

Contents

Glossary	xi
Acronyms	xiii
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	13
1.2.2 Synthetic Lethal Concepts in Genetics	13
1.2.3 Synthetic Lethality in Model Systems	15
1.2.3.1 Synthetic Lethal Pathways and Networks	15
1.2.3.2 Evolution of Synthetic Lethality	16
1.2.4 Synthetic Lethality in Cancer	17
1.2.5 Clinical Impact of Synthetic Lethality in Cancer	18
1.2.6 High-throughput Screening for Synthetic Lethality	20
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	28
1.2.7.5 Data Mining and Machine Learning	29

1.2.7.6	Mutual Exclusivity and Bimodality	32
1.2.7.7	Rationale for Further Development	33
1.3	E-cadherin as a Synthetic Lethal Target	33
1.3.1	The <i>CDH1</i> gene and its Biological Functions	34
1.3.1.1	Cytoskeleton	34
1.3.1.2	Extracellular and Tumour Micro-environment	34
1.3.1.3	Cell-Cell Adhesion and Signalling	35
1.3.2	<i>CDH1</i> as a Tumour (and Invasion) Suppressor	35
1.3.2.1	Breast Cancers and Invasion	35
1.3.3	Hereditary Diffuse Gastric (and Lobular Breast) Cancer	36
1.3.4	Cell Line Models of <i>CDH1</i> Null Mutations	37
1.4	Summary and Research Direction of Thesis	38
1.4.1	Thesis Aims	39
2	Methods and Resources	41
2.1	Bioinformatics Resources for Genomics Research	41
2.1.1	Public Data and Software Packages	41
2.1.1.1	Cancer Genome Atlas Data	42
2.1.1.2	Reactome and Annotation Data	43
2.2	Data Handling	43
2.2.1	Normalisation	43
2.2.2	Sample Triage	43
2.2.3	Metagenes and the Singular Value Decomposition	44
2.2.4	Candidate Triage and Integration with Screen Data	46
2.3	Techniques	46
2.3.1	Statistical Procedures and Tests	47
2.3.2	Gene Set Over-representation Analysis	48
2.3.3	Clustering	48
2.3.4	Heatmap	48
2.3.5	Modelling and Simulations	49
2.3.5.1	Receiver Operating Characteristic Curves	50
2.3.6	Resampling Analysis	50
2.4	Pathway Structure Methods	51
2.4.1	Network and Graph Analysis	51
2.4.2	Sourcing Graph Structure Data	52
2.4.3	Constructing Pathway Subgraphs	52
2.4.4	Network Analysis Metrics	53
2.5	Implementation	54
2.5.1	Computational Resources and Linux Utilities	54
2.5.2	R Language and Packages	55
2.5.3	High Performance and Parallel Computing	58
3	Methods Developed During Thesis	60
3.1	A Synthetic Lethal Detection Methodology	60
3.2	Synthetic Lethal Simulation and Modelling	62
3.2.1	A Model of Synthetic Lethality in Expression Data	63

3.2.2	Simulation Procedure	67
3.3	Detecting Simulated Synthetic Lethal Partners	70
3.3.1	Binomial Simulation of Synthetic Lethality	70
3.3.2	Multivariate Normal Simulation of Synthetic Lethality	72
3.3.2.1	Multivariate Normal Simulation with Correlated Genes	74
3.3.2.2	Specificity with Query-Correlated Pathways	82
3.4	Graph Structure Methods	84
3.4.1	Upstream and Downstream Gene Detection	84
3.4.1.1	Permutation Analysis for Statistical Significance	85
3.4.2	Simulating Gene Expression from Graph Structures	86
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	92
3.5.3.1	Sampling Simulated Data from Graph Structures	92
3.5.3.2	Plotting Directed Graph Structures	92
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	121
4.5	Discussion	122
4.5.1	Strengths of the SLIPT Methodology	122
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	126
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	136
5.2.1	Gene Connectivity and Vertex Degree	137
5.2.2	Gene Importance and Centrality	138
5.2.2.1	Information Centrality	138
5.2.2.2	PageRank Centrality	140
5.3	Relationships between Synthetic Lethal Genes	141
5.3.1	Detecting Upstream or Downstream Synthetic Lethality	142
5.3.2	Resampling for Synthetic Lethal Pathway Structure	144
5.4	Discussion	146
5.5	Summary	148
6	Simulation and Modelling of Synthetic Lethal Pathways	150
6.1	Synthetic Lethal Detection Methods	151
6.1.1	Performance of SLIPT and χ^2 across Quantiles	152
6.1.1.1	Correlated Query Genes affects Specificity	155
6.1.2	Alternative Synthetic Lethal Detection Strategies	157
6.1.2.1	Correlation for Synthetic Lethal Detection	158
6.1.2.2	Testing for Bimodality with BiSEp	159
6.2	Simulations with Graph Structures	160
6.2.1	Performance over Graph Structures	161
6.2.1.1	Simple Graph Structures	161
6.2.1.2	Constructed Graph Structures	164
6.2.2	Performance with Inhibitions	166
6.2.3	Synthetic Lethality across Graph Structures	172
6.2.4	Performance within a Large Simulated Datasets	175
6.3	Simulations in More Complex Graph Structures	180
6.3.1	Simulations over Pathway-based Graphs	181
6.3.2	Pathway Structures in a Large Simulated Datasets	184
6.4	Discussion	187
6.4.1	Simulation Procedure	187
6.4.2	Comparing Methods with Simulated Data	188
6.4.3	Design and Performance of SLIPT	189
6.4.4	Simulations from Graph Structures	191
6.5	Summary	192
7	Discussion	193
7.1	Synthetic Lethality and <i>CDH1</i> Biology	193
7.1.1	Established Functions of <i>CDH1</i>	194
7.1.2	The Molecular Role of <i>CDH1</i> in Cancer	194
7.2	Significance	195

7.2.1	Synthetic Lethality in the Genomic Era	195
7.2.2	Clinical Interventions based on Synthetic Lethality	197
7.3	Future Directions	198
7.4	Conclusions	200
	Bibliography	202
A	Sample Quality	226
A.1	Sample Correlation	226
A.2	Replicate Samples in TCGA Breast Cancer Data	228
B	Software Used for Thesis	232
C	Mutation Analysis in Breast Cancer	241
C.1	Synthetic Lethal Genes and Pathways	241
C.2	Synthetic Lethal Expression Profiles	242
C.3	Comparison to Primary Screen	245
C.3.1	Resampling Analysis	247
C.4	Compare SLIPT genes	249
D	Metagene Analysis	251
D.1	Pathway Signature Expression	251
D.2	Synthetic Lethal Reactome Metagenes	255
E	Intrinsic Subtyping	256
F	Stomach Expression Analysis	258
F.1	Synthetic Lethal Genes and Pathways	258
F.2	Comparison to Primary Screen	262
F.2.1	Resampling Analysis	264
F.3	Metagene Analysis	266
G	Synthetic Lethal Genes in Pathways	267
H	Network Analysis for Mutation SLIPT	274
I	Pathway Structure for Mutation SLIPT	277
J	Performance of SLIPT and χ^2	281
J.1	Correlated Query Genes affects Specificity	287
K	Simulations on Graph Structures	293
K.0.1	Simulations from Inhibiting Graph Structures	294
K.1	Simulation across Graph Structures	297
K.2	Simulations from Complex Graph Structures	301
K.2.1	Simulations from Complex Inhibiting Graphs	304
K.3	Simulations from Pathway Graph Structures	310

List of Figures

1.1	Synthetic genetic interactions	14
1.2	Synthetic lethality in cancer	17
2.1	Read count density	45
2.2	Read count sample mean	45
3.1	Framework for synthetic lethal prediction	61
3.2	Synthetic lethal prediction adapted for mutation	62
3.3	A model of synthetic lethal gene expression	64
3.4	Modelling synthetic lethal gene expression	65
3.5	Synthetic lethality with multiple genes	66
3.6	Simulating gene function	68
3.7	Simulating synthetic lethal gene function	68
3.8	Simulating synthetic lethal gene expression	69
3.9	Performance of binomial simulations	71
3.10	Comparison of statistical performance	71
3.11	Performance of multivariate normal simulations	73
3.12	Simulating expression with correlated gene blocks	75
3.13	Simulating expression with correlated gene blocks	76
3.14	Synthetic lethal prediction across simulations	78
3.15	Performance with correlations	79
3.16	Comparison of statistical performance with correlation structure	80
3.17	Performance with query correlations	81
3.18	Statistical evaluation of directional criteria	82
3.19	Performance of directional criteria	83
3.20	Simulated graph structures	87
3.21	Simulating expression from a graph structure	88
3.22	Simulating expression from graph structure with inhibitions	89
3.23	Demonstration of violin plots with custom features	93
3.24	Demonstration of annotated heatmap	93
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 in the GPCRs	135
5.5	Synthetic lethality and vertex degree	137
5.6	Synthetic lethality and centrality	139
5.7	Synthetic lethality and PageRank	141
5.8	Structure of synthetic lethality resampling	143
6.1	Performance of χ^2 and SLIPT across quantiles	153
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	154
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation	155
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	156
6.5	Performance of negative correlation and SLIPT	159
6.6	Simple graph structures	162
6.7	Performance of simulations on a simple graph	163
6.8	Performance of simulations is similar in simple graphs	164
6.9	Performance of simulations on a pathway	165
6.10	Performance of simulations on a simple graph with inhibition	167
6.11	Performance is higher on a simple inhibiting graph	169
6.12	Performance of simulations on a constructed graph with inhibition	170
6.13	Performance is affected by inhibition in graphs	171
6.14	Detection of synthetic lethality within a graph structure	173
6.15	Performance of simulations including a simple graph	177
6.16	Performance on a simple graph improves with more genes	178
6.17	Performance on an inhibiting graph improves with more genes	179
6.18	Performance of simulations on the PI3K cascade	183
6.19	Performance of simulations including the PI3K cascade	185
6.20	Performance on pathways improves with more genes	186
A.1	Correlation profiles of removed samples	226
A.2	Correlation analysis and sample removal	227
A.3	Replicate excluded samples	228
A.4	Replicate samples with all remaining	229
A.5	Replicate samples with some excluded	230
C.1	Synthetic lethal expression profiles of analysed samples	243
C.2	Comparison of mtSLIPT to short interfering RNA (siRNA)	245
C.3	Compare mtSLIPT and siRNA genes with correlation	249
C.4	Compare mtSLIPT and siRNA genes with correlation	249
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	250
D.1	Pathway metagene expression profiles	253

D.2	Expression profiles for estrogen receptor related genes	254
F.1	Synthetic lethal expression profiles of stomach samples	260
F.2	Comparison of SLIPT in stomach to siRNA	262
G.1	Synthetic lethality in the PI3K/AKT pathway	267
G.2	Synthetic lethality in the PI3K/AKT pathway in cancer	268
G.3	Synthetic lethality in the Extracellular Matrix	269
G.4	Synthetic lethality in the GPCR Downstream	270
G.5	Synthetic lethality in the Translation Elongation	271
G.6	Synthetic lethality in the Nonsense-mediated Decay	272
G.7	Synthetic lethality in the 3' UTR	273
H.1	Synthetic lethality and vertex degree	274
H.2	Synthetic lethality and centrality	275
H.3	Synthetic lethality and PageRank	275
I.1	Structure of synthetic lethality resampling	277
J.1	Performance of χ^2 and SLIPT across quantiles	281
J.2	Performance of χ^2 and SLIPT across quantiles	283
J.3	Performance of χ^2 and SLIPT across quantiles with more genes	285
J.4	Performance of χ^2 and SLIPT across quantiles with query correlation	287
J.5	Performance of χ^2 and SLIPT across quantiles with query correlation	289
J.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	291
K.1	Performance of simulations on a simple graph	293
K.2	Performance of simulations on an inhibiting graph	294
K.3	Performance of simulations on a constructed graph with inhibition	295
K.4	Performance of simulations on a constructed graph with inhibition	296
K.5	Detection of synthetic lethality within a graph structure	297
K.6	Detection of synthetic lethality within an inhibiting graph	299
K.7	Detection of synthetic lethality within an inhibiting graph	300
K.8	Performance of simulations on a branching graph	301
K.9	Performance of simulations on a complex graph	302
K.10	Performance of simulations on a large graph	303
K.11	Performance of simulations on a branching graph with inhibition	304
K.12	Performance of simulations on a branching graph with inhibition	305
K.13	Performance of simulations on a complex graph with inhibition	306
K.14	Performance of simulations on a complex graph with inhibition	307
K.15	Performance of simulations on a large constructed graph with inhibition	308
K.16	Performance of simulations on a large constructed graph with inhibition	309
K.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	310
K.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	311

List of Tables

1.1	Methods for predicting genetic interactions	23
1.2	Methods for predicting synthetic lethality in cancer	24
1.3	Methods used by Wu <i>et al.</i> (2014)	25
2.1	Excluded samples by batch and clinical characteristics.	44
2.2	Computers used during thesis	54
2.3	Linux utilities and applications used during thesis	55
2.4	R installations used during thesis	56
2.5	R Packages used during thesis	56
2.6	R packages developed during thesis	58
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	Examples of candidate metagenes synthetic lethal for <i>CDH1</i> from SLIPT	120
5.1	ANOVA for synthetic lethality and vertex degree	138
5.2	ANOVA for synthetic lethality and information centrality	139
5.3	ANOVA for synthetic lethality and PageRank centrality	140
5.4	Resampling for pathway structure of synthetic lethal detection methods	145
B.1	Complete list of R packages used during this thesis	232
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT . . .	241
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	242
C.3	Pathways for clusters of <i>CDH1</i> partners from mtSLIPT	244
C.4	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA	246
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	247
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	248
D.1	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT . .	255

E.1	Comparison of intrinsic subtypes	256
F.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	258
F.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	259
F.3	Pathways for clusters of <i>CDH1</i> partners in stomach SLIPT	261
F.4	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	263
F.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	264
F.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA	265
F.7	Synthetic lethal metagenes against <i>CDH1</i> in stomach cancer	266
H.1	ANOVA for synthetic lethality and vertex degree	276
H.2	ANOVA for synthetic lethality and information centrality	276
H.3	ANOVA for synthetic lethality and PageRank centrality	276
I.1	Resampling for pathway structure of synthetic lethal detection methods	278

Glossary

centrality	A network metric which identifies important vertices .
edge or link	A relationship connecting a pair of elements of a graph structure or network, may be weighted or directional.
gene expression	A measure of the relative expression of each gene from the mRNA extracted from (pooled) cells.
graph or network	A mathematical structure modelling or depicting the relationships between elements.
information centrality	A network centrality metric which uses the impact of removing a vertex or node on connections in the network.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.
mutation	A change in DNA sequence that disrupts gene function.
PageRank centrality	A network centrality metric which uses eigenvectors with a scaling factor (Brin and Page, 1998).
pathway	A series of biomolecules that produces a particular product or biological function.
shortest path	A path with the fewest possible edges which connects two particular vertices .
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.

vertex degree	A network metric of connectivity of vertices which uses the number of edges connected to each vertex or node .
vertex or node	An element of a graph structure or network.

Acronyms

ANOVA	Analysis of Variance.
GPCR	G Protein Coupled Receptor.
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (against mutation).
NMD	Nonsense-Mediated Decay.
PI3K	Phosphoinositide 3-kinase.
siRNA	Short Interfering RNA.
SLIPT	Synthetic Lethal Interaction Prediction Tool.
UTR	Untranslated Region (of mRNA).

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Appendix G

Synthetic Lethal Genes in Pathways

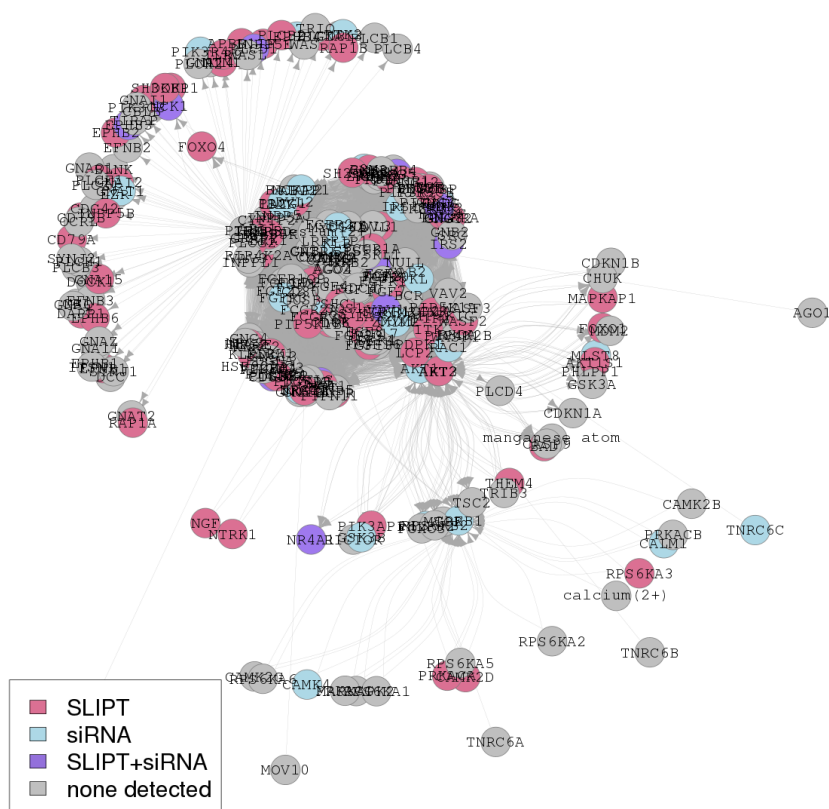


Figure G.1: **Synthetic lethality in the PI3K/AKT pathway.** The Reactome PI3K/AKT pathway with synthetic lethal candidates, coloured as shown in the legend.

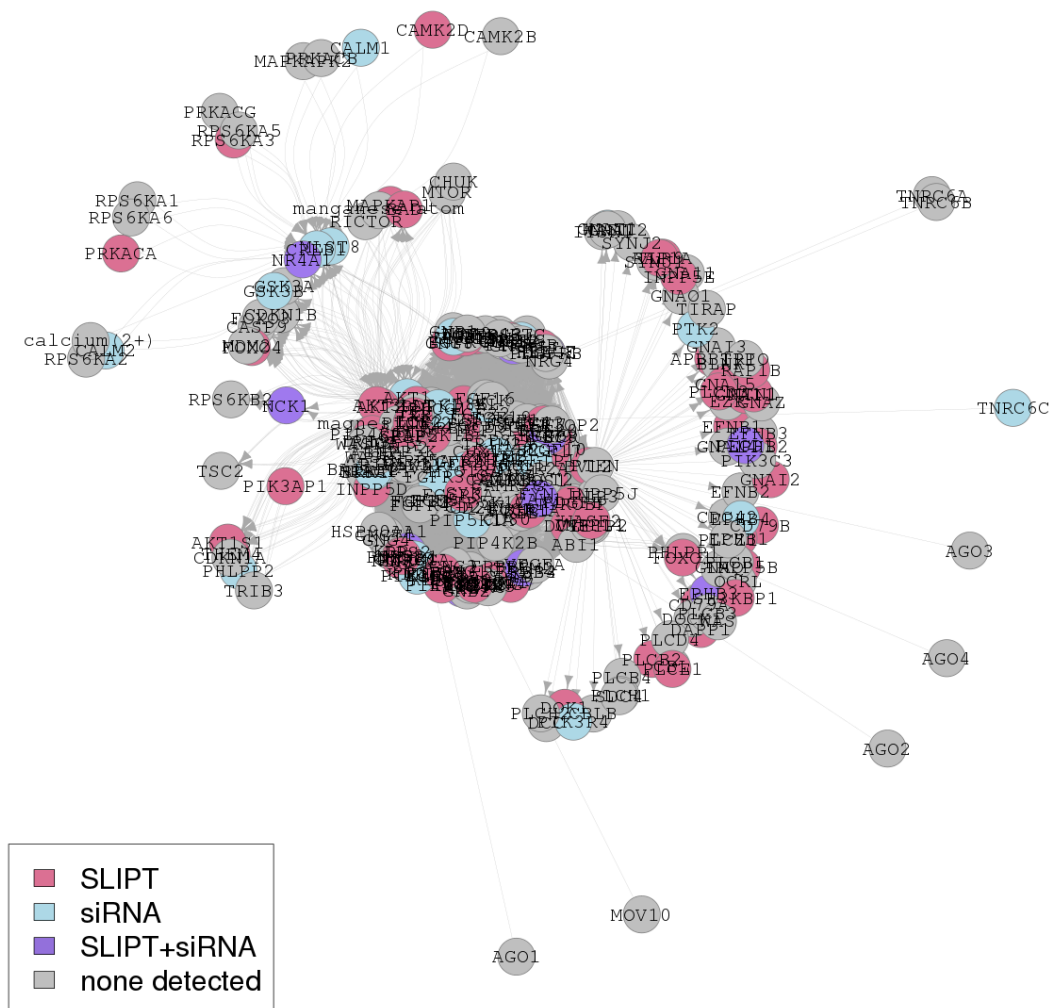


Figure G.2: **Synthetic lethality in the PI3K/AKT pathway in cancer.** The Reactome PI3K/AKT in cancer pathway with synthetic lethal candidates, coloured as shown in the legend.

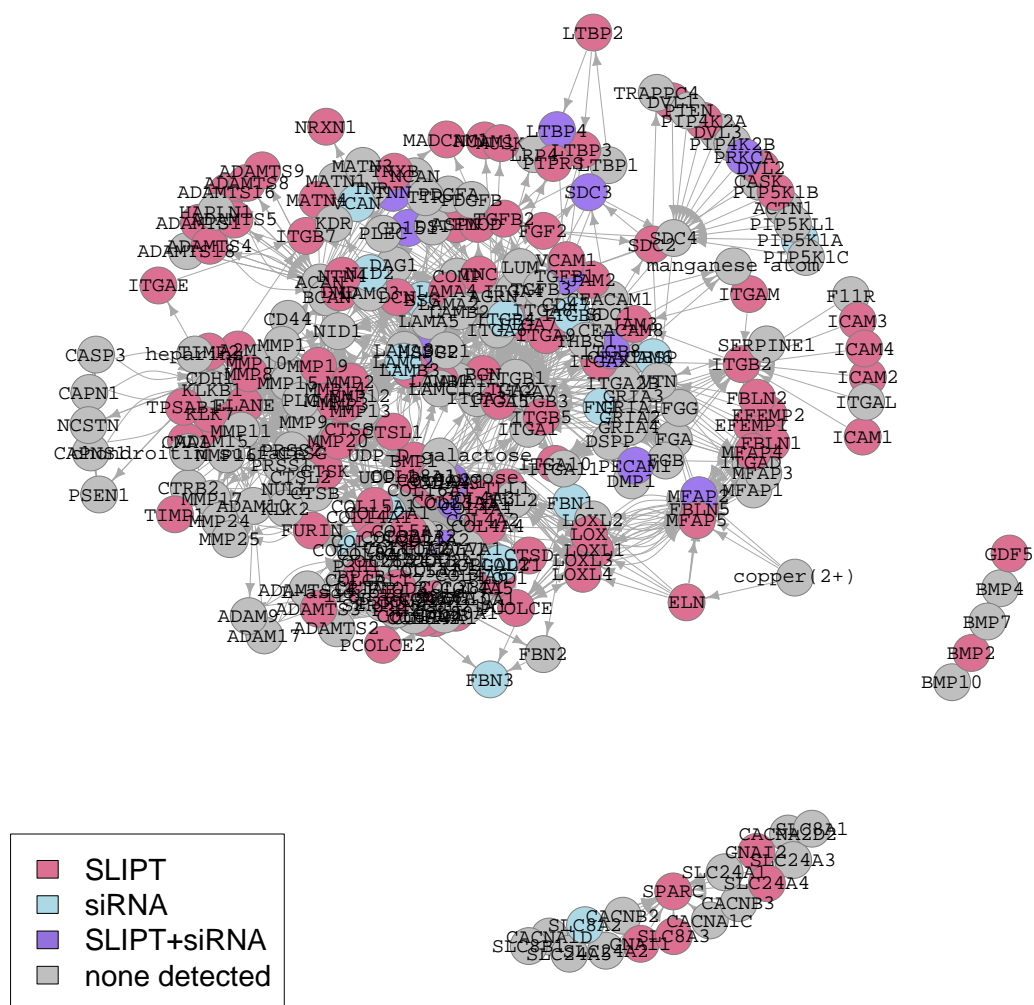


Figure G.3: **Synthetic lethality in the Extracellular Matrix.** The Reactome Extracellular Matrix pathway with synthetic lethal candidates, coloured as shown in the legend.

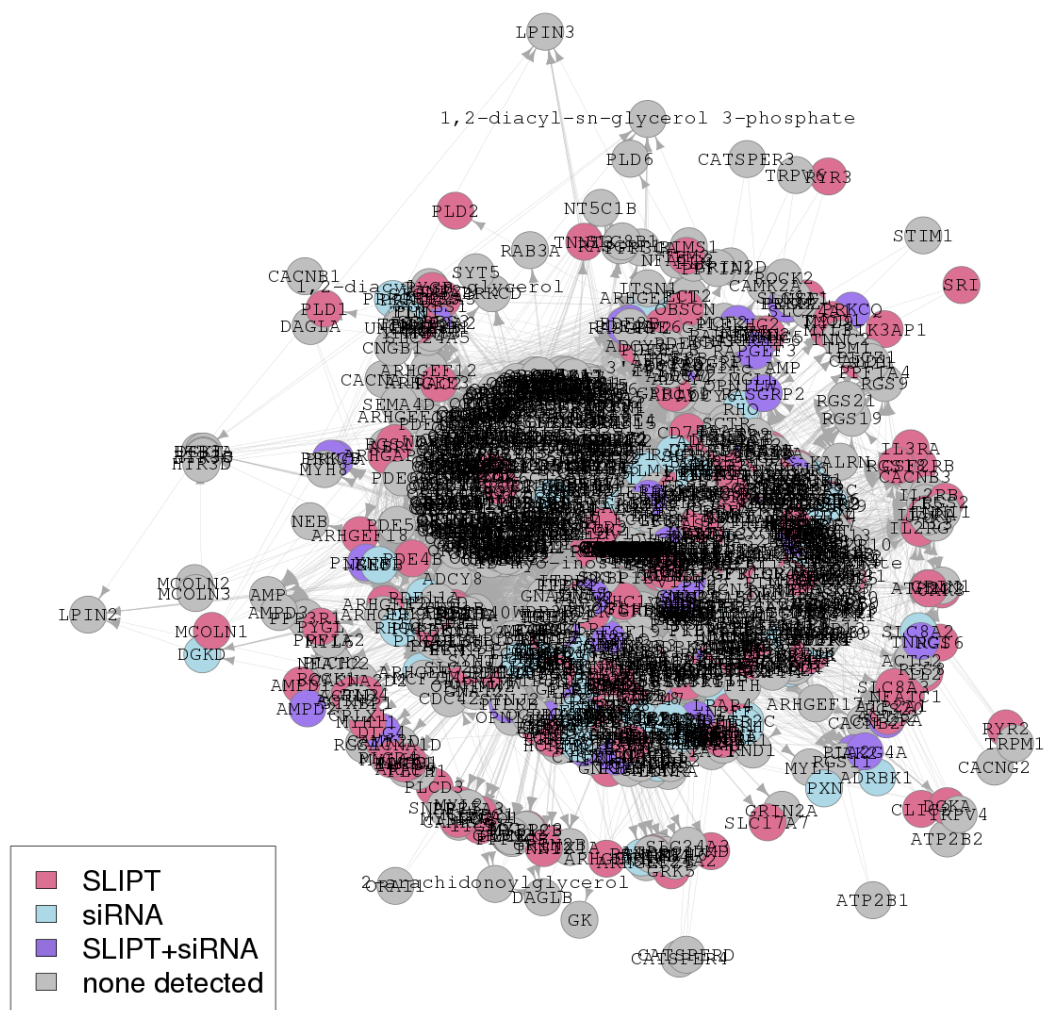


Figure G.4: **Synthetic lethality in the GPCR Downstream.** The Reactome **G protein coupled receptor (GPCR)** Downstream pathway with synthetic lethal candidates, coloured as shown in the legend.

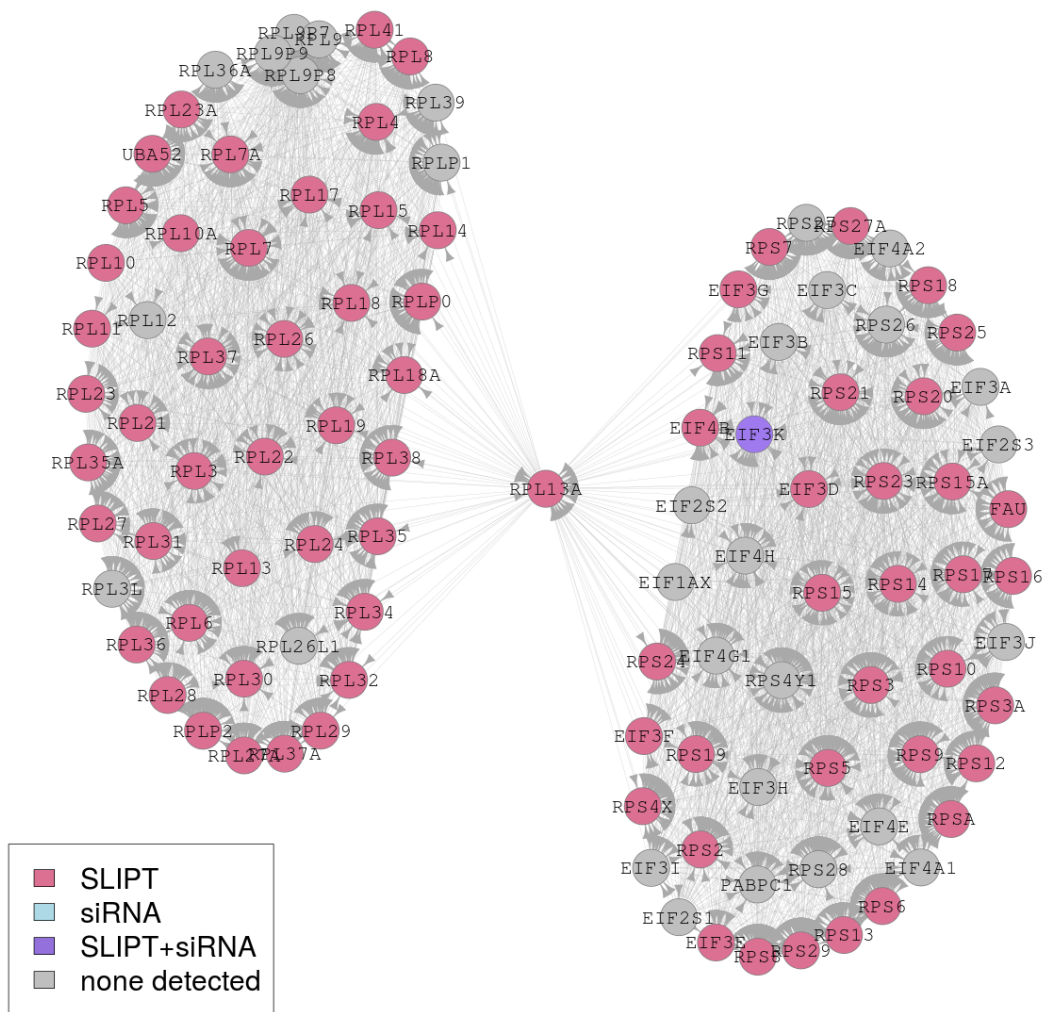


Figure G.7: **Synthetic lethality in the 3' UTR.** The Reactome 3' untranslated region (UTR) pathway with synthetic lethal candidates, coloured as shown in the legend.

Appendix H

Network Analysis for Mutation SLIPT

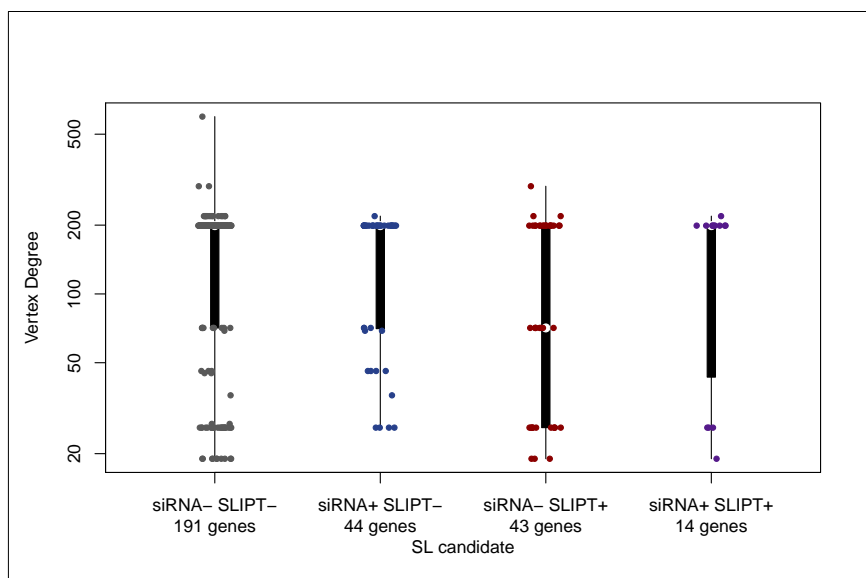


Figure H.1: **Synthetic lethality and vertex degree.** The number of connected genes (**vertex degree**) was compared (on a log-scale) across genes detected by **mtSLIPT** and **siRNA** screening in the Reactome $G_{\alpha i}$ pathway. There were no differences in **vertex degree** between the groups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

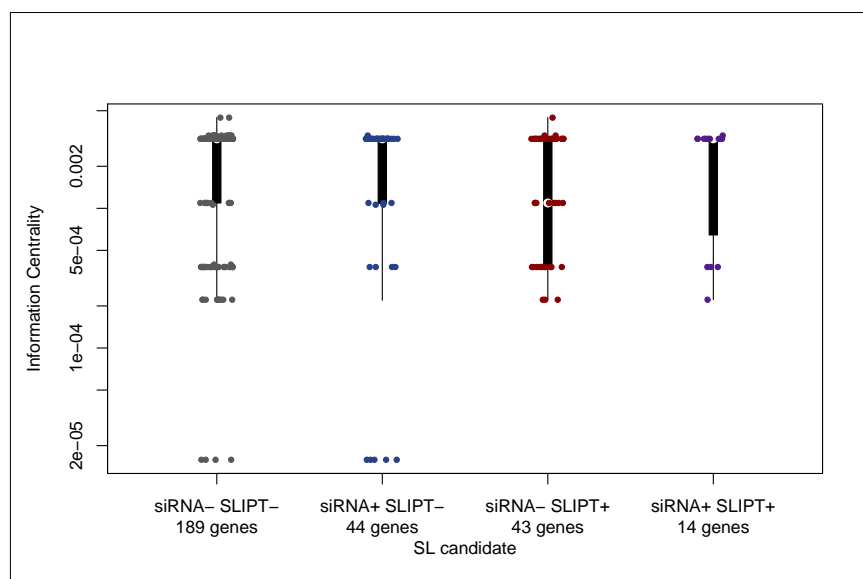


Figure H.2: **Synthetic lethality and centrality.** The [information centrality](#) was compared (on a log-scale) across genes detected by [SLIPT](#) and [siRNA](#) screening in the Reactome $G_{\alpha i}$ pathway. Genes detected by [SLIPT](#) or [siRNA](#) did not have higher centrality than other genes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

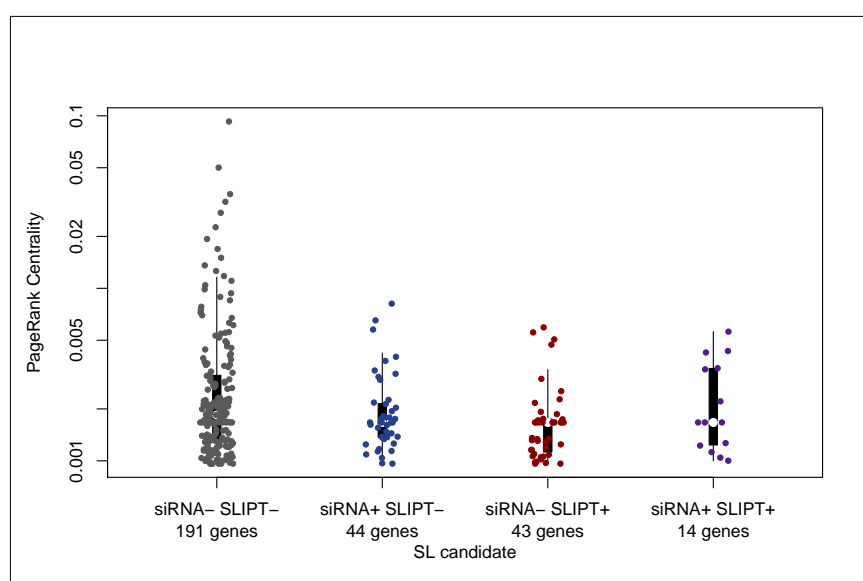


Figure H.3: **Synthetic lethality and PageRank.** The [PageRank centrality](#) was compared (on a log-scale) across genes detected by [mtSLIPT](#) and [siRNA](#) screening in the Reactome $G_{\alpha i}$ pathway. Genes detected by with either [synthetic lethal](#) detection approach had a more restricted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

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

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

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

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

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

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

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

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

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

Appendix I

Pathway Structure for Mutation SLIPT

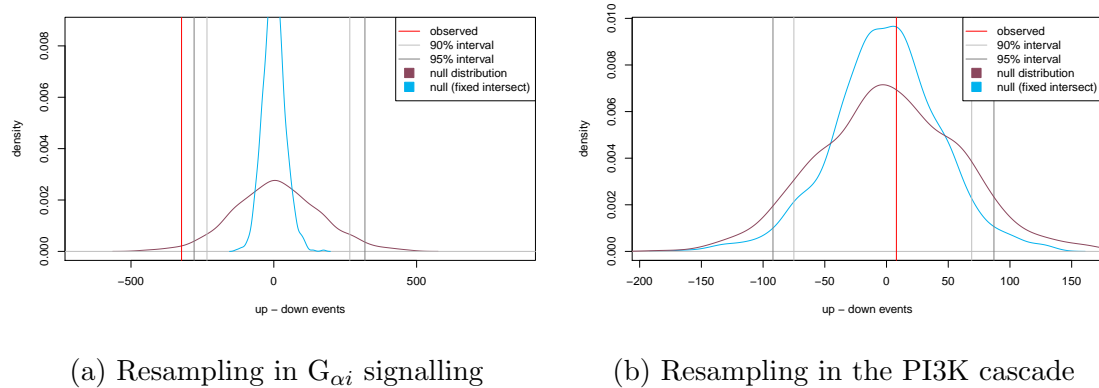


Figure I.1: **Structure of synthetic lethality resampling.** A null distribution with 10,000 iterations of the number of **siRNA** genes upstream or downstream of **mtSLIPT** genes (depicted as the difference of these) in each **pathway**. To assess significance, the observed events (with **shortest paths**) were compared to the 90% and 95% intervals for the null distribution (shown in blue). Genes detected by both methods were not fixed to the same number as observed for the alternative null distribution (shown in red), although the significance of the observed number of events (red) was changed in either case. The genes detected by both approaches were included in computing the number of **shortest paths** (in either direction) between **SLIPT** and **siRNA** genes. The permutations show (a) a significant pathway relationship for $G_{\alpha i}$ signalling and (b) and non-significant relationship for the **phosphoinositide 3-kinase (PI3K)** cascade.

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

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

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

¹ The number of paths where the **siRNA** candidate was upstream of a **mtSLIPT** candidate

² The number of paths where the **siRNA** candidate was downstream of a **mtSLIPT** candidate