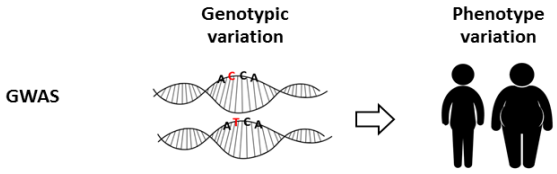
GUEST SPEAKER SEMINAR

Molecular Genetics
UNIVERSITY OF TORONTO

Regulatory variants and human diseases



Challenges when interpreting GWAS signal

Presented by: Dr. Marcelo A. Nóbrega

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While we have known for several years that over 90% of genetic variants associated with complex traits are in the non-protein coding fraction of the human genome, translating these mapping studies to mechanistic insights into disease etiology has lagged significantly behind. Assuming that a sizeable fraction of these noncoding variants impart their effects by altering the properties of distant cis-regulatory elements, the challenges that emerge for the functional follow-up of GWAS include 1) identifying the causal variants; 2) establishing the regulatory potential and tissue-specificity of the cis-regulatory elements harboring the causal variants; 3) assigning the target gene for each enhancer containing regulatory variants of interest; 4) characterizing the phenotypic impact of the altered expression of those genes in physiopathogenesis. To address these challenges, we have developed a comprehensive pipeline to functionally follow-up on GWAS signals. This includes drafting detailed genome-wide maps of chromatin accessibility, gene expression, and long-range genomic interactions in tissues and cell lines relevant to specific diseases. Overlaying these maps with genetic association data and other strategies to fine map disease-associated loci results in the identification of candidate regulatory variants in dozens of loci associated with complex diseases. Some of the insights coming from these studies and the functional follow-up of several leads include: 1) the target genes of genetic associations are often far from the putative causal variants; 2) several variants may contribute to the association of a given locus; 3) as a corollary of the above, multiple regulatory elements harboring variants in a locus may be associated with a trait; 4) these regulatory elements have complex spatial, and temporal specificities; 5) multiple genes are often targeted by regulatory variants in a given disease-associated locus. These insights refine our understanding of the genetic architecture in loci identified by genome-wide genetic associations.

Hosts: Dr. Ian Scott and Dr. Michael Wilson

Date: Monday September 16th, 2019
Time: 2:00 PM
Place: Donnelly Centre CCBR, Red Seminar Room, 160 College Street