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San Francisco

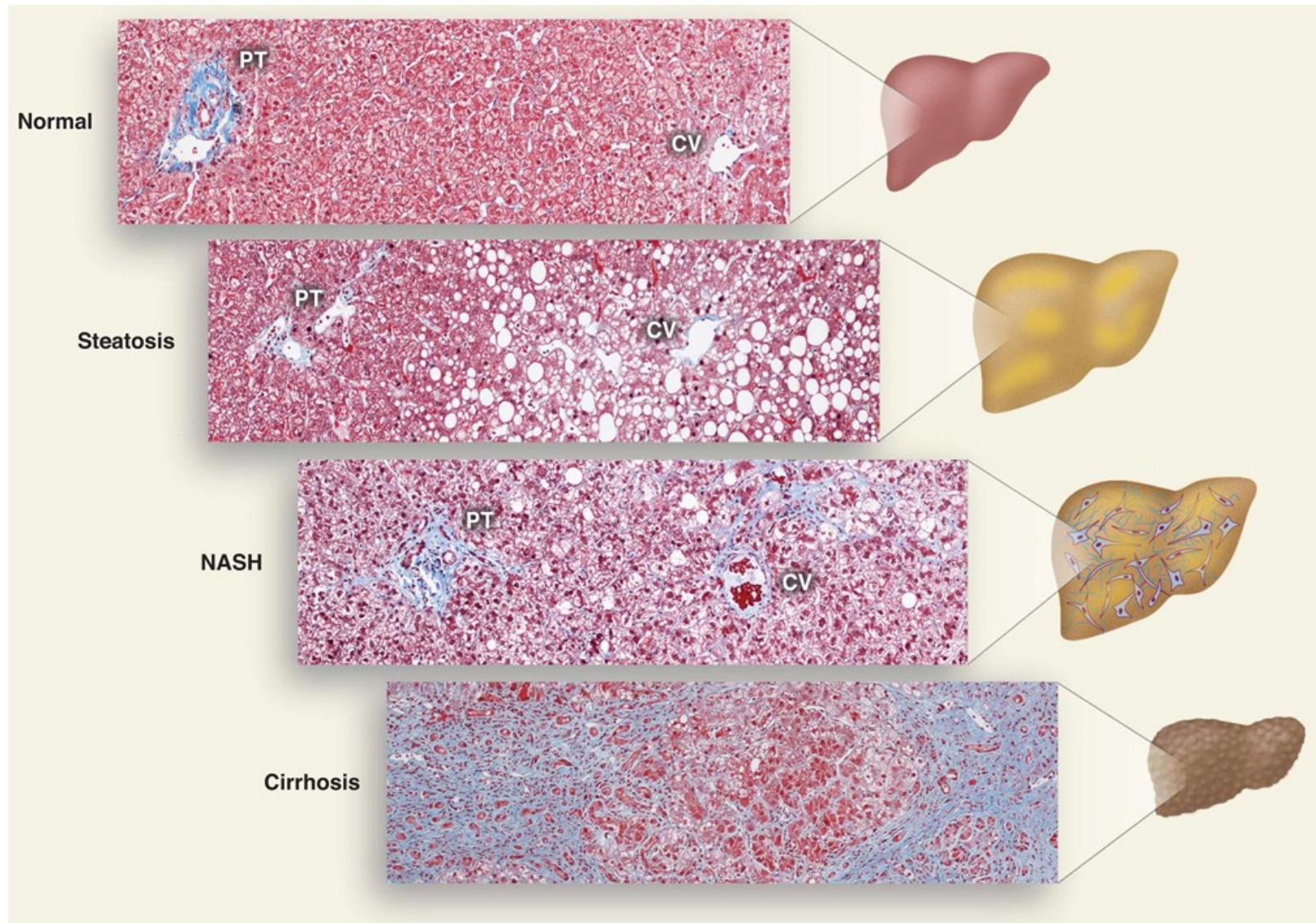


CIRM hiPSC Repository: NAFLD Lines for Disease Modeling

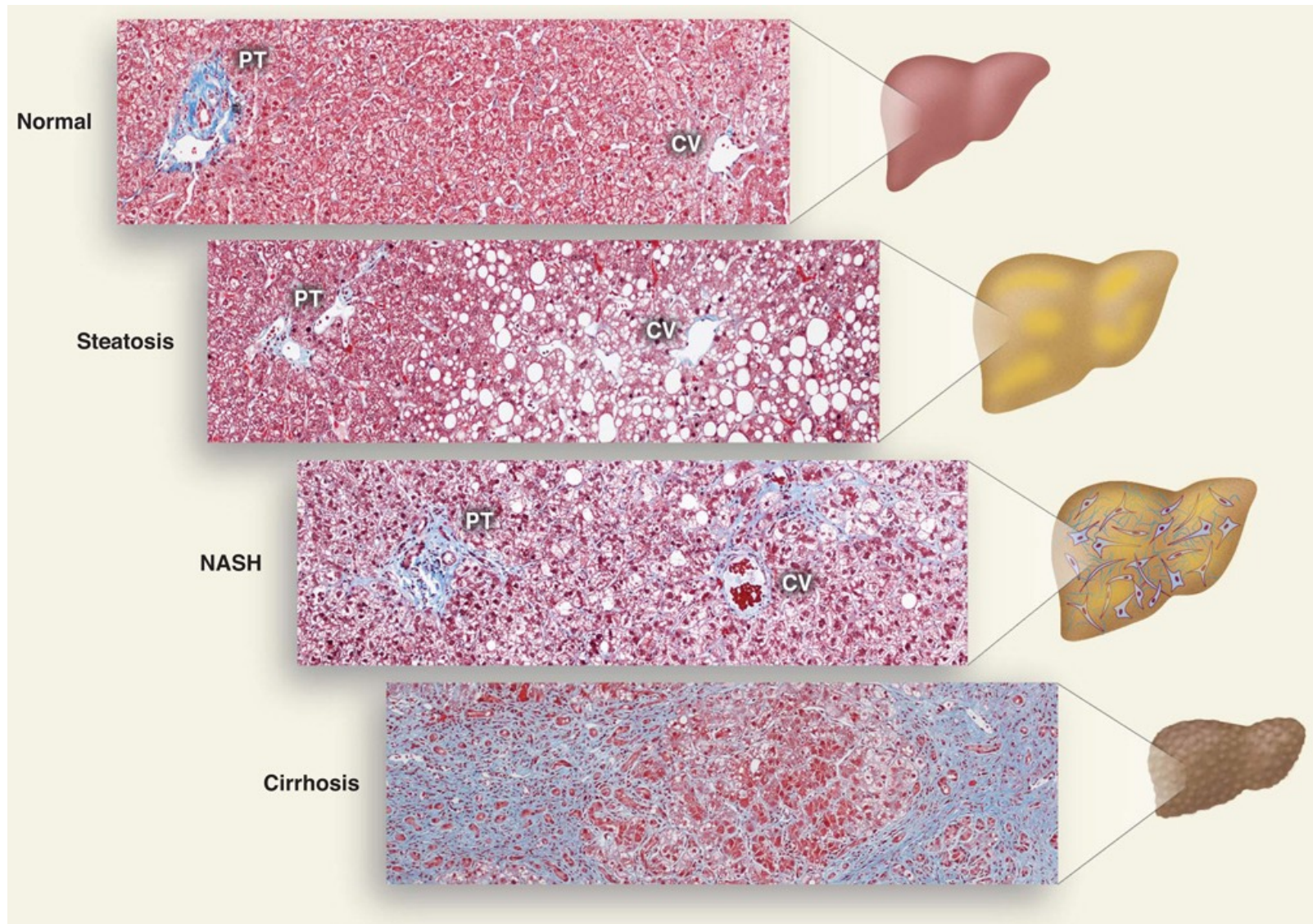
Jacquelyn Maher, MD

University of California, San Francisco

Nonalcoholic fatty liver disease (NAFLD)



Nonalcoholic fatty liver disease (NAFLD)



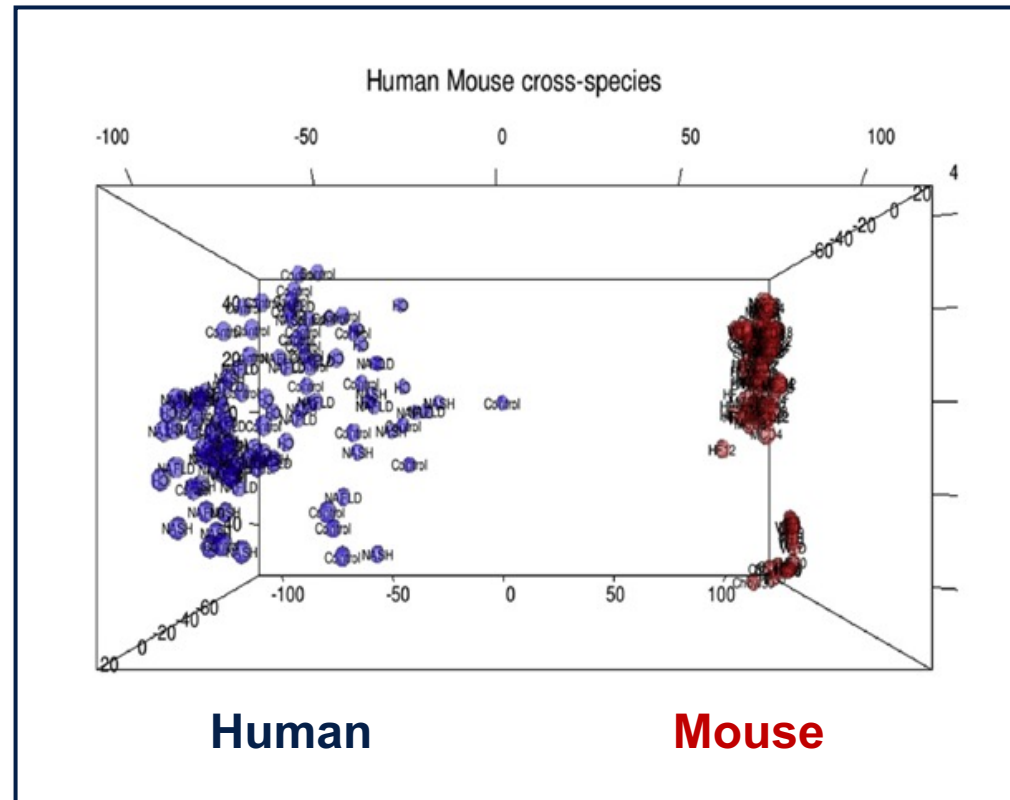
Prevalence

25%

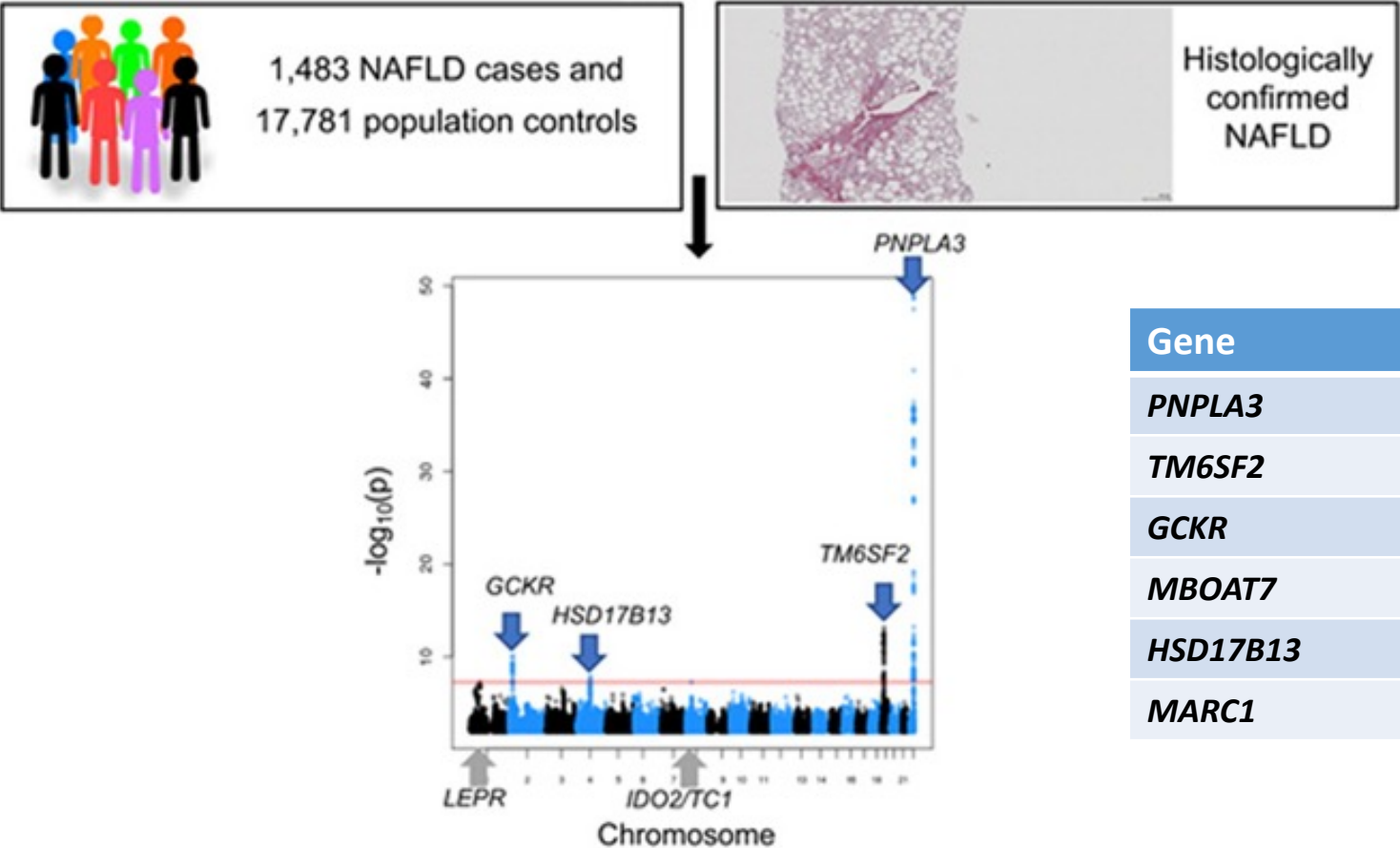
6%

2%

Animal models of NAFLD are imperfect mimics of human disease

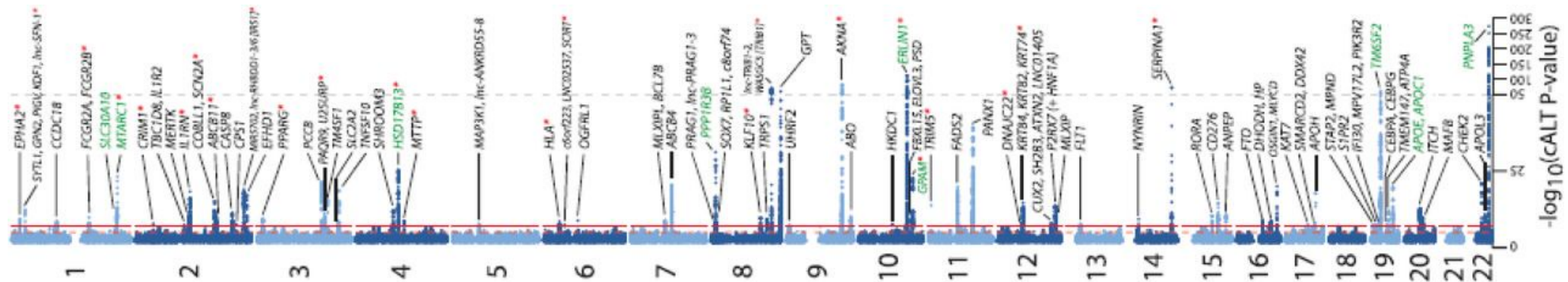


GWAS have uncovered several genetic risk factors for NAFLD

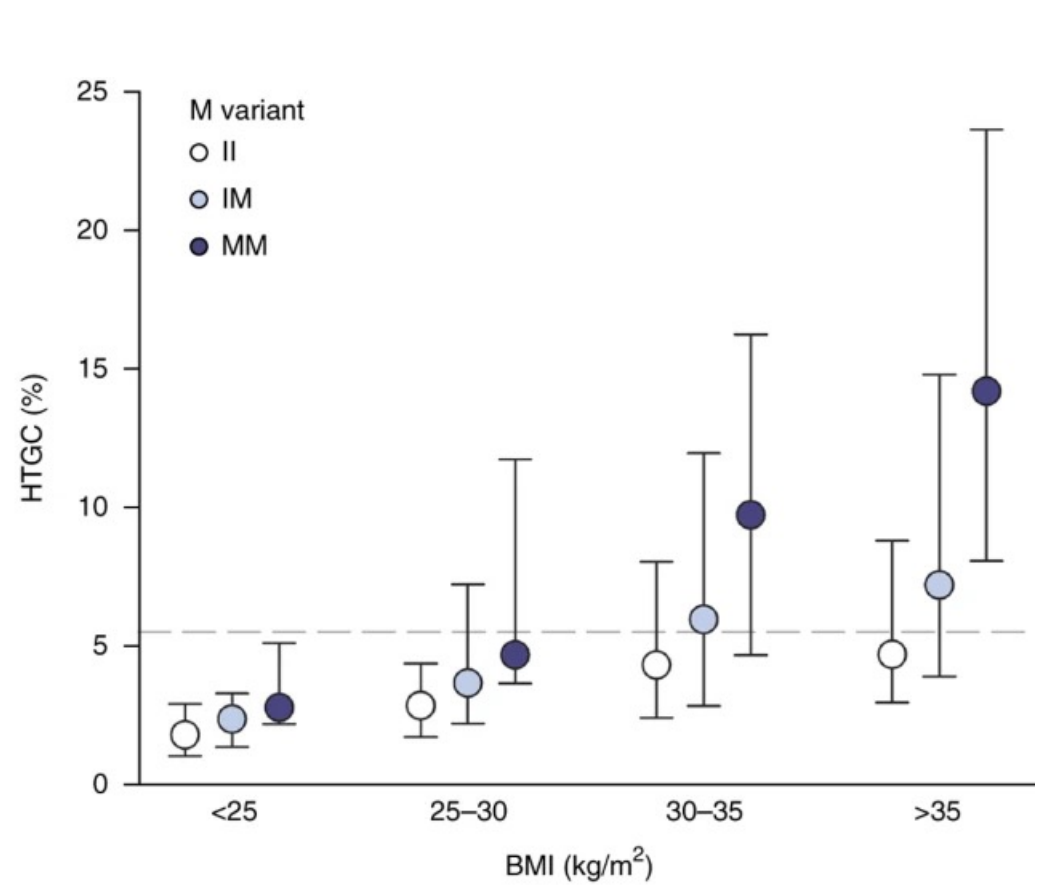


Gene	Association
<i>PNPLA3</i>	Disease
<i>TM6SF2</i>	Disease
<i>GCKR</i>	Disease
<i>MBOAT7</i>	Disease
<i>HSD17B13</i>	Protection
<i>MARC1</i>	Protection

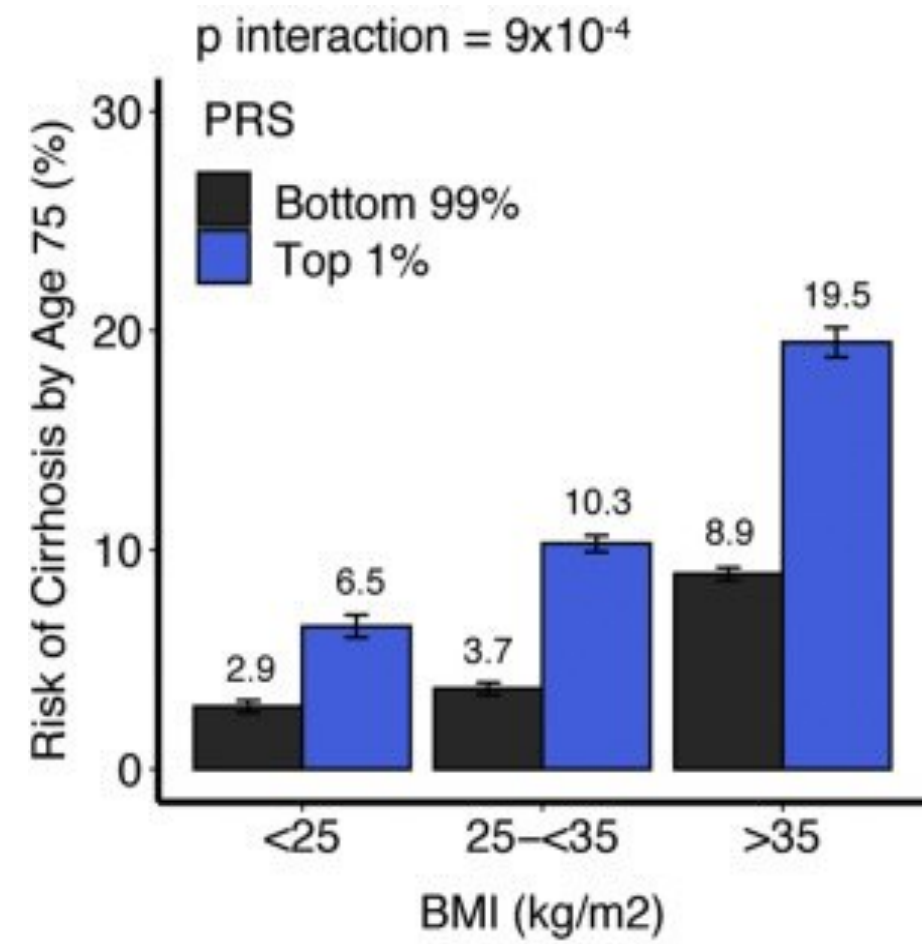
- **90,408 cases and 128,187 controls**
- **77 loci met statistical significance**
- **25 without prior link to NAFLD**
- **Replication cohorts validated 17 SNPs**



Genetic risk alone is not predictive of disease



Liver fat content as a function of PNPLA3 genotype and BMI



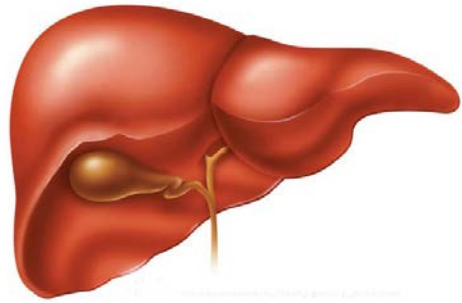
Cirrhosis as function of weighted 12-gene score and BMI

CIRM IT1-06563 - Tissue Collection for Disease Modeling

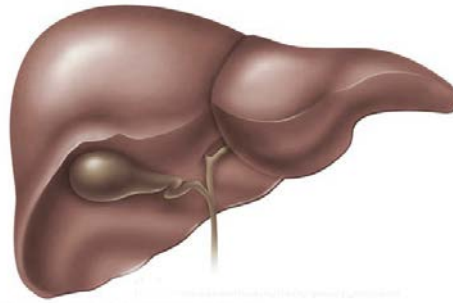
- **Program launched 2013: multiple diseases**
- **Liver disease patients recruited 2014-2016**
- **Limited to 20 healthy controls, suitable for multiple disease cohorts**

CIRM IT1-06563 - Tissue Collection for Disease Modeling

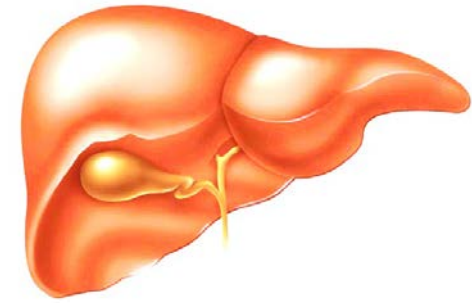
- Program launched 2013: multiple diseases
- Liver disease patients recruited 2014-2016
- Limited to 20 healthy controls, suitable for multiple disease cohorts
- PBMC or skin biopsy collected from 184 subjects; 78% available at Fuji



Normal (19)
Fuji (16)



Hepatitis C (117)
Fuji (91)



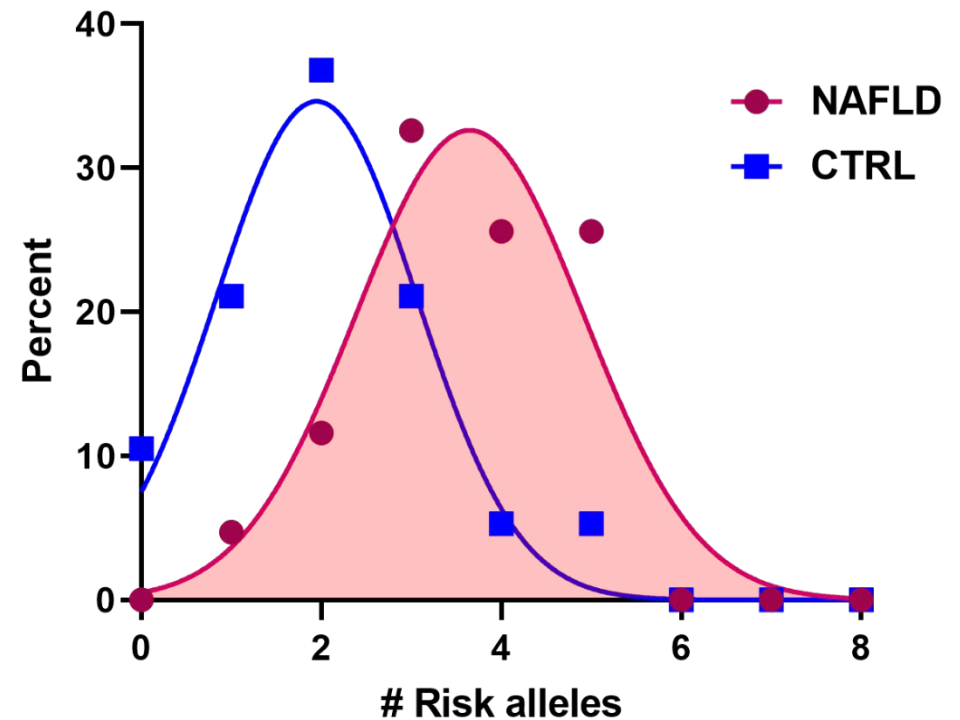
NAFLD (48)
Fuji (38)

Details of the NAFLD cohort

NAFLD iPSC Cohort at UCSF

- 44 NAFLD iPSC lines
- Biopsy-proven NAFLD diagnosis
- Annotated clinical data
- Enriched in Hispanics (67%)
- High frequency of variant *PNPLA3*
 - Any *PNPLA3* risk allele 98%
 - Homozygous *PNPLA3* risk allele 58%
- 19 control iPSC lines

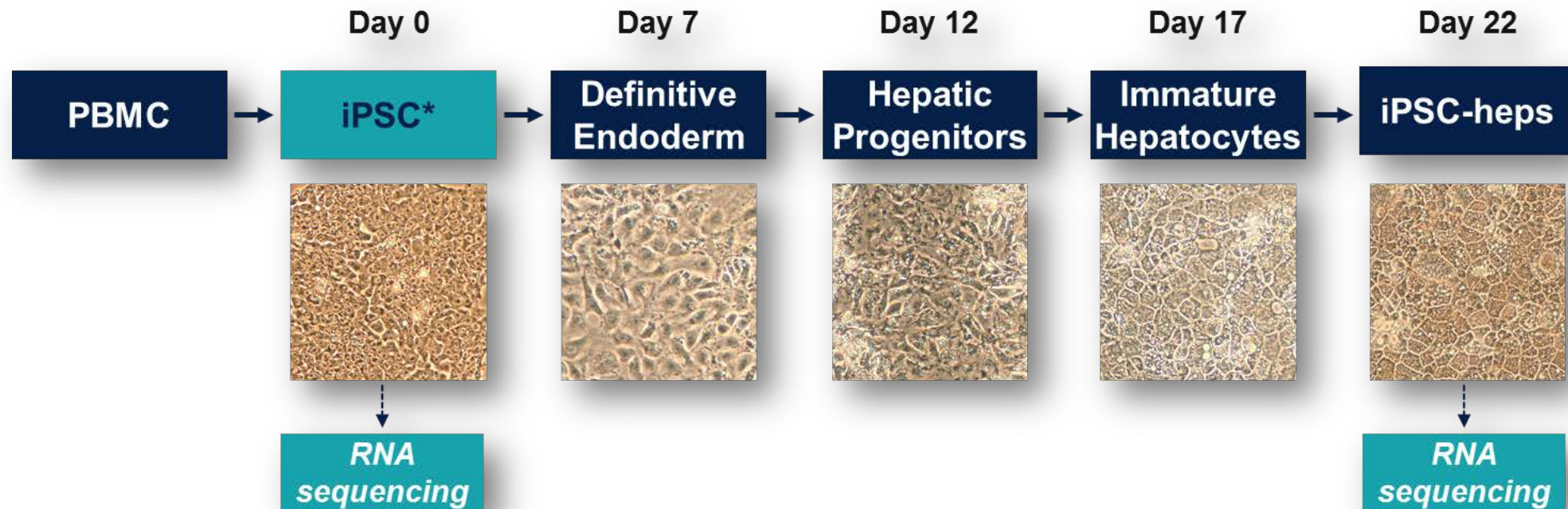
Distribution of NAFLD risk alleles



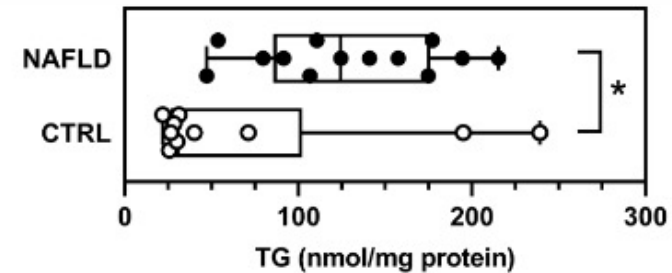
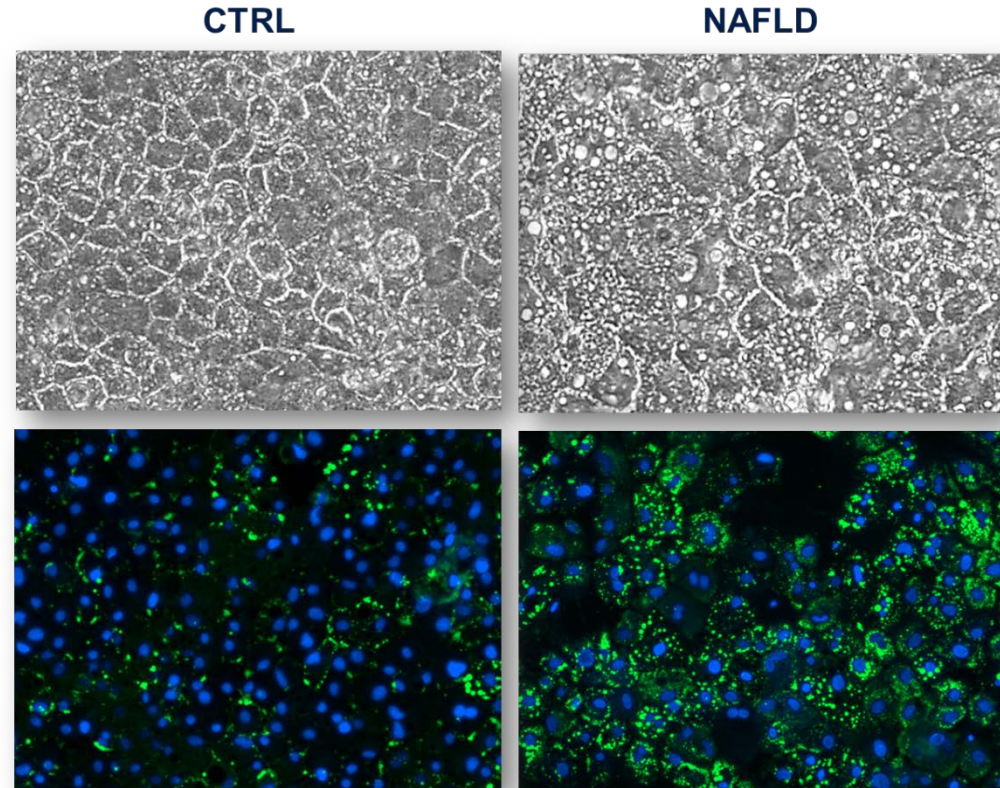
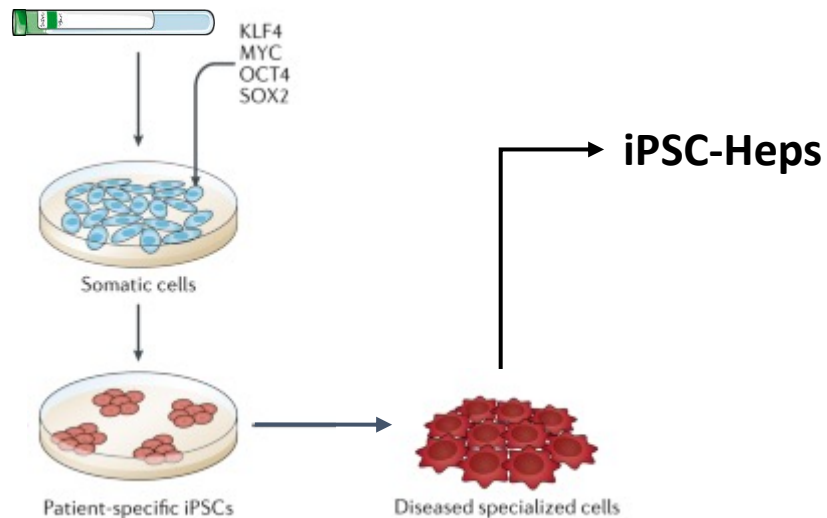
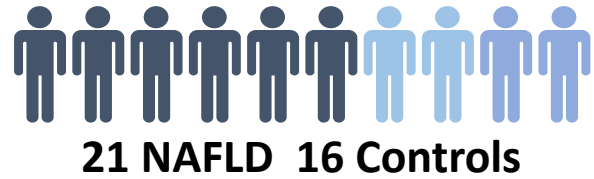
Four established variants: PNPLA3, TM6SF2, GCKR, MBOAT7

Population-based investigation of NAFLD vs. control iPSC-Heps


21 NAFLD (14 with advanced fibrosis)
16 control

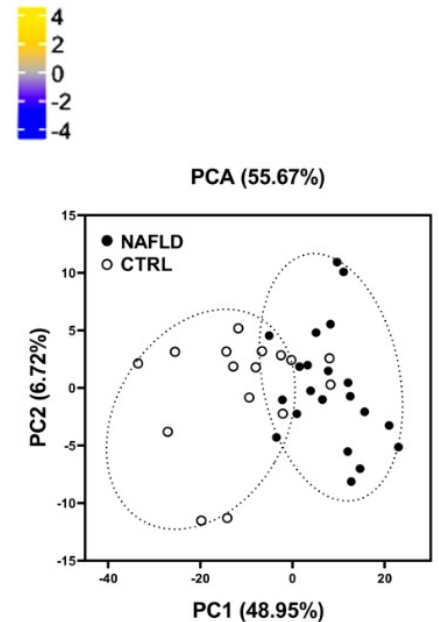
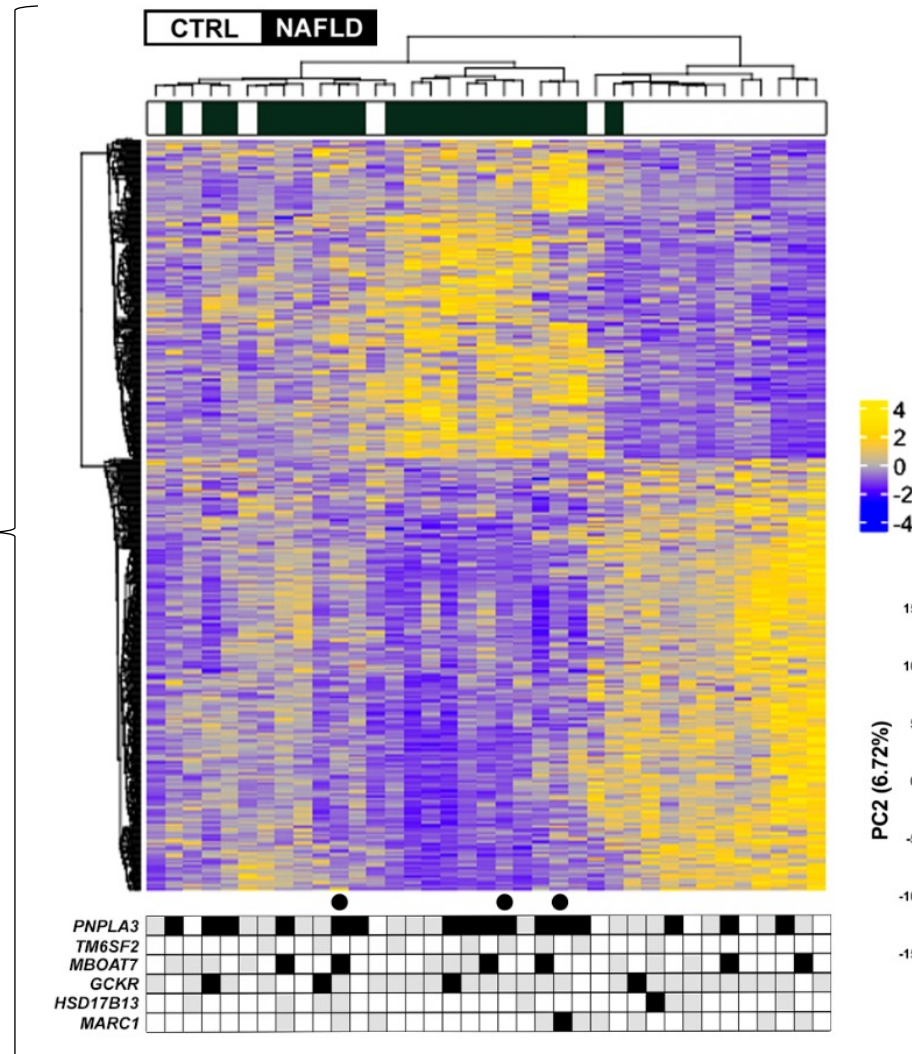
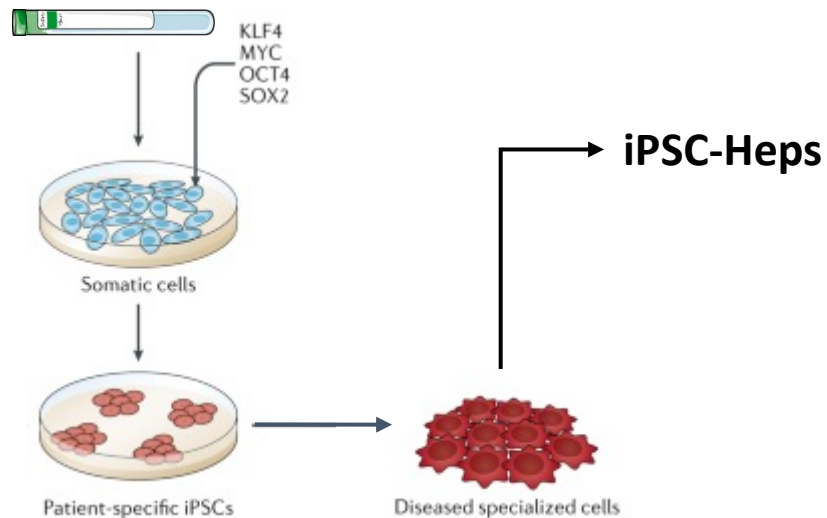


NAFLD iPSC-Heps develop spontaneous steatosis



NAFLD iPSC-Heps display a disease-specific gene signature


21 NAFLD 16 Controls



Opportunities and challenges

- **Opportunities**

- Generate multicellular NAFLD cultures to investigate contribution of other cell types
- CRISPR gene editing to correct or introduce known gene variants
- Uncover new risk variants if (when) disease phenotype persists after gene correction
- Expand cohort: compare iPSC-Hep phenotypes in subjects with similar disease, but from diverse backgrounds

- **Challenges**

- Need controls matched to NAFLD population (ethnicity, gender, weight, genotype)
- Need comparisons between “simple steatosis” and more advanced disease
- Need larger N for NAFLD and controls (ethnic, gender diversity; disease severity)
- Population-based iPSC research is expensive, high-risk; NIH apprehensive



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