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A Bioinformatics Approach to Synthetic Lethal Interactions in Breast Cancer with Gene Expression Data

S. Thomas Kelly

a thesis submitted for the degree of

Doctor of Philosophy

at the University of Otago, Dunedin,

New Zealand.

31 March 2017

Abstract

Background

Synthetic lethal genetic interactions are re-emerging the post-genomics era due to their potential for precision medicine against cancers. Synthetic lethal drug design exploits functional redundancy with genes disrupted in cancers (including tumour suppressors) to develop specific treatments. E-cadherin, encoded by *CDH1*, is a tumour supressor gene with loss of function in breast and btomach cancers. Experimental screens have identified candidate synthetic lethal interactions for drug target triage which can be further supported with bioinformatics analysis. Furthermore, gene expression data is amenable to investigation of the pathway composition and structure of synthetic lethal candidates.

Approach

A computational methodology, the Synthetic Lethal Prediction Tool (SLIPT) was developed to detect synthetic lethal interactions in gene expression data. This methodology was demonstrated on interactions with *CDH1* in breast and stomach cancer data from The Cancer Genomes Atlas (TCGA) project. Synthetic lethal genes and pathways were further investigated with unsupervised clustering, gene set over-representation analysis, metagenes, and permutation resampling. In particular, analyses focused on comparing SLIPT gene candidates to an experimental siRNA screen Telford *et al.* (2015). Graph theory methods were also applied to the most supported pathways to test for pathway structure among between synthetic lethal candidates. Simulation and modelling was used to assess the statistical performance of SLIPT, including simulated data with correlation structures derived from graph stuctures.

Findings

Many candidate synthetic lethal partners of *CDH1* were detected in both TCGA breast cancer. These genes clustered into several distinct groups, with distinct biological functions and elevated expression in different clinical subtypes. While the number of genes detected by both approaches was not significant, these contained significantly enriched pathways. In particular $G_{\alpha i}$ signalling, cytoplasmic microfibres, and extracellular fibrin clotting were robustly supported by both approaches which is consistent with the known cytoskeletal and cell signalling roles of E-cadherin and validation of GPCRs performed by Telford *et al.* (2015). Many of these pathways were replicated in stomach cancer. The pathways supported only by SLIPT included regulation of immune signalling and translational elongation which were unlikely to be detected in an isogenic cell line model but are are still candidates for further investigation.

Synthetic lethal candidates detected by SLIPT and siRNA were compared within graph structures of the candidate synthetic lethal pathways. These genes did not differ by network measures of importance or connectivity in the pathway. There was also little support for SLIPT gene candidates being upstream or downstream of siRNA gene candidates within a pathway, consistently across pathways.

A model of synthetic lethality used to simulate gene expression data with synthetic lethal partners of a gene. The SLIPT methodology had high statistical performance detecting few synthetic lethal partners, although this diminishes with more synthetic lethal partners or lower sample size. The SLIPT methodology performs better than Pearson correlation or the χ^2-test. In particular, it performs well with high specificity for datasets containing thousands of genes or genes positively correlated with the query gene (as expected in human expression data). It was also robust across correlation structures, including those derived from complex pathway structures and often distinguished synthetic lethal genes from those positively or negatively correlated with them. Therefore SLIPT is appropriate to identify synthetic lethal genes within pathways and use candidate synthetic lethal genes (and their correlates) to identify synthetic lethal pathways.

Summary

Thus my thesis has developed, evaluated and refined a bioinformatics approach to discovery of synthetic lethal genes solely from gene expression data. This approach has been demonstrated to detect biologically informative and clinically relevant candidate partners for *CDH1* in breast and stomach cancers. These investigations have also involved the development of network analysis and simulation procedures which may be more widely applicable.

Research Contributions During Candidature

Publications

Kelly, S. T. and Spencer, H. G. (2017) Population-Genetics Models of Sex-Limited Genomic Imprinting. *Theoretical Population Biology* **115**:35-44 doi:10.1016/j.tpb.2017.03.004

Manuscripts Submitted

Kelly, S. T., Single, A. B., Telford, B. J., Beetham, H. G, Godwin, T. D., Chen, A., Black, M., A., and Guilford, P. J. (2017) Towards HDGC chemoprevention: vulnerabilities in E-cadherin-negative cells identified by genomic interrogation of isogenic cell lines and whole tumors. Submitted to *Cancer Prevention Research*.

Kelly, S. T., Chen, A., Guilford, P. J., and Black, M. A. (2017) Synthetic lethal interaction prediction of target pathways in E-cadherin deficient breast cancers. Submitted to *BMC Genomics*.

Conference Presentations

Consortium of Biological Sciences 2017 (Kobe) December TBC

eResearch 2017 (Queenstown) February 20^{th}-22^{nd}

Research Bazaar 2016 (Dunedin) February 2^{nd}-4^{th}

eResearch 2016 (Queenstown) February 9^{th}-11^{th}

Genetics Otago Symposium 2016 (Dunedin) March 7^{th}-8^{th}

DunDead: Zombie Science and Culture Festival 2014 (Dunedin) August 16^{th}-17^{th}

eResearch 2014 (Hamilton) June 30^{th}-July 2^{nd} (Supported by Google)

Poster Presentations

Next Generation Sequencing Asia 2016 (Singapore) October 11^{th}-12^{th} (Supported by the University of Otago Division of Health Sciences; Maurice and Phyllis Paykel Trust)

Research Bazaar 2015 (Melbourne, Australia) February 16^{th}-18^{th} (Supported by the New Zealand eScience Infrastructure)

Otago School of Medical Sciences Postgraduate Symposium 2015 (Dunedin, New Zealand) April 28^{th}-29^{th}

QMB Cancer Drugs Satellite 2014 (Queenstown, New Zealand) August 24^{th}-25^{th}

Seminar Presentations

University of Otago Department of Biochemistry 2017 (Dunedin) November TBC

Tohoku University 2016 (Sendai) November 11th

Okinawa Institute of Science and Technology 2016 (Onna) November 1st

Sokendai Graduate University 2016 (Hayama) October 25th

Tokyo University Institute of Medical Science 2016 (Shirokanedai) October 24th

National Institute of Genetics 2016 (Mishima) October 21st

RIKEN Division of Genomic Technologies 2016 (Yokohama) October 20th

Software Packages

Software packages in the R language have been released. Please refer to the appropriate GitHub repository for more information (including documentation, vignettes, and installation instructions), on the following account: `https://github.com/TomKellyGenetics`

- `slipt` to accompany the synthetic lethal publication above and release SLIPT (Synthetic Lethal Interaction Prediction Tool)
- `vioplotx` to provide enhanced violin plots
- `heatmap.2x` to provide annotated heatmaps
- `igraph.extensions` metapackage for the packages for iGraph objects:
  - `plot.igraph` to provide plotting for directed graphs
  - `info.centrality` to compute network analysis metrics
  - `pathway.structure.permutation` for resampling within pathways
  - `graphsim` to simulate expression (`mvtnorm`) from pathway structures

The `slipt-app` GitHub repository also hosts an application for Synthetic Lethal Interaction Prediction Tool (SLIPT) developed in the R `shiny` environment as part of a related project. There is also a digital copy of this thesis, including high resolution full-colour figures, hosted at:

`https://github.com/TomKellyGenetics/thesis/blob/master/thesis.pdf`

Acknowledgements

I thank my supervisors A/Prof. Mik Black and Prof. Parry Guilford for their support and guidance throughout this my postgraduate studies. It has been a great experience, I look forward to seeing what your research groups produce in the future, may this not be the end.

I am also thankful for the guidance and mentorship of Prof. Hamish Spencer for career advice throughout my studies and time in his research group.

I am also grateful to the past and current members of these research groups, and my peers at the laboratory benches and computers across campus. The peer support, camaraderie, and guidance to newer students has been an incredible part of my time at Otago and has made my thesis studies not just easier but possible at all. The postgraduate community is very special here and have truly made some lifelong friends from all over the world, you are talented researchers and amazing people. May we meet again some day. Where-ever you may end up, there's always time to catch up and I'd be delighted to host some visits while working abroad.

I cannot thank my friends, flatmates, family, and diligent proofreaders enough for their patience and support during such as massive, challenging, and (I'm sure you've heard too often) stressful undertaking during both my PhD and the study leading up to it. There are too many of you to name everyone here without leaving someone out, so thank you all for everything you've done, both the good times and the tough. Thank you for at least pretending to understand complex math oft brought up at the wrong moment. Thank you for checking my writing or slides, even when sprung on you last minute. Thank for your time when what I really needed was a chat, a walk, a drink with "the guys", or a moment to think clearly.

I thank the various organisations that supported this research project:

- This thesis was supported by the Postgraduate Tassell Scholarship in Cancer Research, a University of Otago Doctoral Scholarship.
- The New Zealand eScience Infrastucture (NeSI) provided access to the Intel Pan high-performance computing cluster, support, and training to use it effectively. Various aspects of this thesis would not have been possible without access to such a resource.
- The Health Research Council (HRC) of New Zealand provided funding for experimental research in the Cancer Genetics Laboratory. Again some aspects of this project would not have been possible without access to the data and findings funded by this grant.
- The Allan Wilson Centre and Otago School of Biomedical Sciences provided funding for summer research placements which was a valuable opportunity to gain experience and training used in this thesis project.

I thank the following organisations for support towards presenting findings in this thesis at conference and seminars:

- Google (eResearch 2014 conference, Hamilton)
- NeSI (Software Carpentry training and Research Bazaar 2015, Melbourne)
- REANNZ, NZGL, and NeSI (eResearch 2016 conference, Queenstown)
- Otago Division of Health Sciences, Oxford Global, and Maurice and Phyllis Paykel Trust (NGS Asia 2016, Singapore)
- RIKEN Division of Genomics Technologies and the Okinawa Institue of Science and Technology (funding seminar visits in Japan)

Thanks most of all to my fianceé, Dr Yui Kawagishi, you've been an inspiration. Thank you for your support and encouragement, every day, even from afar: it has always made a difference. It's been incredible to see you flourish in your career and I look forward to joining you again soon. May the next chapter of our adventures involve a bit less Skype across timezones.

どうもありがとう由ちゃん。また来月。頑張った！行きます！

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Glossary

E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by the tumour suppressor gene, *CDH1*.
genome	An analysis of all of the DNA sequence in the genome.
genomic	An approach or technology designed to generate or use data from all genes in the genome.
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.

Acronyms

ANOVA	Analysis of Variance.
GPCR	G Crotein Coupled Receptor.
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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