

ABSTRACT

Schizophrenia is a severe psychiatric illness for which the precise etiology remains unknown. Studies using postmortem human brain have become increasingly important in schizophrenia research, providing an opportunity to directly investigate the diseased brain tissue. Gene expression profiling technologies have been used by a number of groups to explore the postmortem human brain and seek genes which show changes in expression correlated with schizophrenia. While this has been a valuable means of generating hypotheses, there is a general lack of consensus in the findings across studies. Expression profiling of postmortem human brain tissue is difficult due to the effect of various factors that can confound the data. The first aim of this thesis was to use control postmortem human cortex for identification of expression changes associated with such factors, specifically: age, sex, brain pH and postmortem interval. I conducted a meta-analysis across the control arm of eleven microarray datasets (representing over 400 subjects), and identified a signature of genes associated with each factor. These genes provide critical information towards the identification of problematic genes when investigating postmortem human brain in schizophrenia and other neuropsychiatric illnesses. The second aim of this thesis was to evaluate gene expression patterns in the prefrontal cortex associated with schizophrenia by exploring two methods of analysis: differential expression and coexpression. Seven schizophrenia microarray studies of prefrontal cortex were combined for a total of 153 subjects with schizophrenia and 153 healthy controls. Meta-analysis was conducted with careful consideration for the effects of covariates, revealing a robust list of 98 differentially expressed 'schizophrenia genes'. Using the same seven schizophrenia datasets, coexpression networks were generated for control and schizophrenia cohorts within each dataset and then combined across studies using a rank aggregation approach. Topological properties of our 'schizophrenia genes' were evaluated in the context of each network, highlighting differences in correlation structure of these genes in the control and schizophrenia brain. Together these results converge towards a general conclusion, emphasizing that the integration of postmortem human brain expression profiling data improves statistical power and is particularly useful in detecting subtle yet consistent changes in expression associated with schizophrenia.

BIOGRAPHICAL NOTES

Born: August 18, 1982, Brampton, Ontario

Academic Studies: B.Sc. (Hons), McMaster University, 2005

GRADUATE STUDIES

Field of Study: Neuroinformatics/ Neurogenomics

Courses

GENE 501	Special Topics in Bioinformatics
MEDG 548	Problem-based Learning in Bioinformatics
STAT 540	Statistical Methods for High Dimensional Biology
CPSC 445	Algorithms in Bioinformatics
CPSC 504	Data Management
MEDG 520	Advanced Human Molecular Genetics

Instructors

Drs. F. Ouellette and F. Pio
Dr. F. Brinkman
Dr. R. Gottardo
Dr. A. Condon
Dr. R. Pottinger
Dr. A. Brooks-Wilson

AWARDS

MIND Foundation of BC Research Award
McGeer Basic Science Award (UBC Psychiatry)

PUBLICATIONS

Mistry, M., Gillis, J., Pavlidis, P. Genome-wide expression profiling of schizophrenia using a large combined cohort. *Molecular Psychiatry*. 2012. doi: 10.1038/mp.2011.172

Gillis, J., Mistry, M., Pavlidis, P. Gene function analysis in complex datasets using ErmineJ. *Nature Protocols*. 5(5). June 2010.

Mistry, M. and Pavlidis P. A cross-laboratory comparison of expression profiling data from normal human postmortem brain. *Neuroscience*. 167(2):384-95. May 2010.

Mistry M. and Pavlidis P. Gene Ontology term overlap as a measure of gene functional similarity. *BMC Bioinformatics*. 9(1):237. August 2008.

PRESENTATIONS

Meta-analyses of gene expression changes associated with schizophrenia in the postmortem human brain. (May 2012). Trainee Speaker, *Department of Psychiatry Research Day (Life Sciences Institute, UBC)*

Meta-analysis of gene expression in the postmortem human brain: In search of a robust schizophrenia signature. (October 2010). Trainee Speaker, *Centre for High-throughput Biology Annual Retreat (Loon Lake, BC)*

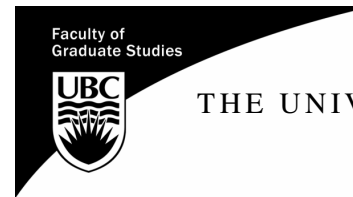
Profiling the postmortem human brain: A meta-analytic approach. (January 2010). Presenter 'SNPs and Chips' panel. *Winter Conference on Brain Research (Breckenridge, CO)*

Cross-laboratory comparison of human postmortem brain expression profiling data. (April 2009). Trainee Speaker, *MSL (Michael Smith Labs) Monthly Colloquia*

Evaluating the Functional Similarity of Gene Pairs. (December 2007). Introductory speaker, *VanBUG (Vancouver Bioinformatics User Group) Monthly Seminar Series*

SUPERVISORY COMMITTEE

Dr. Paul Pavlidis
Dr. Wyeth Wasserman
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THE UNIVERSITY OF BRITISH COLUMBIA

PROGRAMME

The Final Oral Examination
For the Degree of

DOCTOR OF PHILOSOPHY
(Bioinformatics)

MEETA MISTRY

B.Sc. (Hons), McMaster University, 2005

Friday, July 6, 2012, 4:00 pm
Room 200, Graduate Student Centre
Latecomers will not be admitted

“Meta-analyses of Expression Profiling Data in the Postmortem Human Brain”

EXAMINING COMMITTEE

Chair:
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Supervisory Committee:
Dr. Paul Pavlidis, Research Supervisor (Bioinformatics)
Dr. Wyeth Wasserman (Bioinformatics)

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