Leveraging Large iPSC Cohorts and Population Scale Stem Cell Models to Study the Effect of Genetic Variation on Cellular Phenotypes
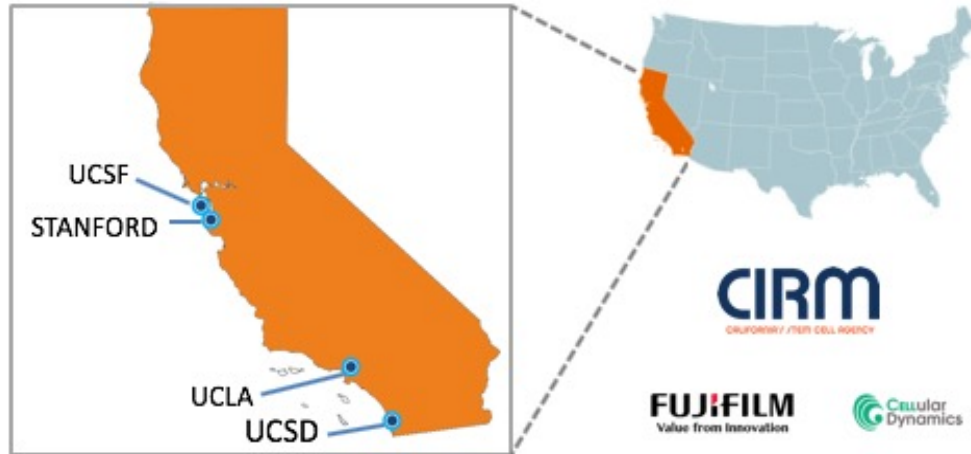
Sulagna (Dia) Ghosh

Computational Biologist

Stanley Center for Psychiatric Research
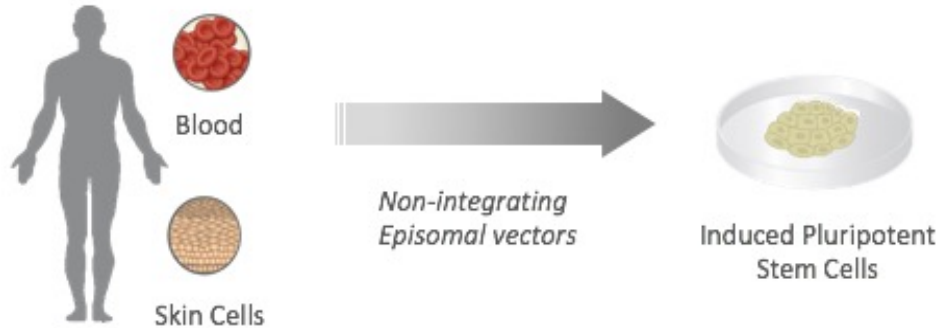
The CIRM-CDI iPSC Repository

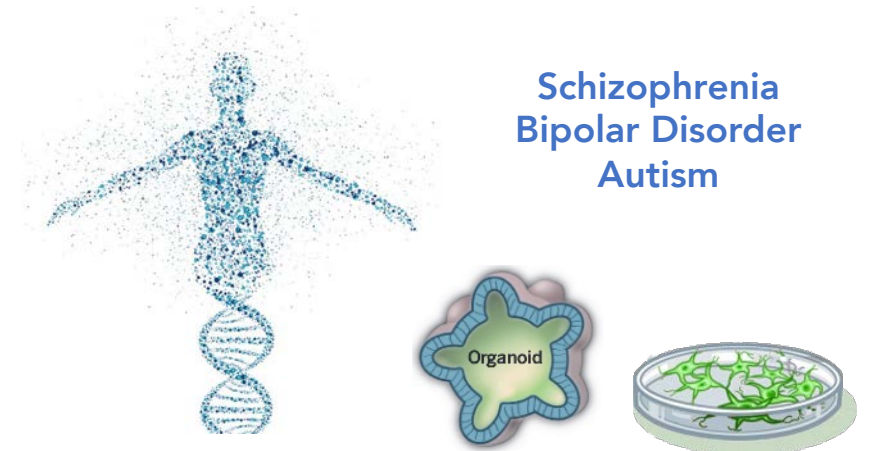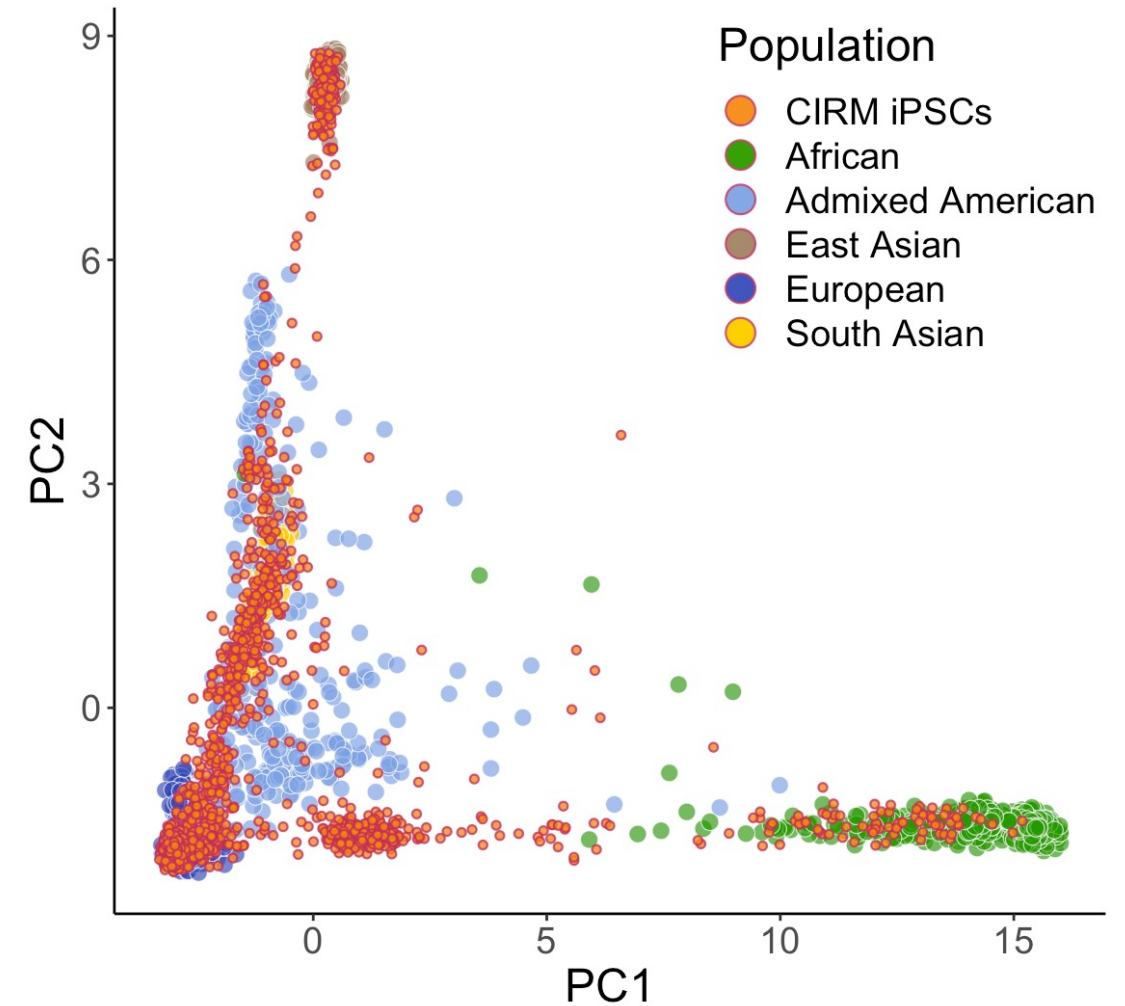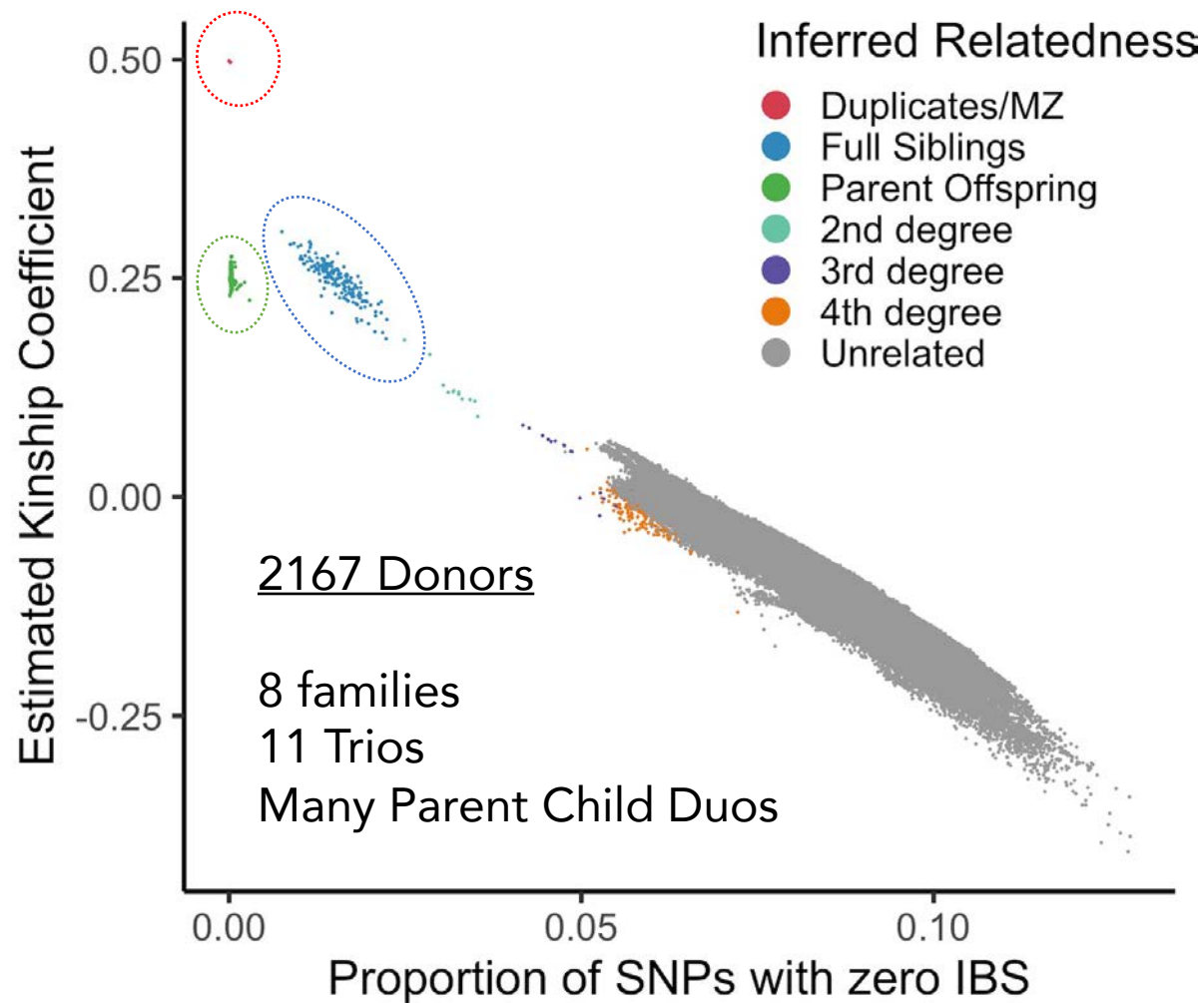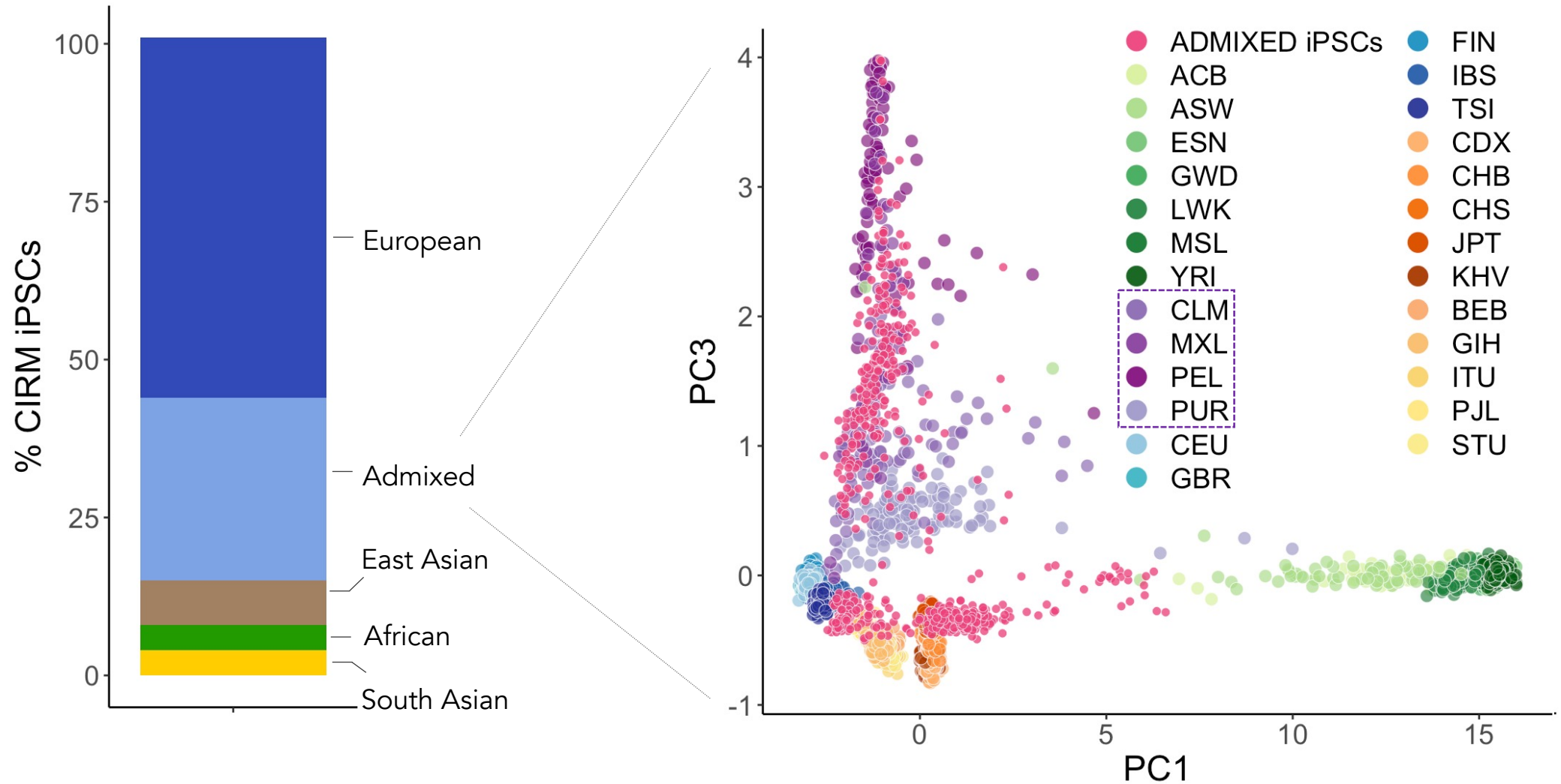*Generating the world's largest induced pluripotent stem cell (iPSC) bank*

CIRM iPSCs have Diverse Genetic Ancestries

CIRM iPSCs have Diverse Genetic Ancestries

Enabling Rational Selection of Lines for Disease Modeling

The value of genotyped cell lines:

o Design experiments informed by ancestry, relatedness and polygenic risk
o Identify lines harboring genetic variants or haplotypes of interest
o Enable identification and validation of cell lines across laboratories
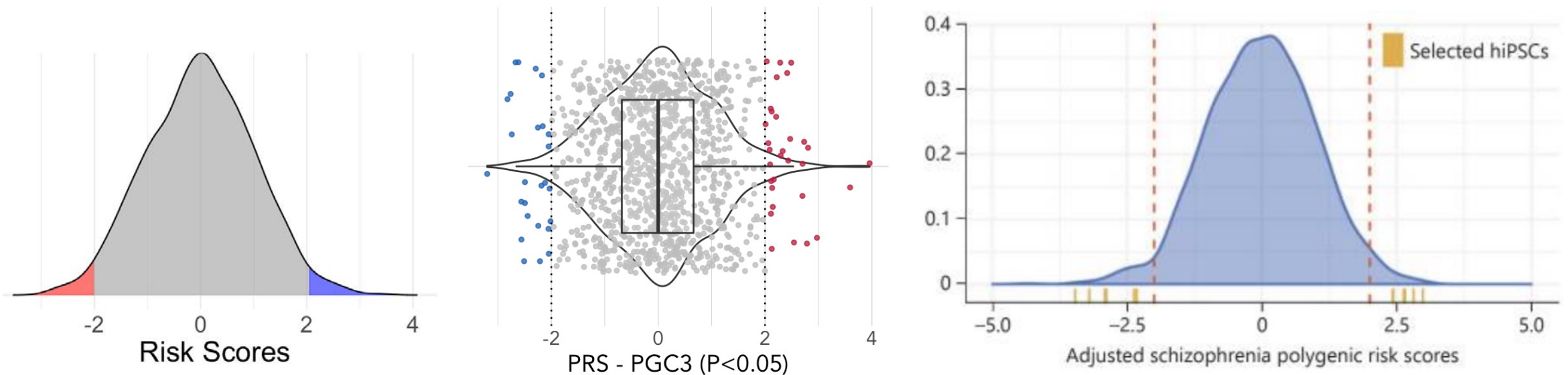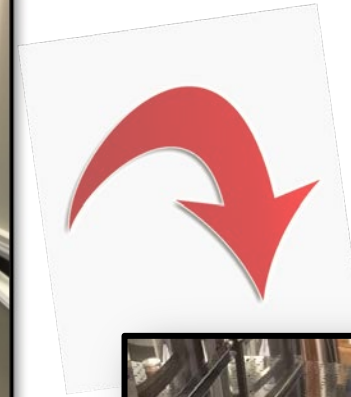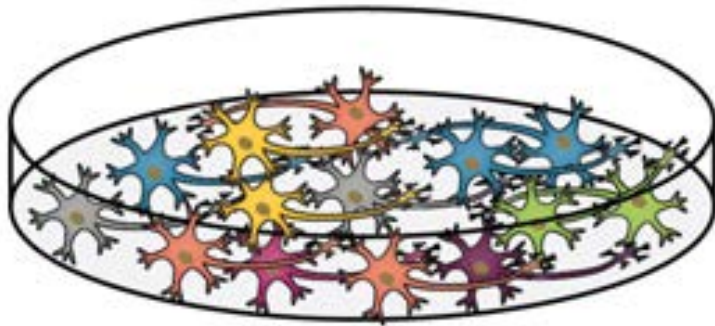

Dobrindt et al, 2021

Population-scale stem cell models

Linking genetic variants to cellular phenotypes

The "Village-in-a-Dish" Experimental Paradigm

Grow cells from 100s of people together, then measure their phenotypes

- Cell environments identical
- Cells processed identically, simultaneously
- Reduce noise from technical variation

Linking Donor Genotypes to Cellular Phenotypes

100s of cell lines pooled, assayed together

+

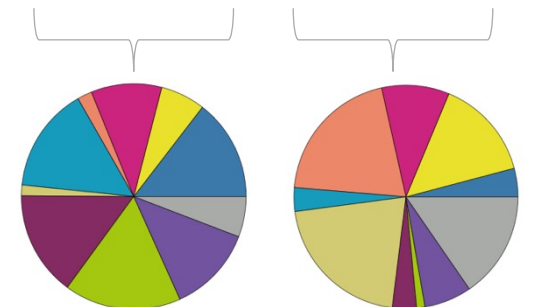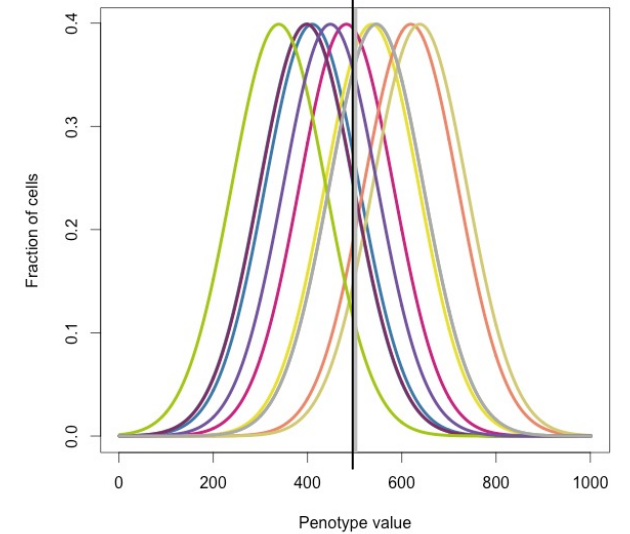Natural sequence variation acts as intrinsic barcode

"Census-seq"

Infer the donor composition of the pool

"Dropulation"

Sorting or selecting cells (based on phenotype) changes the pool's donor composition

Linking Donor Genotypes to Cellular Phenotypes

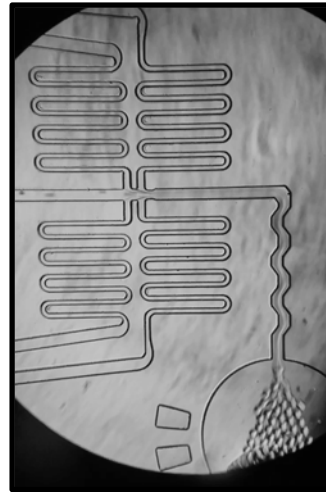100s of cell lines pooled, assayed together
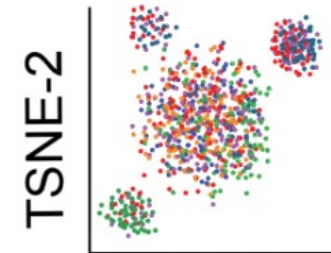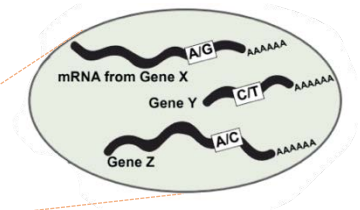
+

Natural sequence variation acts as intrinsic barcode
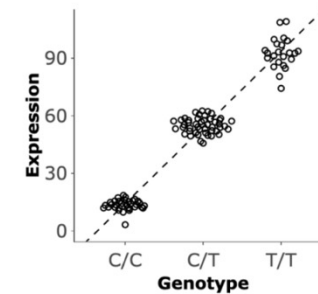
scRNAseq (10X Genomics)

Populations of single-cell droplets analyzed simultaneously

Single Donor Detection

mRNA from Gene X — A/G — AAAAAA
Gene Y — C/T — AAAAAA
Gene Z — A/C — AAAAAA

"Dropulation"

TSNE-2
TSNE-1

Expression
90
60
30
C/C   C/T   T/T
Genotype

Applications of Pooled Experimental Systems

Census: GWAS in a dish

- High throughput association of donor genotypes to cellular phenotypes at low cost
- Pharmacogenetic profiling

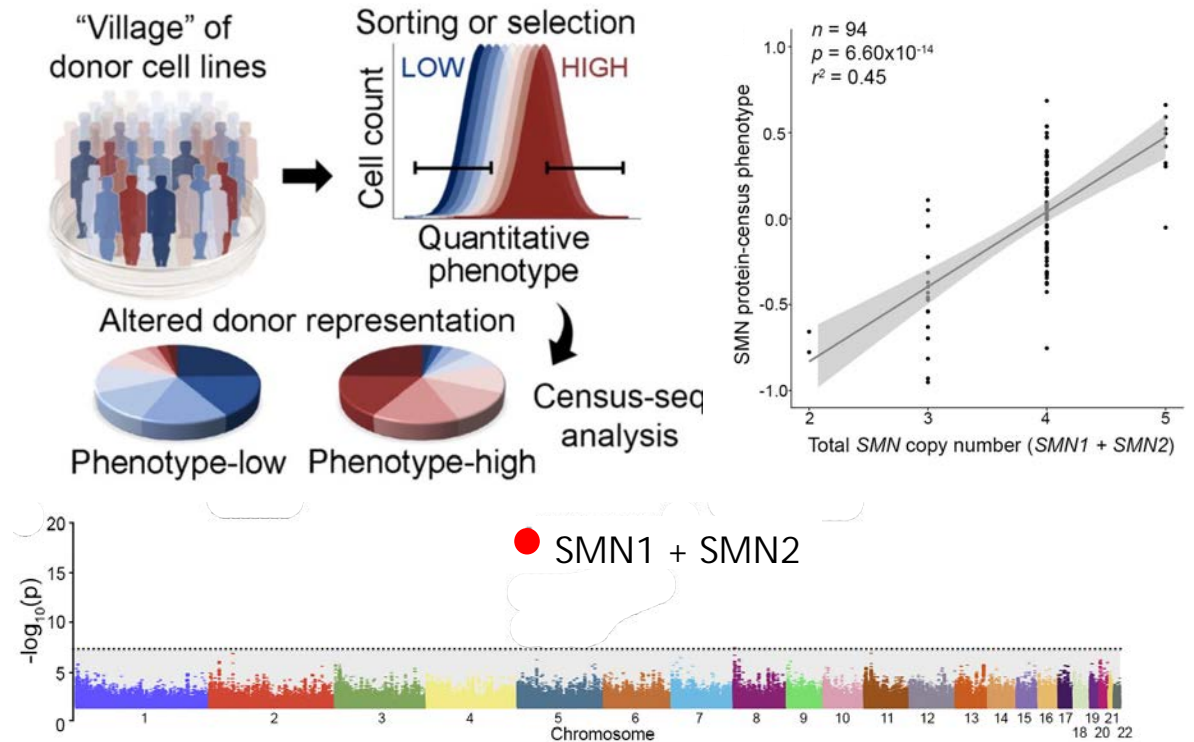# Applications of Pooled Experimental Systems

bioRxiv — THE PREPRINT SERVER FOR BIOLOGY

Natural variation in gene expression and Zika virus susceptibility revealed by villages of neural progenitor cells
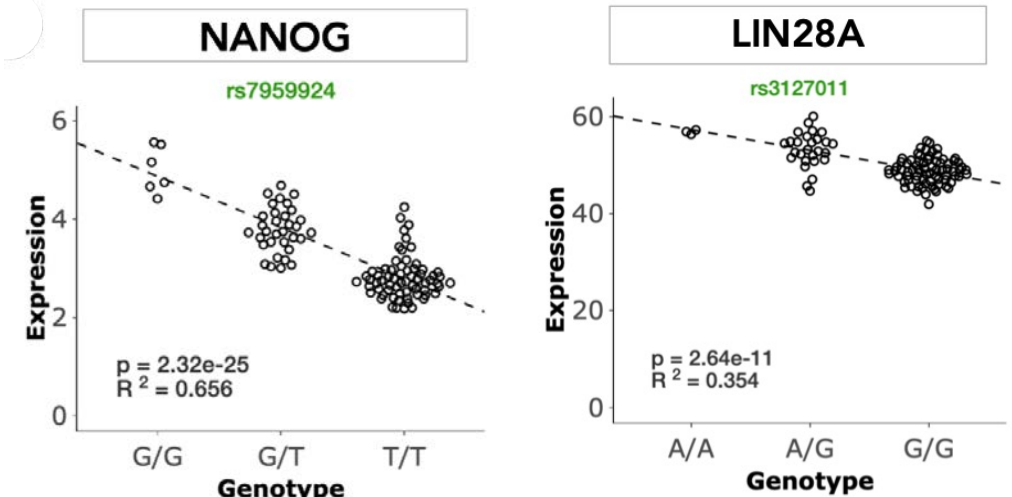
Michael F. Wells, James Nemesh, Sulagna Ghosh, Jana M. Mitchell, Curtis J. Mello, Daniel Meyer, Kavya Raghunathan, Matthew Tegtmeyer, Derek Hawes, Anna Neumann, Kathleen A. Worringer, Joseph J. Raymond, Sravya Kommineni, Karrie Chan, Daniel Ho, Brant K. Peterson, Federica Piccioni, Ralda Nehme, Kevin Eggan, Steven A. McCarroll
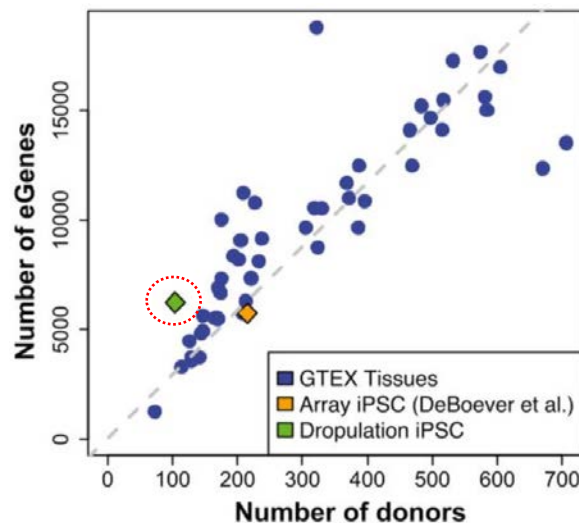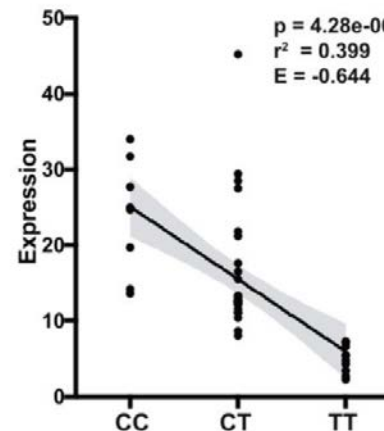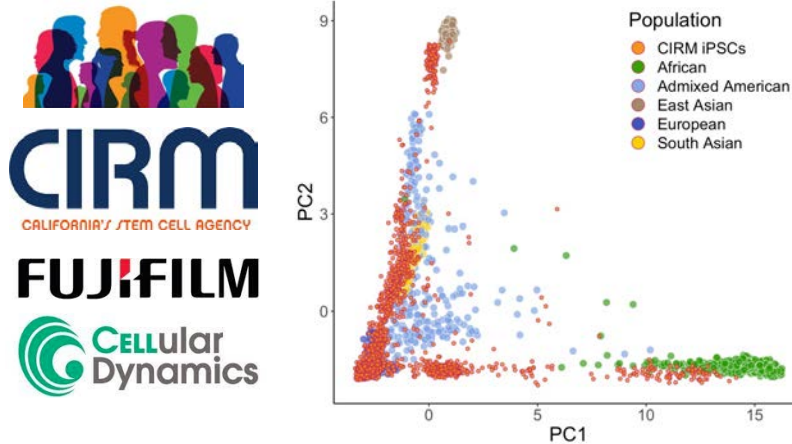
Dropulation: Interindividual Variation

- Discover eQTLs across multiple donors in a dish
- Uncover cell type/state specific eQTLs
- Link disease relevant variants to cellular phenotypes
- Study genetic basis of inter-individual variation

The CIRM-CDI Collection and Cell Villages provide new opportunities for Population-Scale Models of Disease

Publicly accessible genetic data

Cell Villages

eQTL discovery and colocalization with risk variants

Cellular and Genetic Perturbations

Drug Screens and Pharmacogenomic Profiling

Linked Donor Metadata