

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

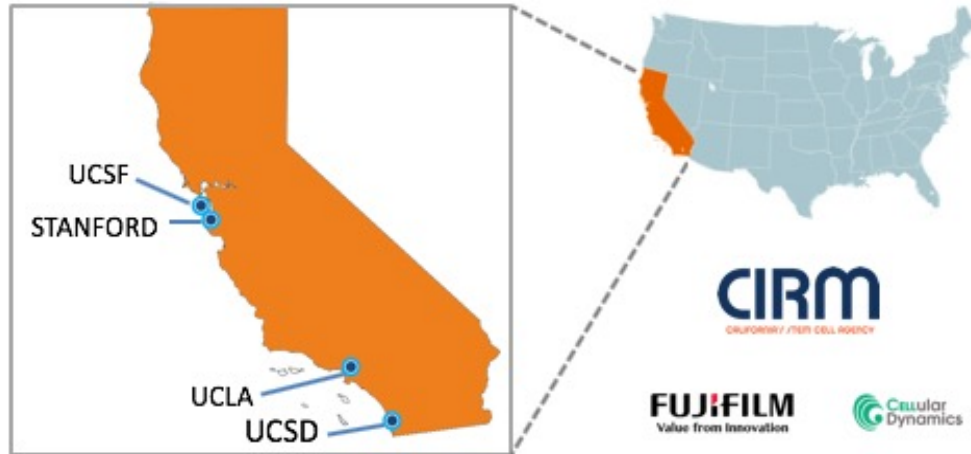
Sulagna (Dia) Ghosh

Computational Biologist

Stanley Center for Psychiatric Research

The CIRM-CDI iPSC Repository

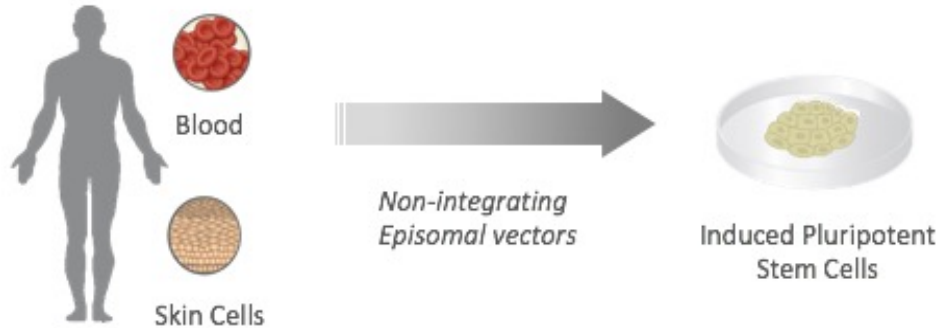
SAMPLE COLLECTION



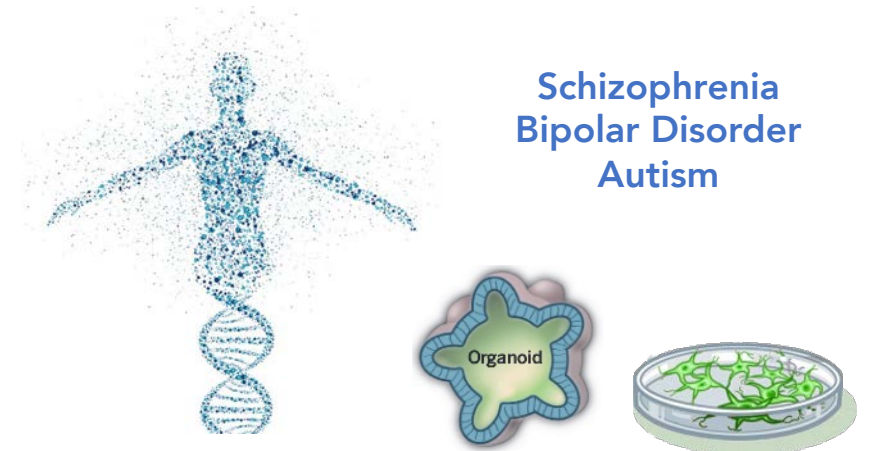
DISORDERS

*Liver Disease
Lung Disease
Heart disease
Blinding eye disease
Childhood neurological disorders
Neurodegenerative disorders*

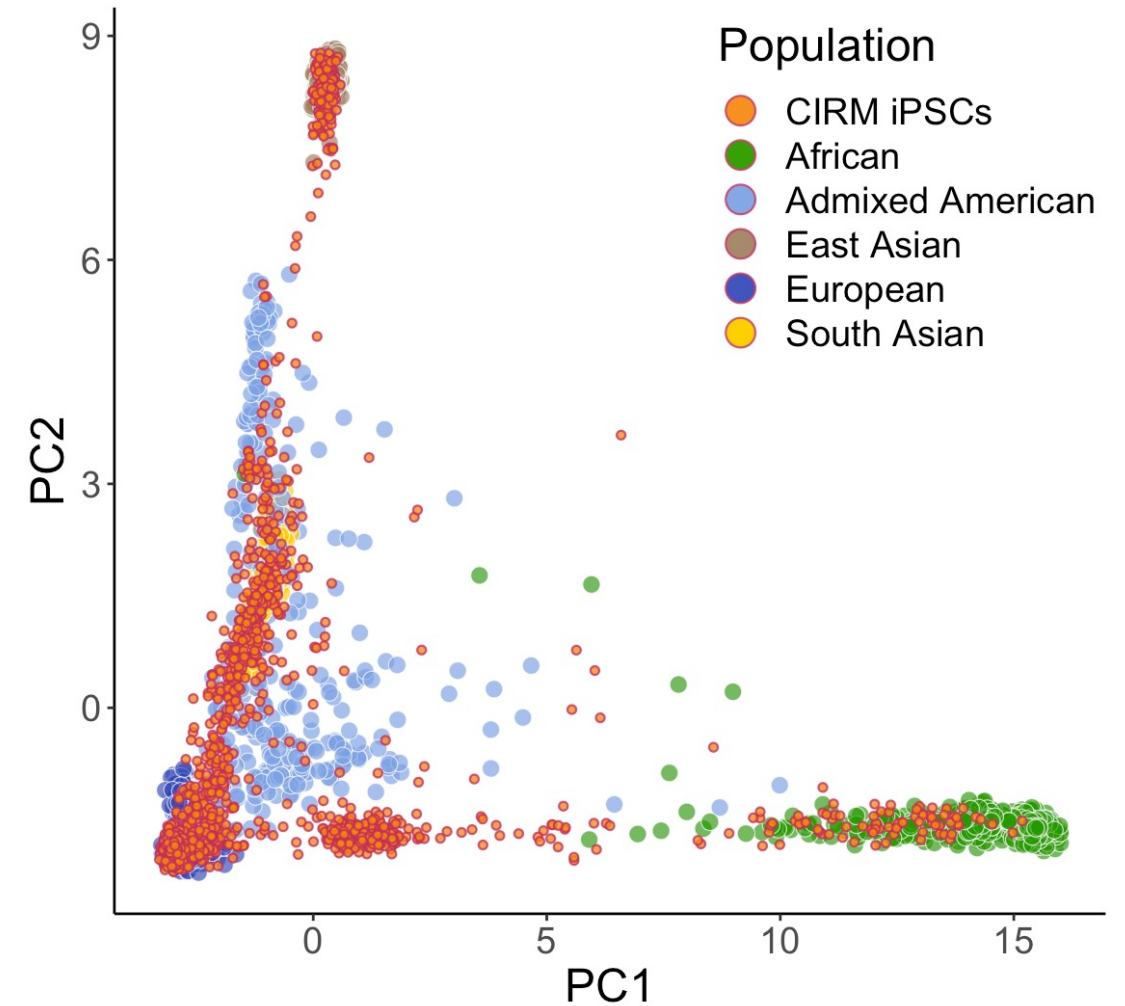
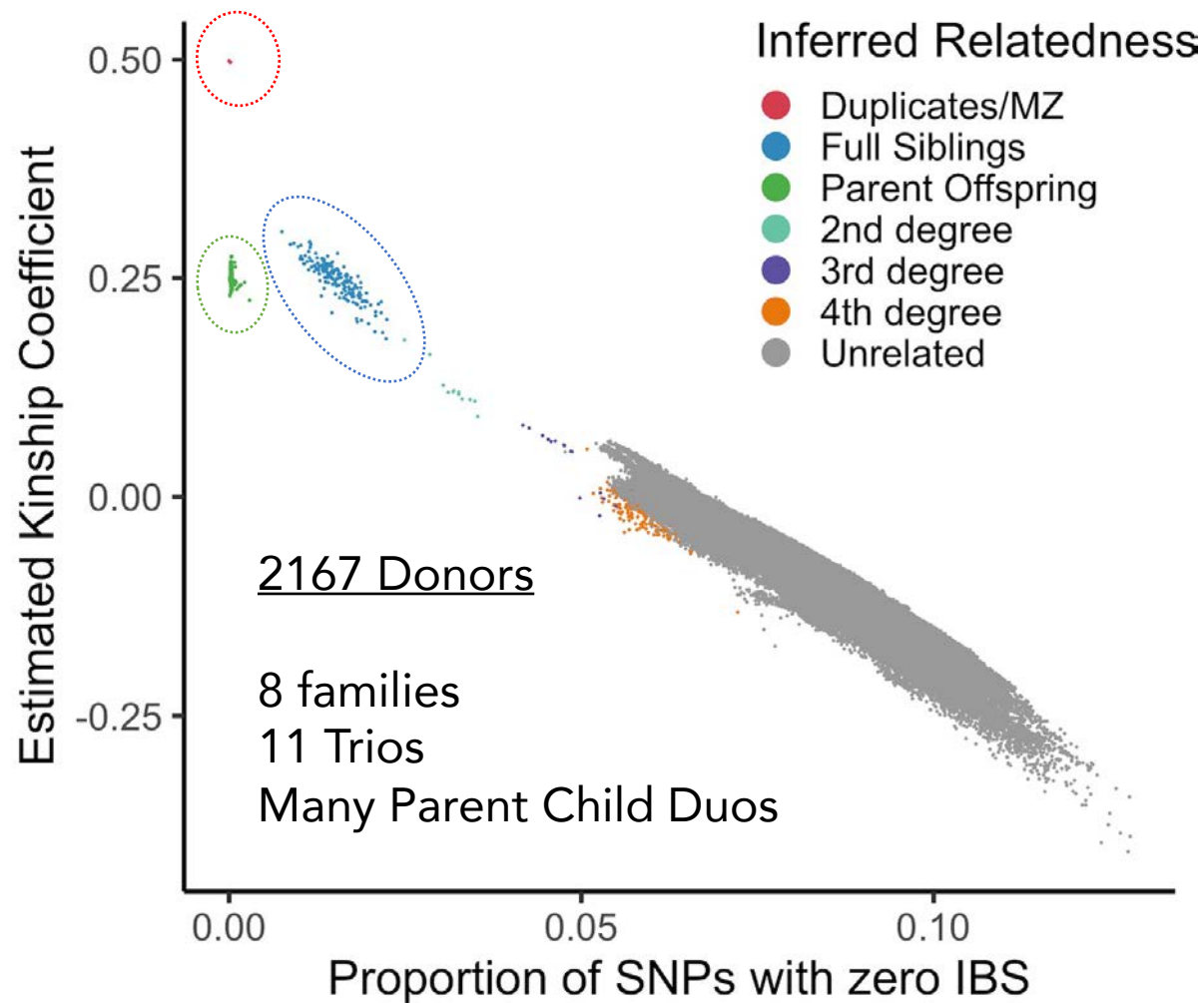
A COLLABORATIVE ENDEAVOR



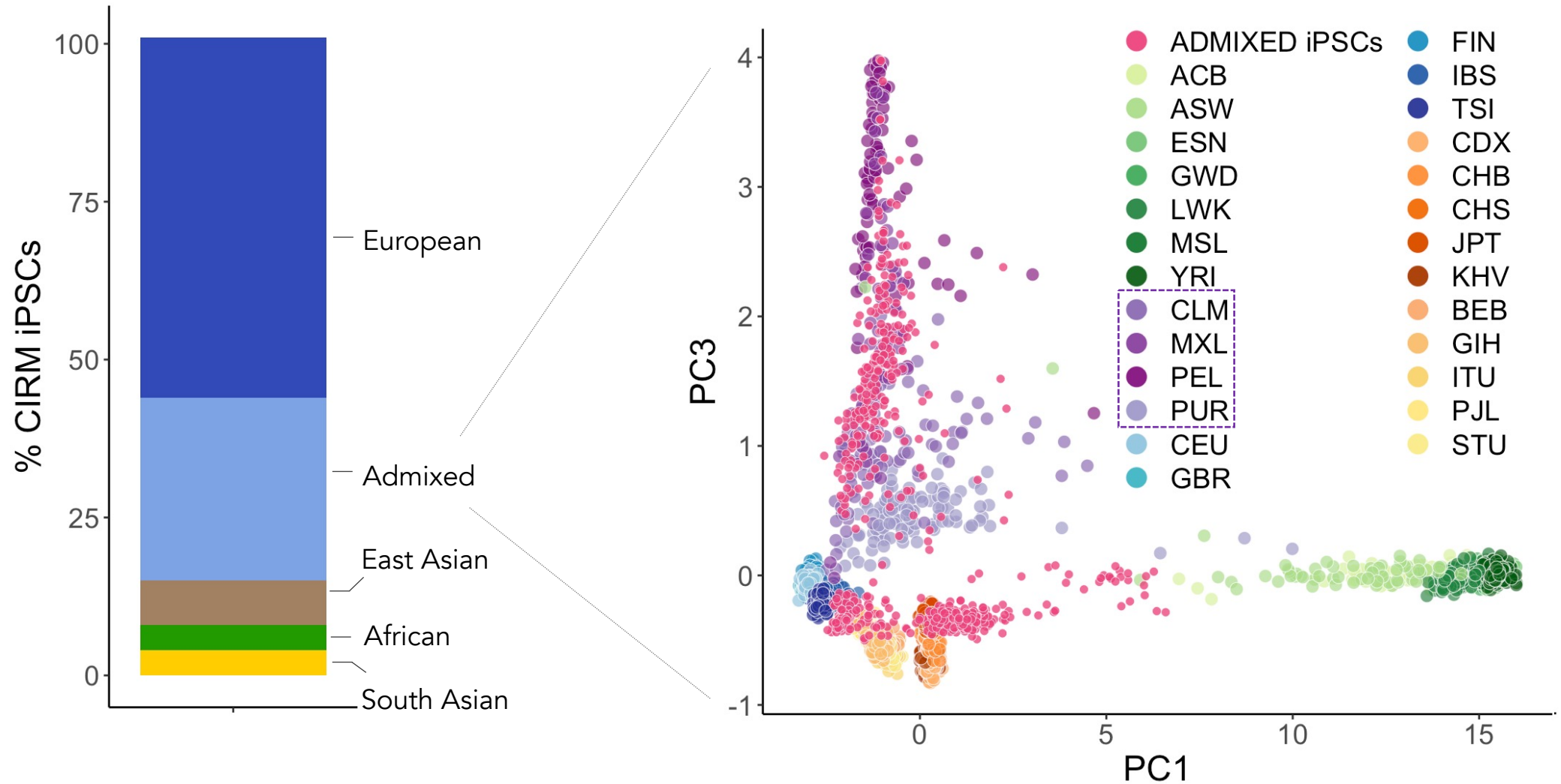
Generating the world's largest induced pluripotent stem cell (iPSC) bank



CIRM iPSCs have Diverse Genetic Ancestries



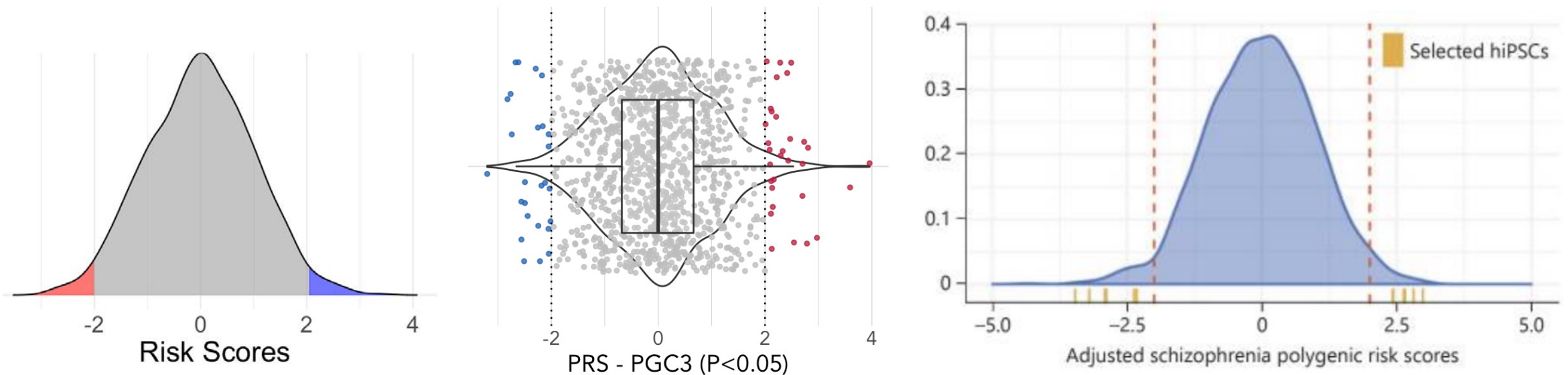
CIRM iPSCs have Diverse Genetic Ancestries



Enabling Rational Selection of Lines for Disease Modeling

The value of genotyped cell lines:

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



Dobrindt et al, 2021

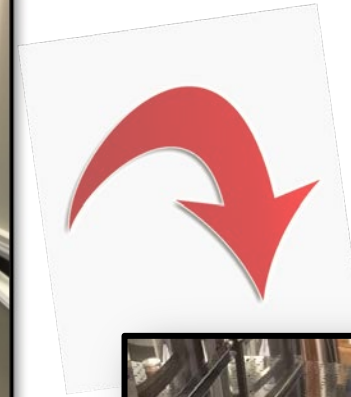
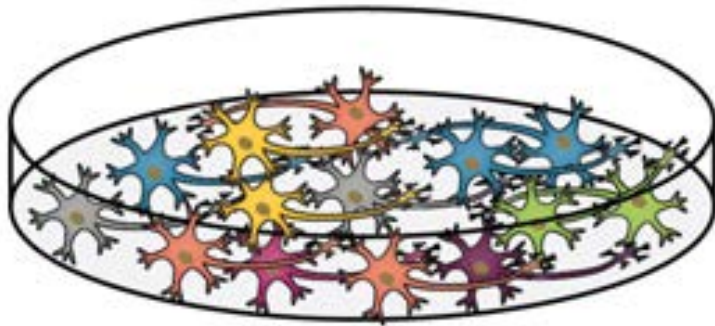
Population-scale stem cell models

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



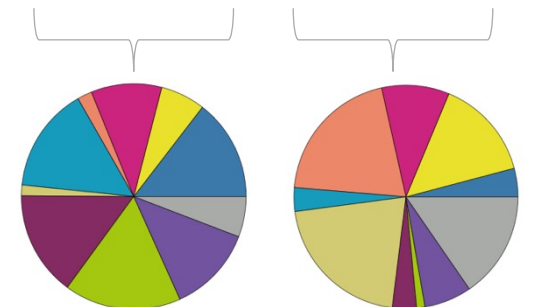
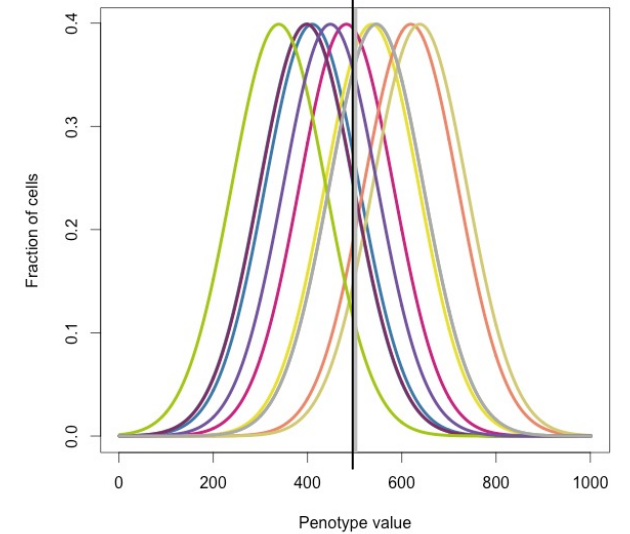
“Census-seq”



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



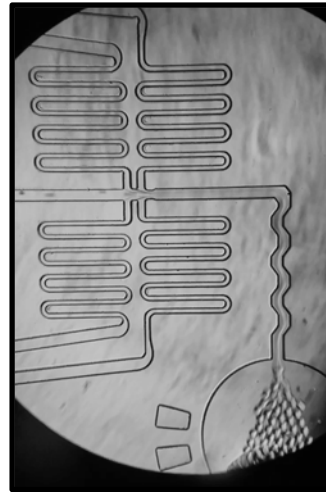
+



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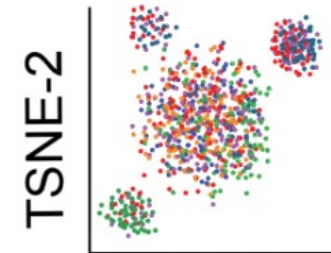
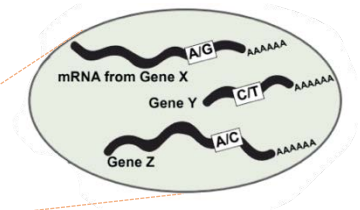
scRNAseq
(10X Genomics)



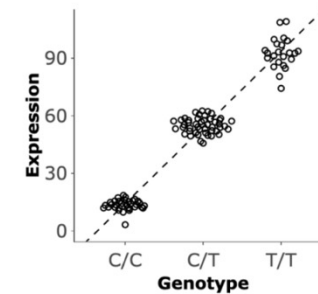
Populations of single-cell
droplets analyzed
simultaneously



Single Donor
Detection



TSNE-1



“Dropulation”


Applications of Pooled Experimental Systems



bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

Mapping genetic effects on cellular phenotypes with “cell villages”

Jana M. Mitchell, James Nemesh, Sulagna Ghosh, Robert E. Handsaker, Curtis J. Mello, Daniel Meyer, Kavya Raghunathan, Heather de Rivera, Matt Tegtmeier, Derek Hawes, Anna Neumann,  Ralda Nehme, Kevin Eggan, Steven A. McCarroll


doi: <https://doi.org/10.1101/2020.06.29.174383>



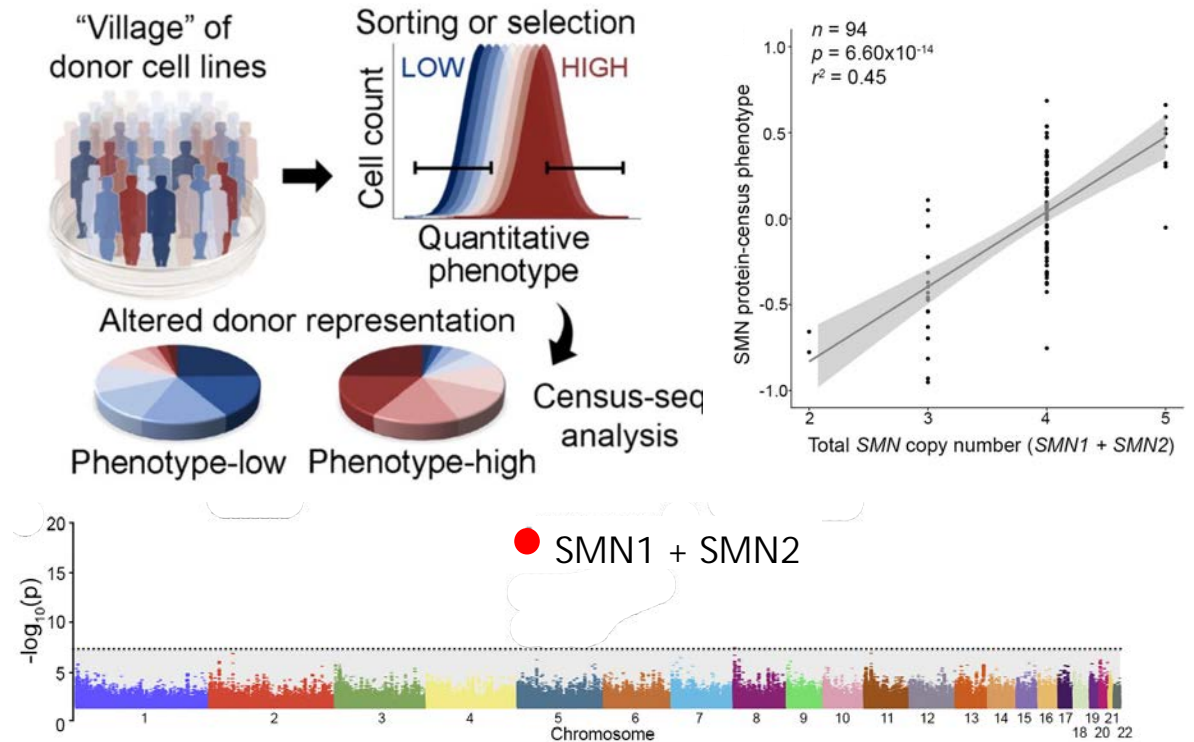
bioRxiv

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 Tegtmeier, 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

Census: GWAS in a dish



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


Applications of Pooled Experimental Systems

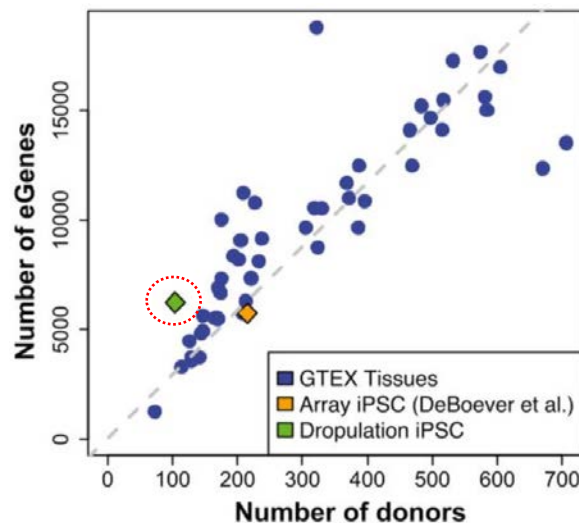


bioRxiv

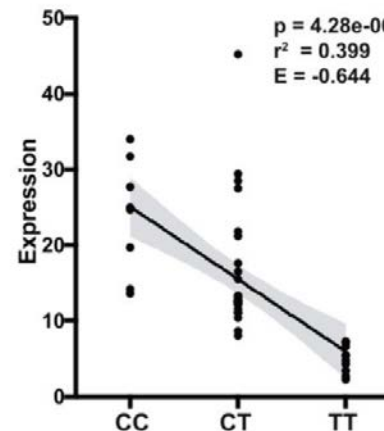
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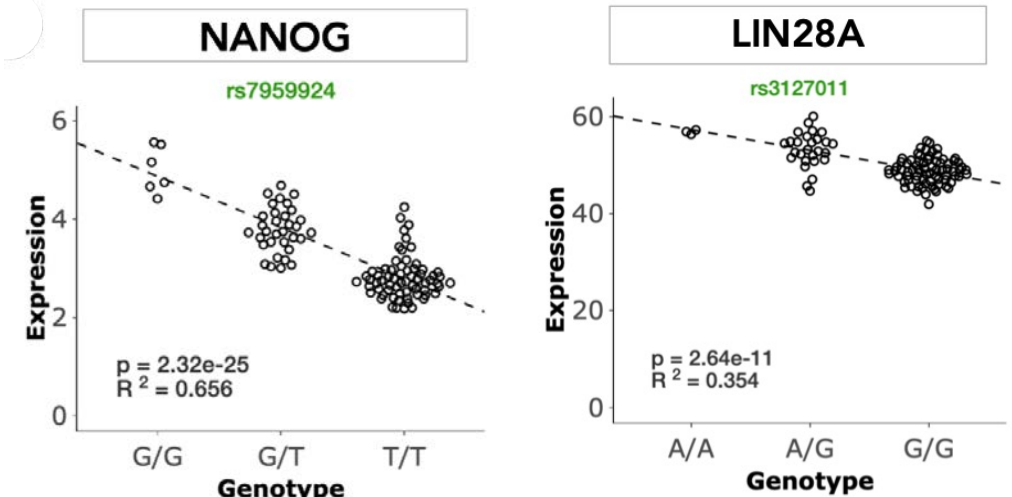
Michael F. Wells, James Nemesh, Sulagna Ghosh, Jana M. Mitchell, Curtis J. Mello, Daniel Meyer, Kavya Raghunathan, Matthew Tegtmeier, Derek Hawes, Anna Neumann, Kathleen A. Worring, Joseph J. Raymond, Sravya Kommineni, Karrie Chan, Daniel Ho, Brant K. Peterson, Federica Piccioni,  Ralda Nehme, Kevin Eggan, Steven A. McCarroll



IFITM3
chr11:320836C>T
SNP rs34481144



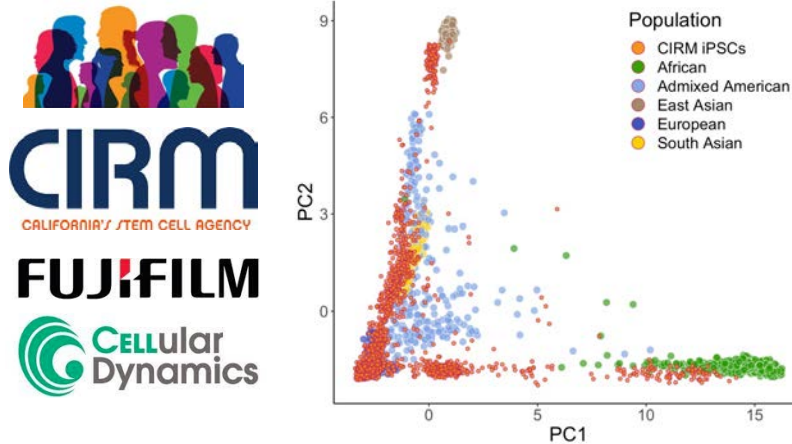
Dropulation: Interindividual Variation



- 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



Linked Donor Metadata

CIRM iPSC Lines Search & Order

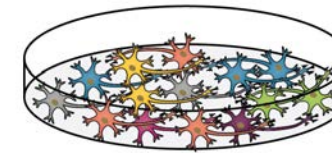
[Hide Filters](#) [Clear all Filters](#) [Instructions](#)

Disease: All Race: All Age at Sampling: 0 to 110
Disease Status: All Ethnicity: All Age at Diagnosis: 0 to 110
Family Status: All Sex: All Age at Onset: 0 to 110

1 to 50 of 1,554 samples Show 50 rows Column visibility Copy CSV Excel PDF Print

Show Clinical	Show Related	Catalog ID	Description	Rel. to Proband	Sampling Age	Sex	Race	Affected	Diagnosis Age	Year of Birth	Onset Age	Available Clones
		CW60261	EPILEPSY	proband	1 Yr.	Female	Caucasian	Yes		2013		B/C
		CW60354	INTELLECTUAL DISABILITY	proband	1 Yr.	Female	Other	Yes		2012		E

Cell Villages



eQTL discovery and
colocalization with risk variants

Cellular and Genetic
Perturbations

Drug Screens and
Pharmacogenomic Profiling