Clinical Utility of Pharmacogenomic Findings: Beyond Single Variants

Hae Kyung Im, PhD

THE UNIVERSITY OF CHICAGO

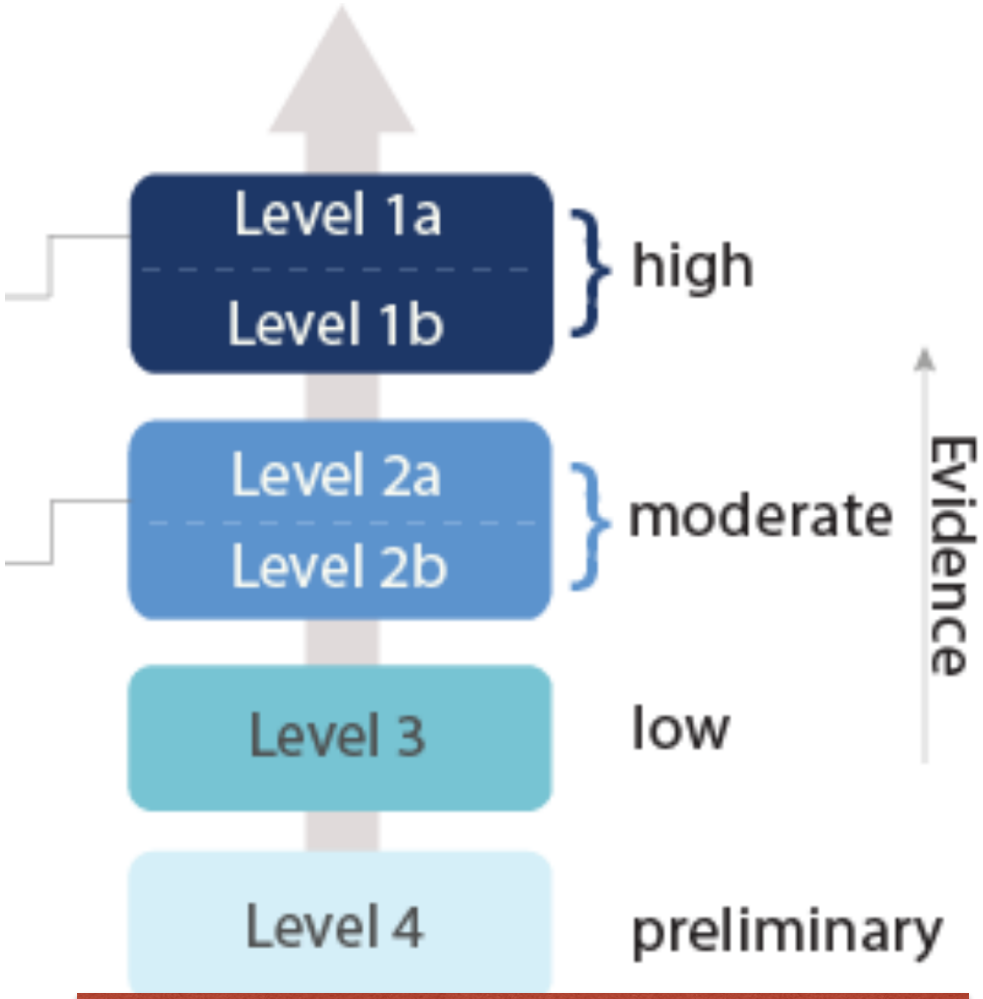
Successes and Challenges of Genome Studies

- GWAS/Sequencing
  - 10K robustly associated genetic variants
- New insights into biology of many traits
- Biological understanding is still lacking

Pharmacogenomic Findings

Evidence Level	Counts	%
1a	40	3
1b	17	1
2a	96	6
2b	74	5
3	1175	76
4	145	9
Total	1547	100

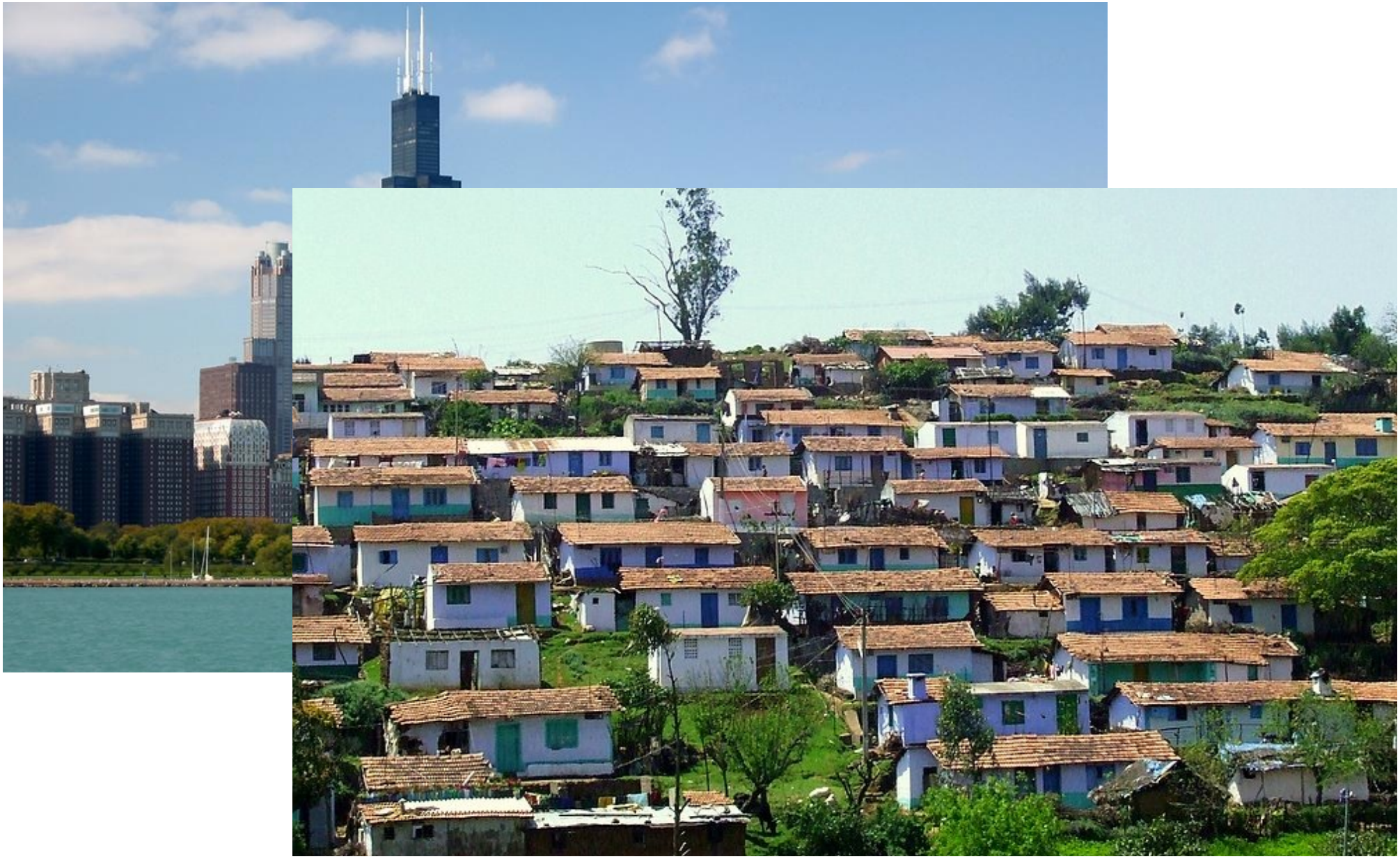
https://www.pharmgkb.org/



Only Level 1a finding have clinical guidelines

Genetic Architecture of Complex Traits

Genetic Architecture of Complex Traits



Genetic Architecture of Complex Traits

Single Variants Not Relevant for Highly Polygenic Traits

Challenges of Pharmacogenomic Studies

- Smaller sample size
- Even more important to integrate prior data
- Integrate other functional data
- Heritability estimates are harder
  - Limited family data
  - Usually samples greater than 1K are needed for GCTA

Bevacizumab Induced Hypertension

- Bevacizumab is a humanized monoclonal antibody that inhibits VEGF induced angiogenesis
- Hypertension is a common adverse event to bevacizumab treatment
- The incidence of hypertension with bevacizumab is 20-30%, while grade 3 or greater hypertension occurs in only 10-15% of patients.

Keston Aquino Michaels

Bevacizumab Trials

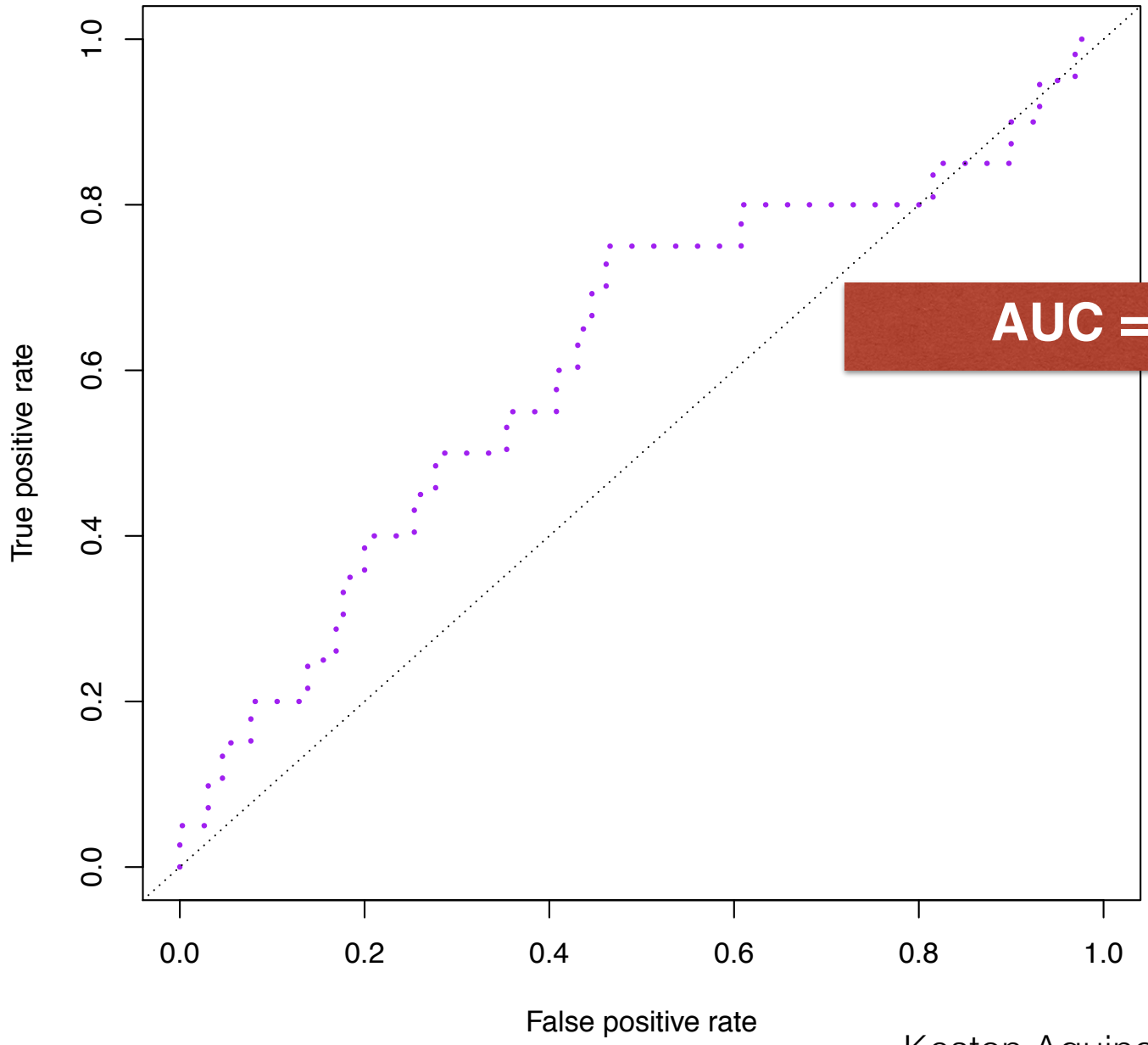
- CALGB 90401
  - a randomized double-blinded placebo controlled phase III trial comparing docetaxel and prednisone with and without bevacizumab in men with hormone refractory prostate cancer
  - n = 664 (with genotype data after QC)
  - PI: Howard McLeod
- CALGB 80303
  - a randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo in patients with advanced pancreatic cancer
  - n = 152 (with genotype data after QC)
  - PI: Federico Innocenti

Bevacizumab Induced Hypertension

- Is primary hypertension risk score predictive of bevacizumab induced hypertension
  - Hypertension results from Cross Consortia Pleiotropy group (n~20K)
- Can we predict drug induced hypertension?
  - 90401 training set
  - 80303 test set
- Dissection of Hypertension

Keston Aquino Michaels & Heather Wheeler

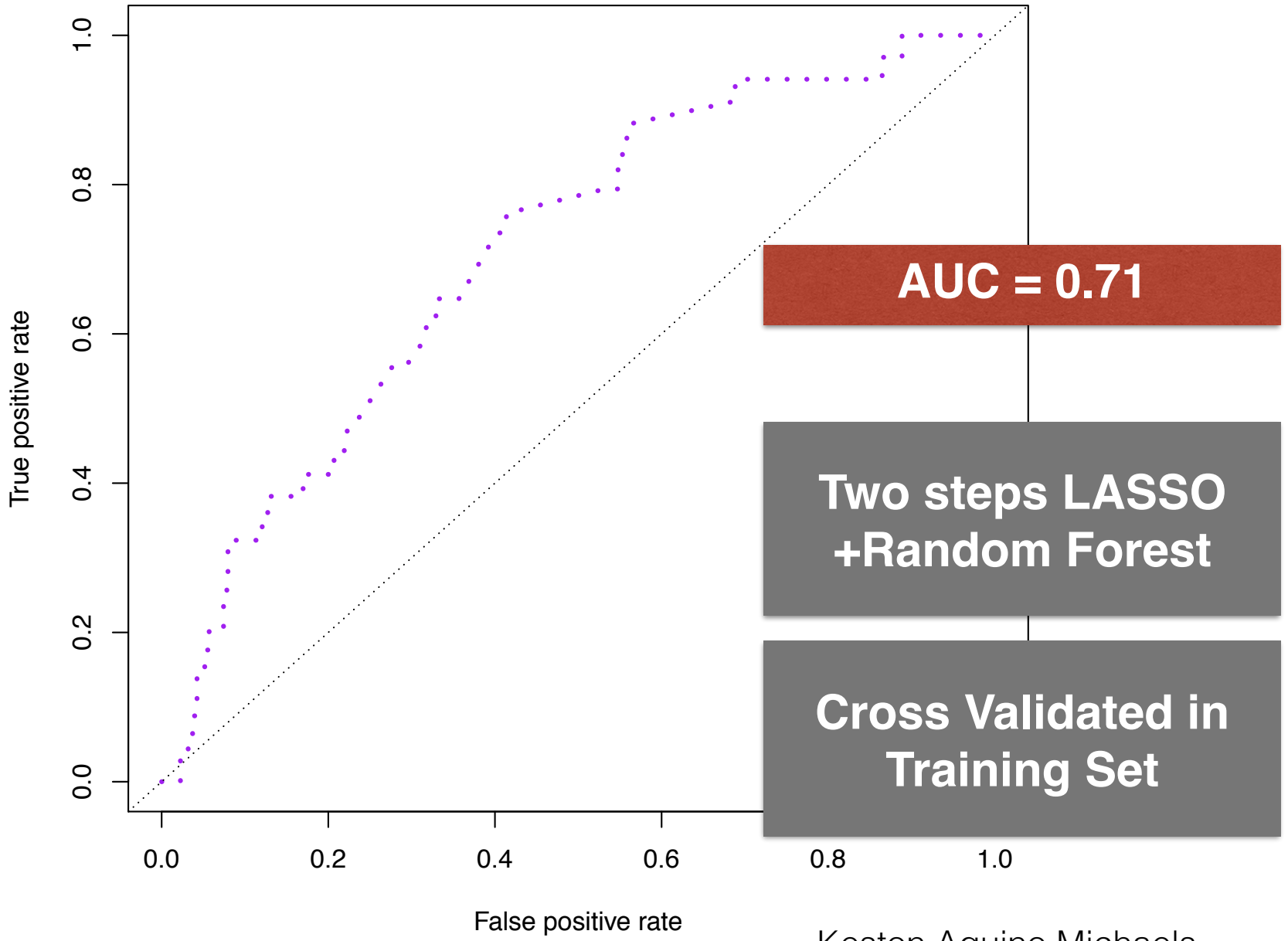
Primary Hypertension score Predicts Bev-induced HT



AUC = 0.62

Keston Aquino Michaels

Bev-Hypertension Predicted Within Study



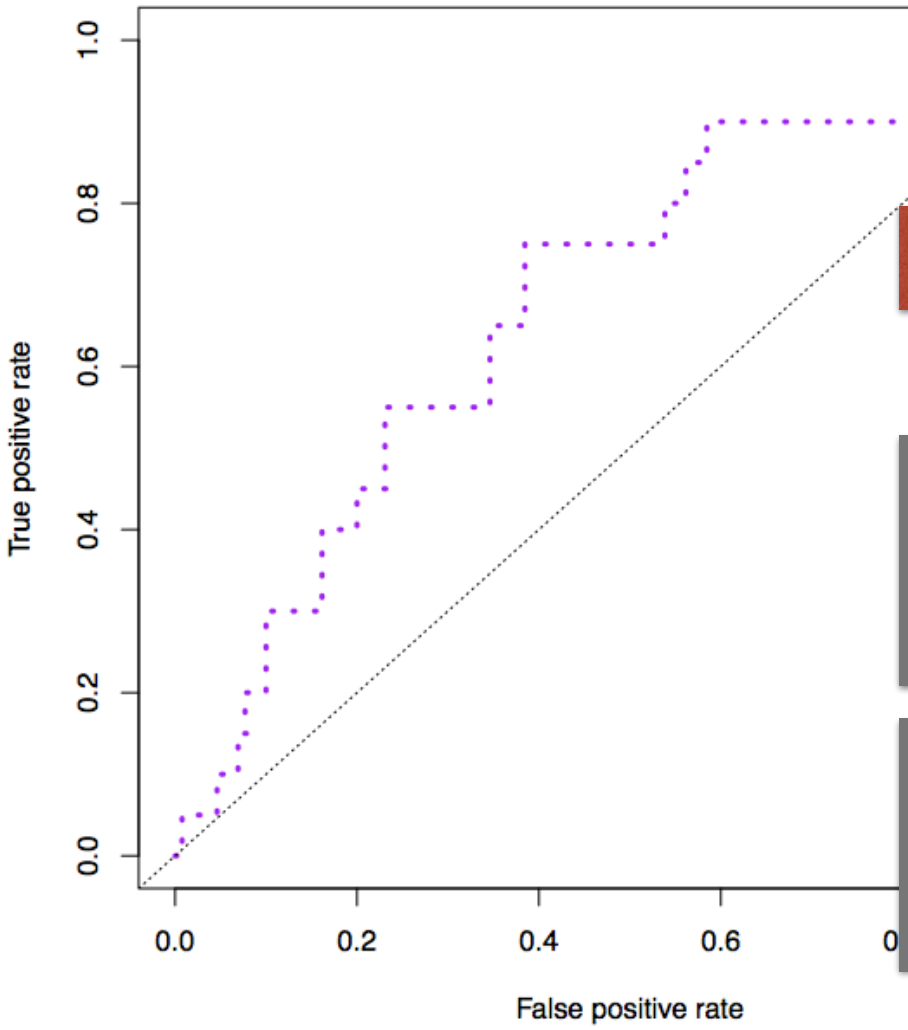
AUC = 0.71

Two steps LASSO +Random Forest

Cross Validated in Training Set

Keston Aquino Michaels

Bev-Hypertension Predicted in Independent Study



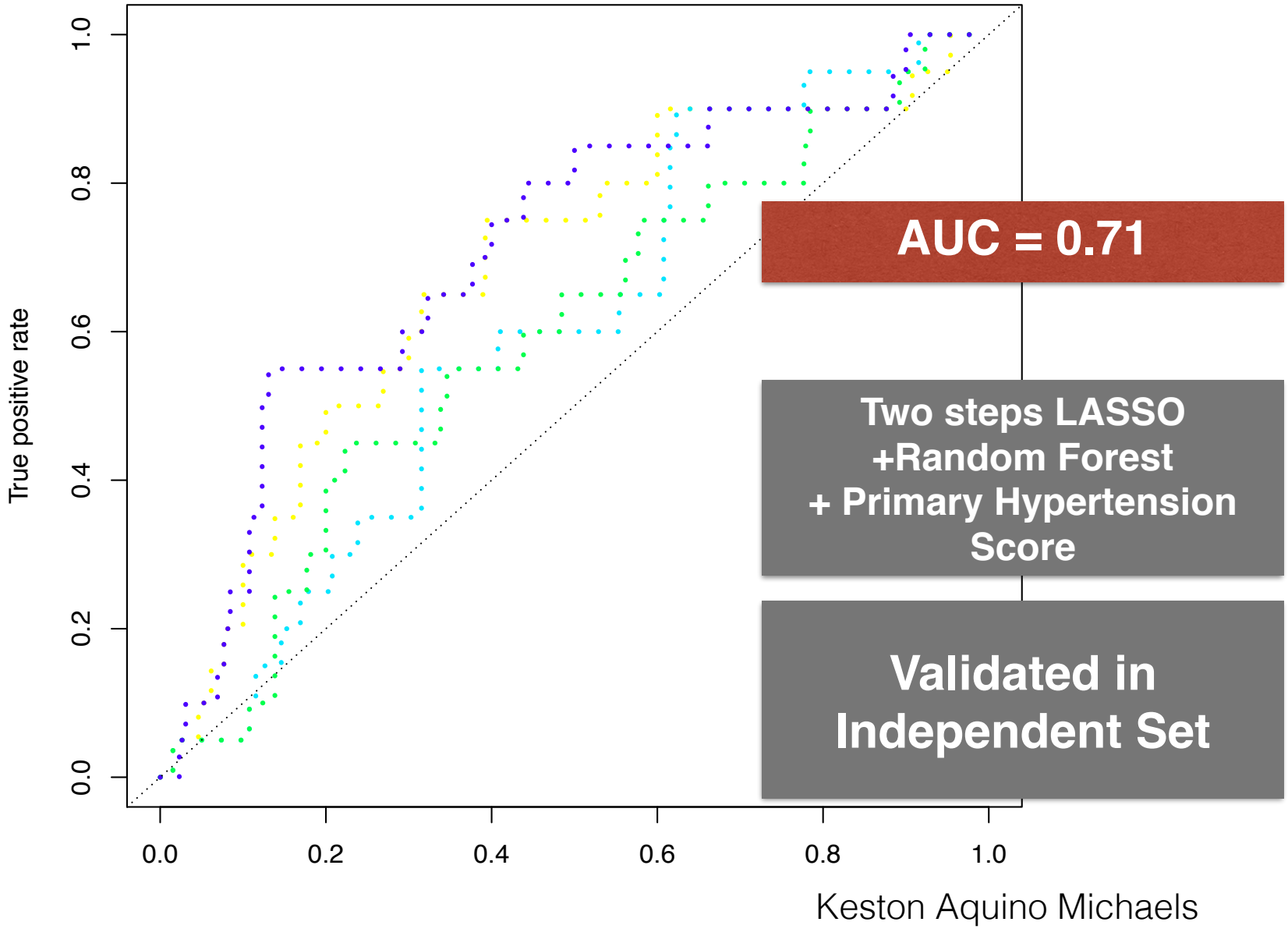
AUC = 0.68

Two steps LASSO +Random Forest

Validated in Independent Set AUC down to 0.68 from 0.71

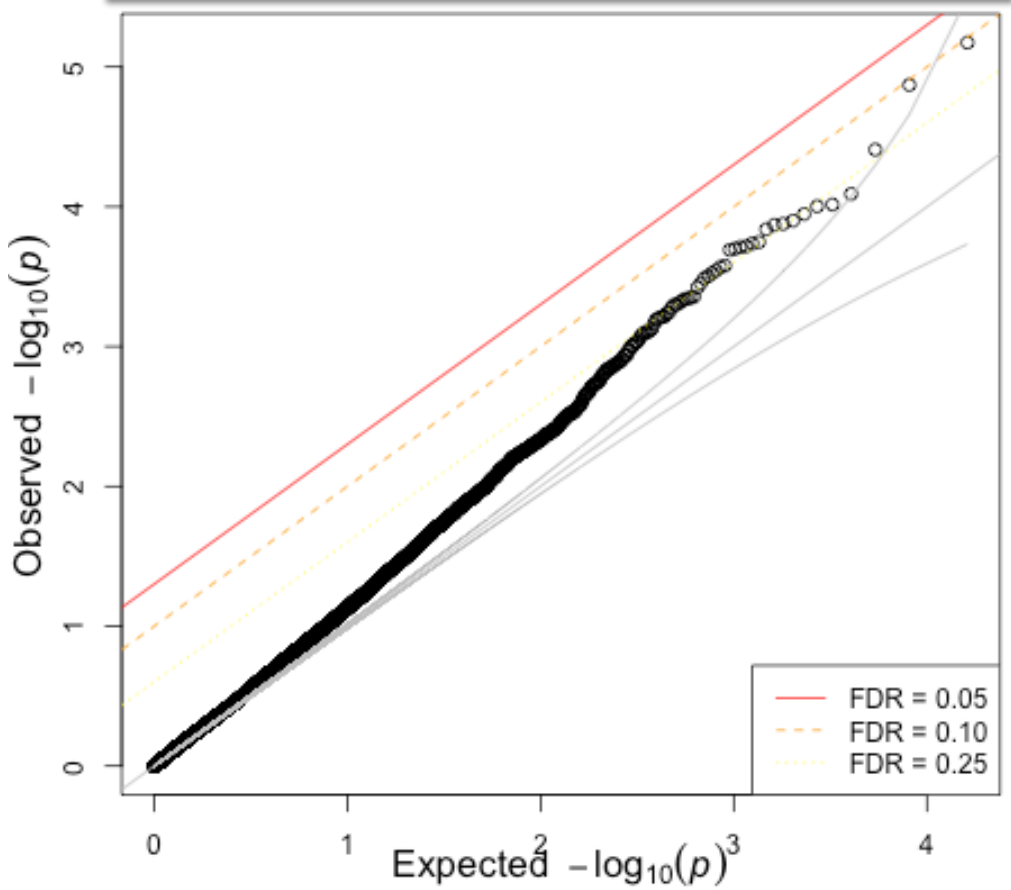
Keston Aquino Michaels

Bev-Hypertension Predicted in Independent Study

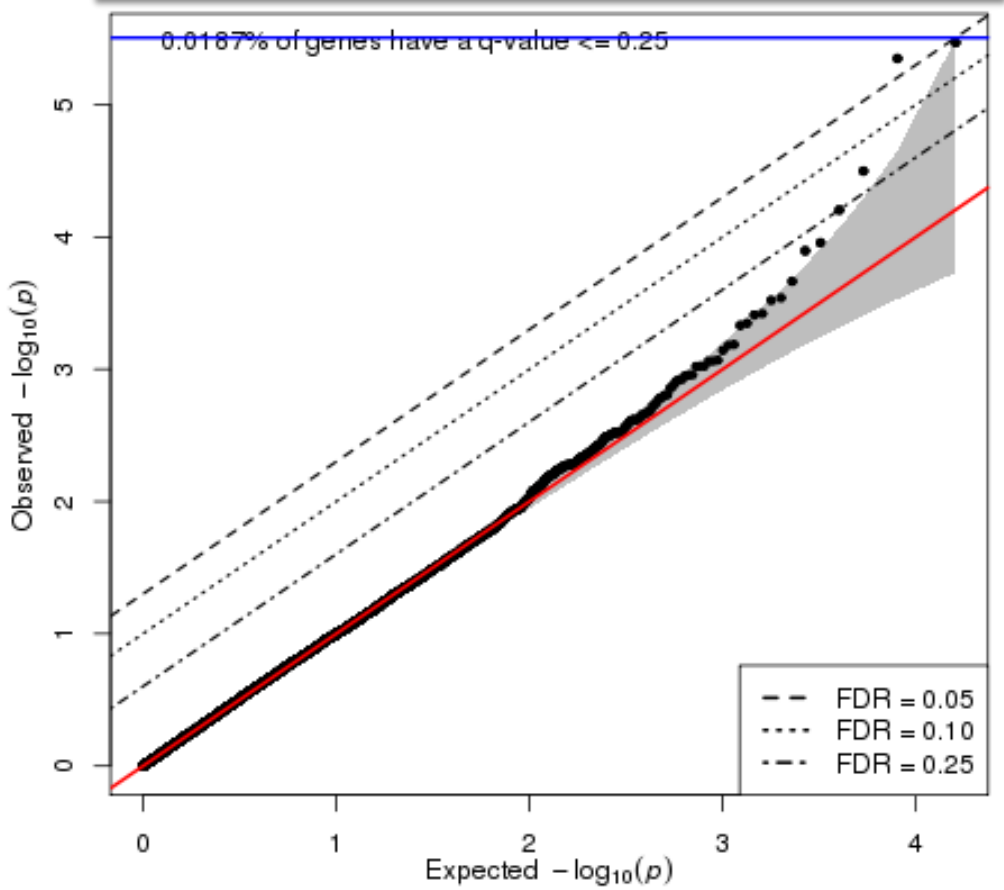


PrediXcan Results Primary and Bev-Hypertension

WTCCC Hypertension



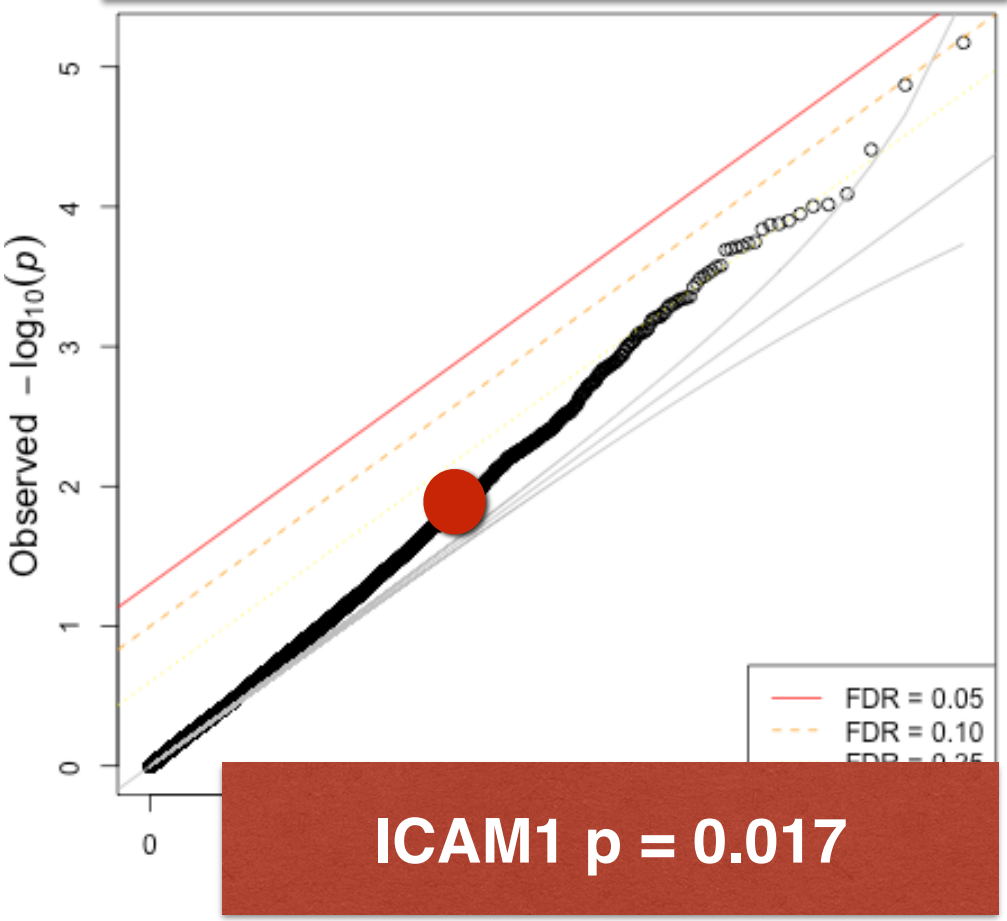
Bevacizumab Hypertension



Heather Wheeler

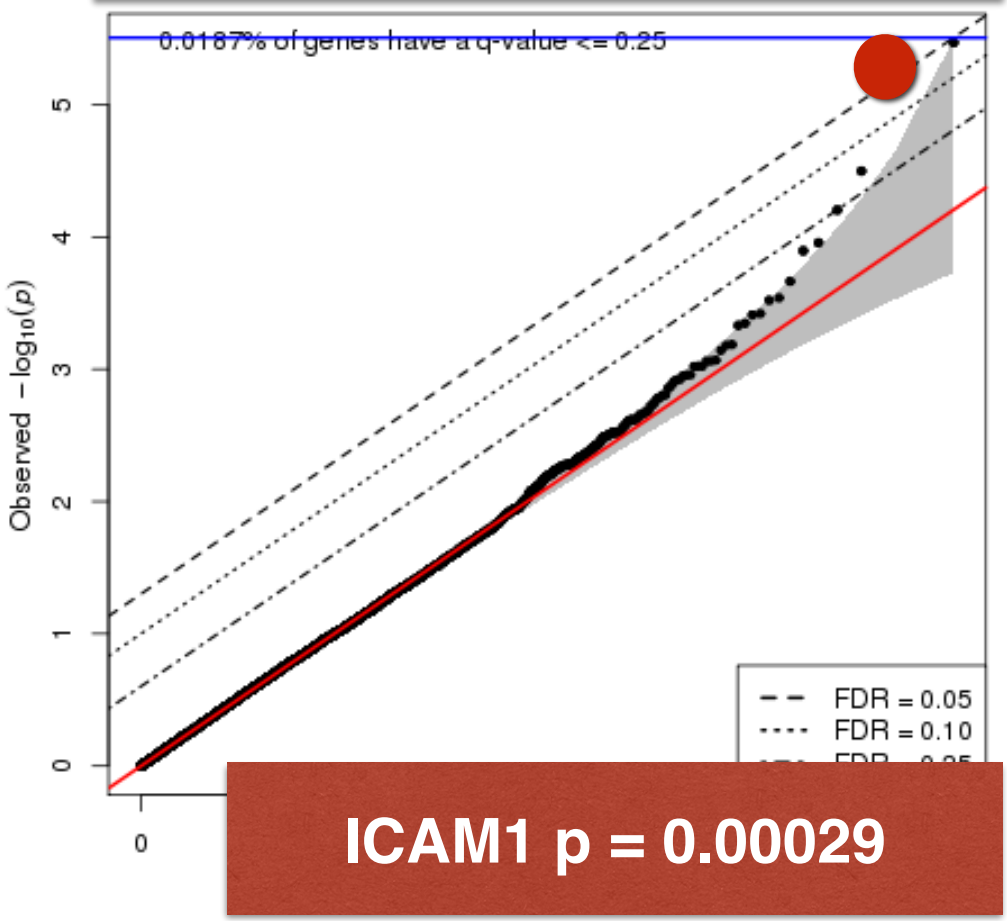
PrediXcan Results Primary and Bev-Hypertension

WTCCC Hypertension



ICAM1 p = 0.017

Bevacizumab Hypertension



ICAM1 p = 0.00029

Heather Wheeler

Hypertension and ICAM1

- Genetically predicted expression levels of ICAM1 was associated with
  - Primary hypertension WTCCC
  - Bevacizumab induced hypertension CALGB 90401
- Genetically predicted serum levels of ICAM1 was associated with
  - Bev induced hypertension CALGB 90401
- Increased levels of ICAM1 were associated with blood pressure in induced hypertension mice model

Summary

- Most single variant findings have limited clinical utility
- Whole genome approaches to prediction improves utility
- Bevacizumab induced hypertension example
  - primary hypertension results help in predicting drug induced hypertension
  - successfully predicted bevacizumab induced hypertension in independent study
  - combining primary + bevacizumab induced HT leads to improved prediction
- PrediXcan: novel gene based test that test mechanism yielded promising findings

Acknowledgements

Contributors

- Keston Aquino Michaels
- Heather Wheeler
- Nancy Cox
- Eileen Dolan
- Kaanan P. Shah
- Sahar Mozaffari
- Eric Gamazon
- Kouros Owzar
- CALGB 80303 Federico Innocenti/Mark Ratain/Yusuke Nakamura
- CALGB 90401 Howard McLeod
- CALGB 40101 Deanna Kroetz
- GTEx Consortium

Data sources

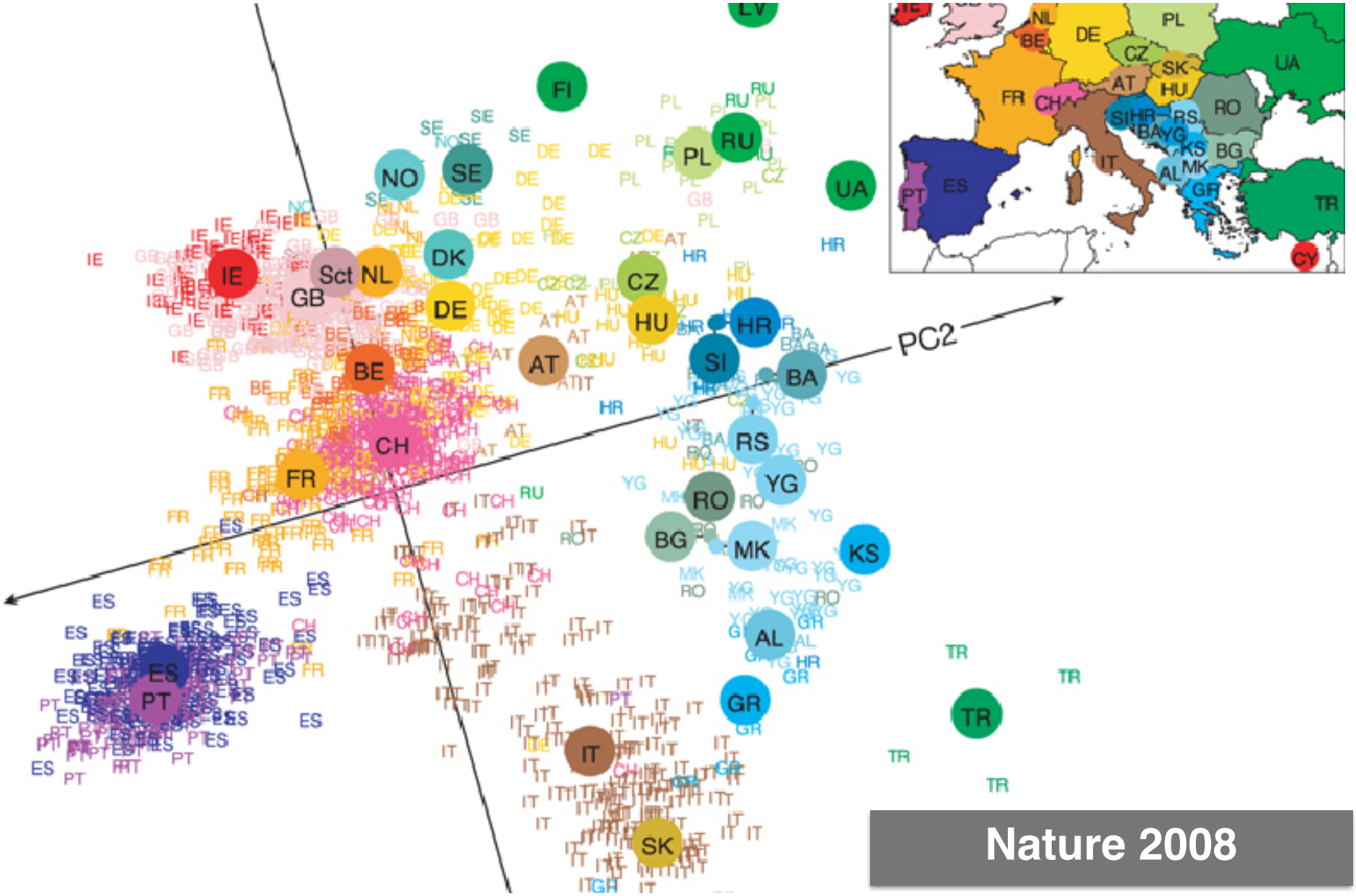
- Cross Consortia Pleiotropy XCP summary results
- WTCCC

Funding

- HKI was funded in part by Uchicago CTSA NCI K12CA139160
- University of Chicago Diabetes Research and Training Center: P60 DK20595, P30 DK020595
- Genotype of Tissue Expression GTEx R01 MH090937 and R01 MH101820
- Pharmacogenomics of Anticancer Agents PAAR UO1GM61393
- Pharmacogenomics Research Network (PGRN) Statistical Analysis Resource (P-STAR) U19 HL065962
- Conte Center grant P50MH094267

Genes mirror geography within Europe

John Novembre[1,2], Toby Johnson[4,5,6], Katarzyna Bryc[7], Zoltán Kutalik[4,6], Adam R. Boyko[7], Adam Auton[7], Amit Indap[7], Karen S. King[8], Sven Bergmann[4,6], Matthew R. Nelson[8], Matthew Stephens[2,3] & Carlos D. Bustamante[7]



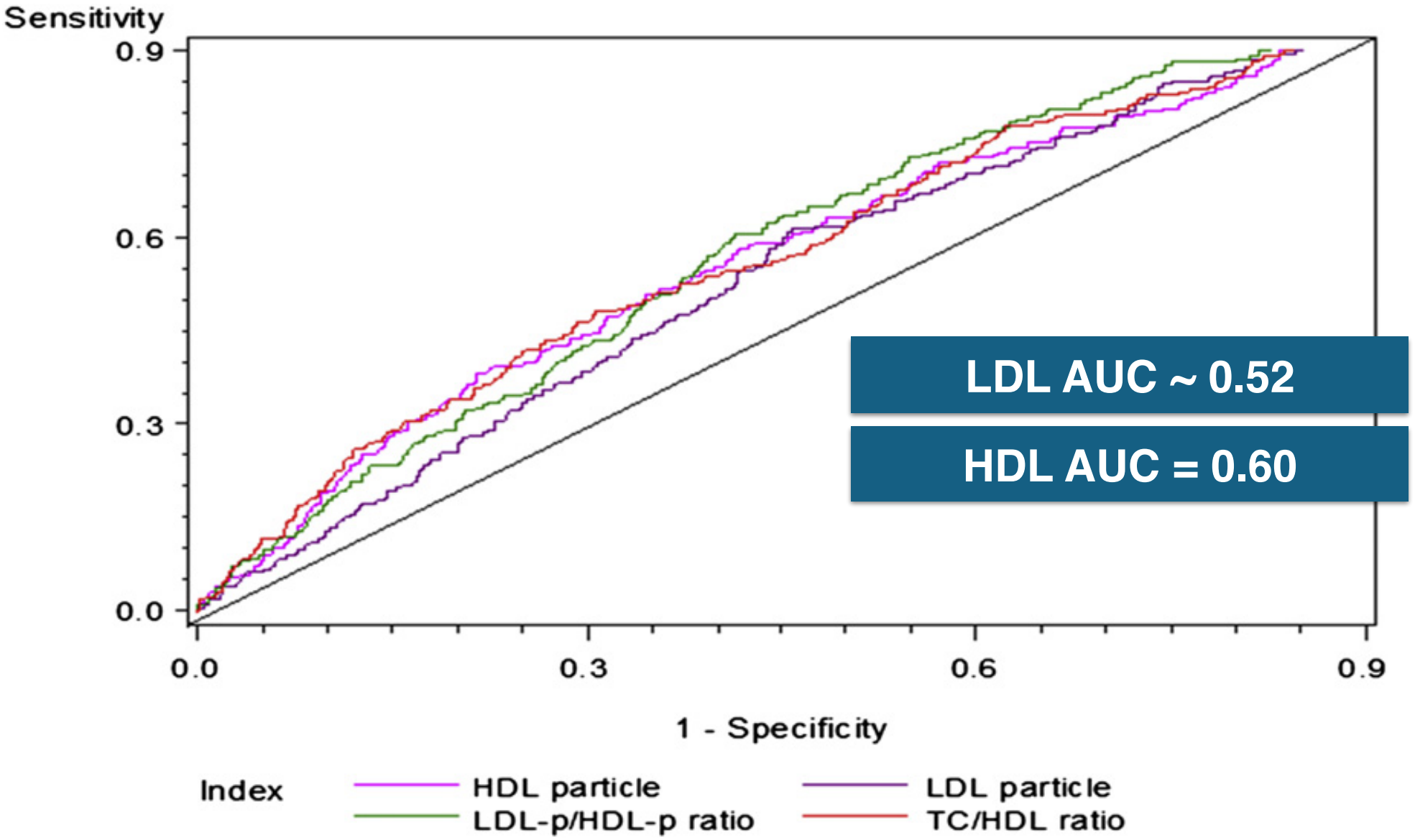
Nature 2008

References

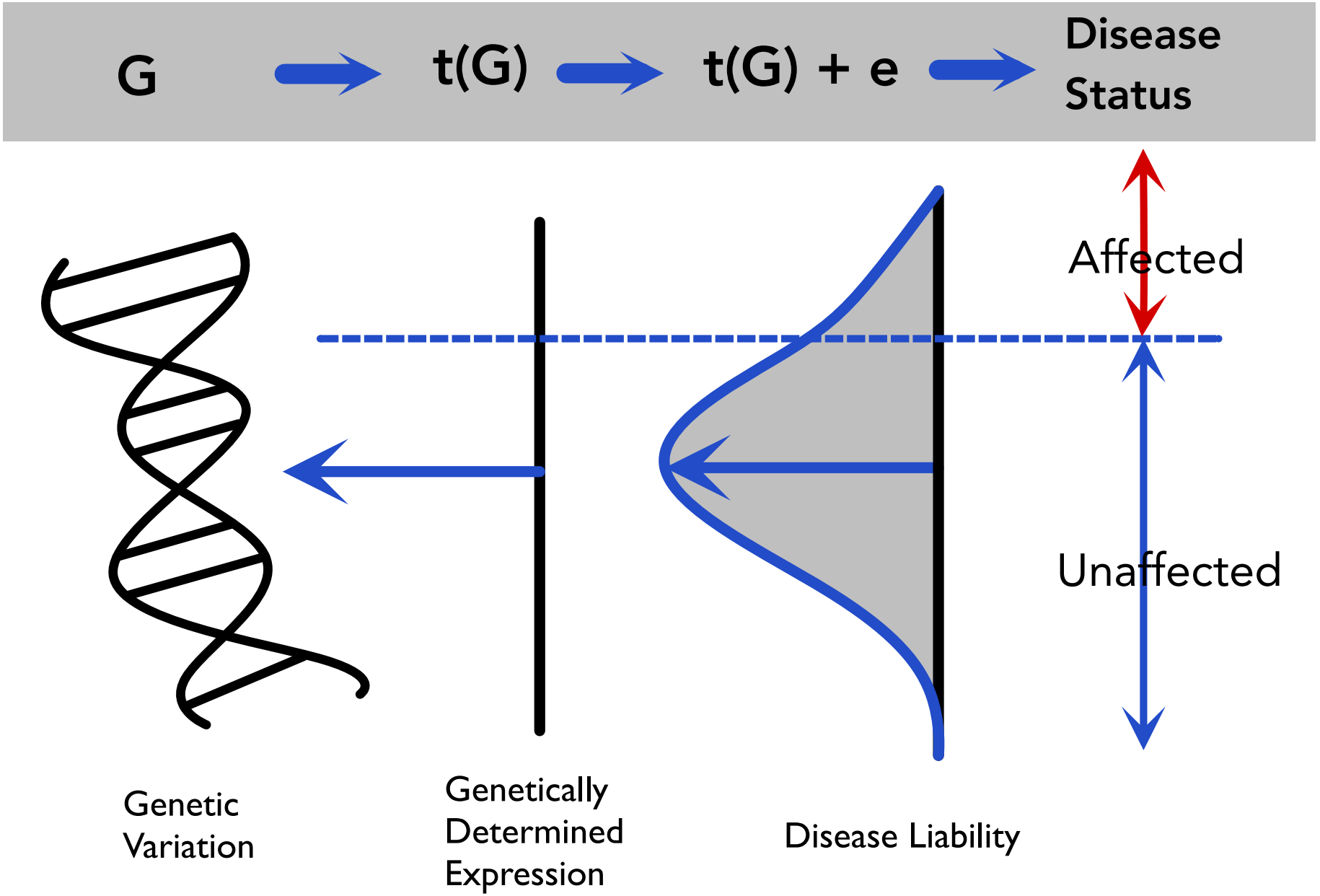
- MPH, Palaniappan Manickam MD, Ankit Rathod MD, Sidakpal Panaich MD, Pawan Hari MD MPH, Vikas Veeranna MD, Apurva Badheka MD, Sony Jacob MD, and Luis Afonso MD FACC. 2011. “Comparative Prognostic Utility of Conventional and Novel Lipid Parameters for Cardiovascular Disease Risk Prediction: Do Novel Lipid Parameters Offer an Advantage?.” Journal of Clinical Lipidology 5 (2). Mosby, Inc: 82–90. doi: 10.1016/j.jacl.2010.12.001.
- Chhibber, A, J Mefford, E A Stahl, S A Pendergrass, R M Baldwin, K Owzar, M Li, et al. 2014. “Polygenic Inheritance of Paclitaxel-Induced Sensory Peripheral Neuropathy Driven by Axon Outgrowth Gene Sets in CALGB 40101 (Alliance)” 14 (4). Nature Publishing Group: 336–42. doi:10.1038/tpj.2014.2.

Lipid Markers AUC

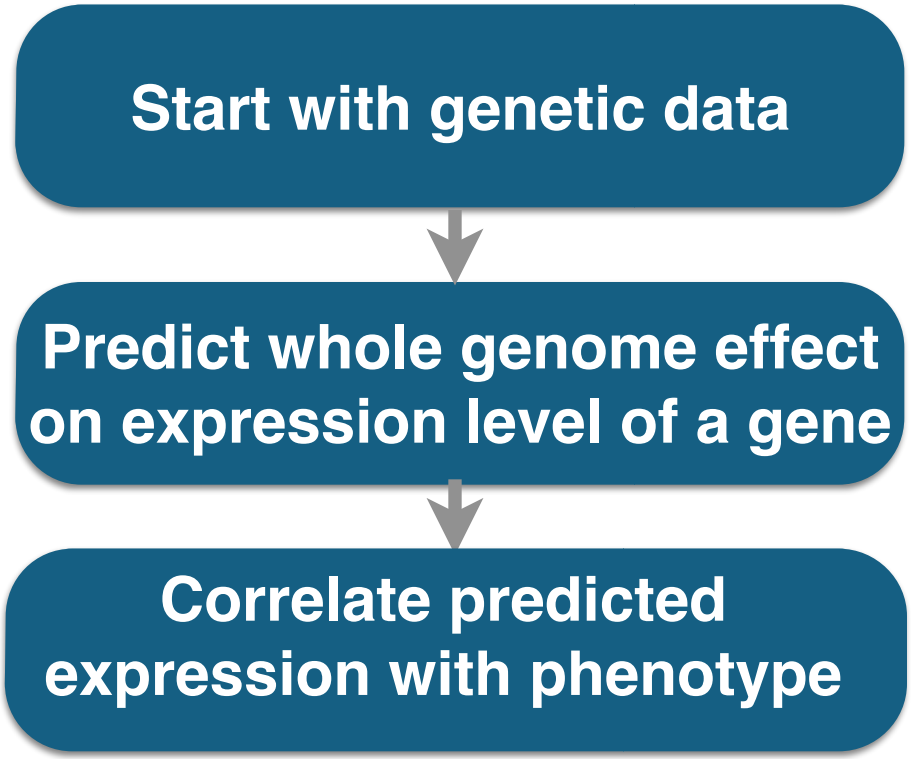
Manickam et al 2011 J Clinical Lipidology



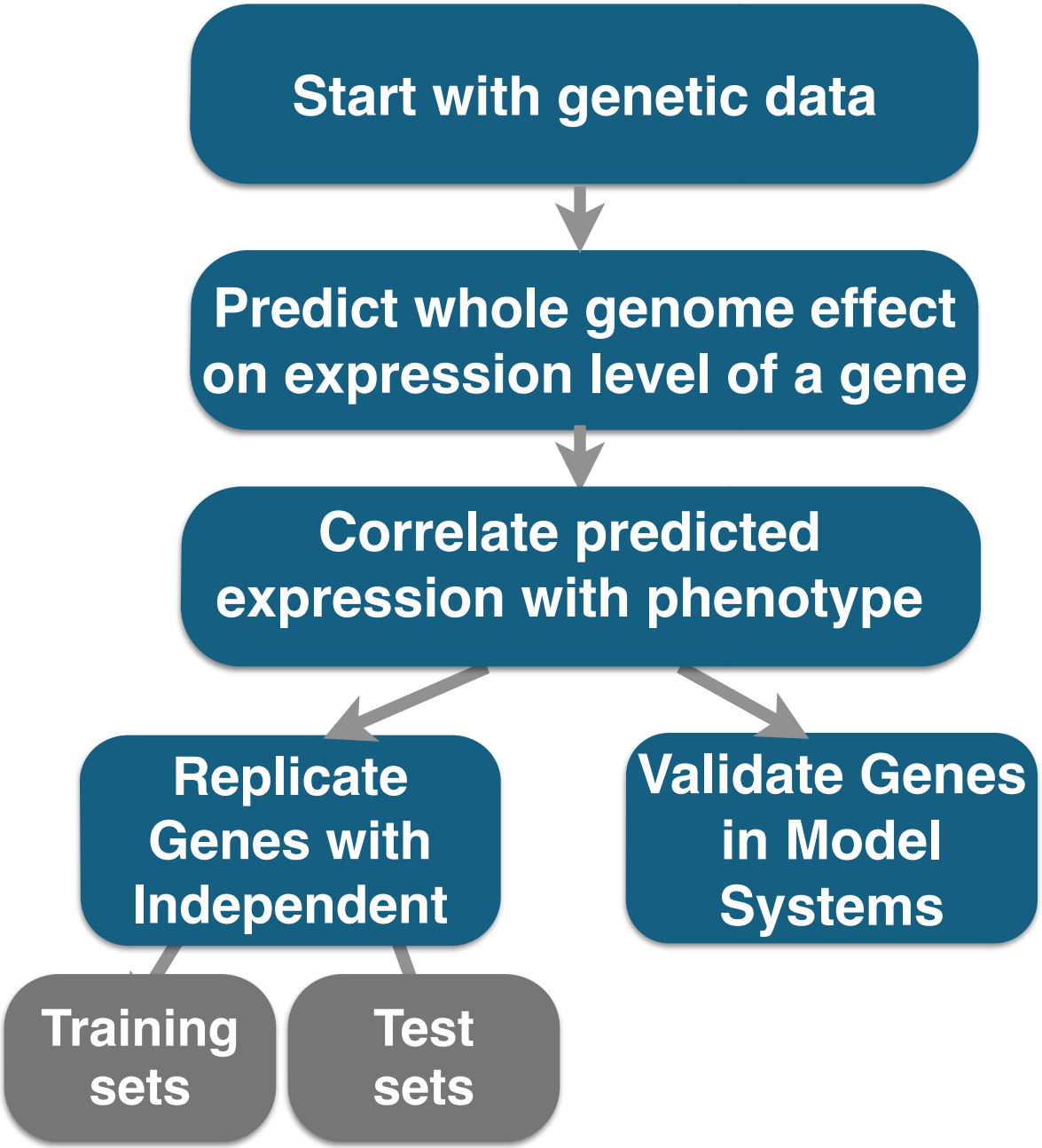
Genetic Control of Disease Through Gene Regulation



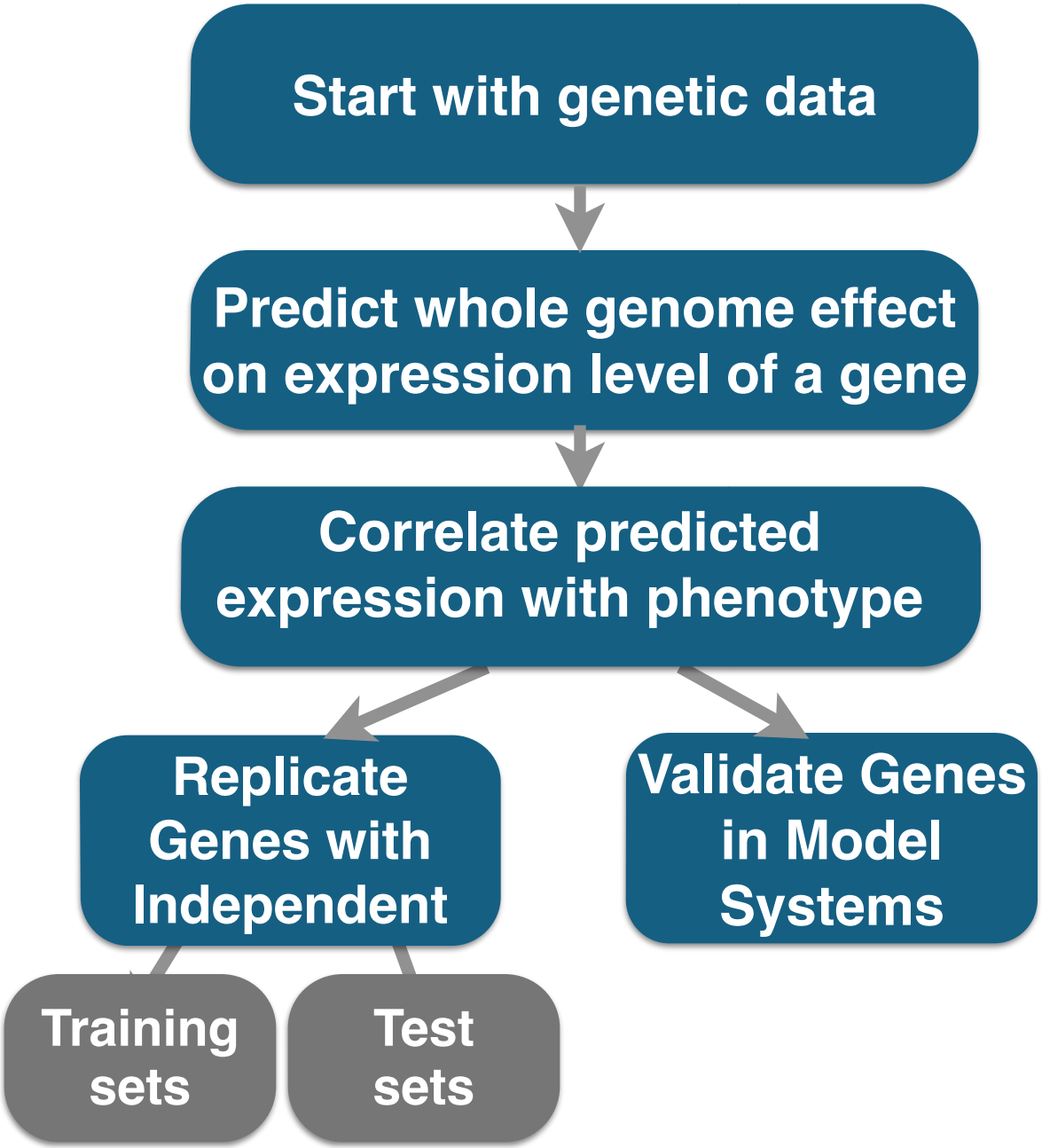
PrediXcan Flow



PrediXcan Flow



PrediXcan Flow



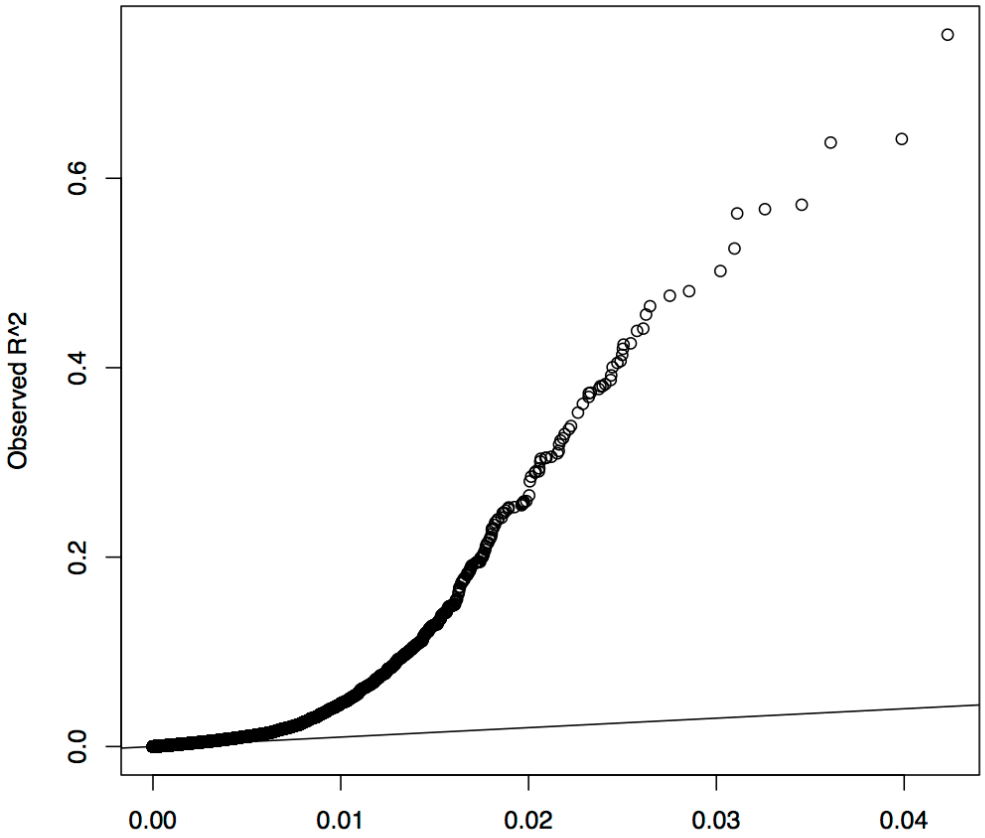
- No transcriptome data is needed
- Only genotype and phenotype data needed
- No reverse causality
- Reduced multiple testing burden
- Mechanism is built in

Expression Data

- GTEx - Genotype of Tissue Expression
  - Large scale Common Fund project
  - 900 organ donors
  - 45 tissues
  - RNAseq, whole exome seq, whole genome seq
- gEUVADIS
  - RNAseq 462 individuals from the 1000 Genomes Project
- Cerebellum expression (Array GSE35974)

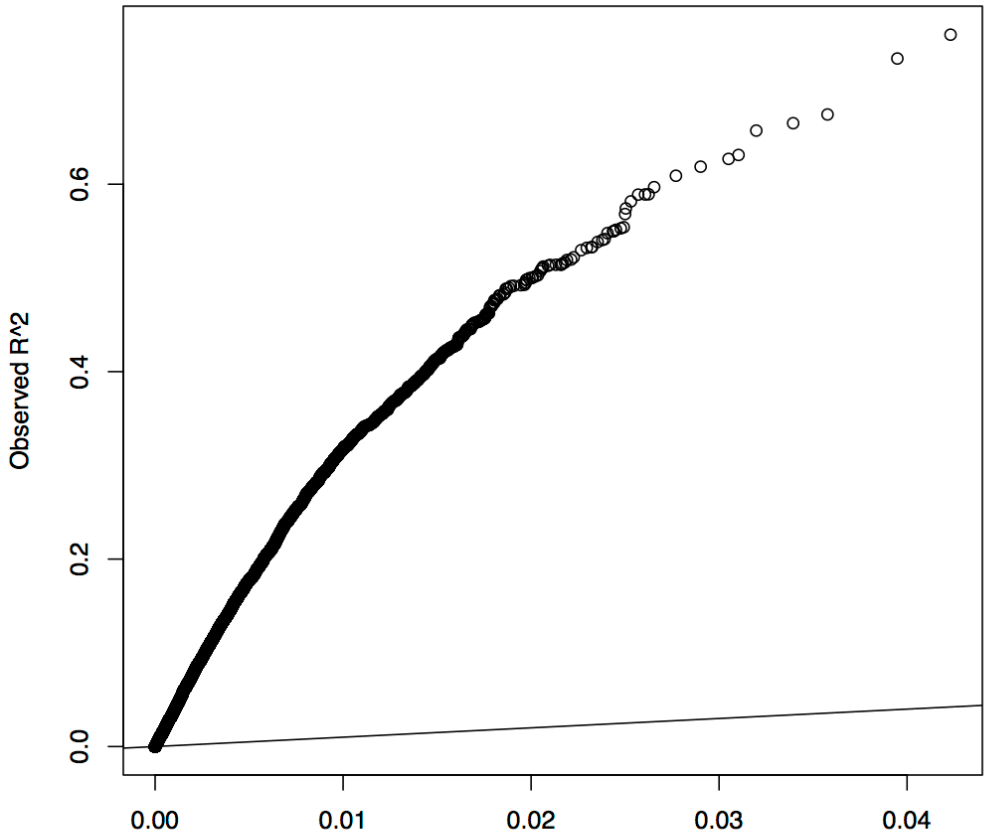
Good Prediction Performance

Prediction R^2



Training with GTEx Testing in 1K Genomes

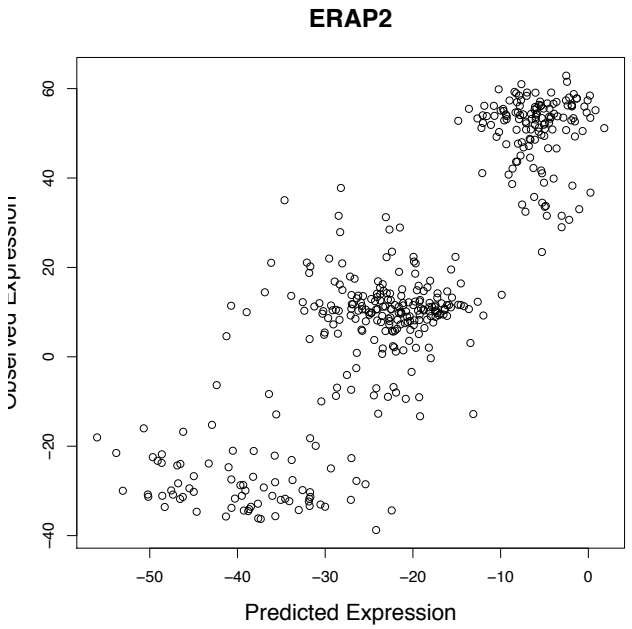
Replication R^2

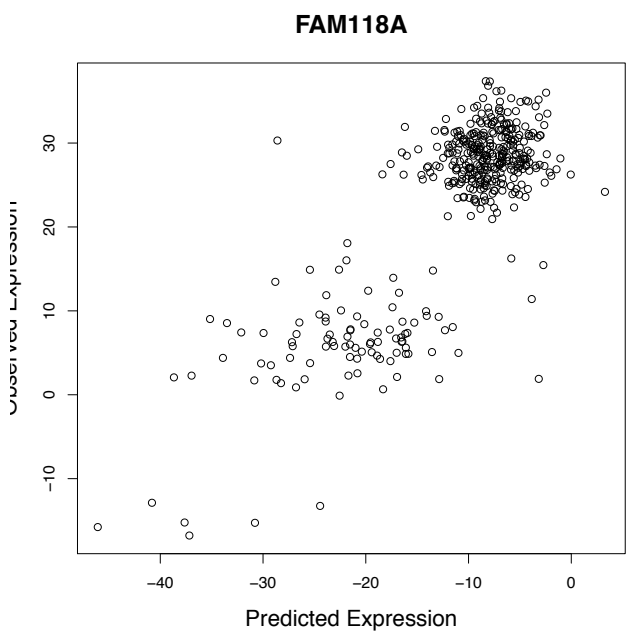


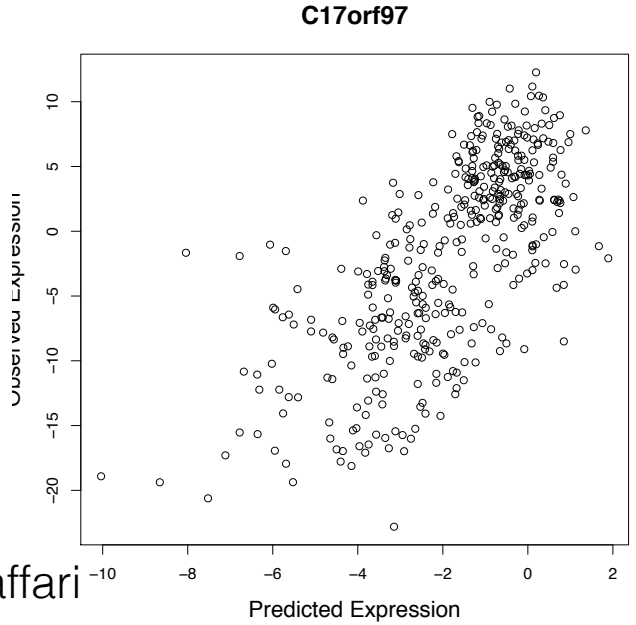
Replicate RNAseq Pickrell et al 2010 vs. 1K Genomes 2013

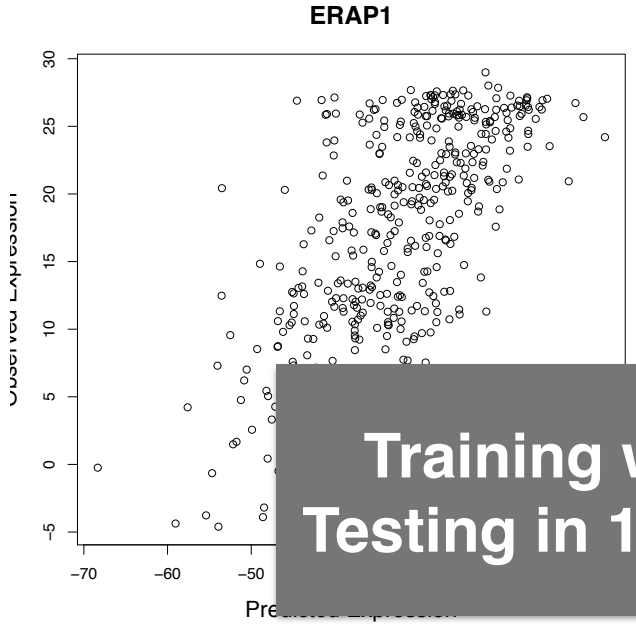
Sahar Mozaffari

Examples of Well Predicted Genes





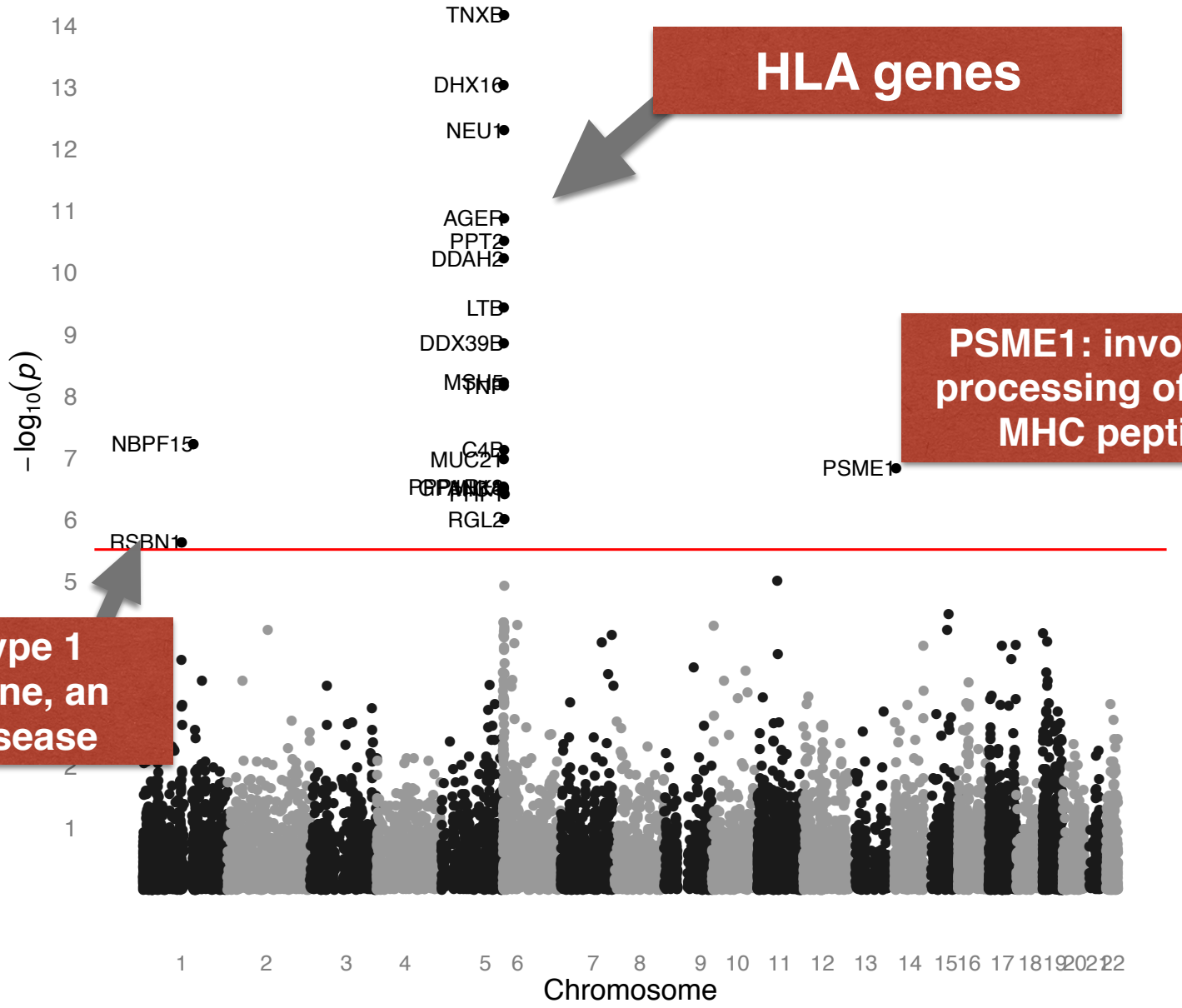




Sahar Mozaffari

Training with GTEx
Testing in 1K Genomes

Genes Associated with Rheumatoid Arthritis



PrediXcan: a Gene Discovery Approach

- PrediXcan is a powerful gene based association test
- It directly tests the molecular mechanism through which genetic variants affect phenotype
- Reduced multiple testing burden compared to single variant approach
- Unlike other gene based tests, it provides direction of effects
- Advantages relative to gene expression studies
  - Applicable to any GWAS datasets
    gene expression levels are predicted from genotype data
  - No reverse causality
    disease status does not affect germline DNA
  - Multiple Tissues can be evaluated
    tissue expressions are only needed to build prediction models