39. Human Genetics

1 unit, Kushal Dey, November 19, 2025

The lecture by Dr. Kushal Dey will delve into the concordance, and discordance, between natural genetic variation and artificial variation from CRISPRi, Perturb-seq, and reporter assay experiments. The lecture will first introduce the study of common and rare genetic variation using Genome wide Association Studies and Whole Exome and Whole Genome Sequencing-based efforts, and downstream functional interpretation of these disease risk variants. We will discuss different variant-to-function approaches to prioritize variants and identify their target genes of action and the cellular pathways they are associated with that play a critical role in disease etiology.

Then, we will delve into how natural genetic variation studies, with and without integration with functional assays, have recently informed small and large-scale perturbation experiments. We will discuss how perturbation datasets present an exciting opportunity to learn the downstream gene programs and cellular processes that are critical for common and rare diseases, opening the path to drug intervention experiments. We will talk about the feedback loop that exists between GWAS/WES and perturbation datasets, where each can be used to inform about the other. We will discuss current machine learning and network-based approaches that have tried to identify important perturbation programs and how they can be related to disease. We will also discuss recent efforts (Siraj et al 2024 bioRxiv, Morris et al 2023 Science) where GWAS data have been used to nominate variants for functional follow-up experiments. We will delve into how for red blood cell traits, CRISPR data in K562 cancer cell line have proved highly informative, as well as, how the current CRISPR data suffer from their limited breadth of data they have been applied to. Finally, we will discuss the harmonization of the CRISPR and GWAS datasets towards benchmarking, and learning optimal combination of, different functional assays and models.

The papers to read are:
Gasperini et al Cell 2019
https://pubmed.ncbi.nlm.nih.gov/30612741/

Additional readings:

Siraj et al 2024 bioRxiv

https://www.biorxiv.org/content/10.1101/2024.05.05.592437v1

Morris et al 2023 Science

https://www.science.org/doi/10.1126/science.adh7699