PhD DEFENCE Thursday, September 21st, 2017
Student: Hani Bagheri
Title: GENOMIC AND FUNCTIONAL CHARACTERISTICS OF DNA COPY NUMBER VARIANTS ASSOCIATED WITH DEVELOPMENTAL ABNORMALITIES
Time and location: 12:30pm PDT; Seminar Room 310, UBC's Eye Care Centre, 2550 Willow Street, Vancouver, BC
Supervisor: Dr. Evica Rajcan Separovic/Cheryl Gregory Evans

ABSTRACT

Small gains and losses of chromosomal DNA, called copy number variants (CNVs), are the cause of many human developmental abnormalities detected before or after birth. Clinically-significant CNVs are found in 2-6% of developmentally arrested embryos and fetuses (termed miscarriage) and in ~15% of children with postnatal developmental abnormalities, typically including abnormal brain function and leading to neuro-developmental delay (NDD).
The overall goal of my PhD project was to characterize CNVs found in both miscarriages and in children with NDD in order to identify candidate genes that cause these two aspects of abnormal development. I used a multi-faceted approach consisting of bioinformatics, human cell-line analysis and transgenic animal model investigations.
I characterized CNVs reported in miscarriages from literature as well as from our laboratory by using bioinformatics approaches to determine the CNVs size, gene content, gene density and function, known gene knockout murine phenotype, and biological pathway enrichment for all miscarriage CNV genes. My analysis identified several genes from miscarriage CNVs with important functions during prenatal development and pregnancy (e.g. *CDKN1C* and *TIMP2*) and enrichment of genes from miscarriage CNVs in biological pathways and processes relevant to embryo/fetal development and feto-maternal interaction (e.g. immune response).
For discovery of candidate genes responsible for childhood NDD, I characterized CNVs mapping to a chromosome region, 2p15p16.1, which are known to be associated with multiple postnatal developmental abnormalities and NDD (termed 2p15p16.1 microdeletion syndrome). I performed detailed phenotype and CNV analysis of 33 patients with 2p15p16.1 microdeletions and identified 3 candidate genes (*XPO1*, *REL*, and *BCL11A*) for the developmental problems. By studying their expression in patient cell-lines as well as phenotypic consequences of the loss or gain of their expression in zebrafish, I confirmed their role in developmental abnormalities associated with this syndrome. I have also explored the role of non-coding sequences from this CNV in regulation of one of the candidate genes, *BCL11A*.
The results of my study provide a blueprint for identification of genes with a role in abnormal development by characterizing CNVs. Understanding the cause of the developmental abnormalities opens paths for exploring possibilities for their improved diagnosis, prevention, and potential cure.