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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

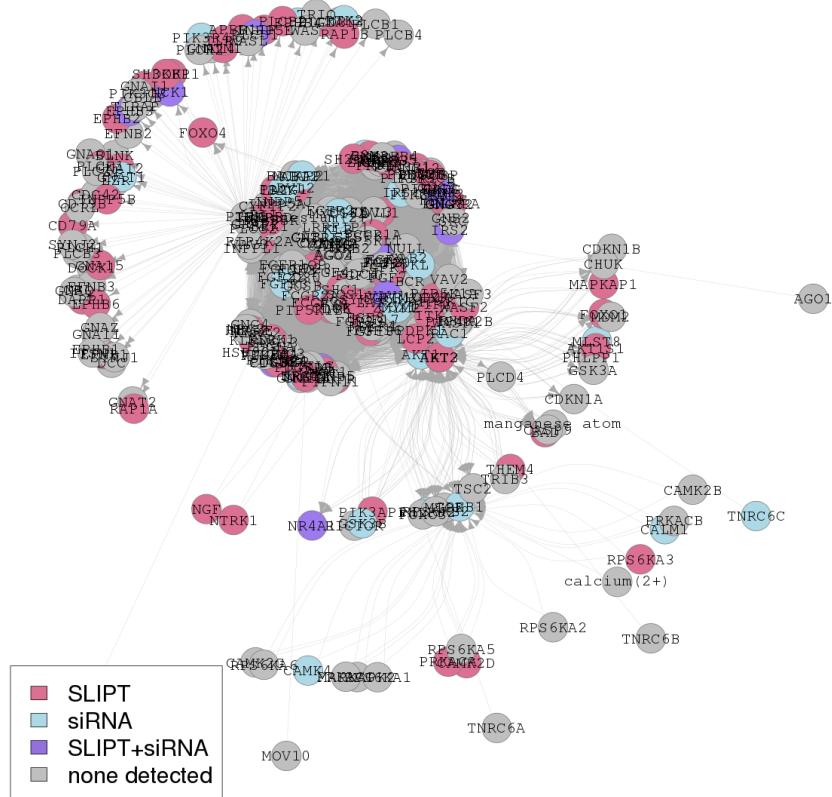


Figure F.1: **Synthetic Lethality in the PI3K/AKT Pathway.** The Reactome PI3K/AKT pathway with synthetic lethal candidates coloured as shown in the legend.

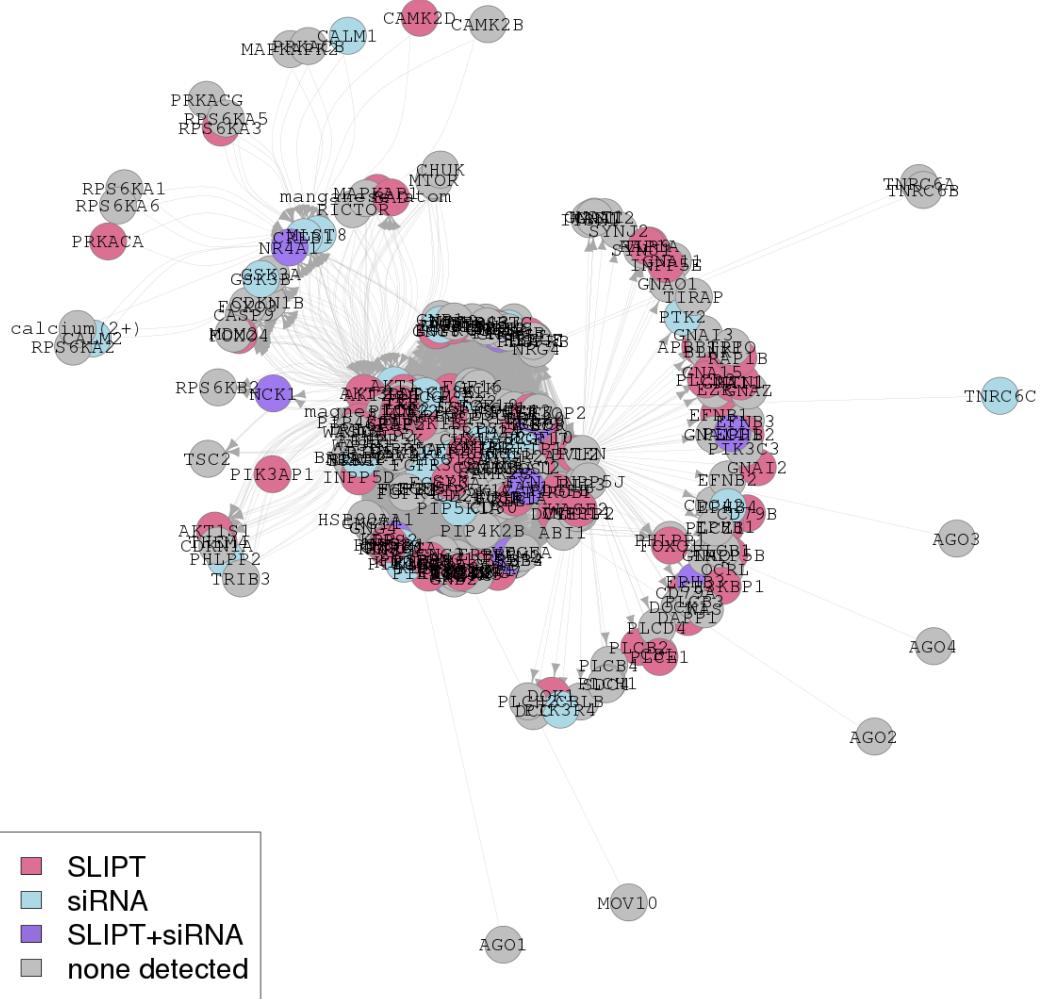


Figure F.2: Synthetic Lethality in the PI3K/AKT Pathway in Cancer. The Reactome PI3K/AKT Pathway in Cancer pathway with synthetic lethal candidates coloured as shown in the legend.

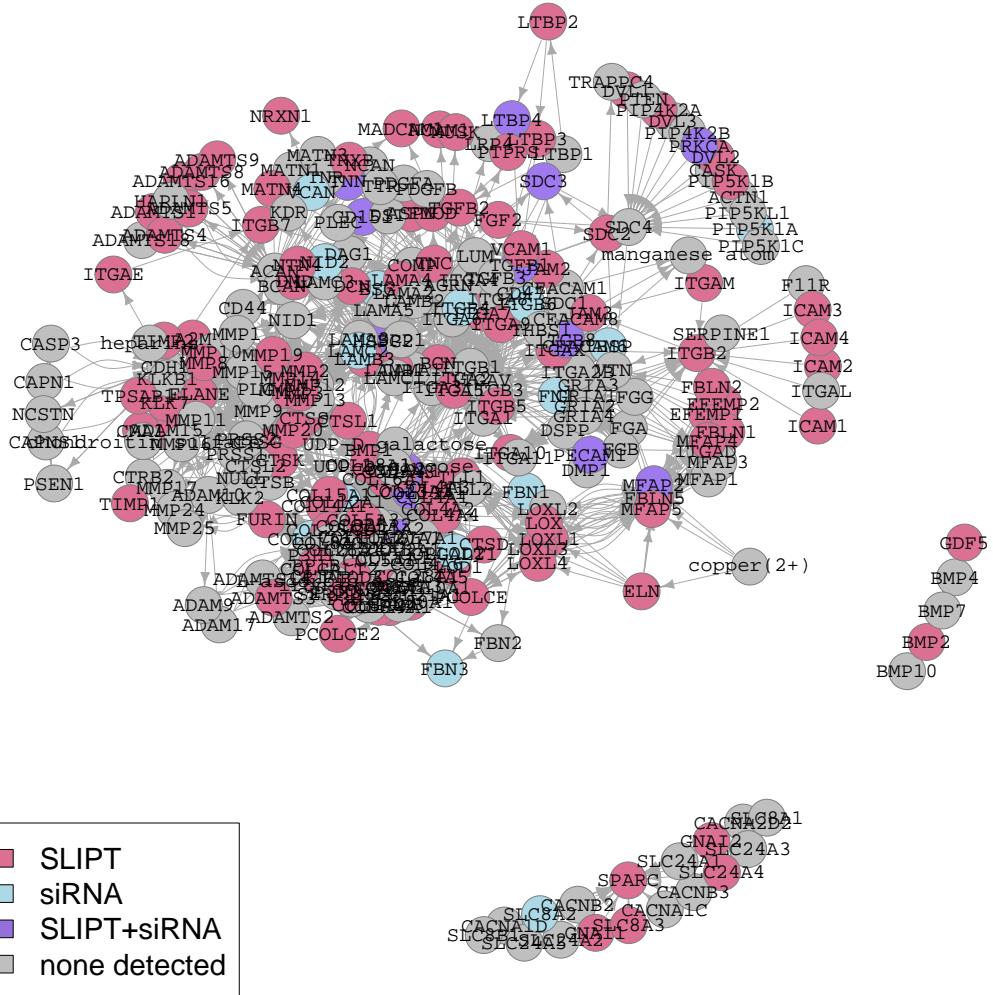


Figure F.3: **Synthetic Lethality in the Extracellular Matrix.** The Reactome Extracellular Matrix pathway with synthetic lethal candidates coloured as shown in the legend.

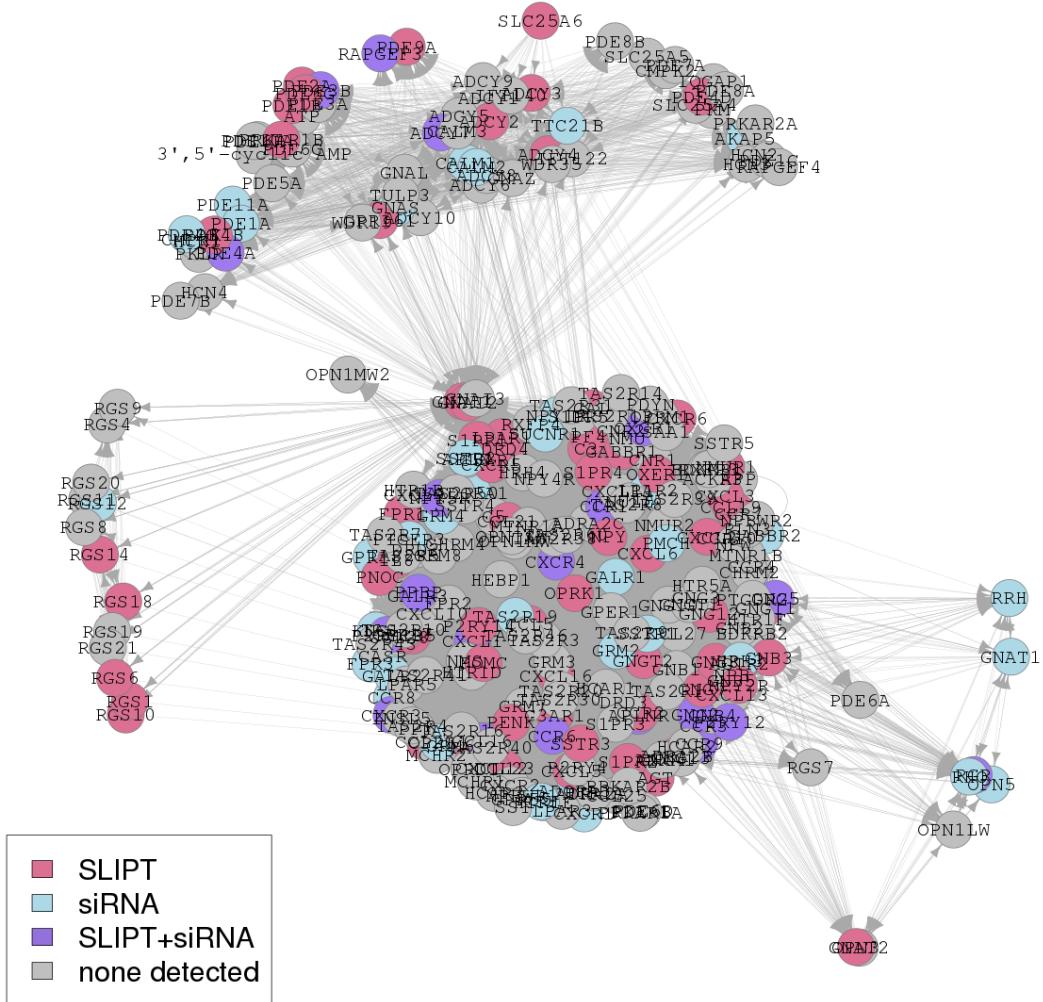


Figure F.4: Synthetic Lethality in the GPCRs. The Reactome $G_{\alpha i}$ pathway with synthetic lethal candidates coloured as shown in the legend.

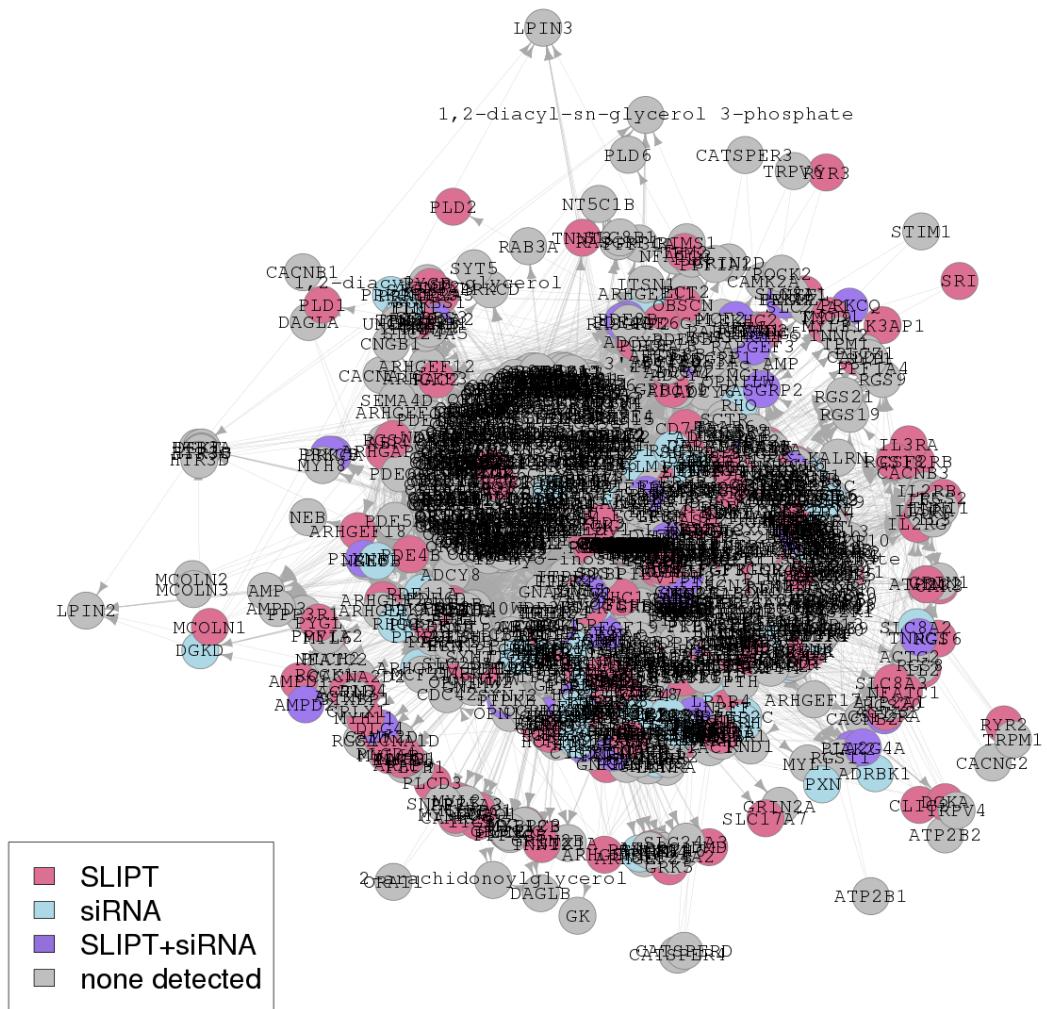


Figure F.5: **Synthetic Lethality in the GPCR Downstream.** The Reactome GPCR Downstream pathway with synthetic lethal candidates coloured as shown in the legend.

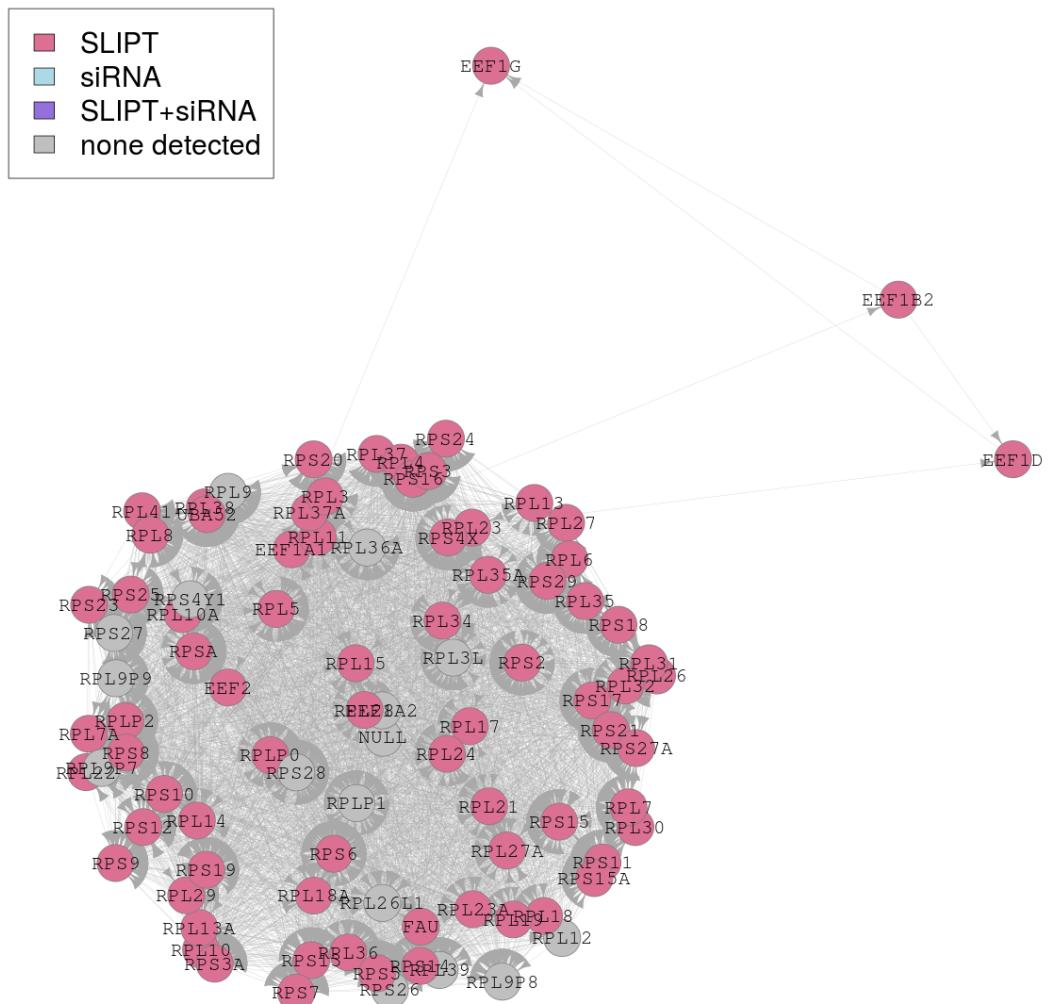


Figure F.6: **Synthetic Lethality in the Translation Elongation**. The Reactome Translation Elongation pathway with synthetic lethal candidates coloured as shown in the legend.

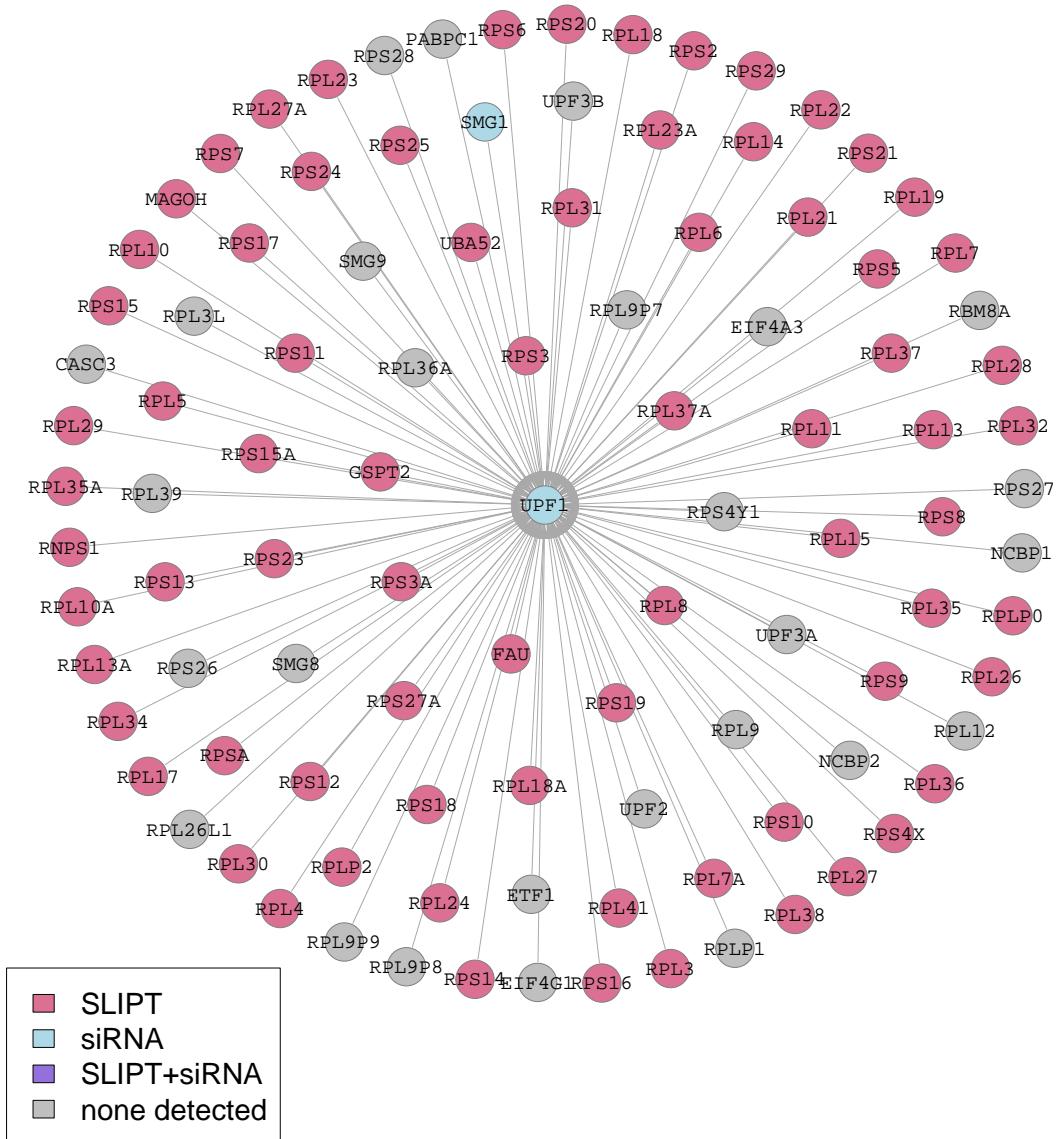


Figure F.7: Synthetic Lethality in the Nonsense-mediated Decay. The Reactome Nonsense-mediated Decay pathway with synthetic lethal candidates coloured as shown in the legend.

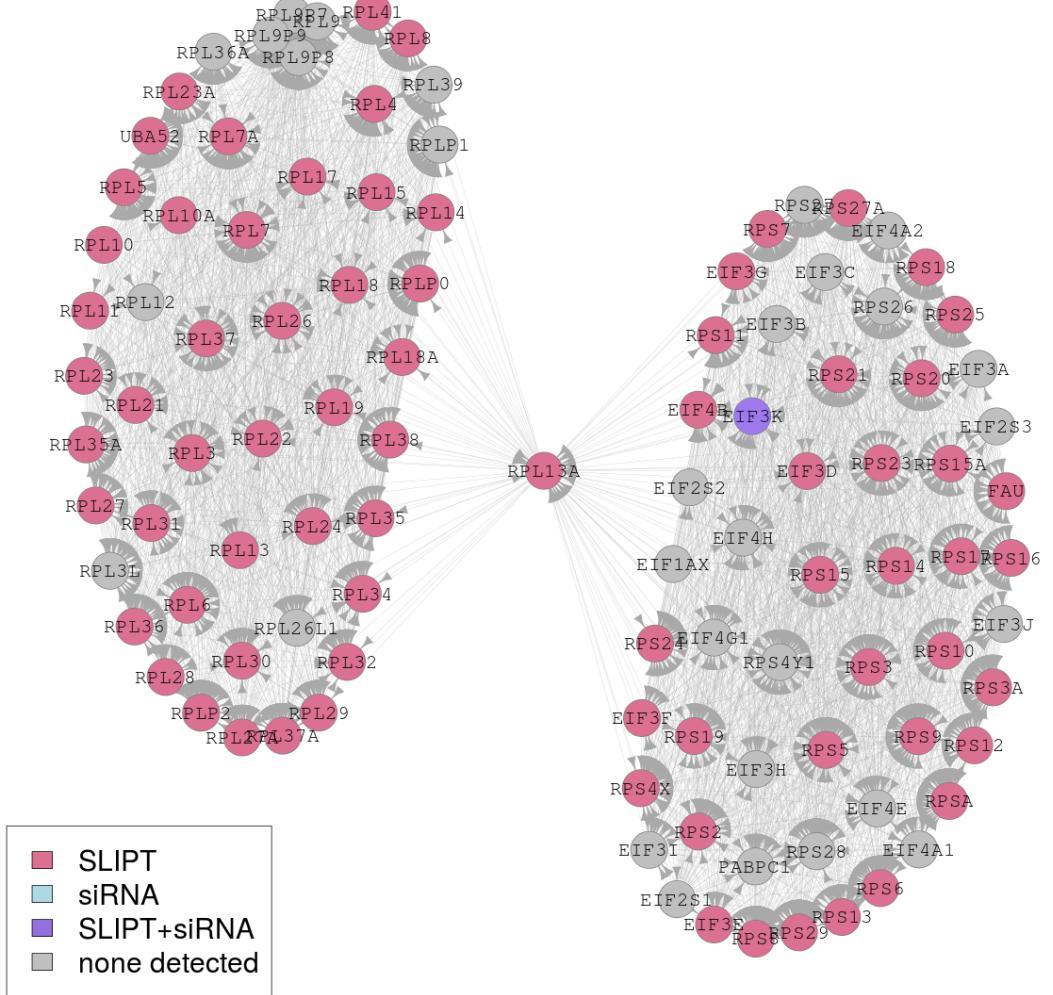


Figure F.8: **Synthetic Lethality in the 3' UTR.** The Reactome 3' UTR pathway with synthetic lethal candidates coloured as shown in the legend.

Appendix G

Pathway Connectivity for Mutation SLIPT

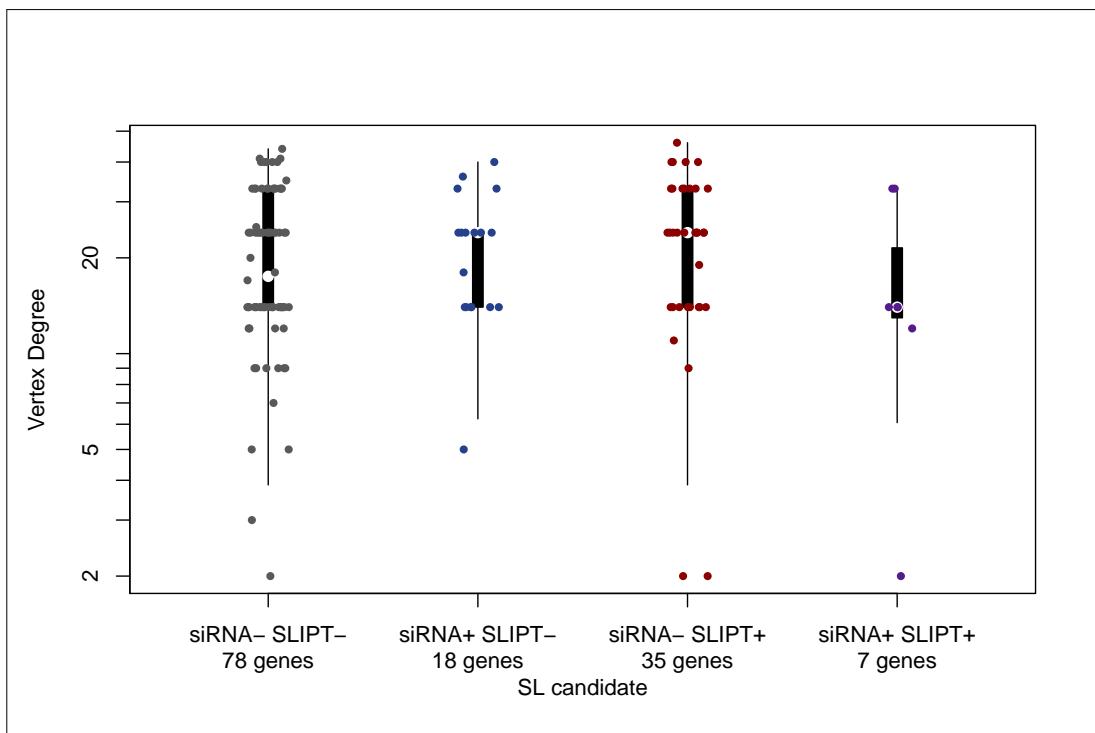


Figure G.1: **Synthetic Lethality and Vertex Degree.** The number of connected genes (vertex degree) was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. There were very few differences in vertex degree between the groups, although genes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

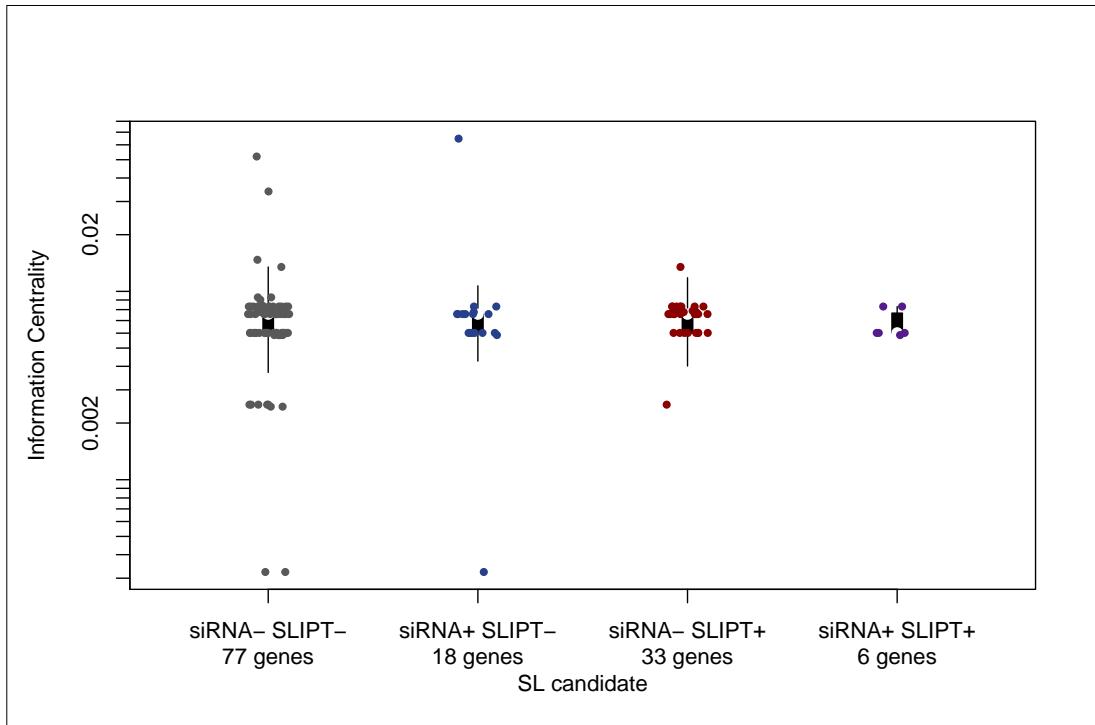


Figure G.2: Synthetic Lethality and Centrality. The information centrality was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. Genes detected by mtSLIPT or siRNA did not have higher connectivity than genes not detected by either approach.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

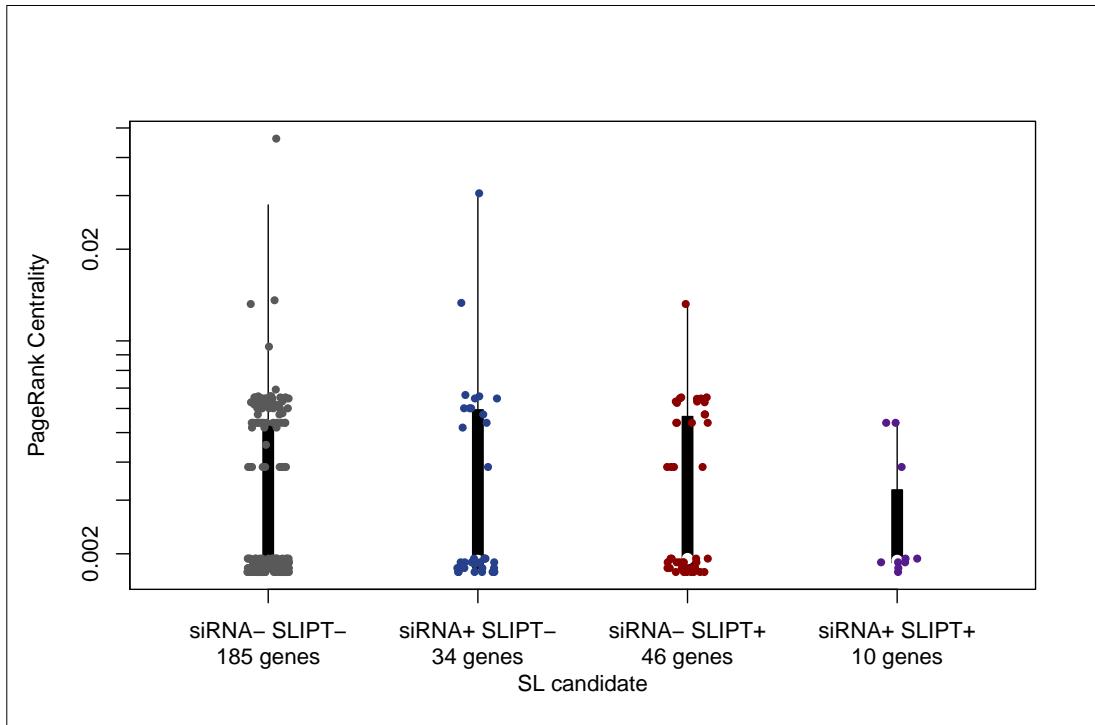


Figure G.3: Synthetic Lethality and PageRank. The PageRank centrality was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. Genes detected by siRNA had a more restricted range of centrality values than other genes not detected by either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

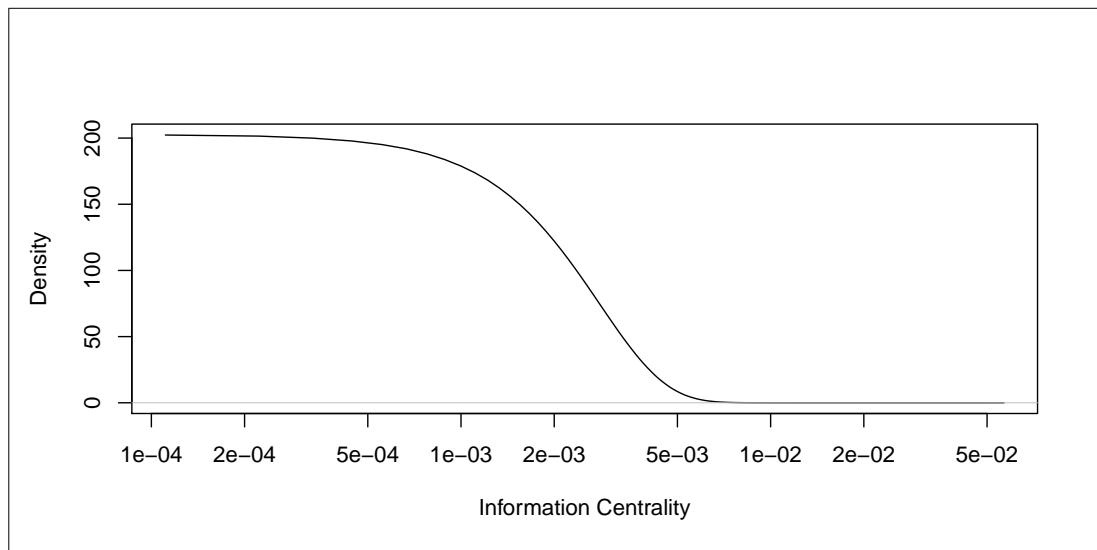


Figure H.1: **Information centrality distribution.** Information centrality in the Reactome network for nodes, including genes/proteins and other biomolecules.

Appendix I

Pathway Structure for Mutation SLIPT

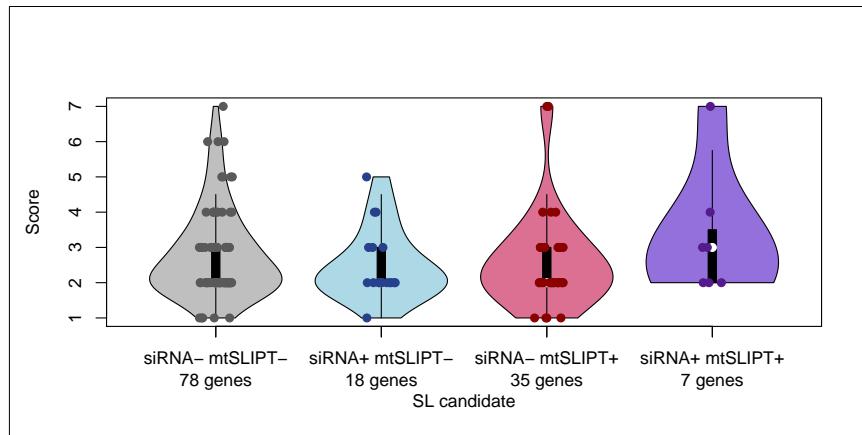


Figure I.1: **Synthetic Lethality and Heirarchy Score in PI3K.** The hierarchical distance scores were similarly distributed across mtSLIPT and siRNA genes. Genes detected by both methods had a higher (downstream) median than either group.

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)

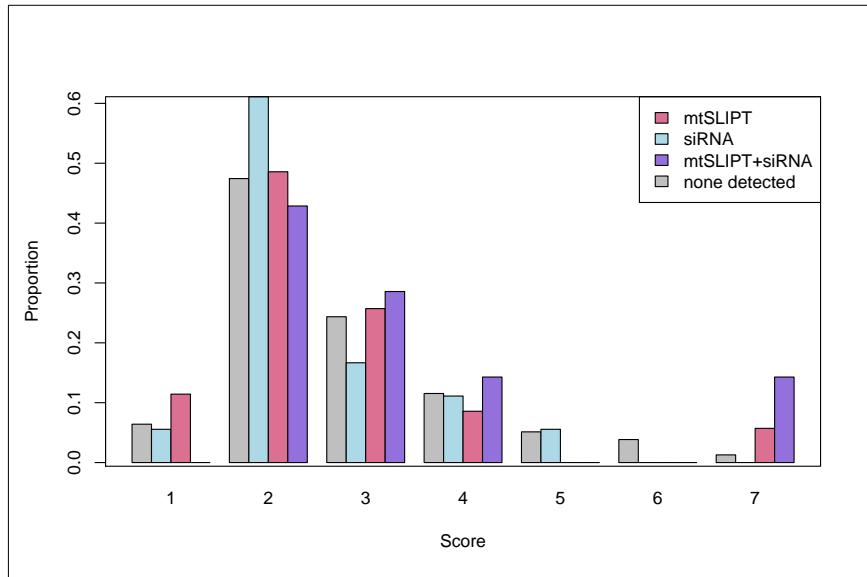


Figure I.2: **Heirarchy Score in PI3K against Synthetic Lethality in PI3K.** The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities.

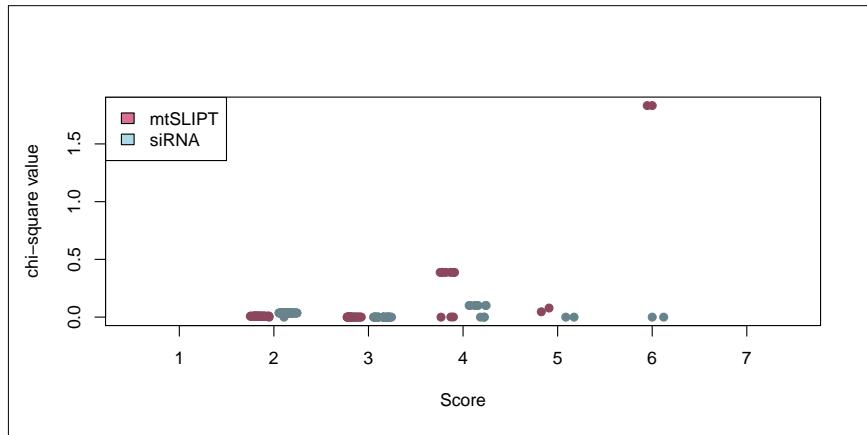


Figure I.3: **Structure of Synthetic Lethality in PI3K.** The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities. The number of mtSLIPT and siRNA genes upstream or downstream 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.

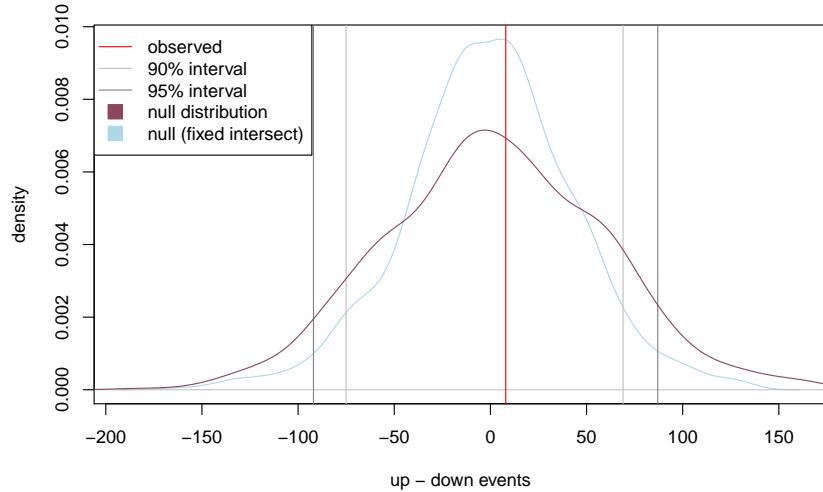


Figure I.4: Structure of Synthetic Lethality Resampling. A null distribution (10,000 iterations) of the siRNA genes upstream or downstream of mtSLIPT genes (shown by the difference) in the PI3K pathway. The observed events (red) were compared to the the distribution (violet) and were not significant.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