Contents

List of Figures

List of Tables

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 Crotein 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

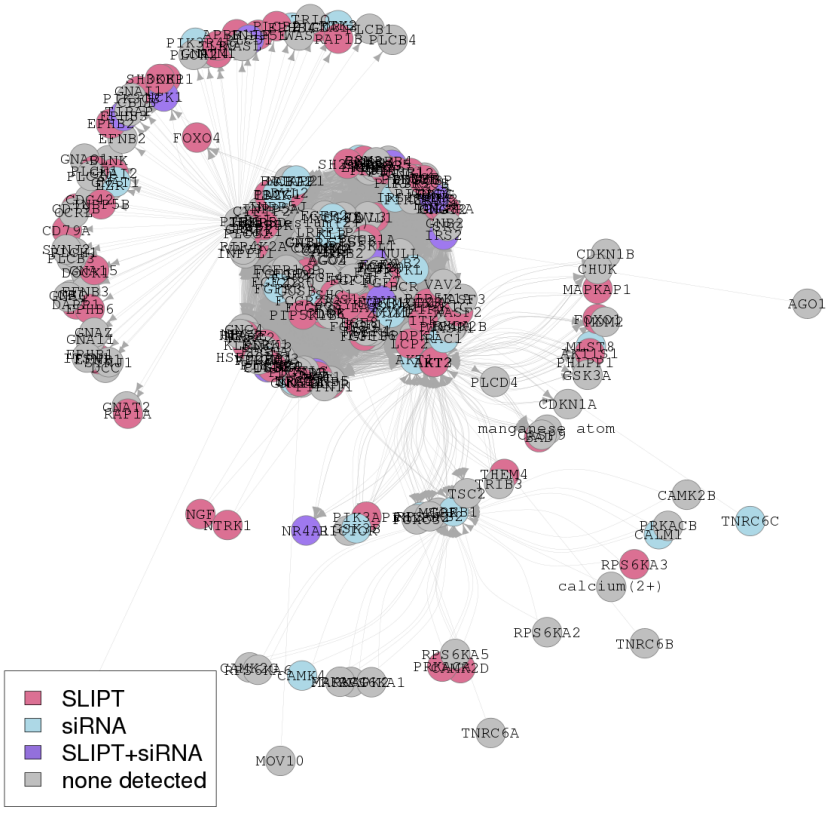


Figure G.1: **Synthetic lethality in the PI3K/AKT pathway.** The Reactome PI3K/AKT pathway with synthetic lethal candidates, coloured as shown in the legend.

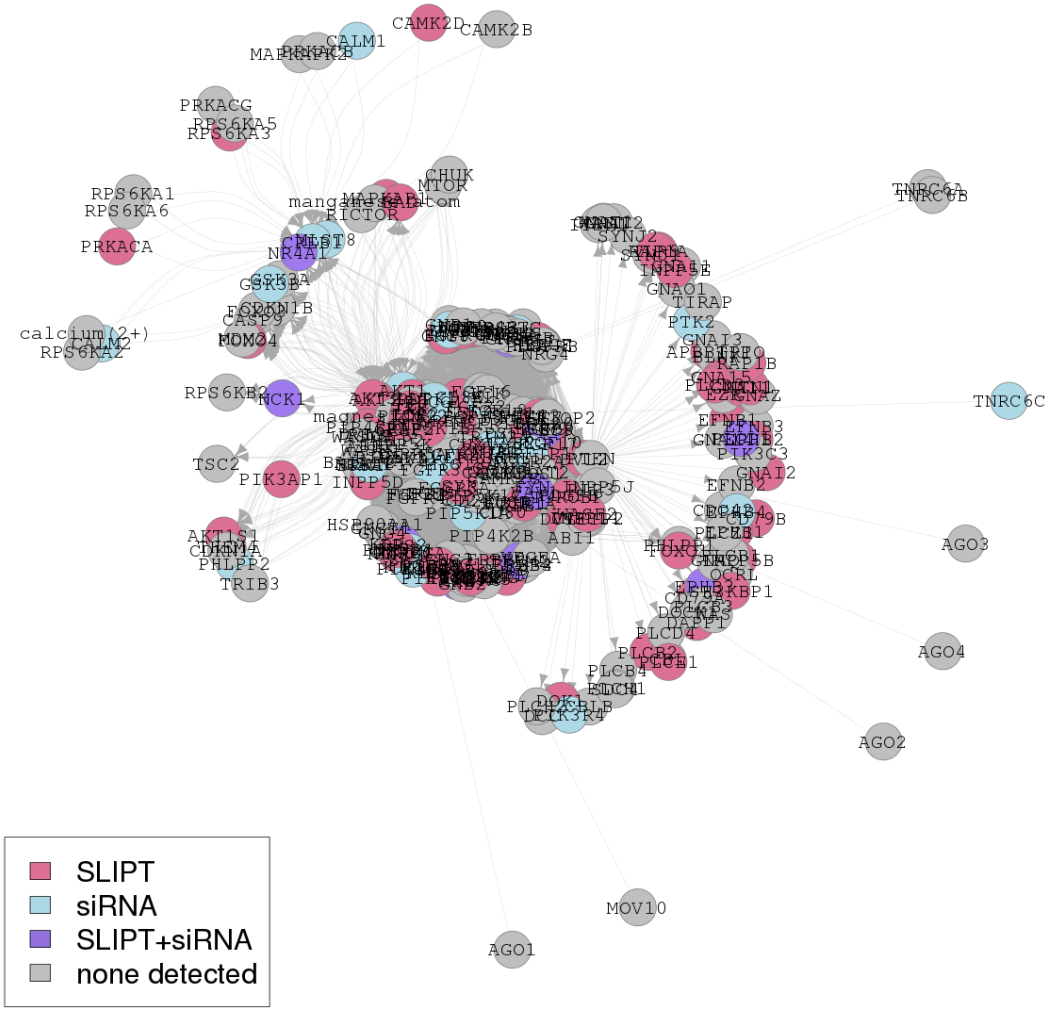


Figure G.2: **Synthetic lethality in the PI3K/AKT pathway in cancer.** The Reactome PI3K/AKT in cancer pathway with synthetic lethal candidates, coloured as shown in the legend.

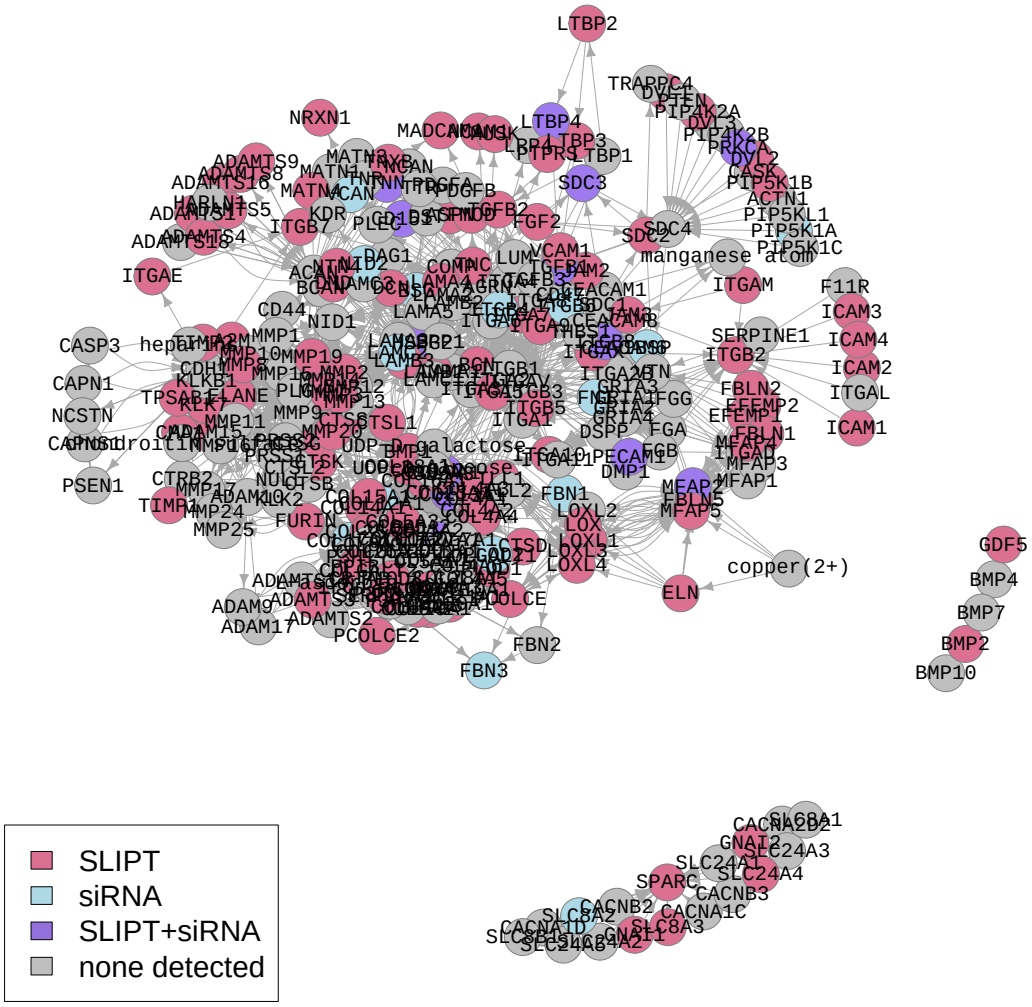


Figure G.3: **Synthetic lethality in the Extracellular Matrix.** The Reactome Extracellular Matrix pathway with synthetic lethal candidates, coloured as shown in the legend.

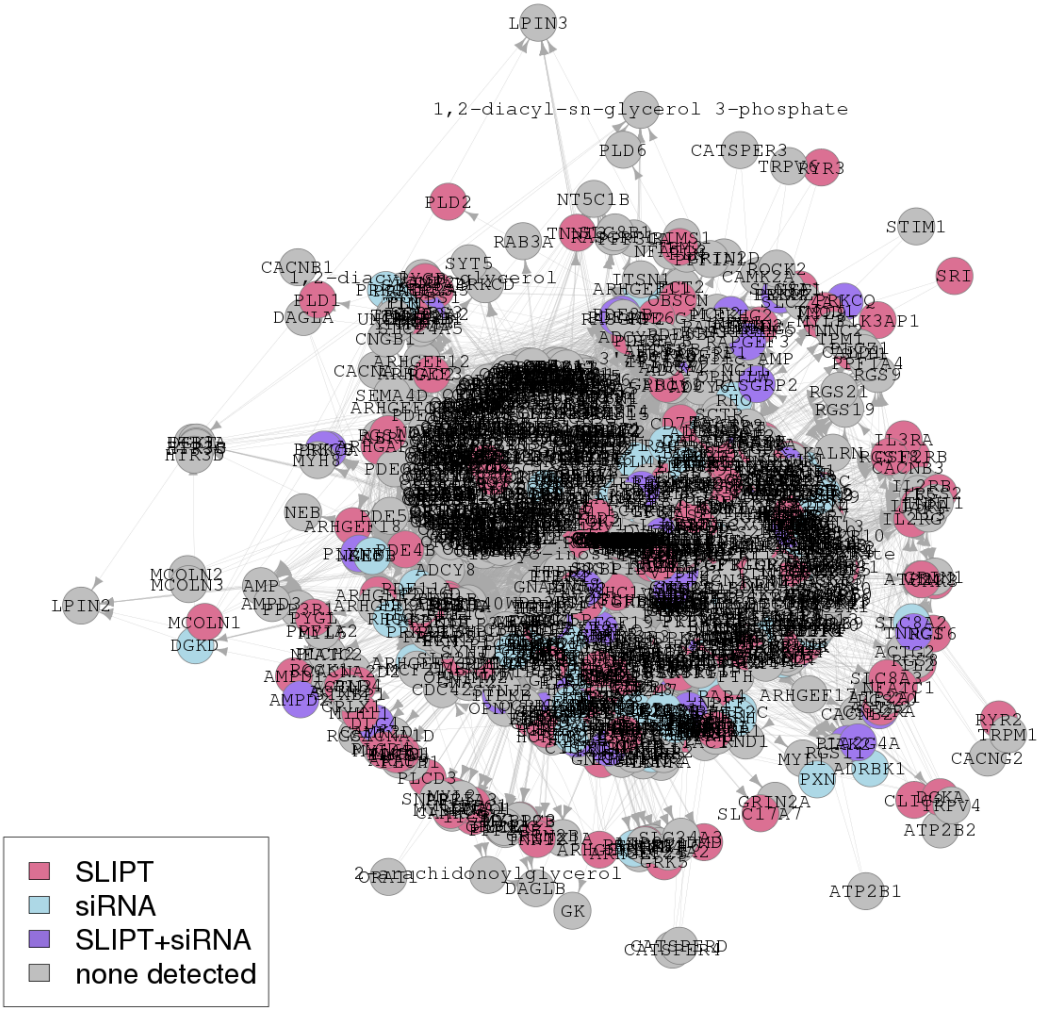


Figure G.4: **Synthetic lethality in the GPCR Downstream.** The Reactome G protein coupled receptor (GPCR) Downstream pathway with synthetic lethal candidates, coloured as shown in the legend.

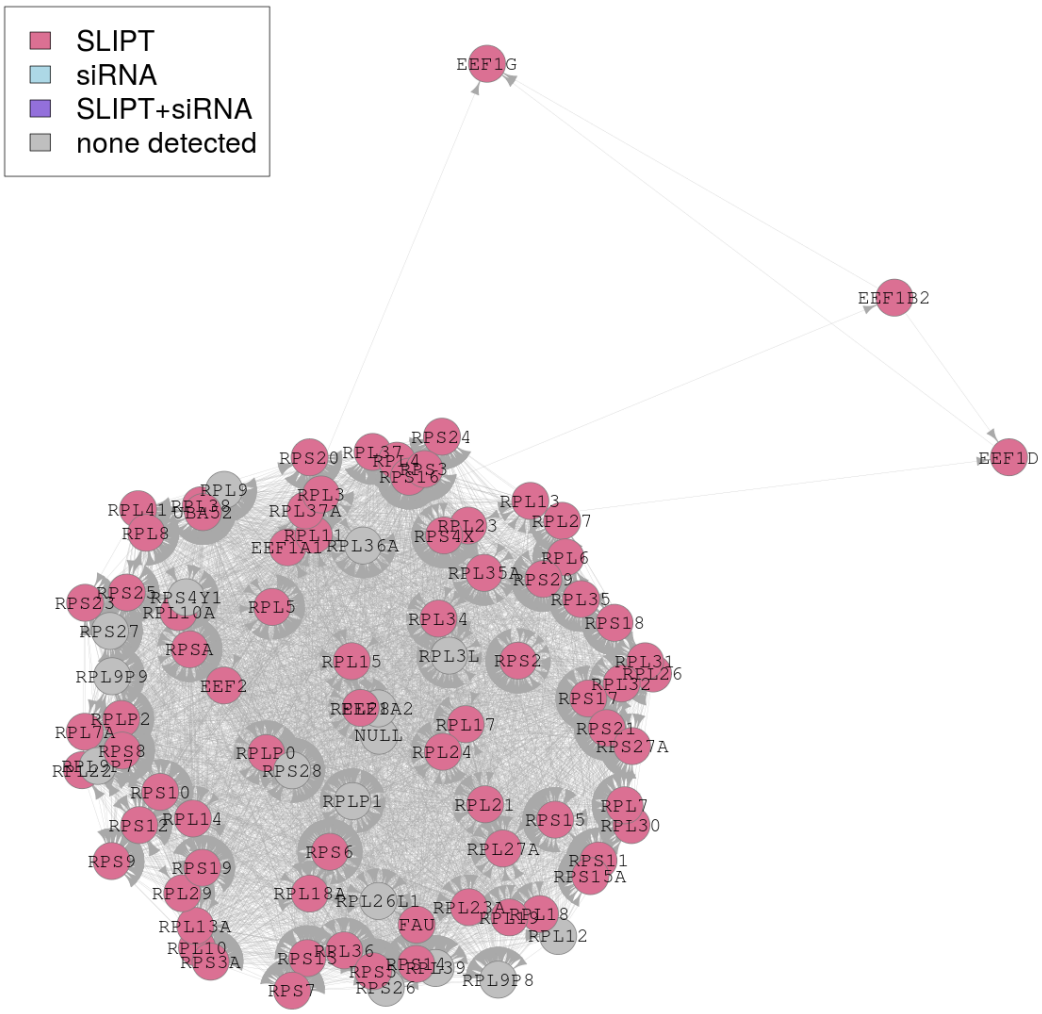


Figure G.5: **Synthetic lethality in the Translation Elongation.** The Reactome Translation Elongation pathway with synthetic lethal candidates, coloured as shown in the legend.

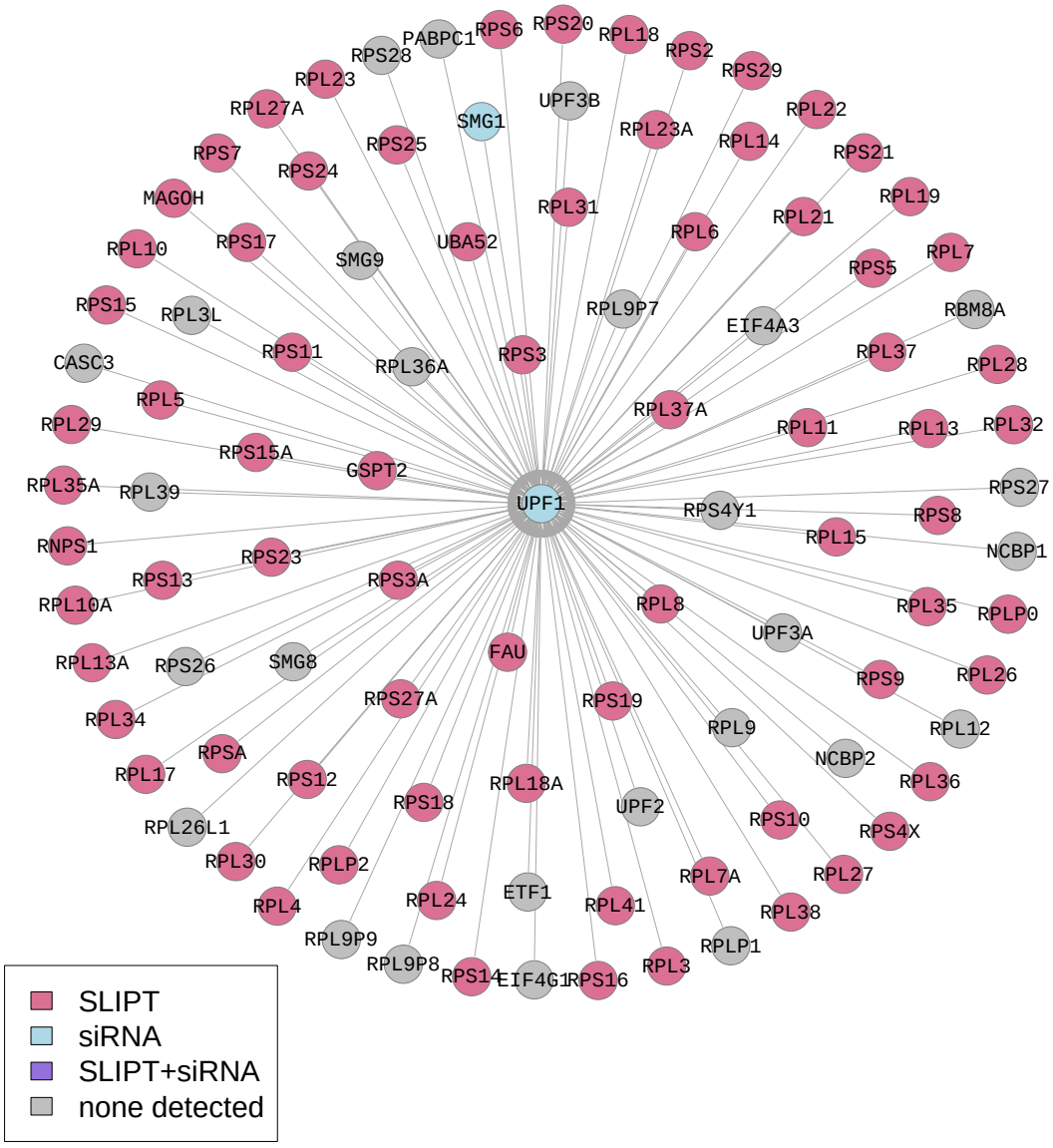


Figure G.6: **Synthetic lethality in the Nonsense-mediated Decay.** The Reactome nonsense-mediated decay (NMD) pathway with synthetic lethal candidates, coloured as shown in the legend.

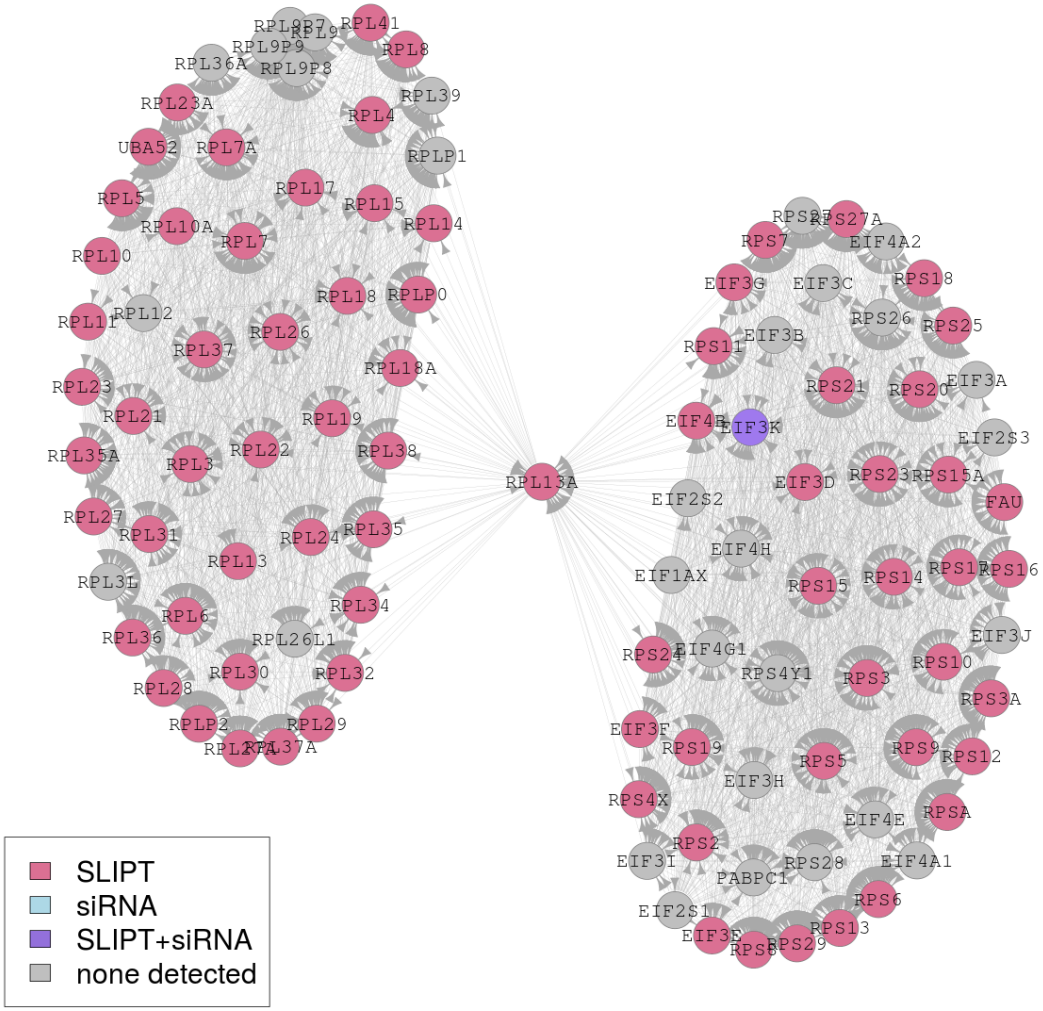


Figure G.7: **Synthetic lethality in the 3′ UTR.** The Reactome 3′ untranslated region (UTR) pathway with synthetic lethal candidates, coloured as shown in the legend.

Appendix H

Network Analysis for Mutation SLIPT

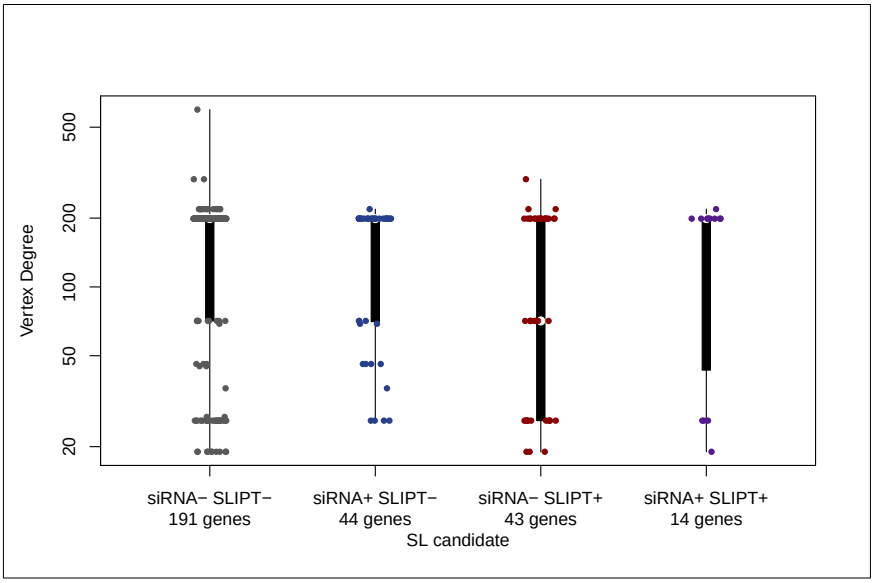


Figure H.1: **Synthetic lethality and vertex degree.** The number of connected genes (vertex degree) was compared (on a log-scale) across genes detected by mtSLIPT and siRNA screening in the Reactome $G_{\alpha i}$ pathway. There were no differences in vertex degree between the groups (shown in Table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

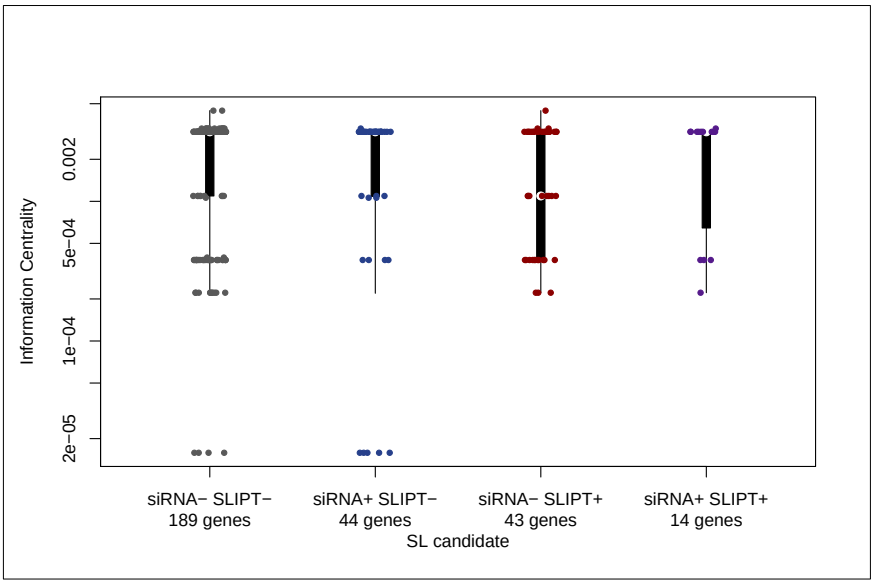


Figure H.2: **Synthetic lethality and centrality.** The information centrality was compared (on a log-scale) across genes detected by SLIPT and siRNA screening in the Reactome $G_{\alpha i}$ pathway. Genes detected by SLIPT or siRNA did not have higher centrality than other genes (shown in Table H.2).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

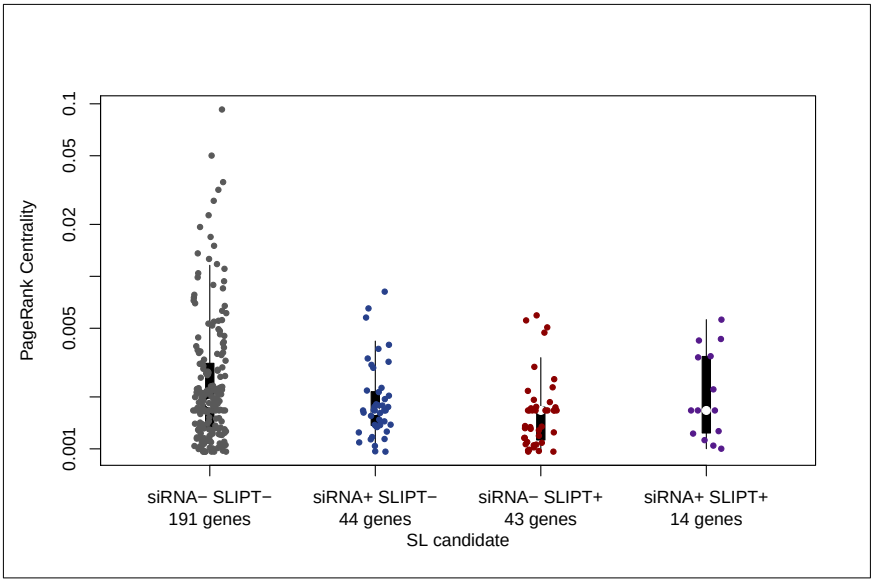


Figure H.3: **Synthetic lethality and PageRank.** The PageRank centrality was compared (on a log-scale) across genes detected by mtSLIPT and siRNA screening in the Reactome $G_{\alpha i}$ pathway. Genes detected by with either synthetic lethal detection approach had a more restricted range of centrality 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)

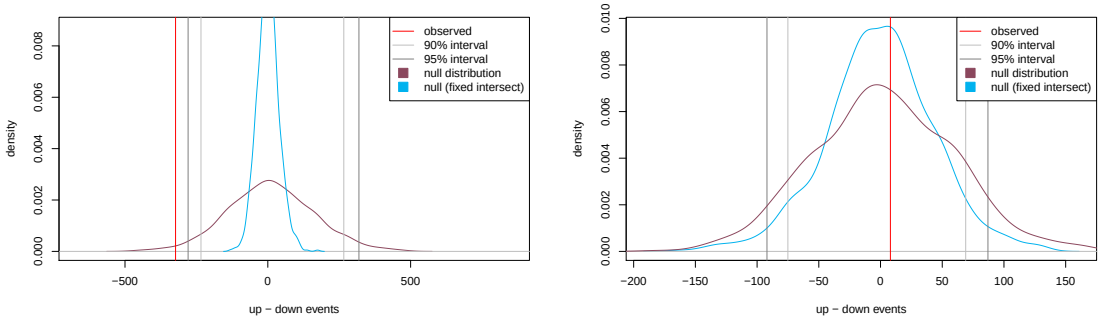
Table H.3: ANOVA for synthetic lethality and PageRank centrality

	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



(a) Resampling in $G_{\alpha i}$ signalling

(b) Resampling in the PI3K cascade

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

	Graph		Candidates		Observed				Permutation p-value		p-value (FDR)
P**Pathway**	**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
$G_{\alpha i}$ 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