Department of Biostatistics and Medical Informatics Seminar

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12:00-1:00 pm
Via Zoom:
https://uwmadison.zoom.us/j/96905602893?pwd=MDliL2VCN2NGOHdWOEtrRHdRVlFpUT09

Genetic regulation: lessons from the human transcriptome

Abstract: During the past decade studies have demonstrated genetic effects on the transcriptome in humans and linked these regulatory mechanisms to complex traits and diseases. In this talk, I will present analyses demonstrating the context specificity of these genetic effects, with special focus on the Genotype-Tissue Expression (GTEx) data, comprised of 15,201 RNA-sequencing samples from 49 tissues of 838 postmortem donors. Genetic associations for gene expression and splicing in cis and trans demonstrate that regulatory associations are found for almost all genes, and contribute contribution to allelic heterogeneity and pleiotropy of complex traits. Importantly, we have identified associations that vary by tissue, cell-type composition, sex, and donor ancestry. We have focused efforts on understanding the impact of biological sex on the transcriptome to investigate the possible basis of the observation that many complex human phenotypes exhibit sex-differentiated characteristics. Here, I will present an extensive catalog comprising sex differences in gene expression and its genetic regulation in the GTEx data. This work demonstrates that sex strongly influences gene expression levels and cellular composition of tissue samples across the human body. The effect of sex on gene expression is widespread, suggesting that many, if not most, biological processes are impacted by sex effects on the transcriptome. We expand the identification of *cis*-eQTLs with sex-differentiated effects by performing a genotype-by-sex interaction eQTL analysis and identified 369 sex-biased eQTLs (sb-eQTLs). By integrating sb-eQTLs with genome-wide association study data, we identify dozens of gene-trait associations that are driven by genetic regulation in a single sex, including novel associations not detected with sex-agnostic approaches. Using the GTEx data as a reference, we have begun an analogous analysis of sex differences in the transcriptome across 25 tumor-types from The Cancer Genome Atlas (TCGA). I will discuss challenges encountered when applying the same statistical approaches to the heterogenous cancer transcriptomes, and describe some possible solutions. Collectively, our integrative analyses provide the most comprehensive characterization of the human transcriptome across tissues and by sex to date, with important implications for complex traits. Our newest efforts with TCGA data are revealing important benchmarking of statistical approaches for removing unwanted sources of variation in heterogenous data, using tumor transcriptomics data as an example.

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