GEN80436 - Thesis proposal

Stephen Coleman

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Abstract

Gene sets are constructed to identify genes linked by some common feature. This can be a function, the location of the gene product, the participation of the product in some metabolic or signalling pathway, the protein structure, the presence of transcription-factor-binding sites or other regulatory elements, the participation in multiprotein complexes, etc. [12][11][6] [1]. However, all of these sets are tissue agnostic. Some attempts to include tissue-specific information has been proposed [4] [5], but this attempts have limitations. We propose to produce tissue specific gene sets by applying multiple dataset integration (MDI) [7] (a Bayesian unsupervised clustering method) to the CEDAR cohort [13], a dataset which includes gene expression data for nine tissue / cell types including six circulating immune cell types (CD4+ T lymphocytes, CD8+ T lymphocytes, CD19+ B lymphocytes, CD14+ monocytes, CD15+ granulocytes, platelets) as well as ileal, colonic, and rectal biopsies (IL, TR, RE datasets respectively).

1 Existing databases

In some of the largest databases (such as the Gene Ontology (GO) Resource [1], the Kyoto Encyclopedia of Genes and Genomes (KEGG) [6], the Molecular Signatures Database (MSigDB) [11] or the STRING protein-protein interaction (PPI) database [12])

2 References to use

Gene set analysis [9] [3]
- Better to look at set fo genes when perturbed diseases state [15][10]
- There exists an abundance of gene set databases .
- Evidence for Tissue specific eQTLs [14]
- Genotype-Tissue Expression (GTEx) project [8] [2]

References

[1] Michael Ashburner, Catherine A. Ball, Judith A. Blake, David Botstein, Heather Butler, J. Michael Cherry, Allan P. Davis, Kara Dolinski, Selina S. Dwight, Janan T. Eppig, Midori A. Harris, David P. Hill, Laurie Issel-Tarver, Andrew Kasarskis, Suzanna Lewis, John C. Matese, Joel E. Richardson, Martin Ringwald, Gerald M. Rubin, and

Gavin Sherlock. Gene Ontology: tool for the unification of biology. *Nature Genetics*, 25(1):25–29, May 2000. ISSN 1061-4036, 1546-1718. doi: 10.1038/75556. URL http://www.nature.com/articles/ng0500_25.

[2] Darren J. Burgess. Gene expression: Principles of gene regulation across tissues. *Nature Reviews Genetics*, 18(12):701–701, November 2017. ISSN 1471-0056, 1471-0064. doi: 10.1038/nrg.2017.94. URL http://www.nature.com/doifinder/10.1038/nrg.2017.94.

[3] Frank Dudbridge. Power and Predictive Accuracy of Polygenic Risk Scores. *PLoS Genetics*, 9(3):e1003348, March 2013. ISSN 1553-7404. doi: 10.1371/journal.pgen.1003348. URL https://dx.plos.org/10.1371/journal.pgen.1003348.

[4] H Robert Frost. Computation and application of tissue-specific gene set weights. *Bioinformatics*, 34(17):2957–2964, September 2018. ISSN 1367-4803, 1460-2059. doi: 10.1093/bioinformatics/bty217. URL https://academic.oup.com/bioinformatics/article/34/17/2957/4962491.

[5] Casey S Greene, Arjun Krishnan, Aaron K Wong, Emanuela Ricciotti, Rene A Zelaya, Daniel S Himmelstein, Ran Zhang, Boris M Hartmann, Elena Zaslavsky, Stuart C Sealfon, Daniel I Chasman, Garret A FitzGerald, Kara Dolinski, Tilo Grosser, and Olga G Troyanskaya. Understanding multicellular function and disease with human tissue-specific networks. *Nature Genetics*, 47(6):569–576, June 2015. ISSN 1061-4036, 1546-1718. doi: 10.1038/ng.3259. URL http://www.nature.com/articles/ng.3259.

[6] Minoru Kanehisa, Yoko Sato, Miho Furumichi, Kanae Morishima, and Mao Tanabe. New approach for understanding genome variations in KEGG. *Nucleic Acids Research*, 47(D1):D590–D595, January 2019. ISSN 0305-1048, 1362-4962. doi: 10.1093/nar/gky962. URL https://academic.oup.com/nar/article/47/D1/D590/5128935.

[7] Paul Kirk, Jim E. Griffin, Richard S. Savage, Zoubin Ghahramani, and David L. Wild. Bayesian correlated clustering to integrate multiple datasets. *Bioinformatics*, 28(24):3290–3297, December 2012. ISSN 1460-2059, 1367-4803. doi: 10.1093/bioinformatics/bts595. URL https://academic.oup.com/bioinformatics/article-lookup/doi/10.1093/bioinformatics/bts595.

[8] John Lonsdale, Jeffrey Thomas, Mike Salvatore, Rebecca Phillips, Edmund Lo, Saboor Shad, Richard Hasz, Gary Walters, Fernando Garcia, Nancy Young, Barbara Foster, Mike Moser, Ellen Karasik, Bryan Gillard, Kimberley Ramsey, Susan Sullivan, Jason Bridge, Harold Magazine, John Syron, Johnelle Fleming, Laura Siminoff, Heather Traino, Maghboeba Mosavel, Laura Barker, Scott Jewell, Dan Rohrer, Dan Maxim, Dana Filkins, Philip Harbach, Eddie Cortadillo, Bree Berghuis, Lisa Turner, Eric Hudson, Kristin Feenstra, Leslie Sobin, James Robb, Phillip Branton, Greg Korzeniewski, Charles Shive, David Tabor, Liqun Qi, Kevin Groch, Sreenath Nampally, Steve Buia, Angela Zimmerman, Anna Smith, Robin Burges, Karna Robinson, Kim Valentino, Deborah Bradbury, Mark Cosentino, Norma Diaz-Mayoral, Mary Kennedy, Theresa Engel, Penelope Williams, Kenyon Erickson, Kristin Ardlie, Wendy Winckler, Gad Getz, David DeLuca, Daniel MacArthur, Manolis Kellis, Alexander Thomson, Taylor Young, Ellen Gelfand, Molly Donovan, Yan Meng, George Grant, Deborah Mash,

Yvonne Marcus, Margaret Basile, Jun Liu, Jun Zhu, Zhidong Tu, Nancy J Cox, Dan L Nicolae, Eric R Gamazon, Hae Kyung Im, Anuar Konkashbaev, Jonathan Pritchard, Matthew Stevens, Timothèe Flutre, Xiaoquan Wen, Emmanouil T Dermitzakis, Tuuli Lappalainen, Roderic Guigo, Jean Monlong, Michael Sammeth, Daphne Koller, Alexis Battle, Sara Mostafavi, Mark McCarthy, Manual Rivas, Julian Maller, Ivan Rusyn, Andrew Nobel, Fred Wright, Andrey Shabalin, Mike Feolo, Nataliya Sharopova, Anne Sturcke, Justin Paschal, James M Anderson, Elizabeth L Wilder, Leslie K Derr, Eric D Green, Jeffery P Struewing, Gary Temple, Simona Volpi, Joy T Boyer, Elizabeth J Thomson, Mark S Guyer, Cathy Ng, Assya Abdallah, Deborah Colantuoni, Thomas R Insel, Susan E Koester, A Roger Little, Patrick K Bender, Thomas Lehner, Yin Yao, Carolyn C Compton, Jimmie B Vaught, Sherilyn Sawyer, Nicole C Lockhart, Joanne Demchok, and Helen F Moore. The Genotype-Tissue Expression (GTEx) project. *Nature Genetics*, 45(6):580–585, June 2013. ISSN 1061-4036, 1546-1718. doi: 10.1038/ng.2653. URL http://www.nature.com/articles/ng.2653.

[9] Michael A. Mooney and Beth Wilmot. Gene set analysis: A step-by-step guide. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 168(7):517–527, October 2015. ISSN 15524841. doi: 10.1002/ajmg.b.32328. URL http://doi.wiley.com/10.1002/ajmg.b.32328.

[10] A. C. Nica and E. T. Dermitzakis. Expression quantitative trait loci: present and future. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1620):20120362–20120362, May 2013. ISSN 0962-8436, 1471-2970. doi: 10.1098/rstb.2012.0362. URL http://rstb.royalsocietypublishing.org/cgi/doi/10.1098/rstb.2012.0362.

[11] A. Subramanian, P. Tamayo, V. K. Mootha, S. Mukherjee, B. L. Ebert, M. A. Gillette, A. Paulovich, S. L. Pomeroy, T. R. Golub, E. S. Lander, and J. P. Mesirov. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the National Academy of Sciences*, 102(43):15545–15550, October 2005. ISSN 0027-8424, 1091-6490. doi: 10.1073/pnas.0506580102. URL http://www.pnas.org/cgi/doi/10.1073/pnas.0506580102.

[12] Damian Szklarczyk, Annika L Gable, David Lyon, Alexander Junge, Stefan Wyder, Jaime Huerta-Cepas, Milan Simonovic, Nadezhda T Doncheva, John H Morris, Peer Bork, Lars J Jensen, and Christian von Mering. STRING v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Research*, 47(D1):D607–D613, January 2019. ISSN 0305-1048, 1362-4962. doi: 10.1093/nar/gky1131. URL https://academic.oup.com/nar/article/47/D1/D607/5198476.

[13] The International IBD Genetics Consortium, Yukihide Momozawa, Julia Dmitrieva, Emilie Théâtre, Valérie Deffontaine, Souad Rahmouni, Benoît Charloteaux, François Crins, Elisa Docampo, Mahmoud Elansary, Ann-Stephan Gori, Christelle Lecut, Rob Mariman, Myriam Mni, Cécile Oury, Ilya Altukhov, Dmitry Alexeev, Yuri Aulchenko, Leila Amininejad, Gerd Bouma, Frank Hoentjen, Mark Löwenberg, Bas Oldenburg, Marieke J. Pierik, Andrea E. vander Meulen-de Jong, C. Janneke van der Woude, Marijn C. Visschedijk, Mark Lathrop, Jean-Pierre Hugot, Rinse K. Weersma, Martine

De Vos, Denis Franchimont, Severine Vermeire, Michiaki Kubo, Edouard Louis, and Michel Georges. IBD risk loci are enriched in multigenic regulatory modules encompassing putative causative genes. *Nature Communications*, 9(1):2427, December 2018. ISSN 2041-1723. doi: 10.1038/s41467-018-04365-8. URL http://www.nature.com/articles/s41467-018-04365-8.

[14] The Multiple Tissue Human Expression Resource (MuTHER) Consortium, Elin Grundberg, Kerrin S Small, Åsa K Hedman, Alexandra C Nica, Alfonso Buil, Sarah Keildson, Jordana T Bell, Tsun-Po Yang, Eshwar Meduri, Amy Barrett, James Nisbett, Magdalena Sekowska, Alicja Wilk, So-Youn Shin, Daniel Glass, Mary Travers, Josine L Min, Sue Ring, Karen Ho, Gudmar Thorleifsson, Augustine Kong, Unnur Thorsteindottir, Chrysanthi Ainali, Antigone S Dimas, Neelam Hassanali, Catherine Ingle, David Knowles, Maria Krestyaninova, Christopher E Lowe, Paola Di Meglio, Stephen B Montgomery, Leopold Parts, Simon Potter, Gabriela Surdulescu, Loukia Tsaprouni, Sophia Tsoka, Veronique Bataille, Richard Durbin, Frank O Nestle, Stephen O'Rahilly, Nicole Soranzo, Cecilia M Lindgren, Krina T Zondervan, Kourosh R Ahmadi, Eric E Schadt, Kari Stefansson, George Davey Smith, Mark I McCarthy, Panos Deloukas, Emmanouil T Dermitzakis, and Tim D Spector. Mapping cis- and trans-regulatory effects across multiple tissues in twins. *Nature Genetics*, 44(10):1084–1089, October 2012. ISSN 1061-4036, 1546-1718. doi: 10.1038/ng.2394. URL http://www.nature.com/articles/ng.2394.

[15] Naomi R. Wray, Sang Hong Lee, Divya Mehta, Anna A.E. Vinkhuyzen, Frank Dudbridge, and Christel M. Middeldorp. Research Review: Polygenic methods and their application to psychiatric traits. *Journal of Child Psychology and Psychiatry*, 55(10):1068–1087, October 2014. ISSN 00219630. doi: 10.1111/jcpp.12295. URL http://doi.wiley.com/10.1111/jcpp.12295.