Abstract:
One of the central challenges in genetics is to understand the mapping from genetic variation to phenotypic variation. During the past 15 years, genome-wide association studies (GWAS) have been used to study the genetic basis of a wide variety of complex diseases and other traits. One striking finding from this work has been that for a wide range of complex traits such as height or schizophrenia, even the most important loci in the genome contribute just a small fraction of the phenotypic variance. Instead, most of the variance comes from tiny contributions from tens to hundreds of thousands of variants spread across most of the genome. Our group has argued that these observations do not fit neatly into standard conceptual models of genetics. In recent papers, we have proposed one model to explain this, which we refer to as the "omnigenic" model.

In this talk, I will review our past work in this area, and describe new work that we have done on the genetic basis of three molecular traits—urate, IGF-1, and testosterone—that are biologically simpler than most diseases, and for which we know a great deal in advance about the core genes and pathways. For these molecular traits, we observe huge enrichment of significant signals near genes involved in the relevant biosynthesis, transport, or signaling pathways. However, even these molecular traits are highly polygenic, with most of the variance coming not from core genes, but from thousands to tens of thousands of variants spread across most of the genome. In summary, our models help to illustrate why so many variants affect risk for any given disease.

Suggested Readings:
- Boyle/Li/Pritchard 2017: https://www.ncbi.nlm.nih.gov/pubmed/28622505
- Liu/Li/Pritchard 2019: https://www.ncbi.nlm.nih.gov/pubmed/31051098
- Sinnott-Armstrong/Naqvi/Rivas/Pritchard 2020: https://www.biorxiv.org/content/10.1101/2020.04.20.051631v1