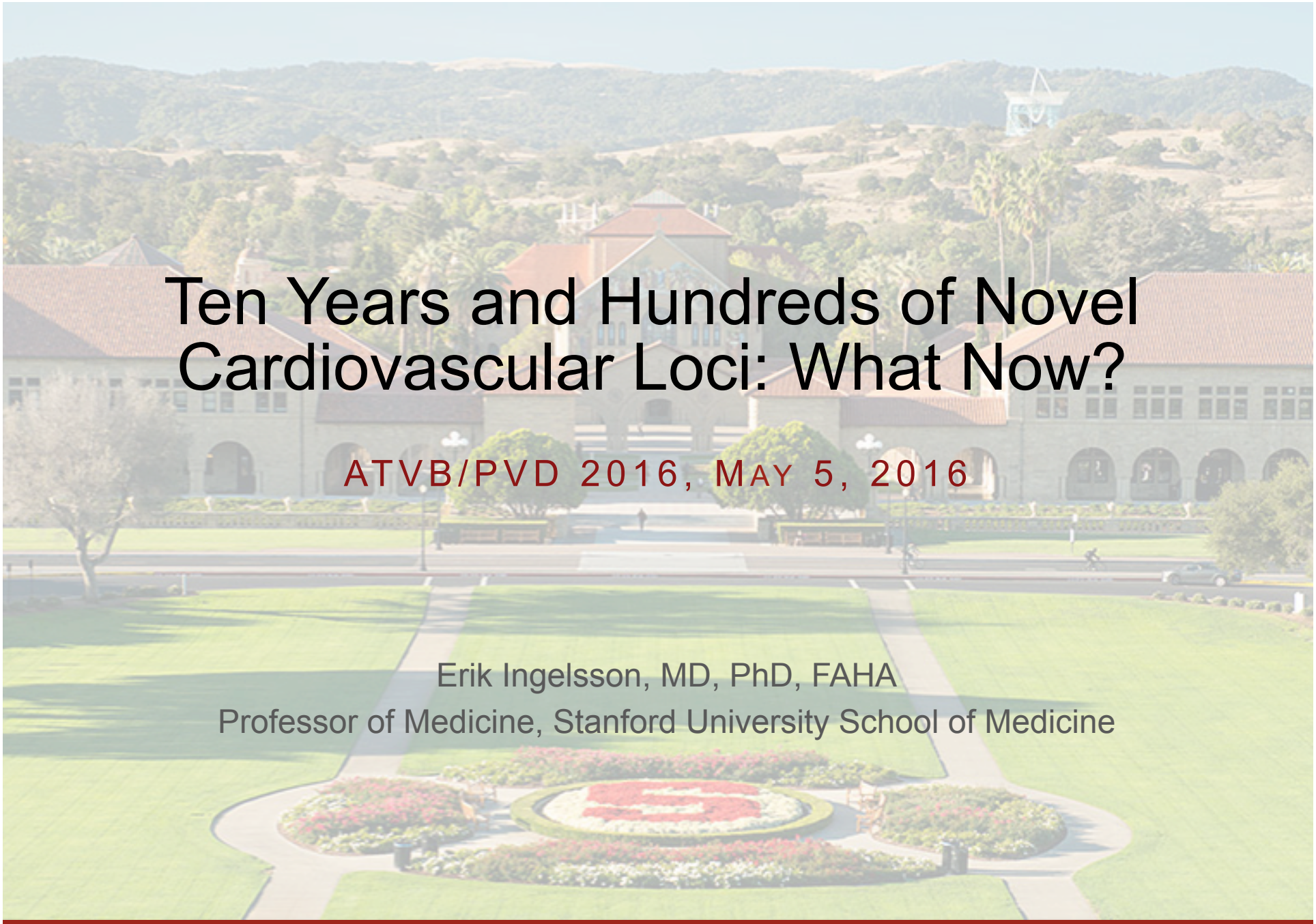


Ten Years and Hundreds of Novel Cardiovascular Loci: What Now?

ATVB/PVD 2016, May 5, 2016

Erik Ingelsson, MD, PhD, FAHA
Professor of Medicine, Stanford University School of Medicine

Stanford University

Disclosure Information

FINANCIAL DISCLOSURE:

None.

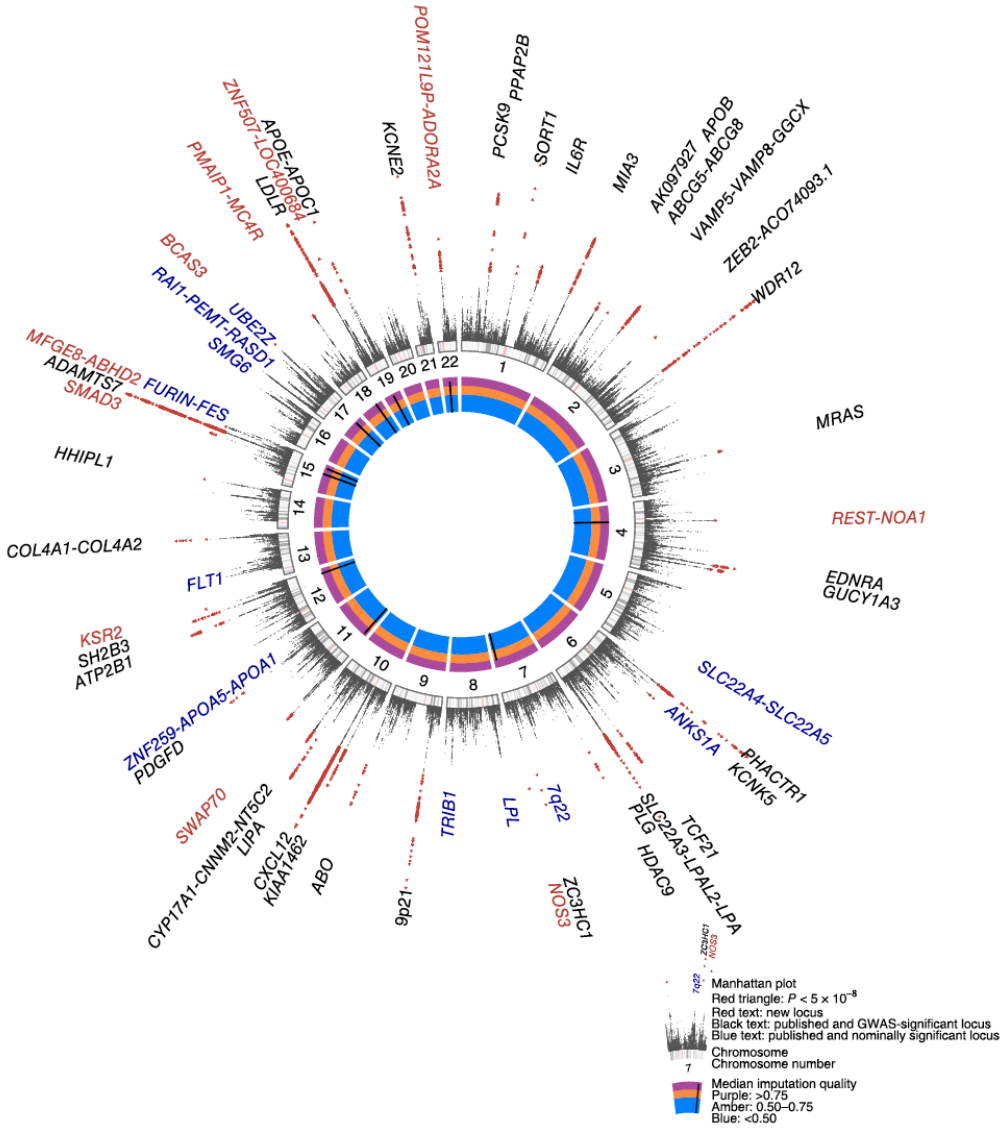
UNLABELED/UNAPPROVED USES DISCLOSURE:

None.

Outline

- What have we learned from ten years of GWAS?
- Overall strategies for post-GWAS studies
- Examples of follow-up studies informed by cardiovascular GWAS

GWAS have discovered hundreds of CVD-related loci



Ref: CARDIoGRAMplusC4D. Nat Genet. 2015;47(10):1121-30; https://www.ebi.ac.uk/gwas/.

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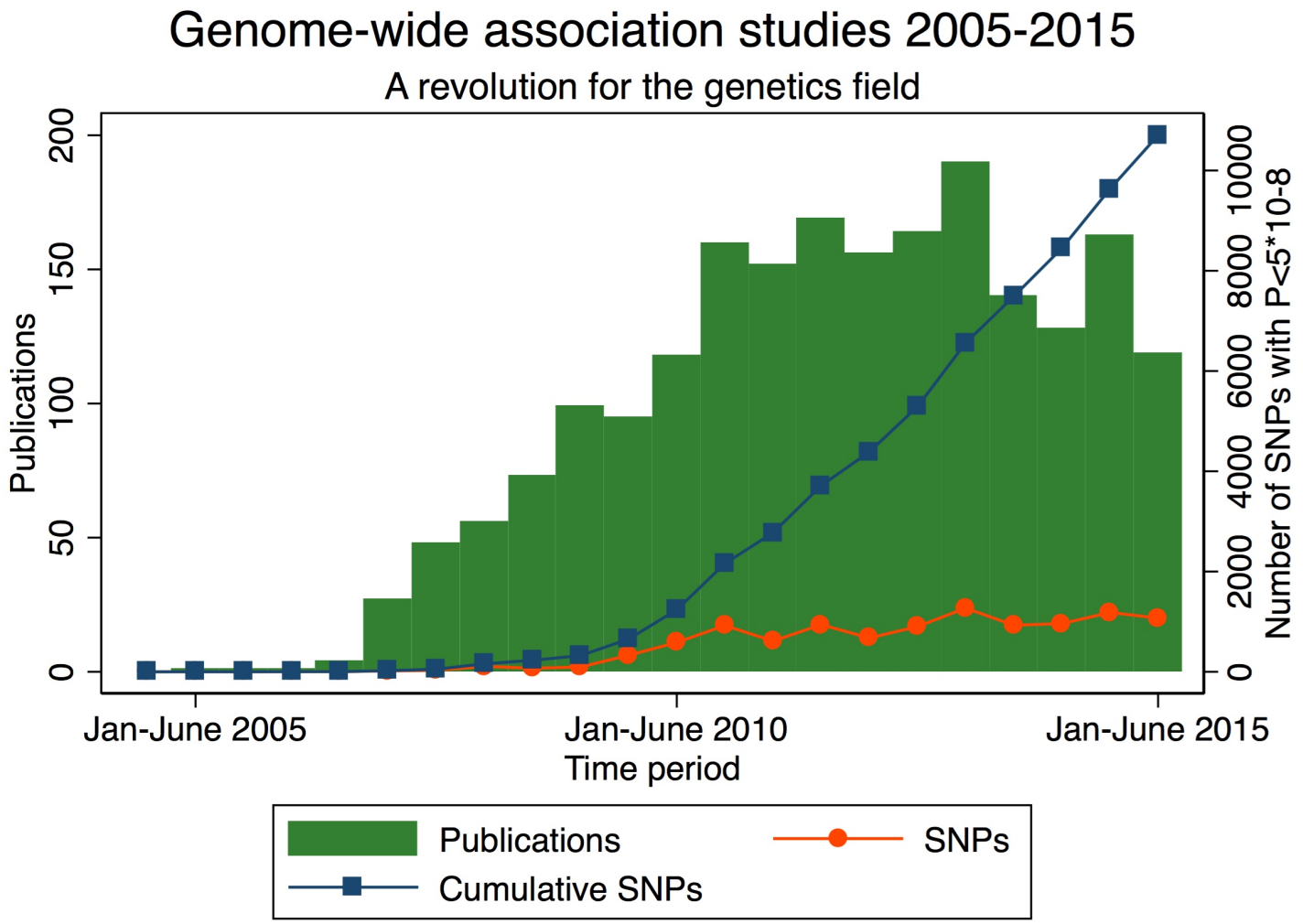
GWAS have discovered hundreds of CVD-related loci



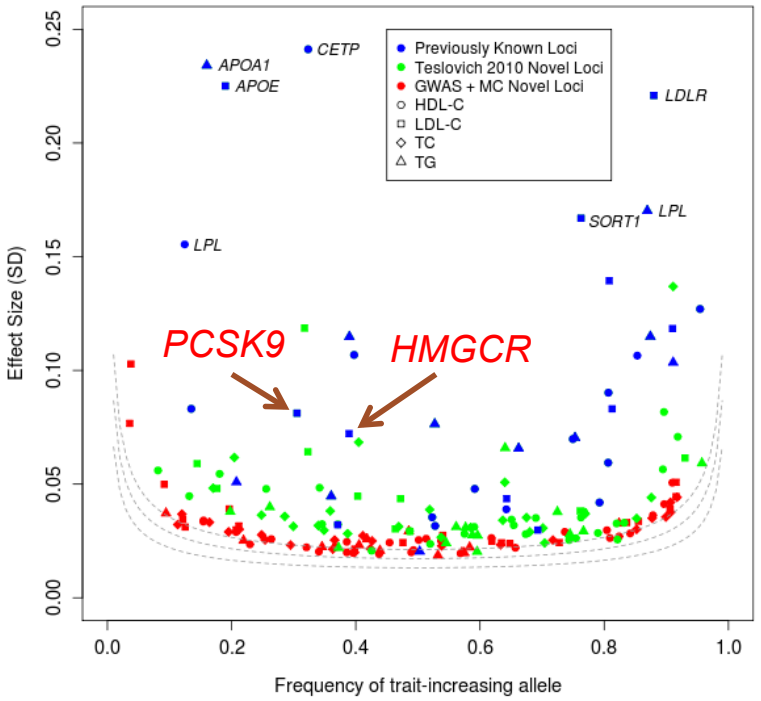
Ref: CARDIoGRAMplusC4D. Nat Genet. 2015;47(10):1121-30; https://www.ebi.ac.uk/gwas/.

GWAS have discovered hundreds of CVD-related loci

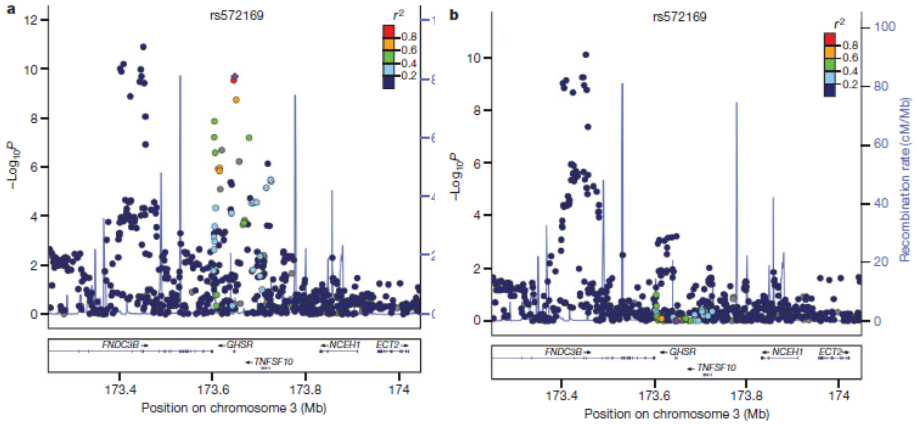
Cardiovascular disease: 179
Cardiovascular measurements: 217
Lipids: 309
Body weight and measures: 388
Metabolic disease: 142

Ref: CARDIoGRAMplusC4D. Nat Genet. 2015;47(10):1121-30; https://www.ebi.ac.uk/gwas/.

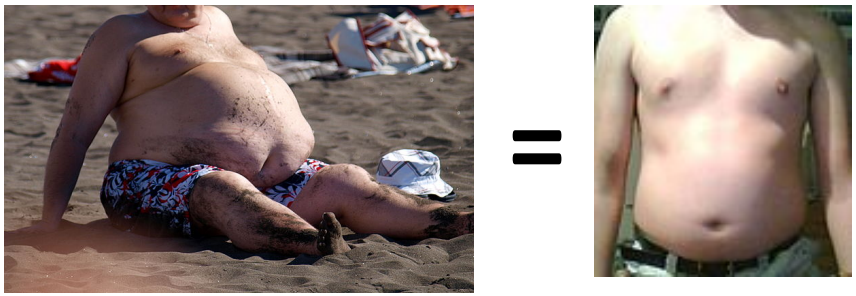
Lessons learned: Genetic architecture



Many loci with tiny effects



Allelic heterogeneity is common



Genetic architecture of extremes is similar to overall trait

Ref: Willer CJ. Nat Genet. 2013;45(11):1274-83; Wood AR. Nat Genet 2014; 46(11):1173-86; Berndt SI et al. Nat Genet 2013;45(5):501-12.

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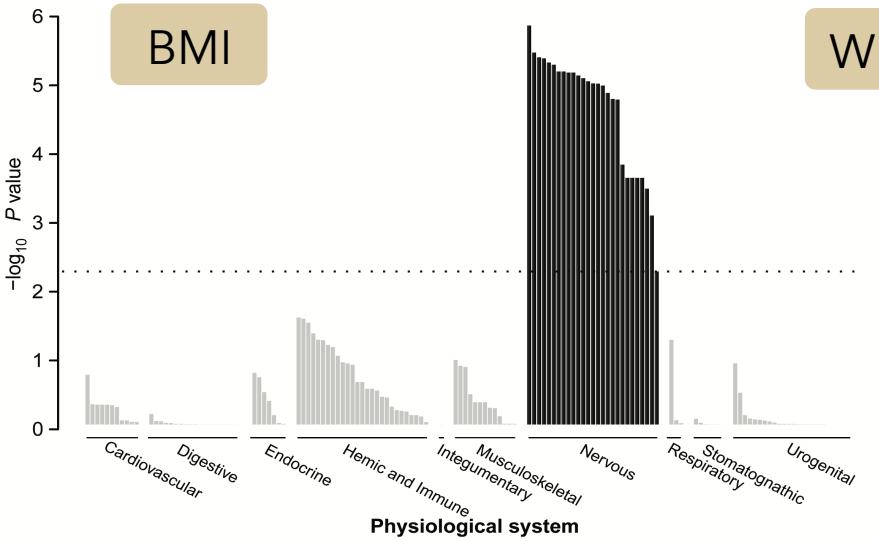
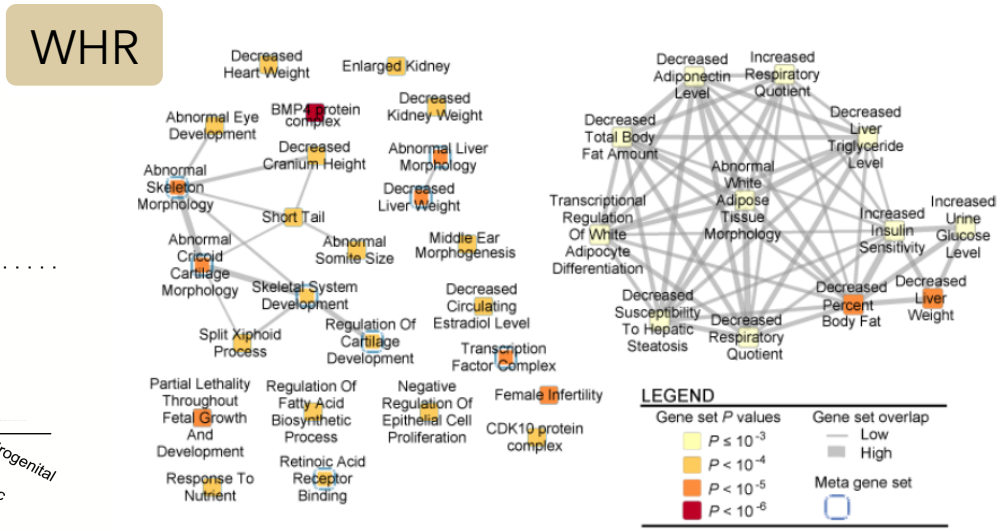
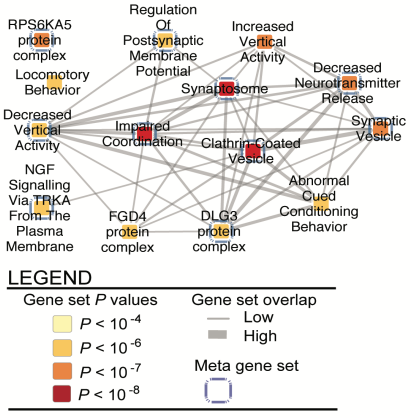
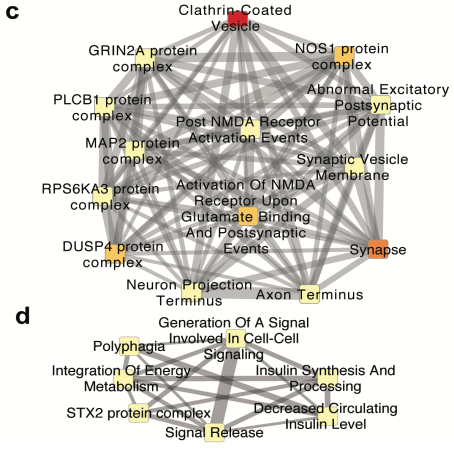
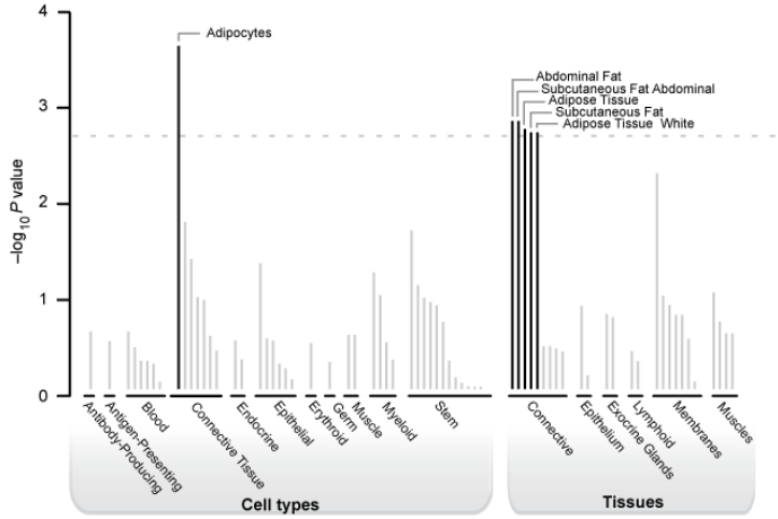
Lessons learned: Biological insights directly from GWAS











Ref: Locke AE. Nature 2015;518(7538):197-206); Shungin D. Nature 2015. 518(7538):187-96.

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Lessons learned: Follow-up with deeper phenotyping

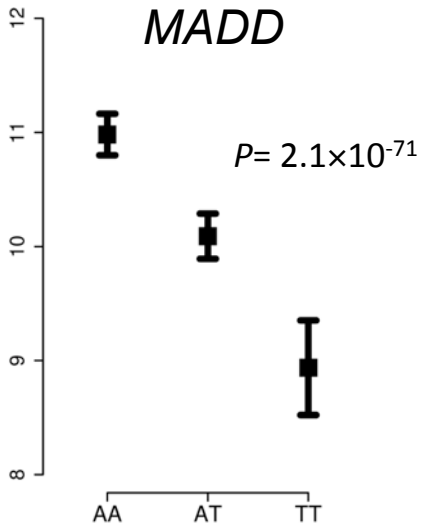
Known FG or FI loci

1. Implicated in abnormal insulin processing

2. Associated with abnormal insulin processing and lower insulin secretion

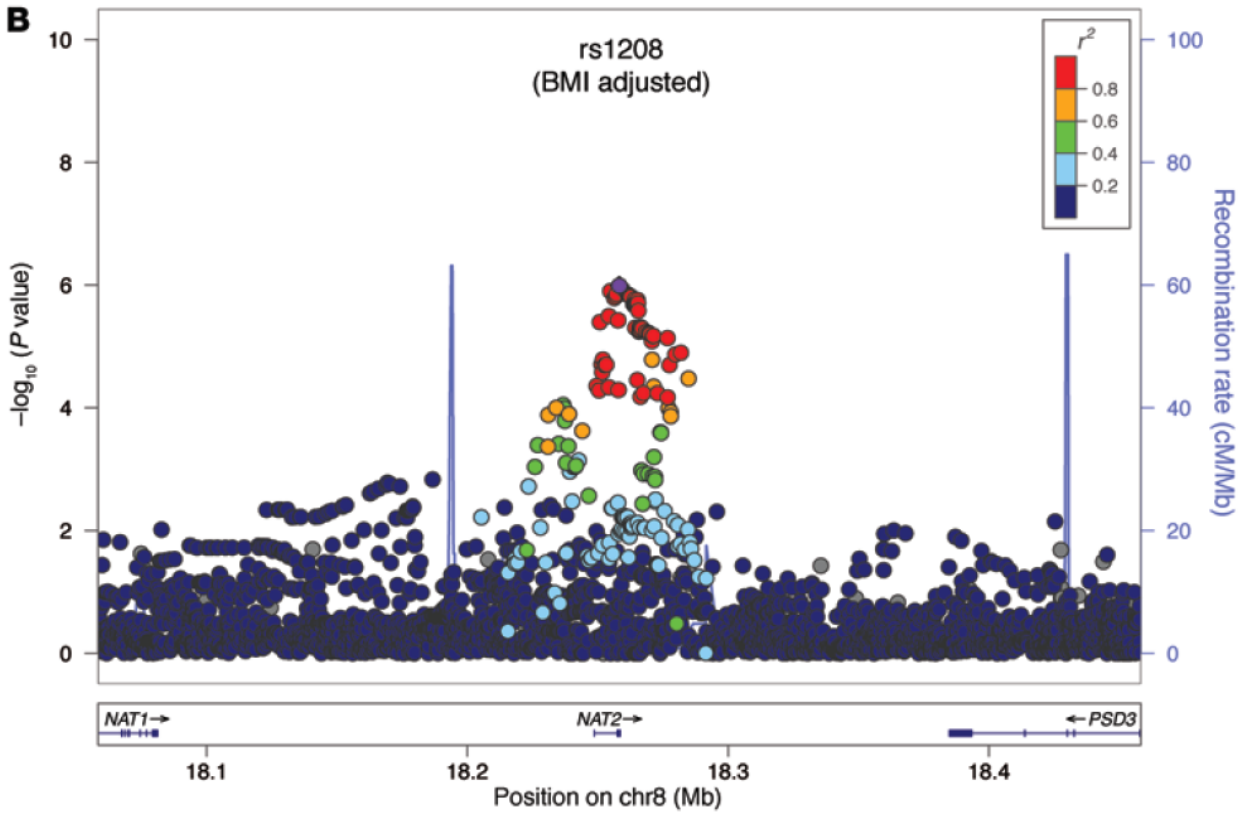
3. Associated with abnormalities in early insulin secretion

4. Involved in regulation of insulin sensitivity



Ref: Ingelsson et al. Diabetes 2010; 59:1266–1275.

Lessons learned: Functional follow-up in model systems



Ref: Knowles JW. J Clin Invest 2015;125(4):1739-51.

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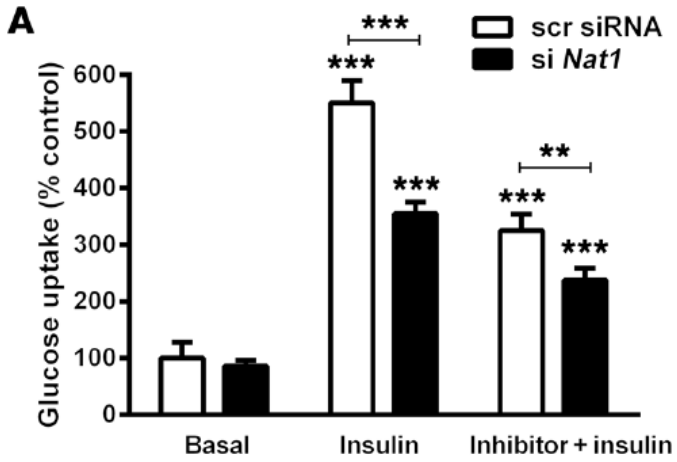
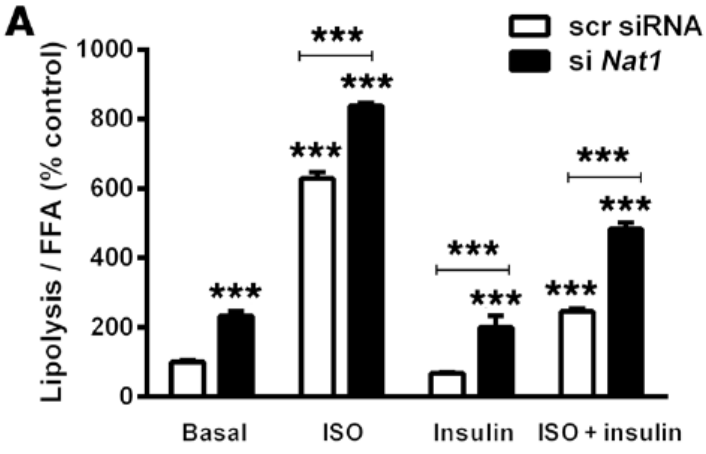
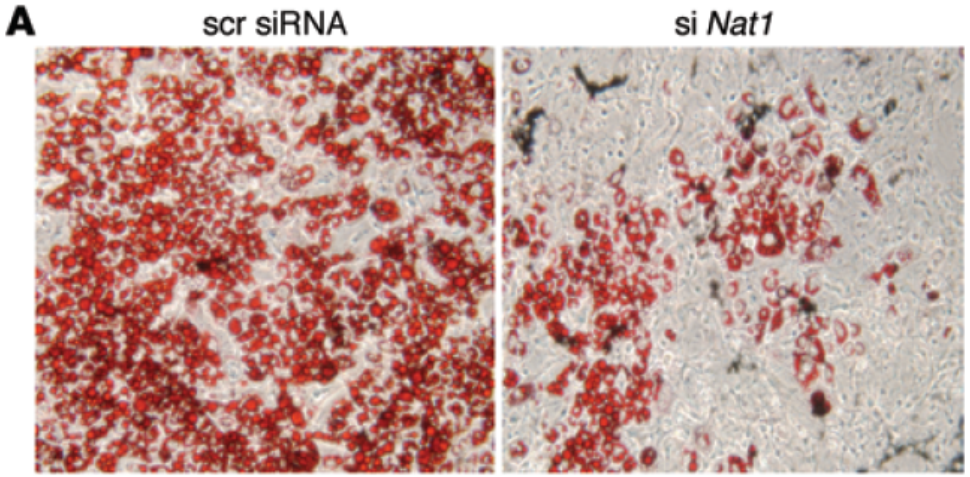
Lessons learned: Functional follow-up in model systems







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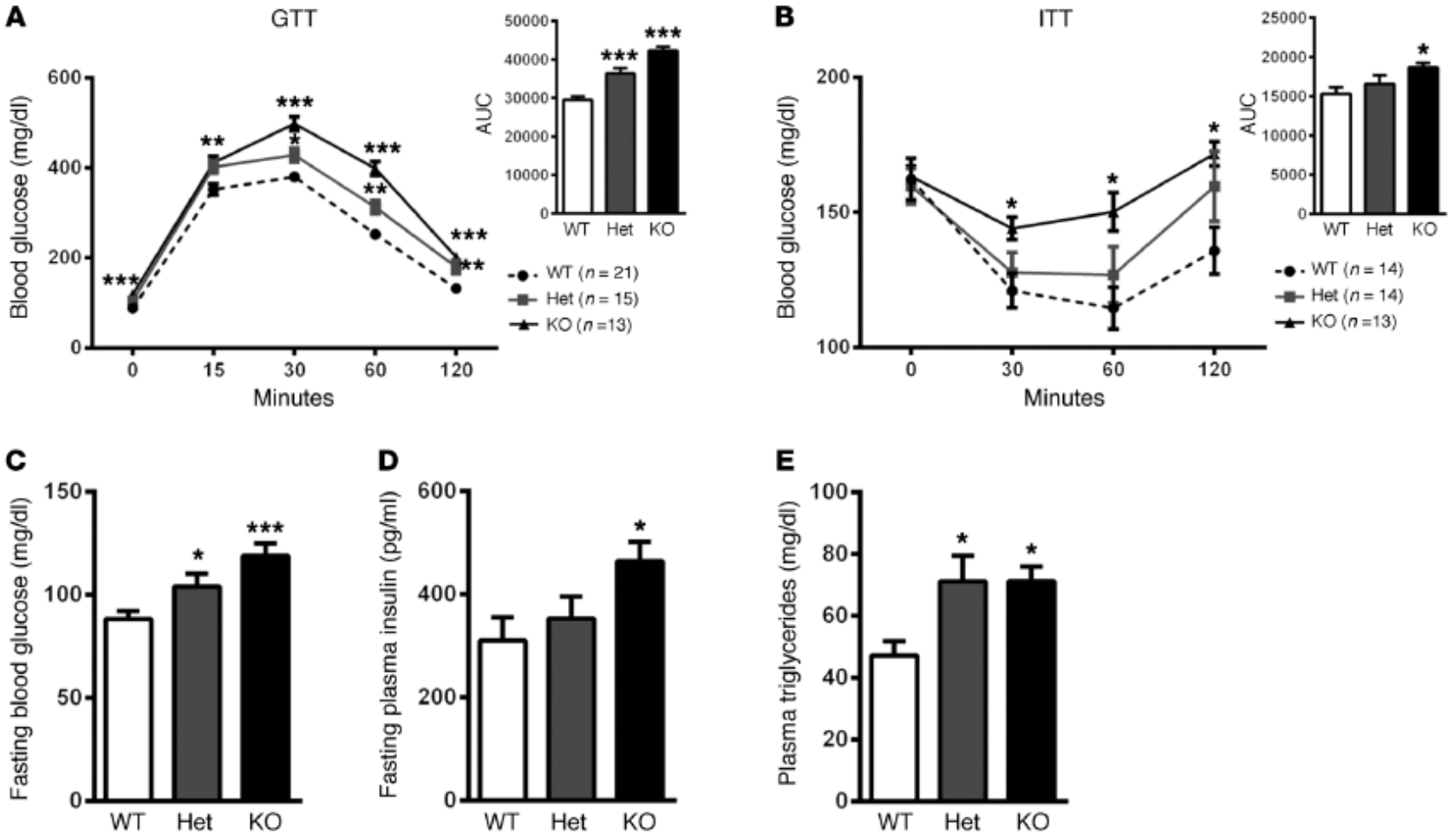
Lessons learned: Functional follow-up in model systems



Ref: Knowles JW. J Clin Invest 2015;125(4):1739-51.

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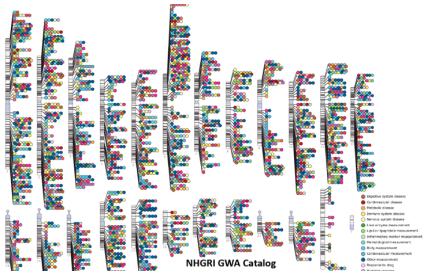
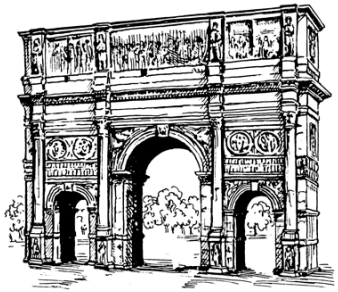
Outline

- What have we learned from ten years of GWAS?

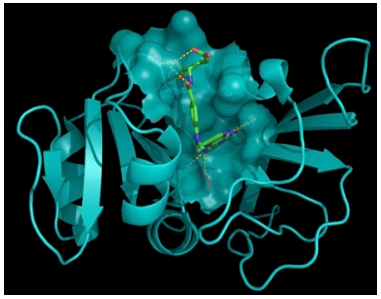
Hundreds of loci



Insights to genetic architecture



New biology

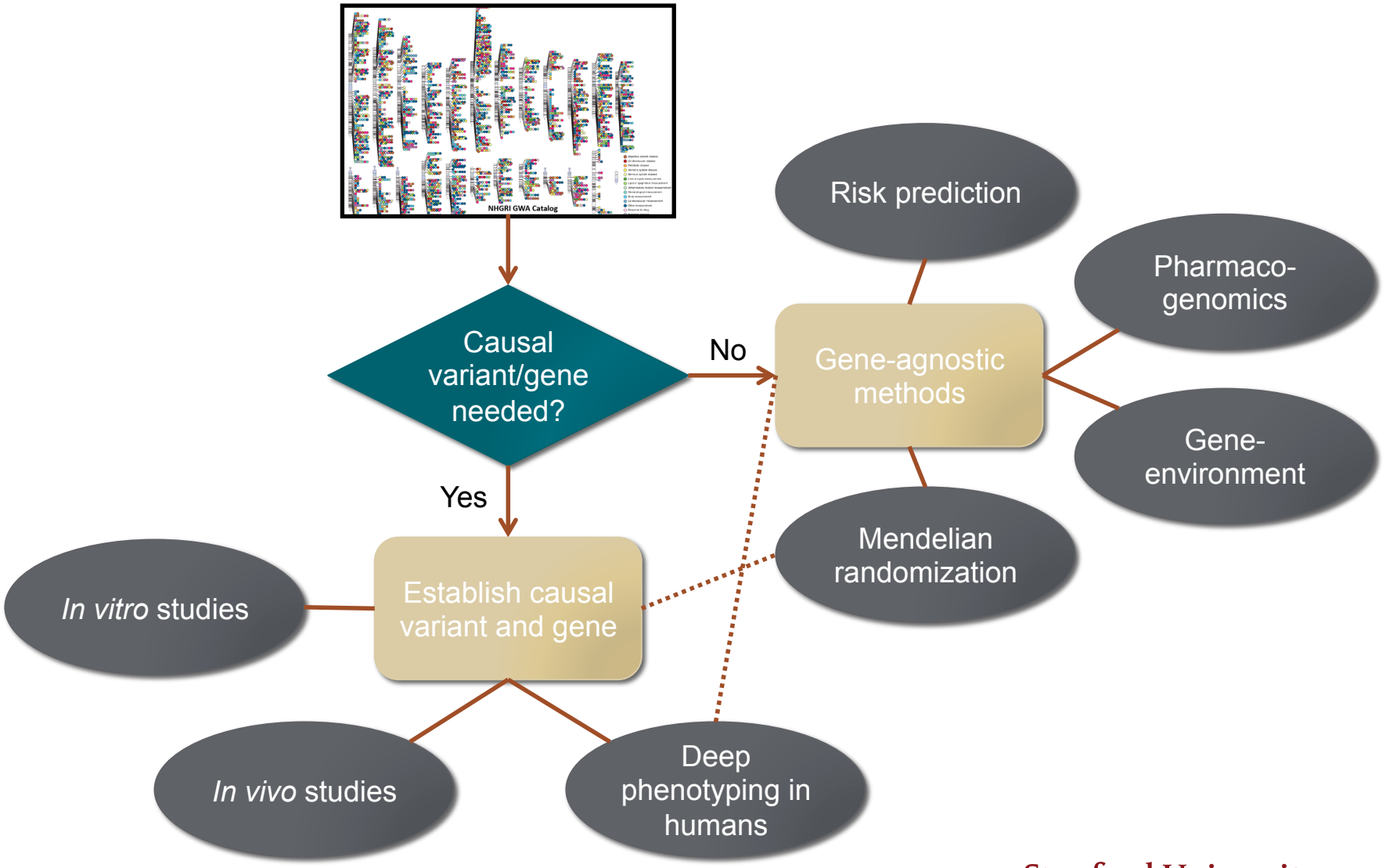


Few clinical applications

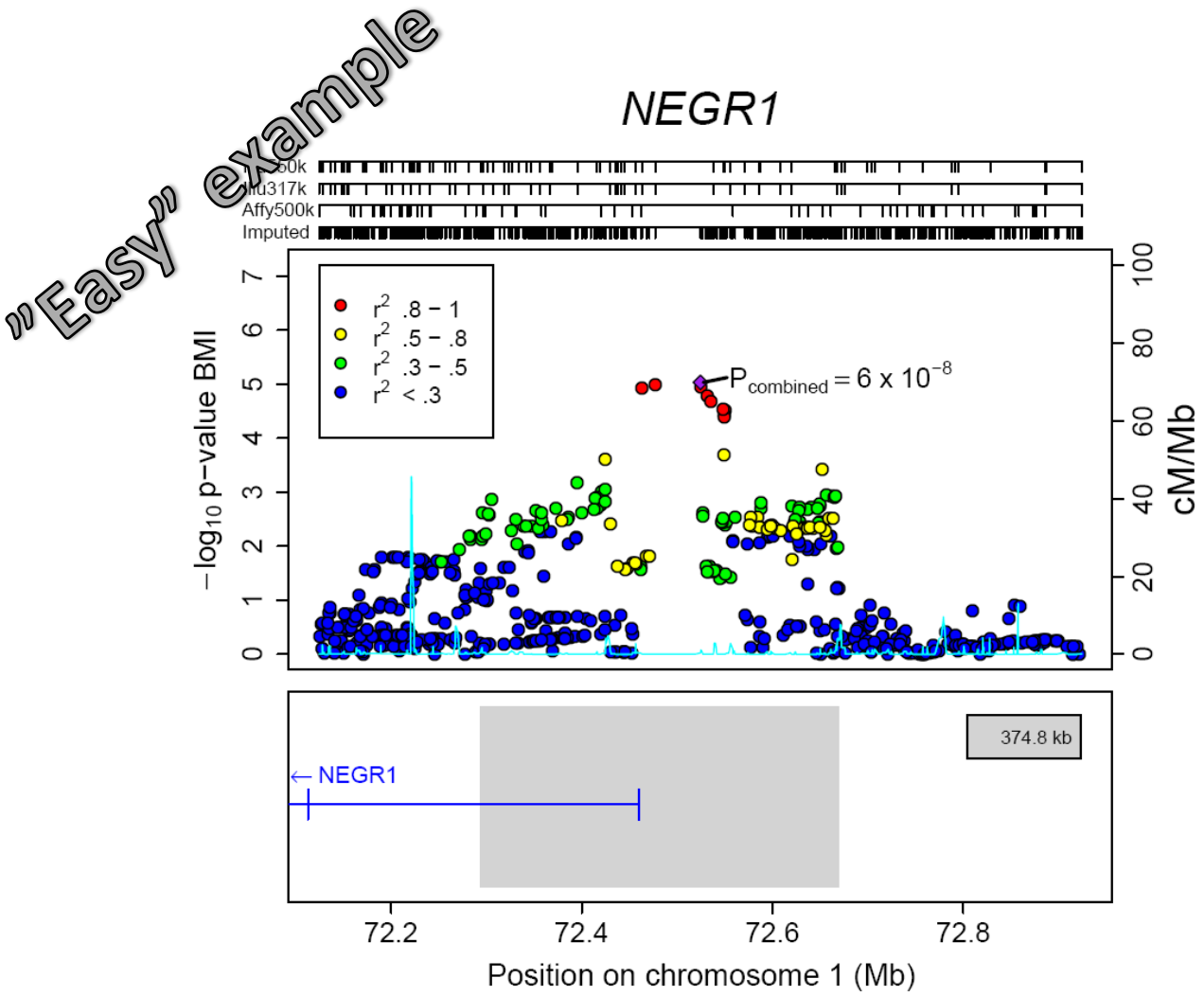
Outline

- Overall strategies for post-GWAS studies

Overall goals and strategies of post-GWAS studies



Challenges of identifying the causal gene



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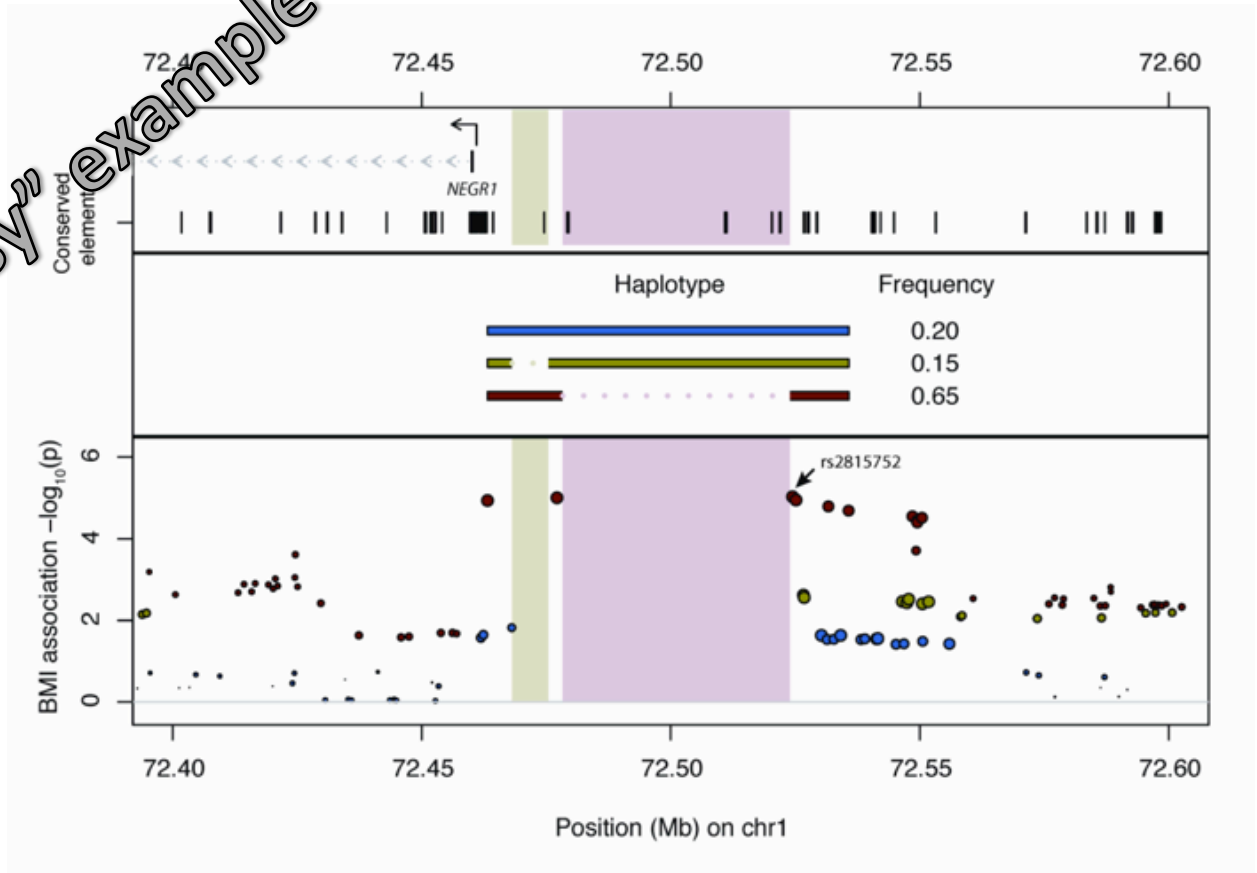
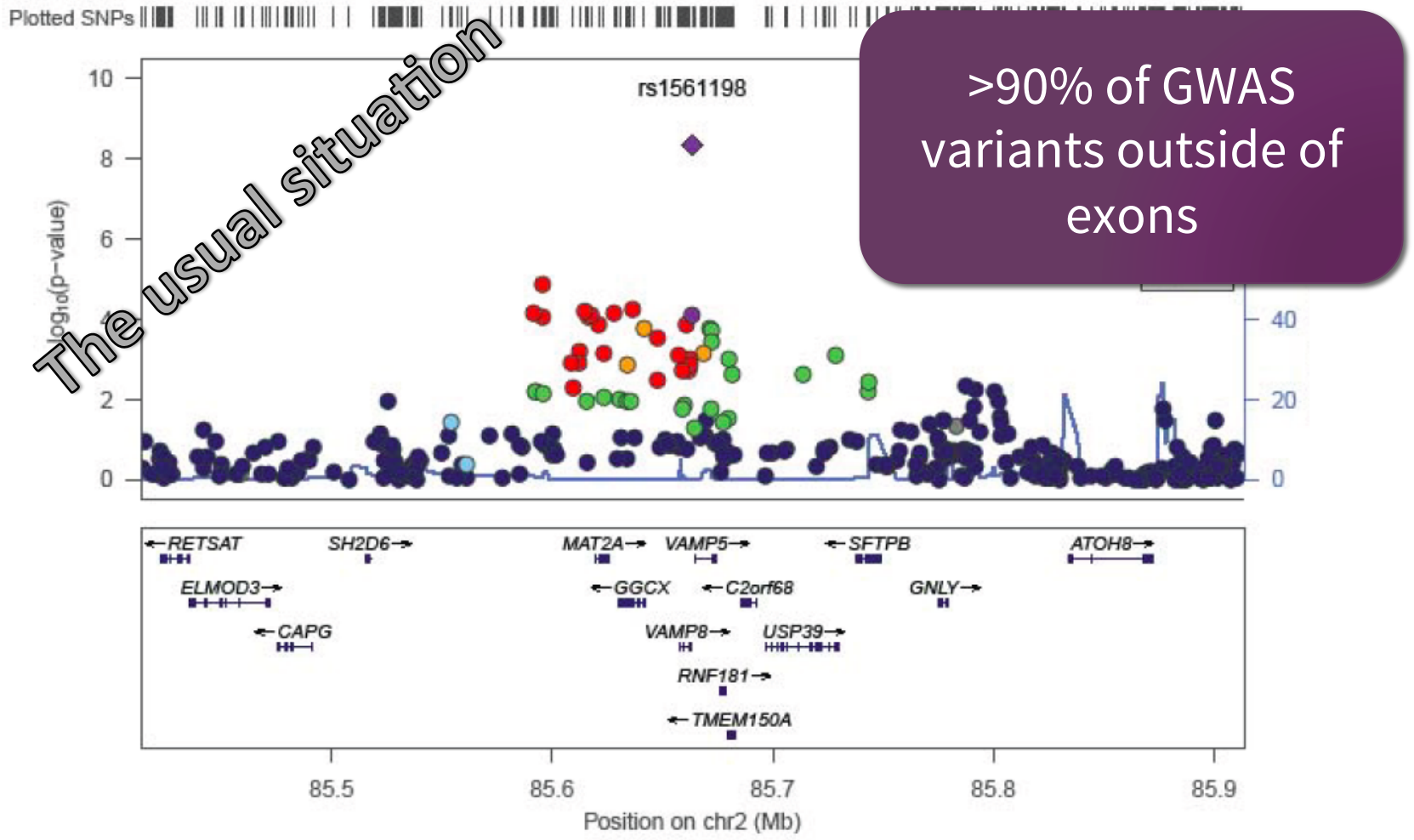
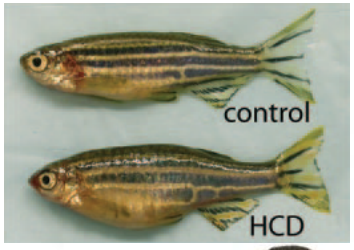


Challenges of identifying the causal gene

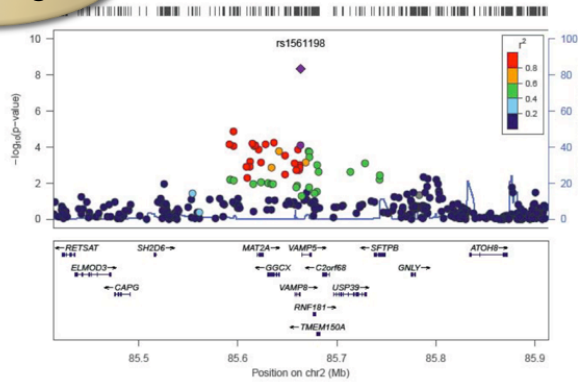


Approaches to identify causal variants and genes

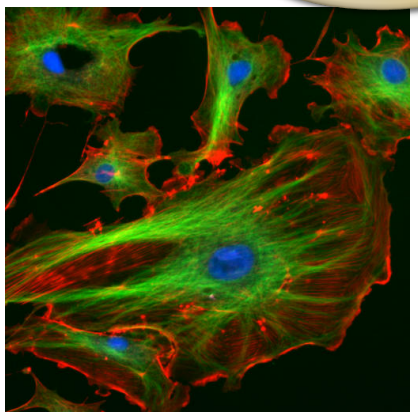
In vivo models



Fine-mapping

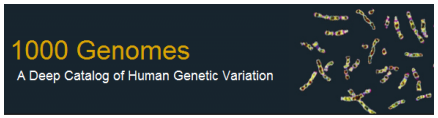


In vitro models

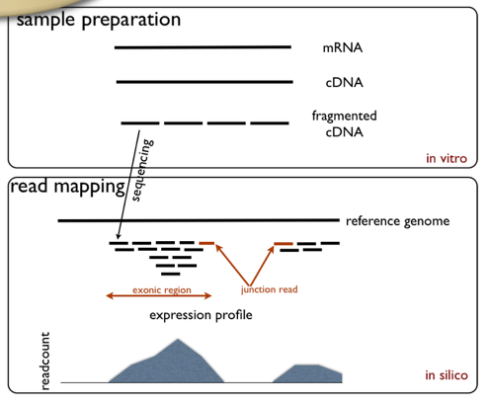


In silico information

ExAC



eQTLs



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Outline

- Examples of follow-up studies informed by cardiovascular GWAS

Studies of insulin resistance and fat distribution loci in adipocytes, hepatocytes and myocytes

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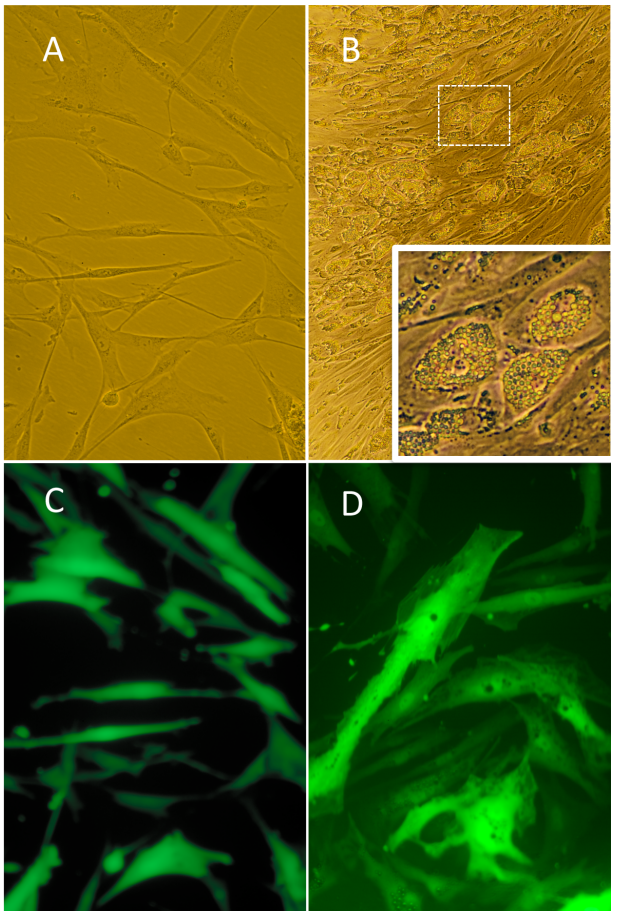
- Phenotypes
  - Glucose uptake
  - Lipolysis
  - Adipogenesis
  - Glycogen metabolism
  - Insulin signaling
  - Gene and protein expression
- SGBS, 3T3-L1, primary preadipocytes, HepG2 and C2C12
- CRISPR-Cas9 with lentiviral transduction
- Compound incubation




Casimiro Castillejo-Lopez


Naomi Cook


Susanne Trombley


Christoph Nowak

Stanford University

Screening and characterization of causal genes using zebrafish

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$F_{0\text{-}pool1}$: CRISPR-Cas9 target sites in early exons of eight candidate genes

$F_{0\text{-}pool2}$: Second set of CRISPR-Cas9 target sites in early exons of the same eight candidate genes

Crossing $F_{0\text{-}pool1}$ and $F_{0\text{-}pool2}$ to create F_1 with 0-2 functional knocks at 8 genes

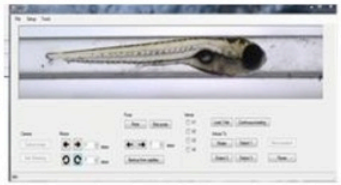
5 dpf

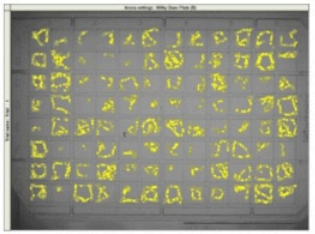
10 days of control (CD) or high-energy diet (HED)

8*96 fish (at 5 dpf)

8*96 fish (CD)

8*96 fish (HED)



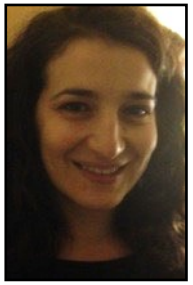


High-throughput imaging using VAST (adiposity or atherosclerosis) and DanioVision (physical activity)

Euthanization and homogenization

Sequencing at 16 targets
Lipid fractions
Glucose and insulin

Marcel den Hoed

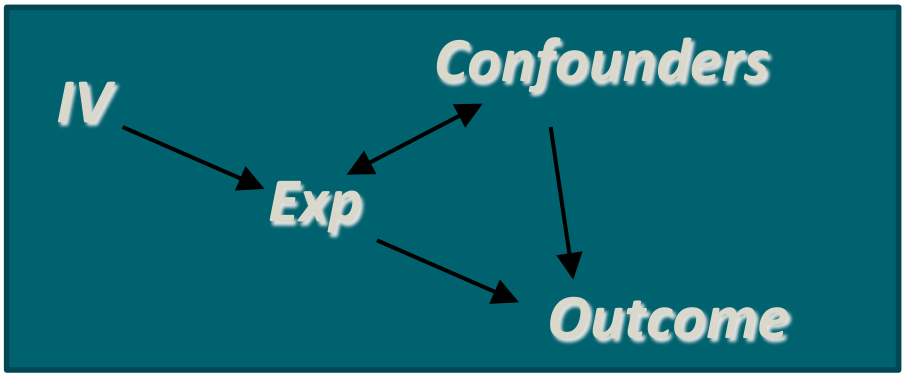


Anastasia Emmanouilidou

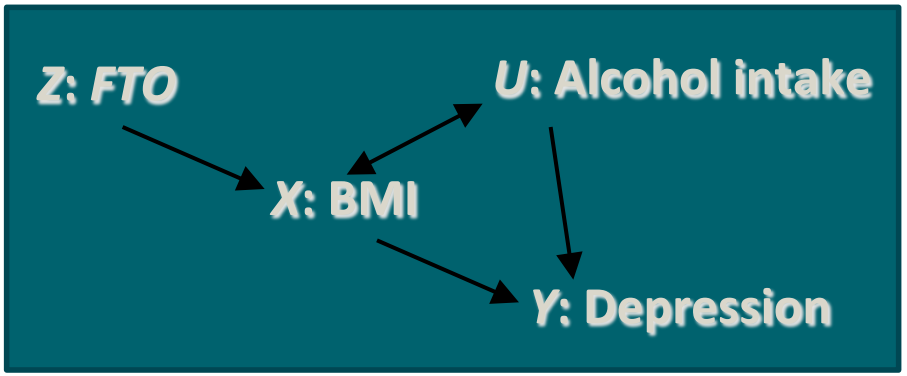
Manoj Bandaru

Stanford University

Mendelian randomization to address causality



Mendelian randomization to address causality



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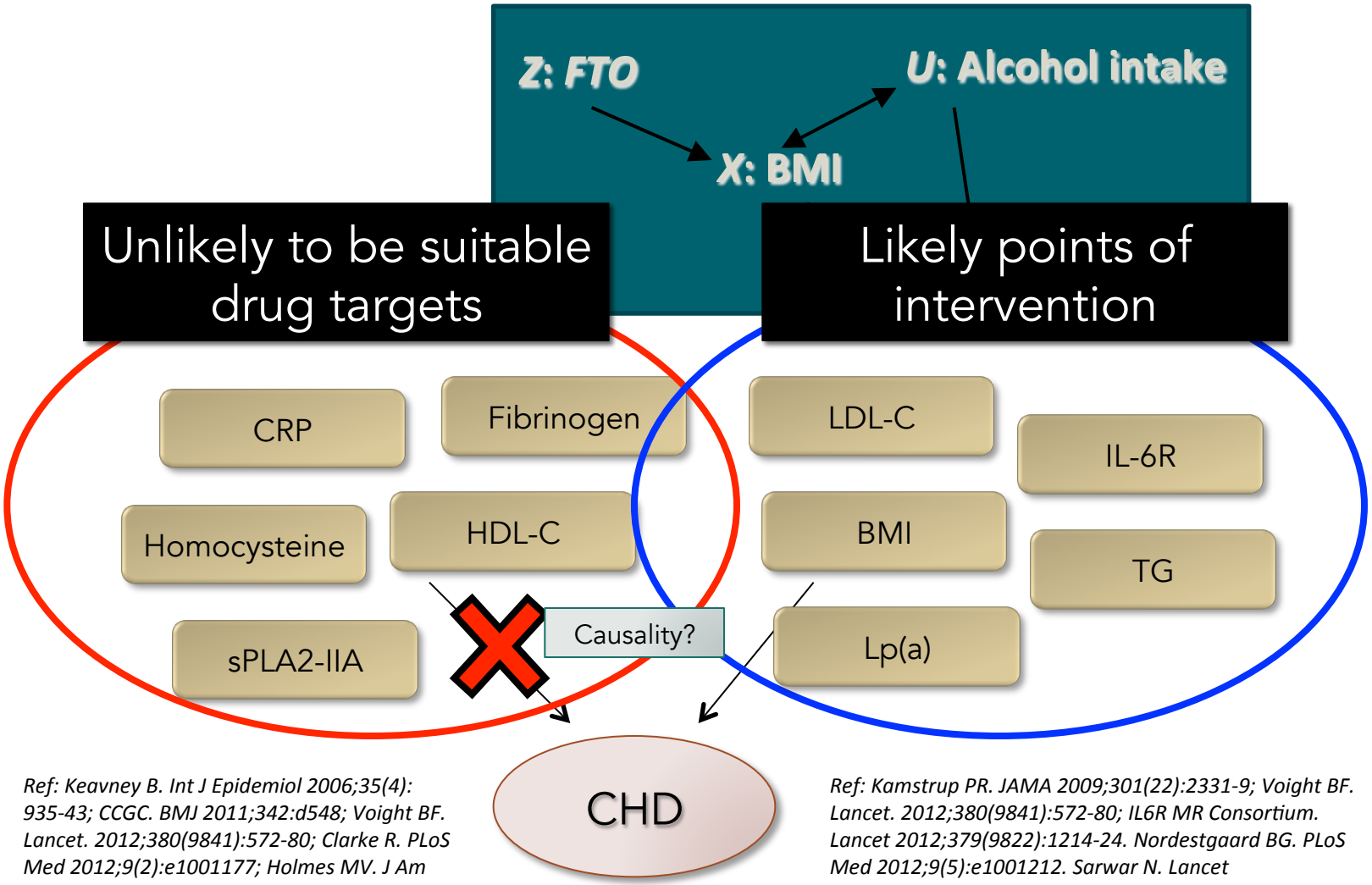
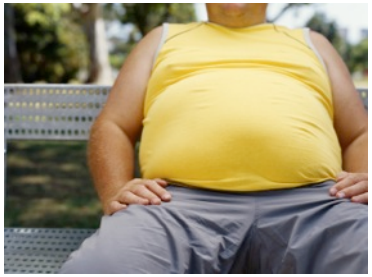
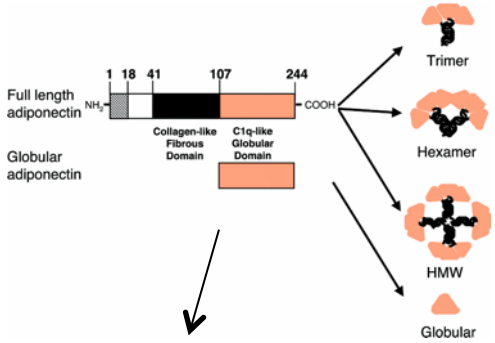


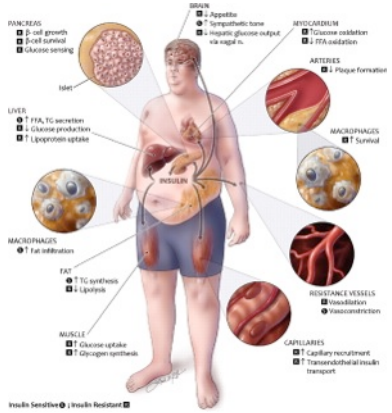
Ref: Keavney B. Int J Epidemiol 2006;35(4): 935-43; CCGC. BMJ 2011;342:d548; Voight BF. Lancet. 2012;380(9841):572-80; Clarke R. PLoS Med 2012;9(2):e1001177; Holmes MV. J Am Coll Cardiol 2013; 62(21):1966-76.

Ref: Kamstrup PR. JAMA 2009;301(22):2331-9; Voight BF. Lancet. 2012;380(9841):572-80; IL6R MR Consortium. Lancet 2012;379(9822):1214-24. Nordestgaard BG. PLoS Med 2012;9(5):e1001212. Sarwar N. Lancet 2010;375(9726):1634-9. GLGC. Nat Genet 2013;45(11): 1345-52

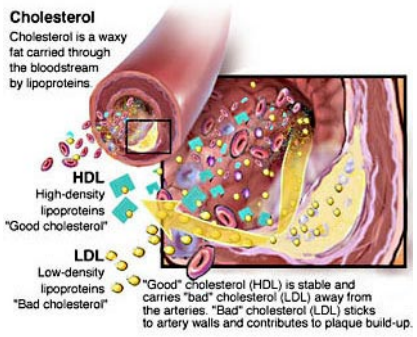
MR studies of obesity and insulin resistance







Tove Fall



Ref: Gao H et al. Diabetes 2013; 62(4):1338-44; Fall T et al. PLoS Med 2013; 10(6):e1001474; Fall T et al. Diabetes 2015; 64(5):1841-52; Fall T et al. Diabetes 2015; 64(7):2676-84; Hägg S et al. Int J Epidemiol. 2015;44(2):578-86.

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Concluding remarks

- GWAS has provided us with:
  - Hundreds of cardiovascular loci to follow-up upon
  - New knowledge about genetic architecture
  - Initial biological insights
- Now, we need to:
  - Establish causal variants and genes
  - Perform various kinds of follow-up studies to better understand biology and initiate translation
- Plenty of work, but many important discoveries to be made

Thanks for your attention!
Questions or comments?

THANKS TO MY SPONSORS: