PhD DEFENCE – Tuesday, December 15th, 2015
Student: Chansonette Badduke
Title: **FUNCTIONAL GENOMIC ANALYSIS OF NOVEL MICRODELETIONS AND MICRODUPLICATIONS ASSOCIATED WITH INTELLECTUAL DISABILITY**
Time and Location: 11:00 am, Room 203, Graduate Student Centre, 6371 Crescent Road, UBC Campus
Supervisor: Dr. Evica Rajcan-Separovic

ABSTRACT
Intellectual disability (ID) is a diagnosis given to persons who have life-long cognitive and adaptive impairments that begin early in life. ID affects about 1-3% of the population. Extremely small chromosome losses and gains, called microdeletions and microduplications respectively (collectively Copy Number Variants, CNVs), are the cause of ID in ~15% of cases and their identification has helped to pinpoint genomic regions that contain ID-genes.
The objective of my PhD research was to search for ID candidate genes in subjects with ID, focusing on the functional genomic analysis of genes from CNVs and in the rest of the genome. I studied individuals with unique *de novo* pathogenic CNVs at chromosomal position 2p15-16.1 and with familial CNVs at chromosomal position 1q21.1. I used a multi-faceted approach that included the study of candidate genes': 1) expression, 2) sequence changes, 3) knock down consequences in *C. elegans* and 4) imprinting potential.
My results show that the best candidate genes from the 2p15-16.1 CNV are XPO1, USP34 and REL because their expression is reduced in individuals with deletions. In case of the 1q21.1 CNV, I identified two candidate genes (CHD1L and PRKAB2) from the CNV that had altered expression and cellular function. I also identified a pathogenic sequence change in ATF6 in individuals with a familial 1q21.1 duplication. ATF6 is located outside the 1q21.1 CNV and is part of the Endoplasmic Reticulum (ER) stress response pathway which may contribute to the phenotypic variability in this family. Finally, I identified 3 CNVs in children with ID that overlap putative imprinted regions.
The results of my study therefore led to the identification of genes which could contribute to ID as their function is altered in patients with the CNV or their characteristics suggest that they can be sensitive to copy number changes. This work contributes to an improved understanding of how CNVs and additional genetic changes in the rest of the genome can lead to ID.