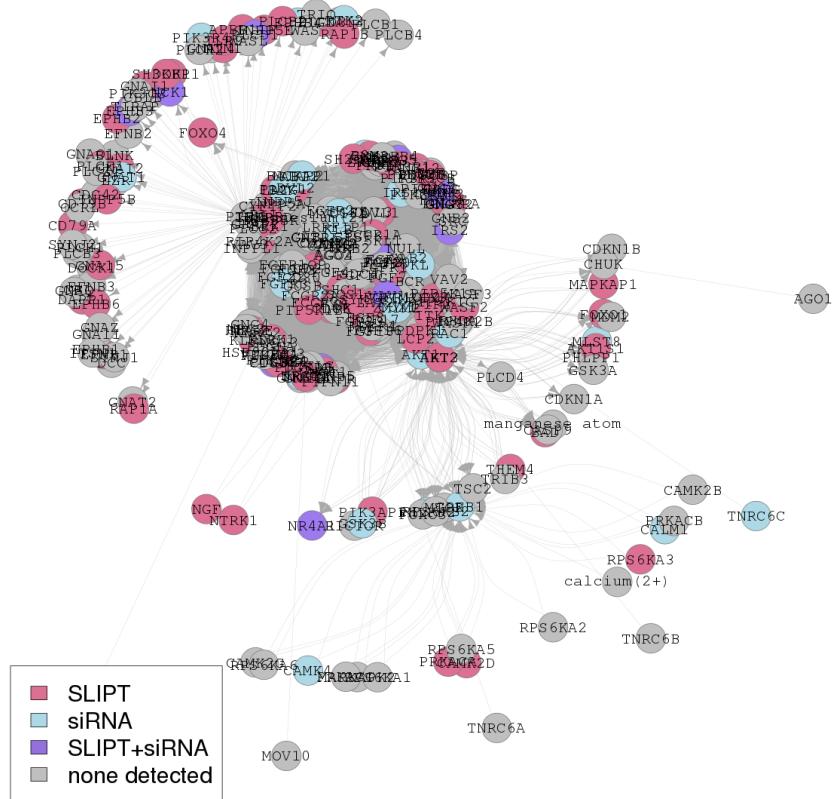


Figure F.1: **Synthetic Lethality in the PI3K/AKT Pathway.** The Reactome PI3K/AKT pathway with synthetic lethal candidates coloured as shown in the legend.

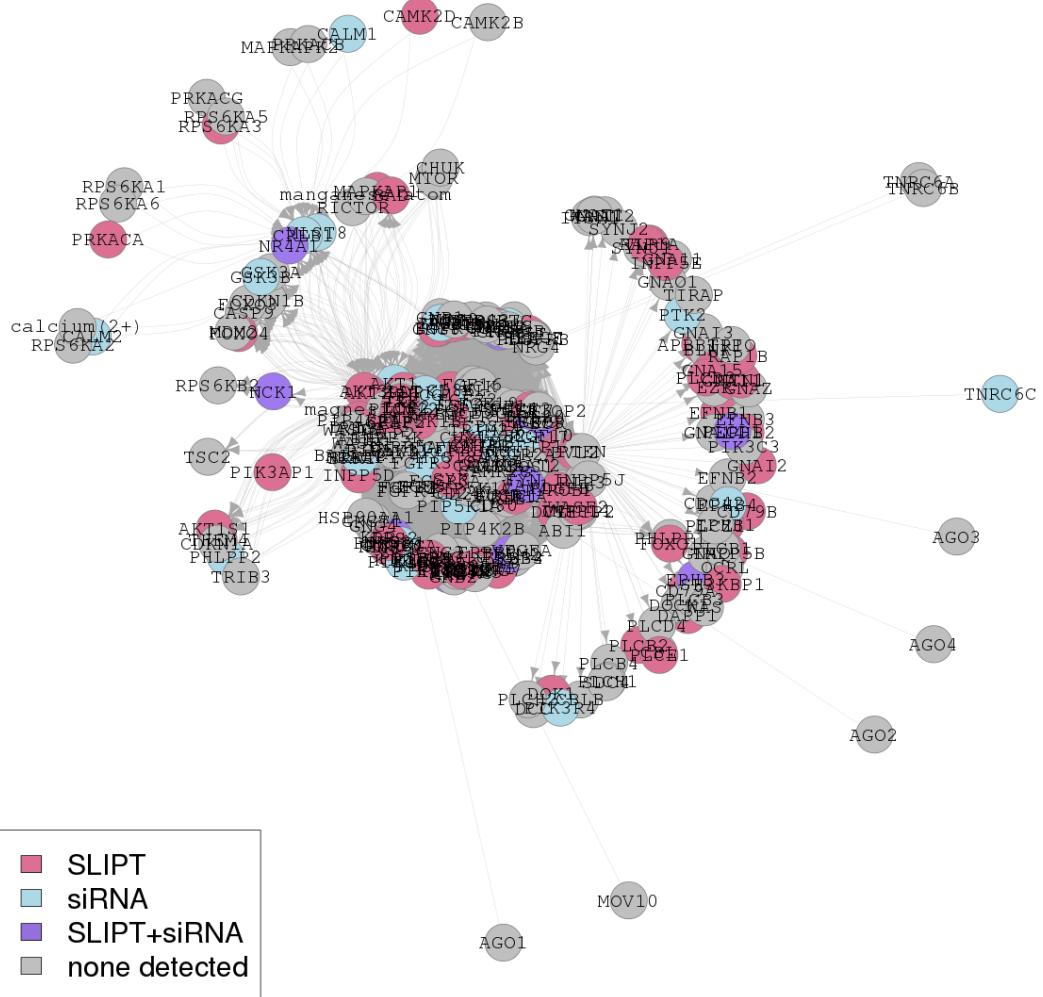


Figure F.2: Synthetic Lethality in the PI3K/AKT Pathway in Cancer. The Reactome PI3K/AKT Pathway in Cancer pathway with synthetic lethal candidates coloured as shown in the legend.

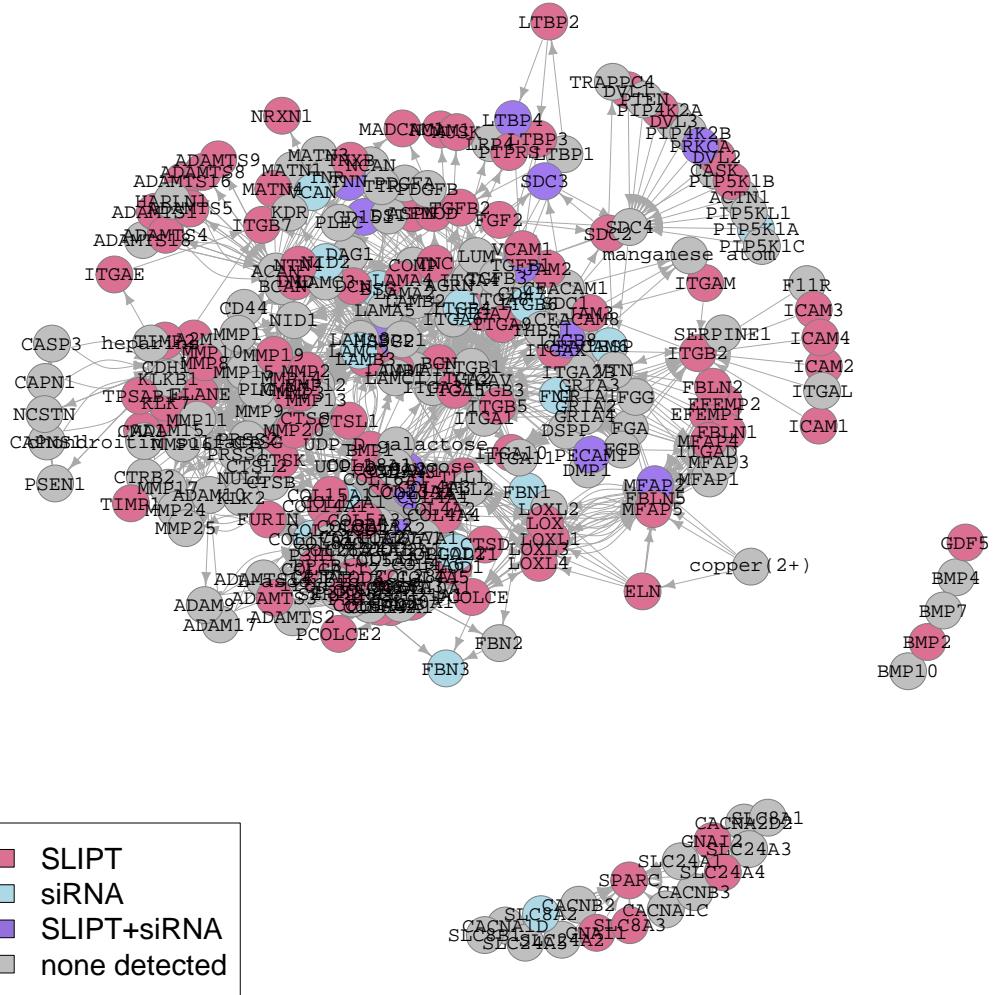


Figure F.3: Synthetic Lethality in the Extracellular Matrix. The Reactome Extracellular Matrix pathway with synthetic lethal candidates coloured as shown in the legend.

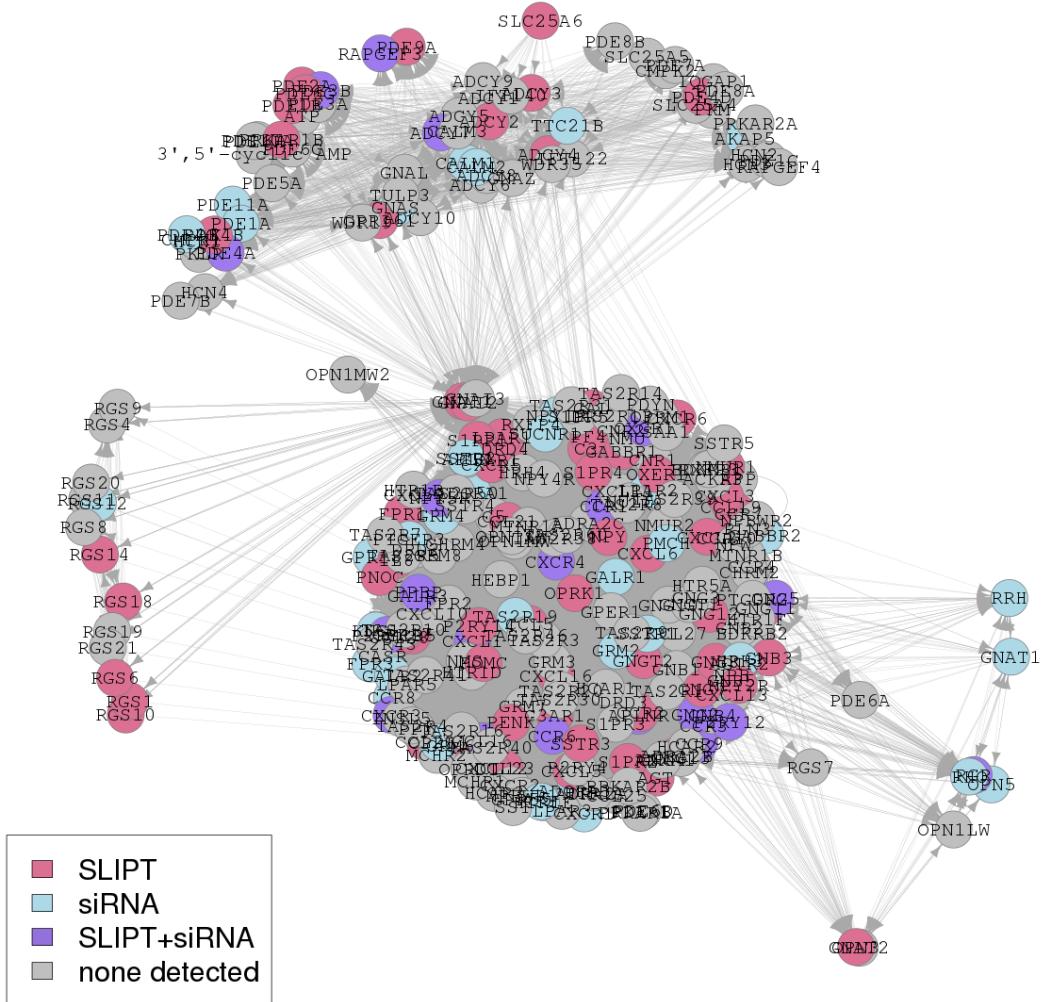


Figure F.4: Synthetic Lethality in the GPCRs. The Reactome $G_{\alpha i}$ pathway with synthetic lethal candidates coloured as shown in the legend.

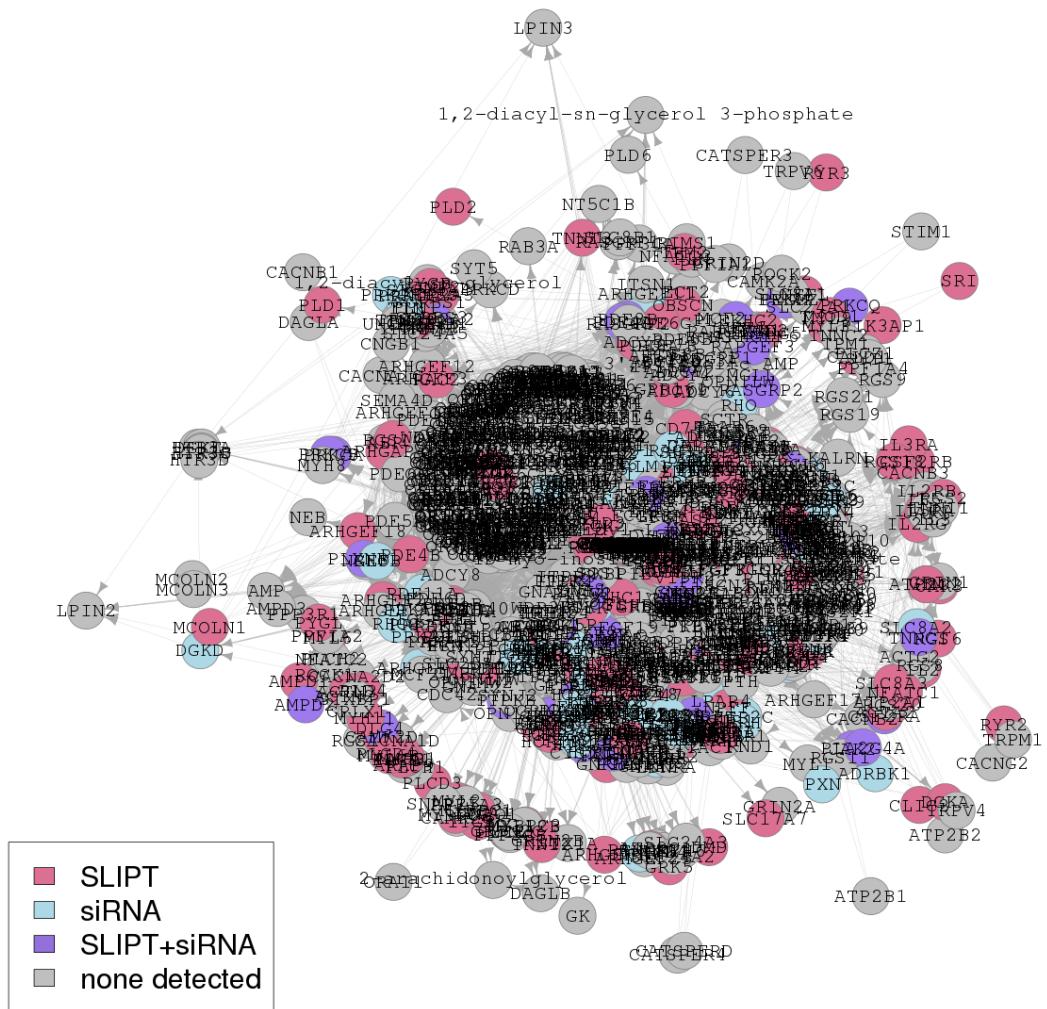


Figure F.5: **Synthetic Lethality in the GPCR Downstream.** The Reactome GPCR Downstream pathway with synthetic lethal candidates coloured as shown in the legend.

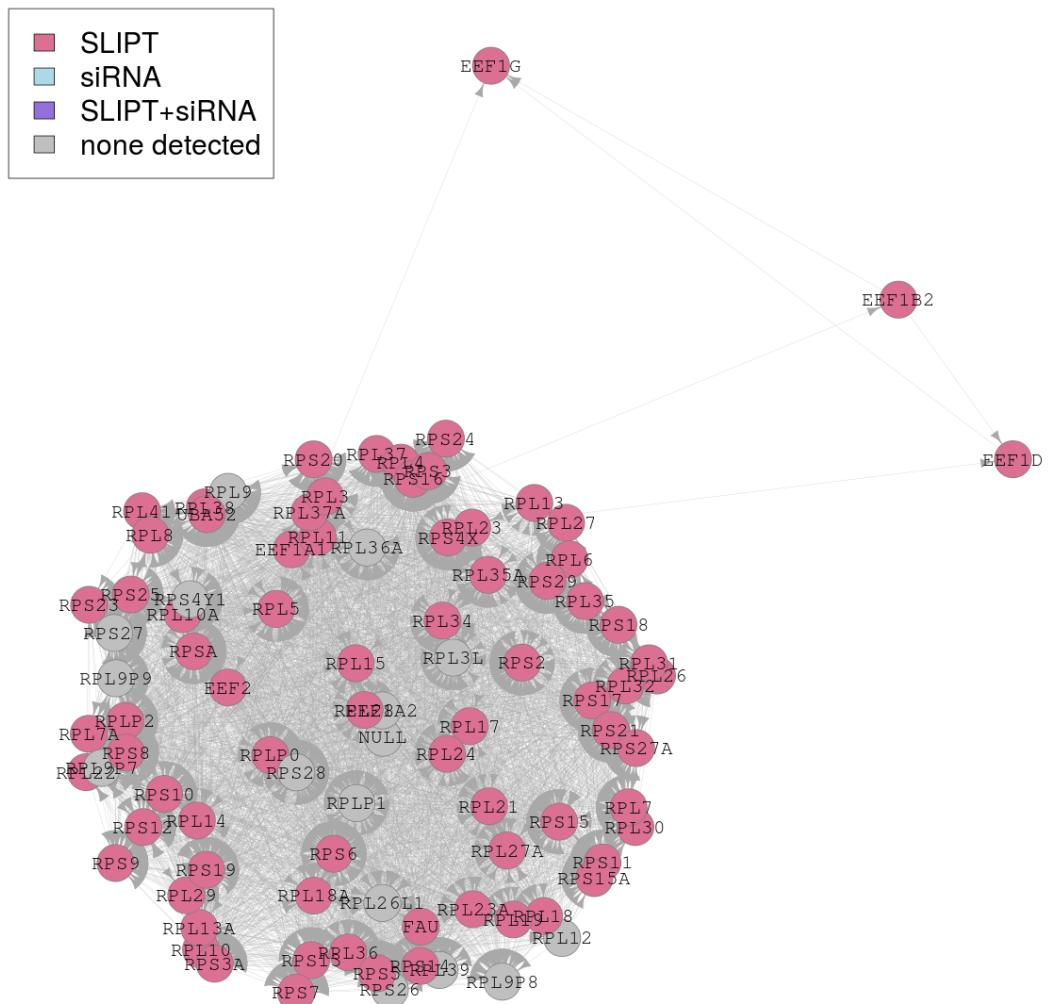


Figure F.6: **Synthetic Lethality in the Translation Elongation**. The Reactome Translation Elongation pathway with synthetic lethal candidates coloured as shown in the legend.

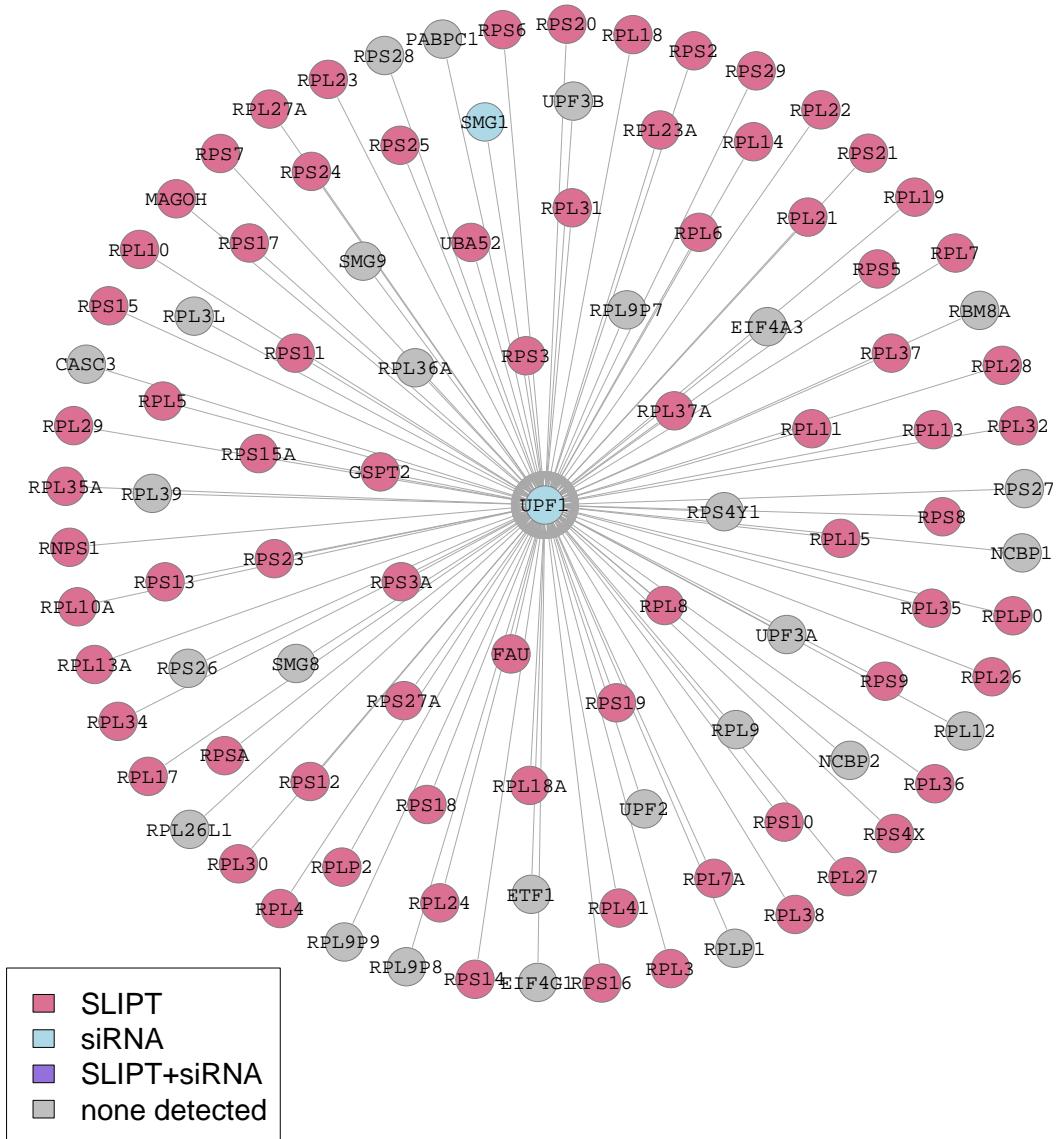


Figure F.7: Synthetic Lethality in the Nonsense-mediated Decay. The Reactome Nonsense-mediated Decay pathway with synthetic lethal candidates coloured as shown in the legend.

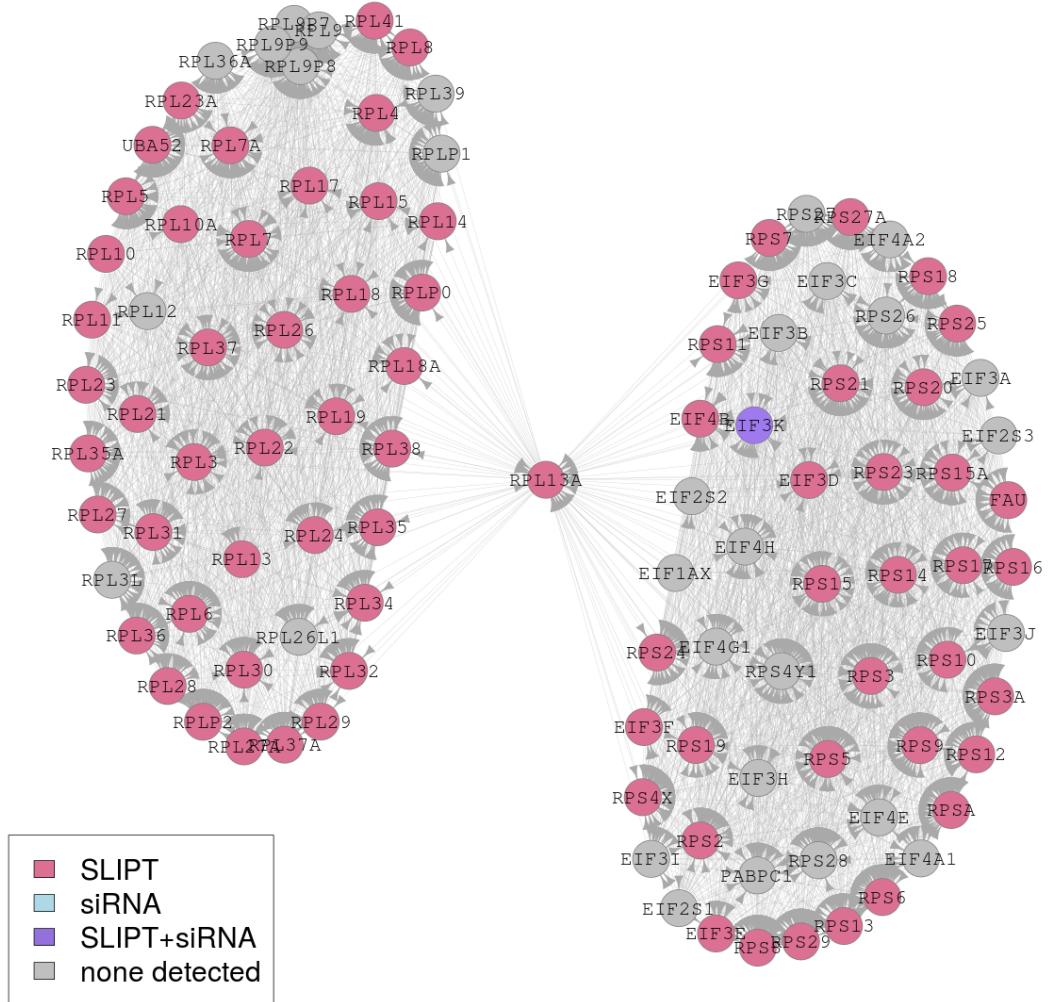


Figure F.8: **Synthetic Lethality in the 3' UTR.** The Reactome 3' UTR pathway with synthetic lethal candidates coloured as shown in the legend.

Appendix G

Pathway Connectivity for Mutation SLIPT

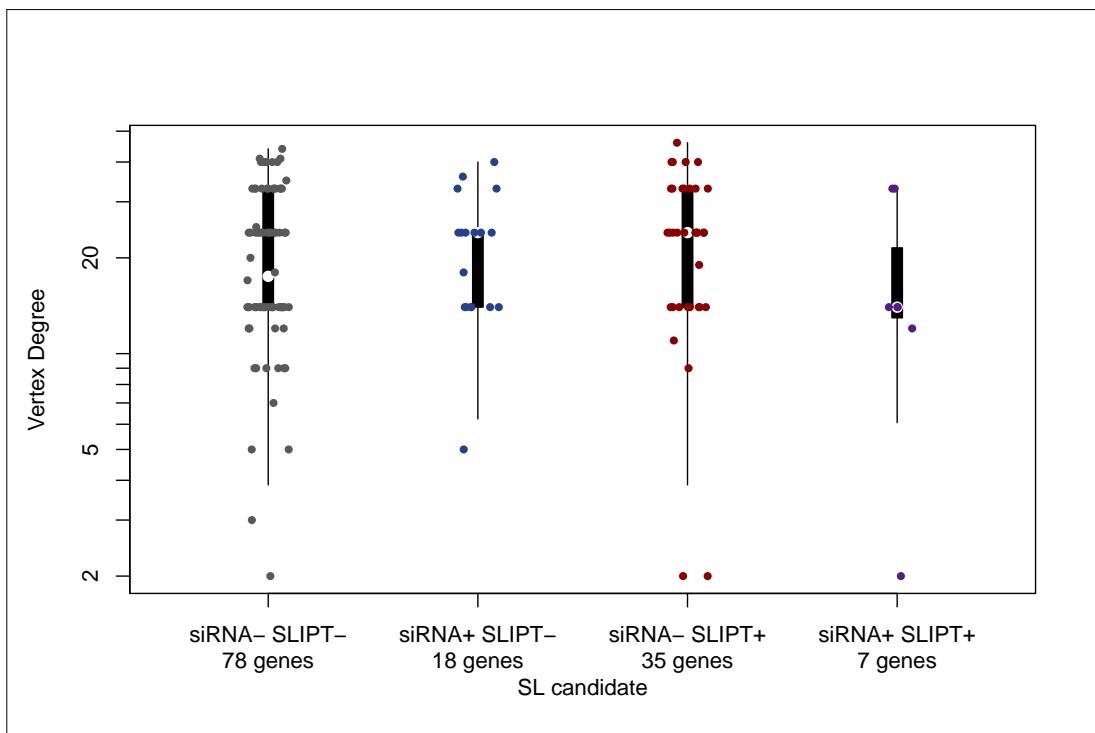


Figure G.1: **Synthetic Lethality and Vertex Degree.** The number of connected genes (vertex degree) was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. There were very few differences in vertex degree between the groups, although genes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

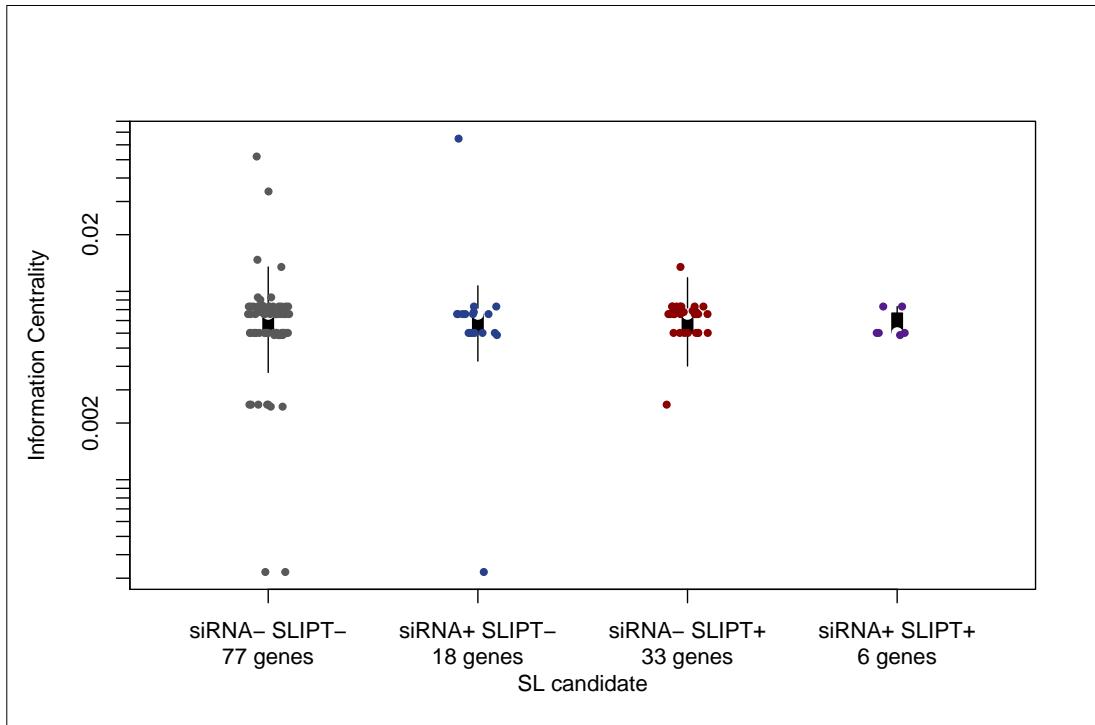


Figure G.2: Synthetic Lethality and Centrality. The information centrality was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. Genes detected by mtSLIPT or siRNA did not have higher connectivity than genes not detected by either approach.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

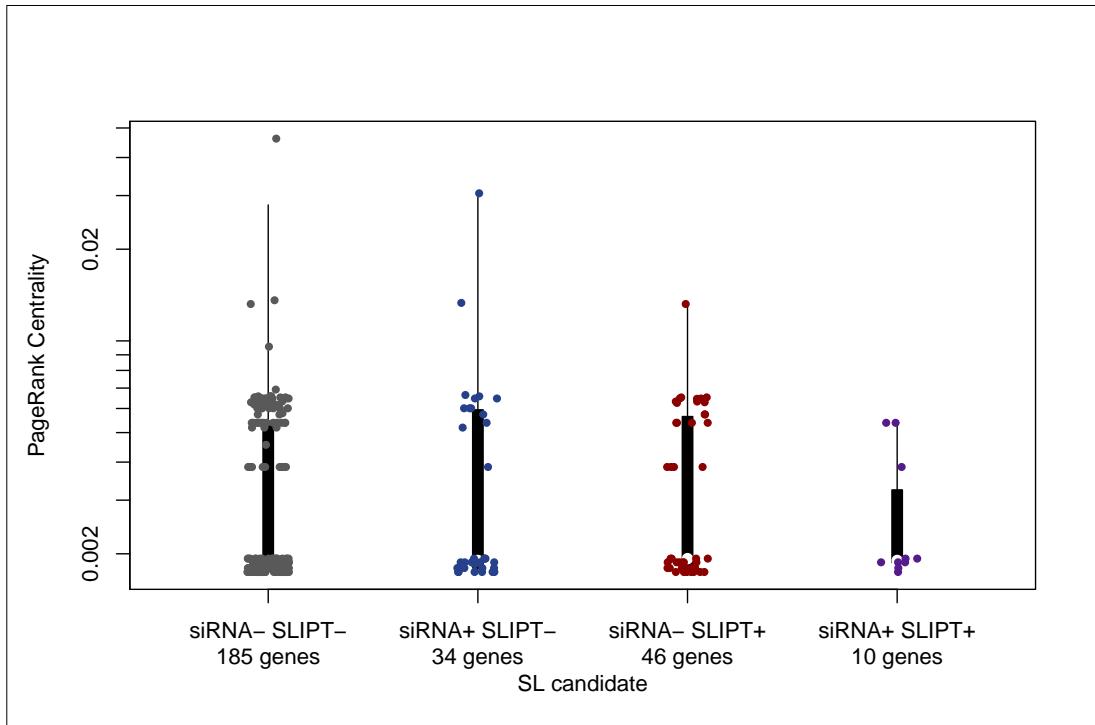


Figure G.3: Synthetic Lethality and PageRank. The PageRank centrality was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. Genes detected by siRNA had a more restricted range of centrality values than other genes not detected by either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

Table G.1: ANOVA for Synthetic Lethality and Vertex Degree

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

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

Table G.2: ANOVA for Synthetic Lethality and Information Centrality

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

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

Table G.3: ANOVA for Synthetic Lethality and PageRank Centrality

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

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

Appendix H

Information Centrality for Gene Essentiality

Network structure is another useful strategy to analyse gene function and this has been used to investigate network properties of a network constructed from of Reactome pathways imported via Pathway Commons with Paxtools (Cerami *et al.*, 2011; Demir *et al.*, 2013). Most notably, information centrality which has been proposed as a measure of gene essentiality was calculated as performed by Kranthi *et al.* (2013) using the efficiency and shortest path between each pair of nodes in the network before and after a node of interest is removed to test the importance of a node to network connectivity. Reactome contains substrates and cofactors in addition to genes or proteins. In support of centrality as a measure of essentiality, a number of nodes with the highest centrality (shown in Table H.1) were essential nutrients including Mg²⁺, Ca²⁺, Zn²⁺, and Fe. In addition, there were genes important in development of epithelial tissues and breast cancer such as *IL8*, *GATA3*, and *CTNNB1* detected with relatively high information centrality.

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

Node	Centrality
<i>ZNF473</i>	0.0510
magnesium(2+)	0.0082
<i>XBP1</i>	0.0053
calcium(2+)	0.0050
zinc(2+)	0.0048
iron atom	0.0041
<i>FMN</i>	0.0040
<i>AGT</i>	0.0037
<i>HSP90AA1</i>	0.0029
phosphatidyl-L-serine	0.0029
<i>P2RX7</i>	0.0026
<i>PANX1</i>	0.0024
<i>NCAM1</i>	0.0022
<i>NUDT1</i>	0.0021
<i>PLAUR</i>	0.0020
<i>IL8</i>	0.0020
<i>HSPA8</i>	0.0019
<i>TYROBP</i>	0.0019
<i>CASP3</i>	0.0017
<i>GNAL</i>	0.0015
<i>CBLB</i>	0.0015
<i>HBB</i>	0.0014
<i>GATA4</i>	0.0013
<i>TGS1</i>	0.0013
<i>CTNNB1</i>	0.0012

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

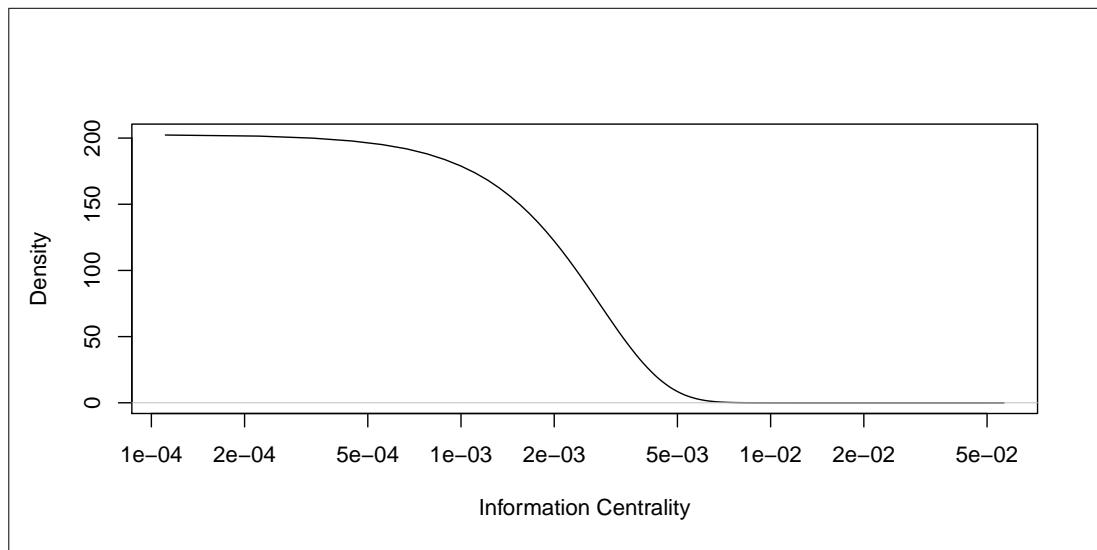


Figure H.1: **Information centrality distribution.** Information centrality in the Reactome network for nodes, including genes/proteins and other biomolecules.

Appendix I

Pathway Structure for Mutation SLIPT

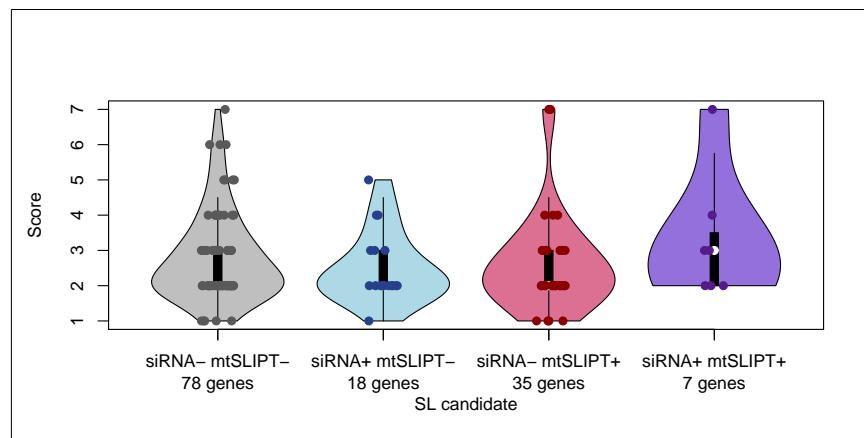


Figure I.1: **Synthetic Lethality and Heirarchy Score in PI3K.** The hierarchical distance scores were similarly distributed across mtSLIPT and siRNA genes. Genes detected by both methods had a higher (downstream) median than either group.

Table I.1: ANOVA for Synthetic Lethality and PI3K Hierarchy

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

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

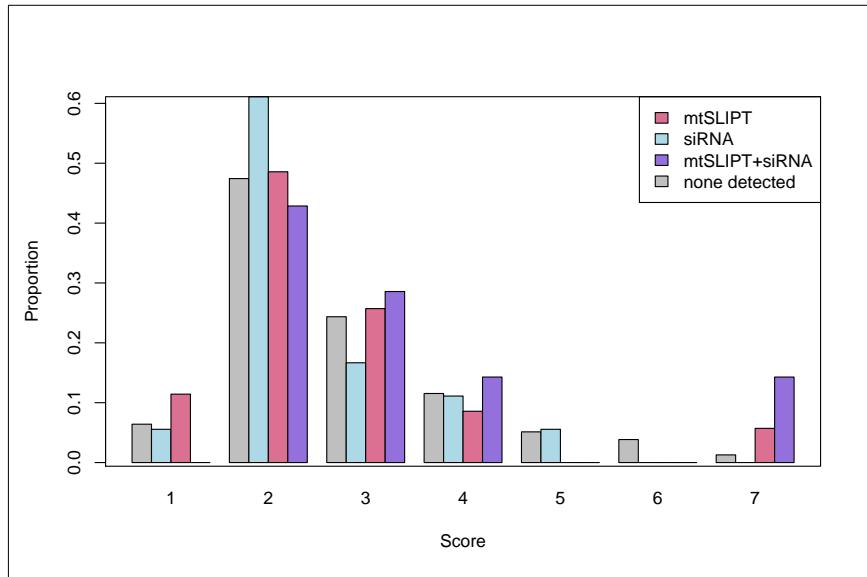


Figure I.2: **Heirarchy Score in PI3K against Synthetic Lethality in PI3K.** The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities.

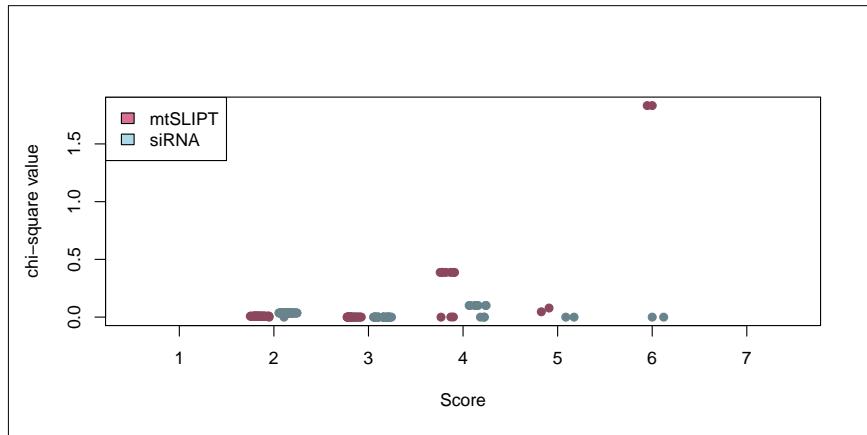


Figure I.3: **Structure of Synthetic Lethality in PI3K.** The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities. The number of mtSLIPT and siRNA genes upstream or downstream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

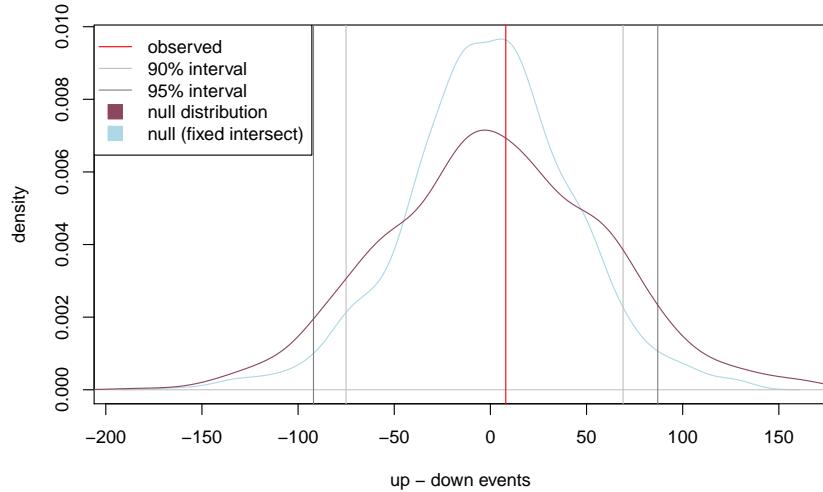


Figure I.4: Structure of Synthetic Lethality Resampling. A null distribution (10,000 iterations) of the siRNA genes upstream or downstream of mtSLIPT genes (shown by the difference) in the PI3K pathway. The observed events (red) were compared to the the distribution (violet) and were not significant.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

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

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

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