ABSTRACT

New massively parallel sequencing technologies offer opportunities to profile genomes and transcriptomes for copy number variations; polymorphisms; somatic point mutations; chromosomal rearrangements and can capture gene expression and splicing information. A suite of methods was developed to analyze both RNA-seq and whole genome/exome sequence data from malignant cells for the purpose of identifying somatic point mutations and fusion transcripts. This work reports the application of these and other tools to gain insights into the somatic mutations involved in two common classes of lymphoid malignancies, namely non Hodgkin lymphoma and acute lymphoblastic leukemia. Analysis of multiple cases by a combination of RNA-seq, genome and exome sequencing revealed genes significantly mutated in non Hodgkin lymphoma including many not previously known to be mutated in these or any other cancers. These included multiple genes involved in altering the methylation or acetylation state of histones such as *EZH2, MLL2, CREBBP* and *MEF2B,* suggesting a previously unappreciated role of deregulated or altered epigenetic gene regulation in lymphomagenesis. Some of the mutated genes, such as *MLL2,* had clear patterns of inactivating mutations, indicating they act as tumour suppressors in NHL. Others had mutation hot spots that can be indicative of an oncogenic gain of function and this was proven to be the case for the mutation hot spot identified in *EZH2.* Analysis of acute lymphoblastic leukemia revealed both novel point mutations and fusion transcripts. The latter included fusions that potentially deregulate known oncogenes such as *JAK2* and *ABL1.* These data may indicate new treatment options for patients with ALL and NHL and lend new insights into the molecular nature of these diseases.

BIOGRAPHICAL NOTES

Born:	September 26, 1980, Comox, BC
Academic Studies:	B. Sc. Simon Fraser University, 2003 M. Sc. University of British Columbia, 2007
Current Position:	Ph. D. Candidate, BC Cancer Agency

GRADUATE STUDIES

Field of Study: Cancer Genomics

Courses	**Instructors**
N/A	N/A

AWARDS

Vanier Canada Graduate Scholarship (CIHR)
Senior Graduate Studentship (MSFHR)
Lloyd Skarsgard Graduate Student Research Excellence Prize (BCCA)
Four Year Doctoral Fellowship (UBC)

SELECTED PUBLICATIONS

Morin, R.D. et al., 2011. Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. *Nature,* 476(7360), pp.298–303.

Morin, R.D. et al., 2010. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nature Genetics,* 42(2), pp.181–185.

Yap D.B. et al., 2011. Somatic mutations at EZH2 Y641 act dominantly through a mechanism of selectively altered PRC2 catalytic activity, to increase H3K27 trimethylation. Blood. 2011 Feb 24;117(8):2451-9.

Shah, S.P. et al., 2009. Mutational evolution in a lobular breast tumour profiled at single nucleotide resolution. *Nature,* 461(7265), pp.809–813.

SELECTED PRESENTATIONS

Diffuse Large B-Cell Lymphoma in BC: From Bench to Bedside. BC Cancer Agency Seminar Series, Vancouver, BC. (Sep 2011)

Identification of Genes Frequently Mutated In FL and DLBCL with Transcriptome, Genome and Exome Sequencing. 52nd ASH Annual Meeting. Orlando, FL. (Dec 2010)

Using Genomic and Transcriptomic Sequencing to Identify Recurrent Somatic Mutations in Non Hodgkin Lymphoma. Beyond Sequencing, San Francisco, CA. (Jun 2010)

Tyrosine 641 of the *EZH2* Oncogene is Frequently Mutated in Non Hodgkin Lymphomas of Germinal Center Origin. 51st ASH Annual Meeting, New Orleans, LA. (Dec 2009)

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Dr. Steven Jones
Dr. Joseph Connors

Faculty of Graduate Studies

THE UNIVERSITY OF BRITISH COLUMBIA

PROGRAMME

The Final Oral Examination
For the Degree of

DOCTOR OF PHILOSOPHY
(Bioinformatics)

RYAN DAVID MORIN

B. Sc., Simon Fraser University, 2003
M. Sc., University of British Columbia, 2007

Friday, December 15, 2011, 12:30 pm
Room 203, Graduate Student Centre
Latecomers will not be admitted

"Mutation Discovery and Characterization in Lymphoid Neoplasms using Massively Parallel RNA and DNA Sequencing"

EXAMINING COMMITTEE

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Supervisory Committee:
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Dr. Paul Pavlidis (Bioinformatics)
Dr. Joseph Connors (Pathology)

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