

Integrative omics

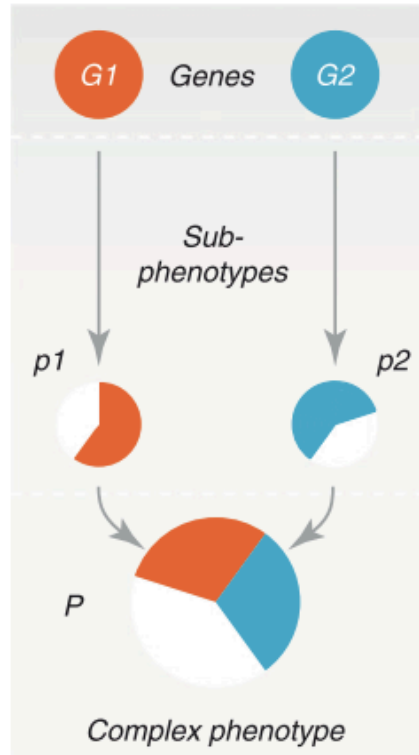
Michael Inouye
Baker Heart and Diabetes Institute
Univ of Melbourne / Monash Univ

Summer Institute in Statistical Genetics 2017
Integrative Genomics Module
Seattle

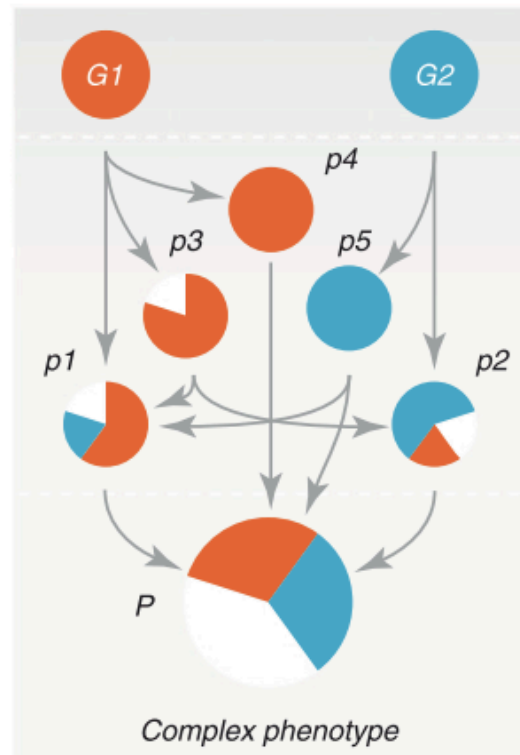
[@minouye271](https://twitter.com/minouye271)
www.inouyelab.org

Background

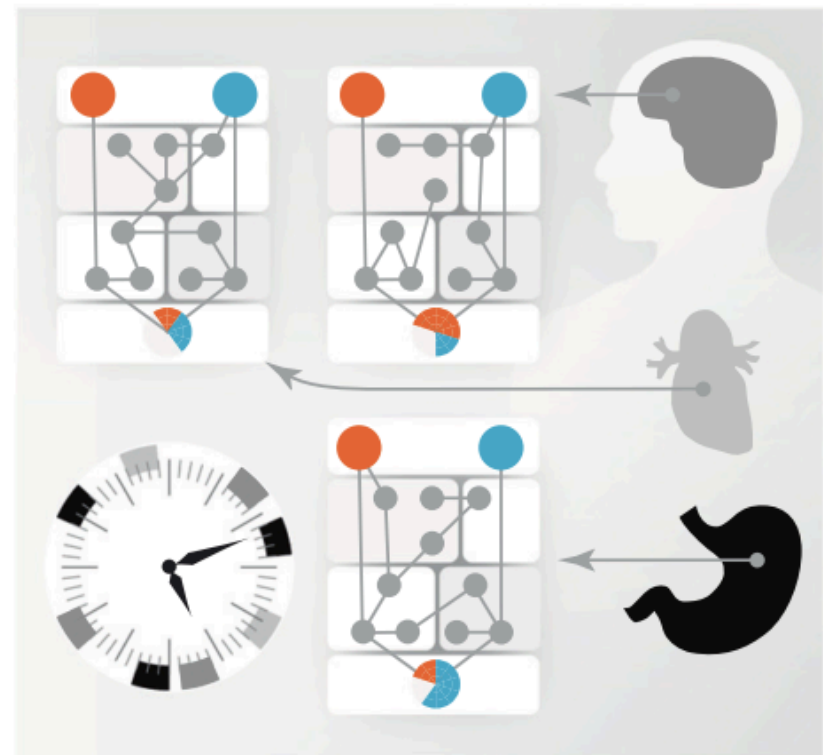
(a) Sub-phenotypes



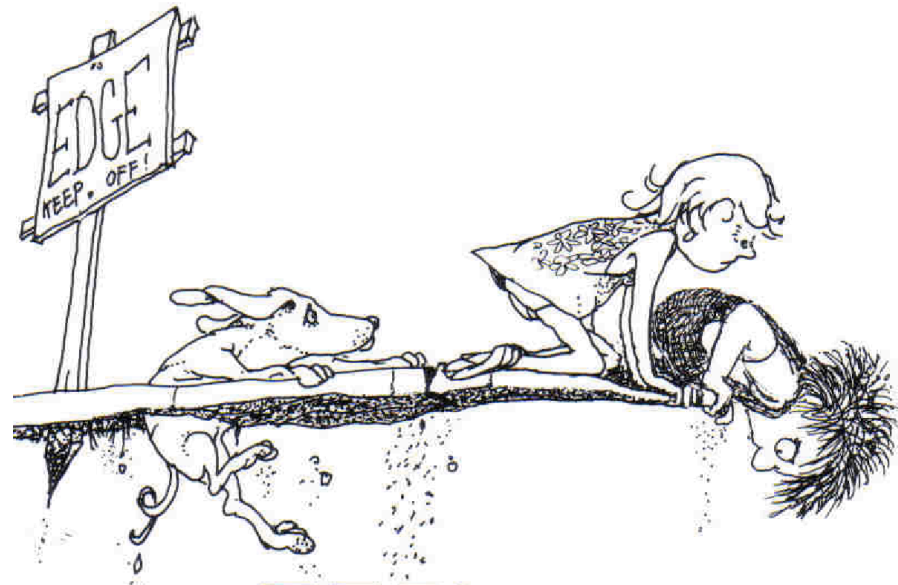
(b) Additional sub-phenotypes



(c) Multiple tissues, 'omics and time points



Where the sidewalk ends...



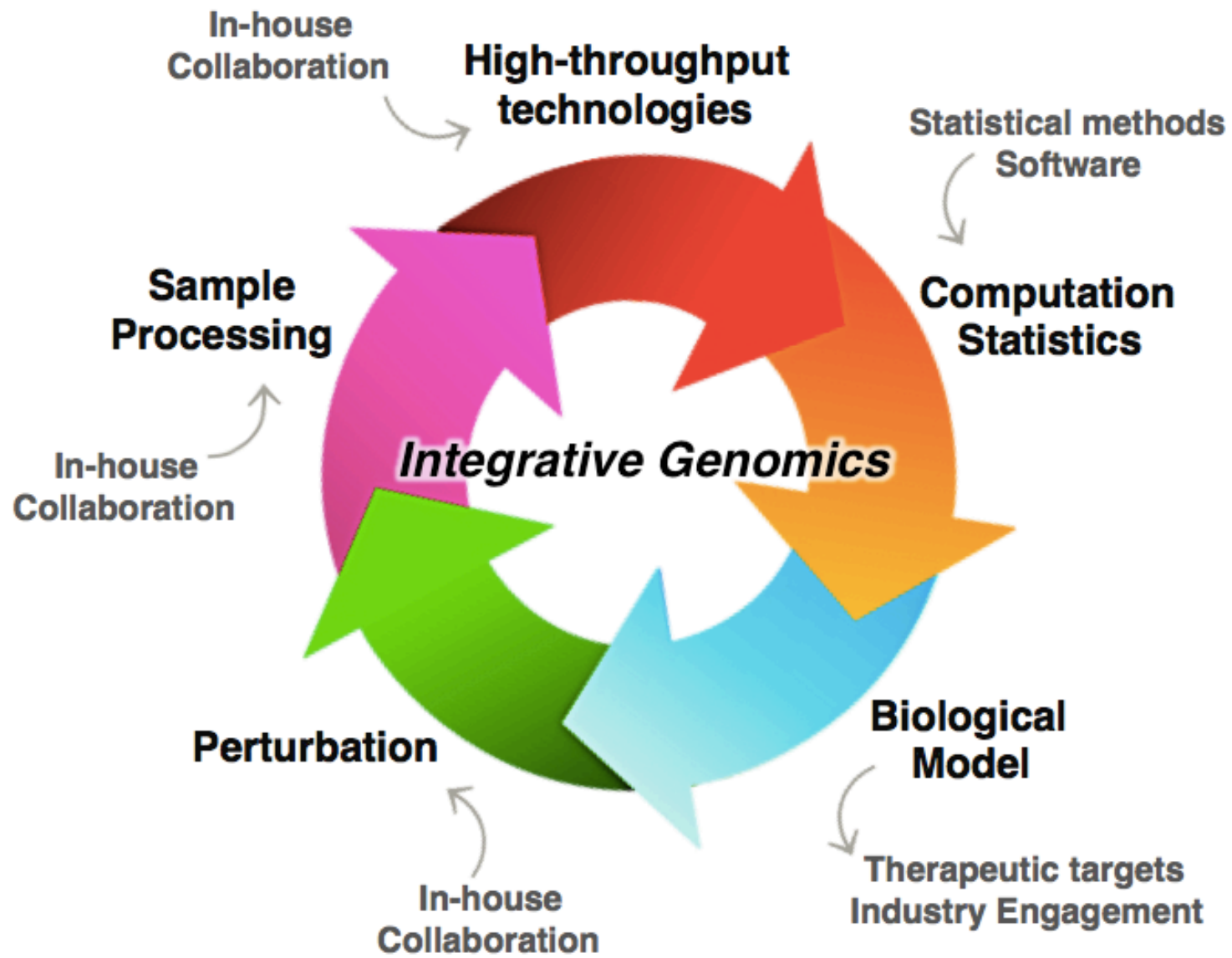
Integrative analysis is a relatively undeveloped area

Lots of scope for development and novel ideas

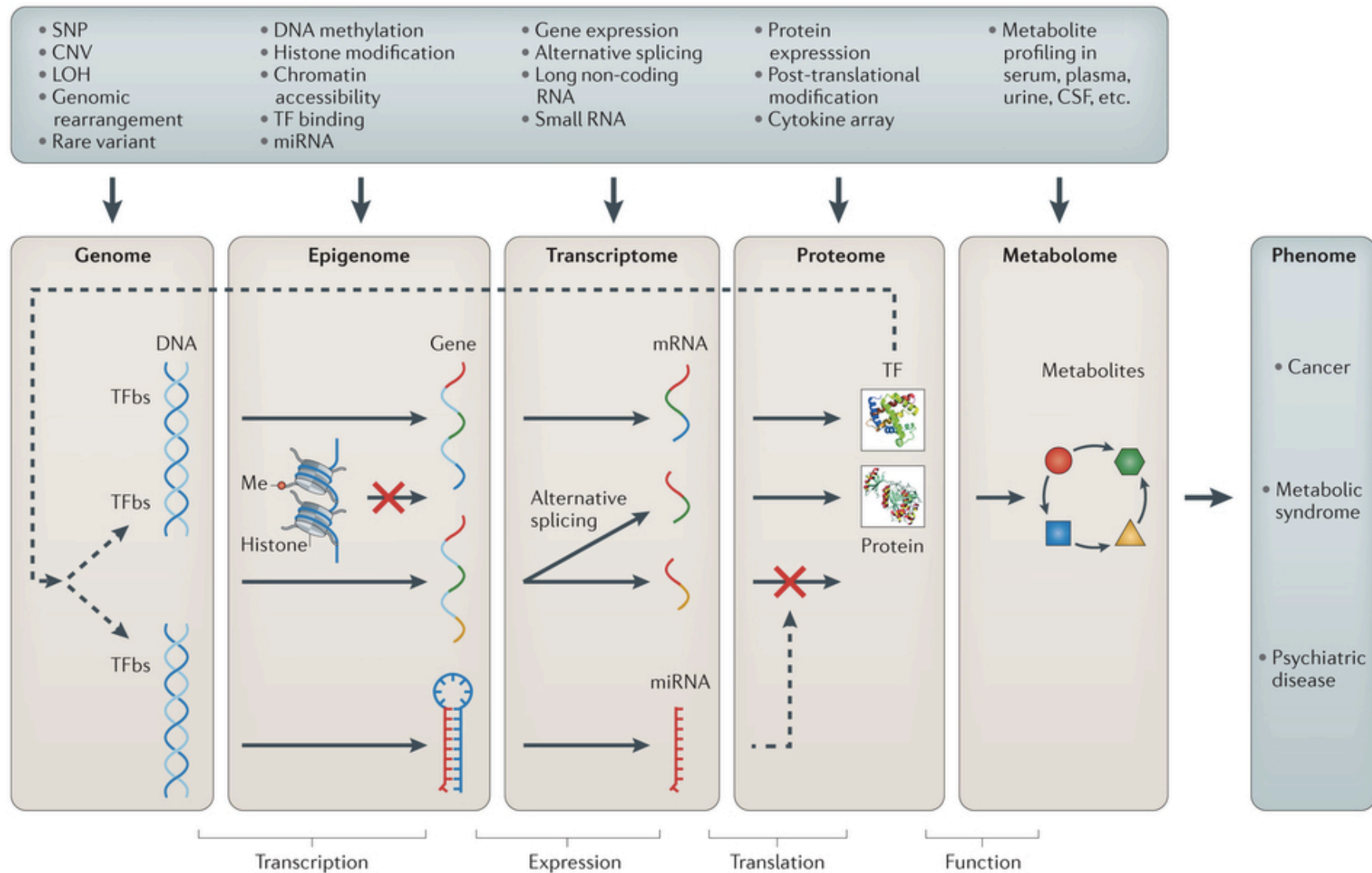
**Nothing close to consensus on analytical approaches
and strategies**

Why integrate?

- It's likely that variation within a single omic data type (e.g. genome) will not capture the complexity of the phenotype
- It may not explain all of phenotypic variance nor identify all the causal factors
- Integration may better explain phenotype and identify/characterise (multiple) pathways and intervention points to control phenotype



Biological framework for multi-omics



Challenges

- **Large P: High dimensionality**
 - 10K, 100K, 100M variables per sample
- **Small N**
- **Heterogeneous data**
 - Different molecules
 - Different technologies
 - Different sampling strategies
- **Correlation**
- **Computational efficiency/feasibility**

Main things to be aware of

- **Understand the biological models underlying the data**
 - Context and interpretation
- **Know the technology**
 - Batches, biases, error profiles, sensitivities/specificities, missing data
- **Know the sampling strategy(s)**
 - Group-wise (case/control), population-based, enrichments, stimuli?
- **Spend time exploring the data**
 - Without exception, you will see things that require follow up
- **Build analysis pipelines and log all analyses**
- **The data may be complex but your analysis and presentation doesn't have to be**

Role of transcriptome in integrative analyses

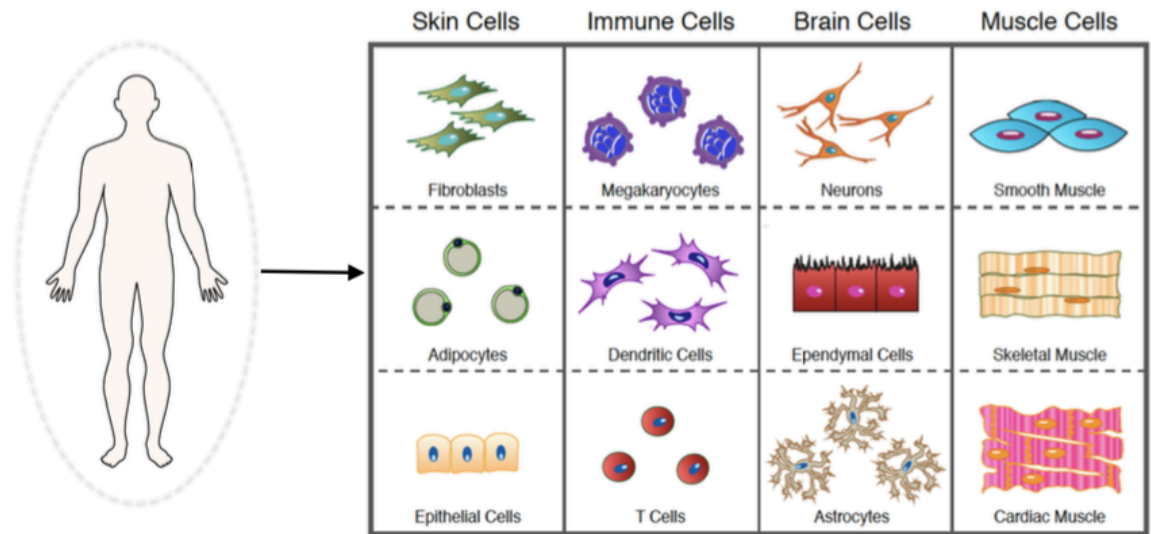
- Insights into biomolecular networks
- Less technical variability than proteomics
- Relatively affordable
- Stable tissues and cell types are (usually) readily available
- Many network methods have been applied to gene expression data in the past
- Gene expression is thus a convenient way to characterise the average biological state of the cell population(s) being assessed

A Google Maps for the Human Body

A group of scientists has taken the first important steps towards creating the Human Cell Atlas—a complete inventory of our staggeringly diverse cells.

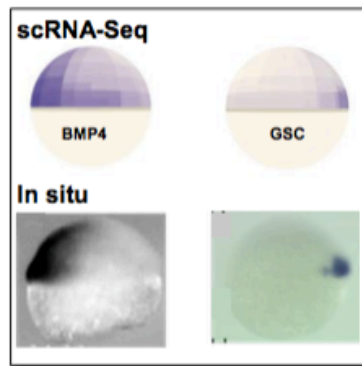
ED YONG | OCT 14, 2016 | SCIENCE

www.humancellatlas.org



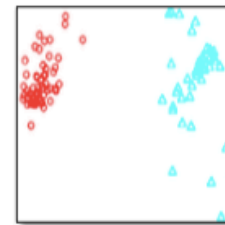
Human adult 2×10^{13} cells

LOCATION



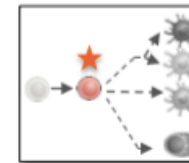
Fish embryo

TYPE



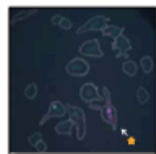
Retina neurons

LINEAGE

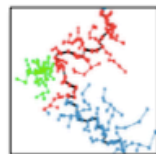


New human immune blood progenitor

TRANSITIONS

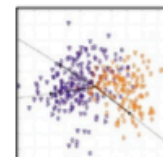


'Early responder' immune cells

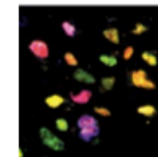


Muscle cell differentiation

STATE



Pathogenic T cells in MS model



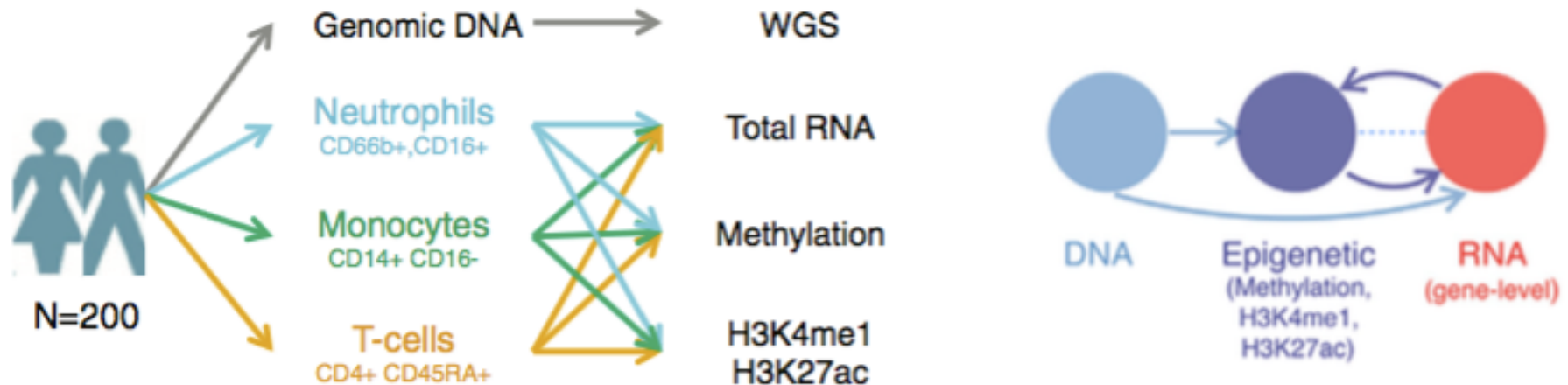
CSC spectrum in glioma

Regev & Teichmann

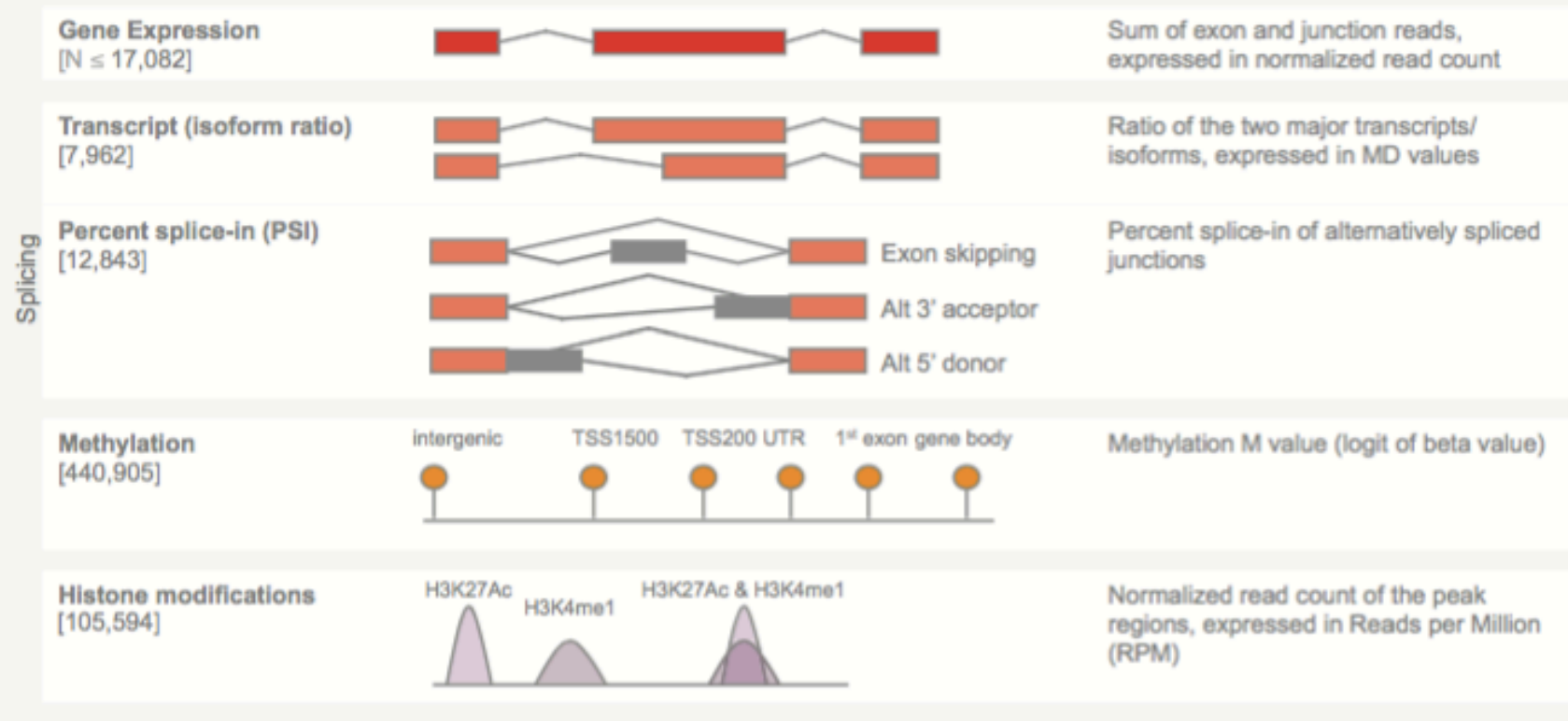
Genetic Drivers of Epigenetic and Transcriptional Variation in Human Immune Cells

Lu Chen,^{1,2,28} Bing Ge,^{3,28} Francesco Paolo Casale,^{4,28} Louella Vasquez,^{1,28} Tony Kwan,³ Diego Garrido-Martín,^{5,6} Stephen Watt,¹ Ying Yan,¹ Kousik Kundu,^{1,2} Simone Ecker,^{7,8} Avik Datta,⁹ David Richardson,⁹ Frances Burden,^{2,18} Daniel Mead,¹ Alice L. Mann,¹ Jose Maria Fernandez,⁷ Sophia Rowlston,^{2,18} Steven P. Wilder,¹⁰ Samantha Farrow,^{2,18} Xiaojian Shao,³ John J. Lambourne,^{3,2,18} Adriana Redensek,³ Cornelis A. Albers,^{13,16} Vyacheslav Amstislavskiy,¹⁴ Sofie Ashford,^{2,18} Kim Berentsen,¹⁵ Lorenzo Bomba,¹ Guillaume Bourque,³ David Bujold,³ Stephan Busche,³ Maxime Caron,³ Shu-Huang Chen,³ Warren Cheung,³ Oliver Delaneau,¹² Emmanouil T. Dermitzakis,¹² Heather Elding,¹ Irina Colgiu,¹⁷ Frederik O. Bagger,^{2,4,18} Paul Flicek,⁹ Ehsan Habibi,¹⁵ Valentina Iotchkova,^{1,11} Eva Janssen-Megens,¹⁵ Bowon Kim,¹⁵ Hans Lehrach,¹⁴ Ernesto Lowy,⁹ Amit Mandoli,¹⁵ Filomena Matarese,¹⁵ Matthew T. Maurano,¹⁹ John A. Morris,³ Vera Pancaldi,⁷ Farzin Pourfarzad,²⁰ Karola Rehnstrom,^{2,18} Augusto Rendon,^{2,21} Thomas Risch,¹⁴ Nilofar Sharifi,¹⁵ Marie-Michelle Simon,³ Marc Sultan,¹⁴ Alfonso Valencia,⁷ Klaudia Walter,¹ Shuang-Yin Wang,¹⁵ Mattia Frontini,^{2,18,22} Stylianos E. Antonarakis,¹² Laura Clarke,⁹ Marie-Laure Yaspo,¹⁴ Stephan Beck,⁸ Roderic Guigo,^{5,6,23} Daniel Rico,^{7,24} Joost H.A. Martens,¹⁵ Willem H. Ouwehand,^{1,2,18,22,25} Taco W. Kuijpers,^{2,20,26} Dirk S. Paul,^{8,27} Hendrik G. Stunnenberg,¹⁵ Oliver Stegle,⁴ Kate Downes,^{2,18} Tomi Pastinen,^{3,*} and Nicole Soranzo^{1,2,22,25,29,*}

Cell 167, 1398–1414 (2016)



Molecular Data Traits



Variance
Decomposition

Quantitative
Trait Loci

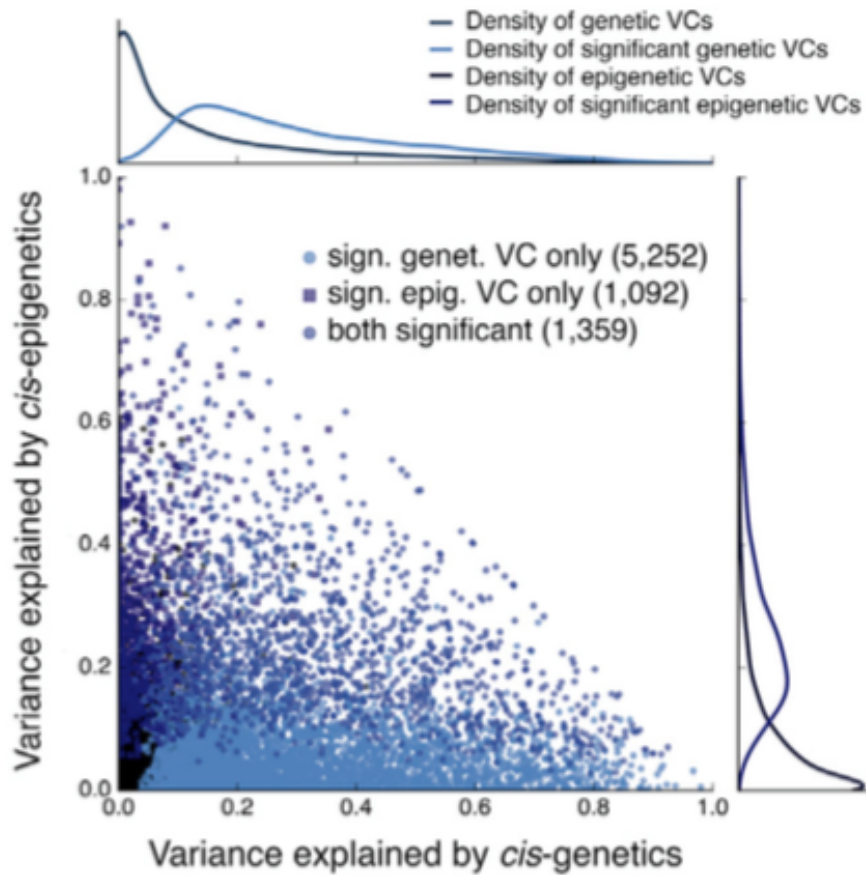
Alleles-specific
Analysis

Disease
Integration

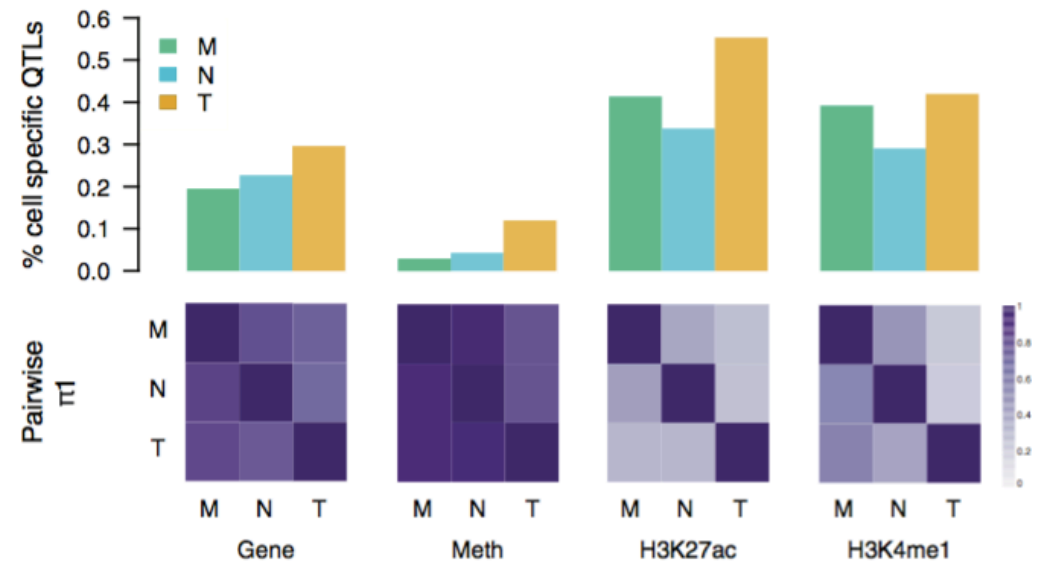
LIMIX: Lippert et al, *BioRxiv* 2016

Chen et al, *Cell* 2016

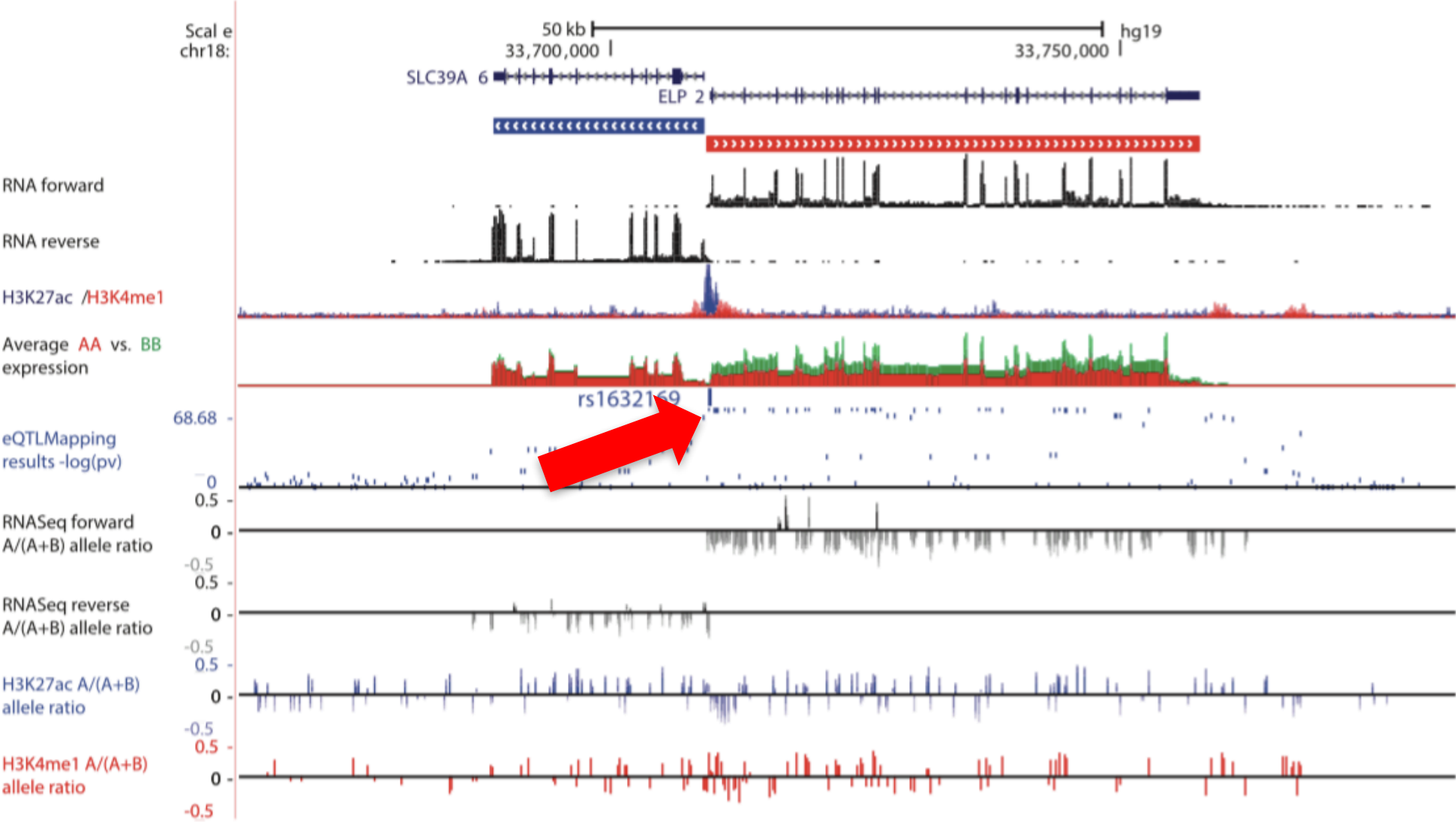
Is a gene's (monocyte) transcription dominated by genetic or epigenetic effects?



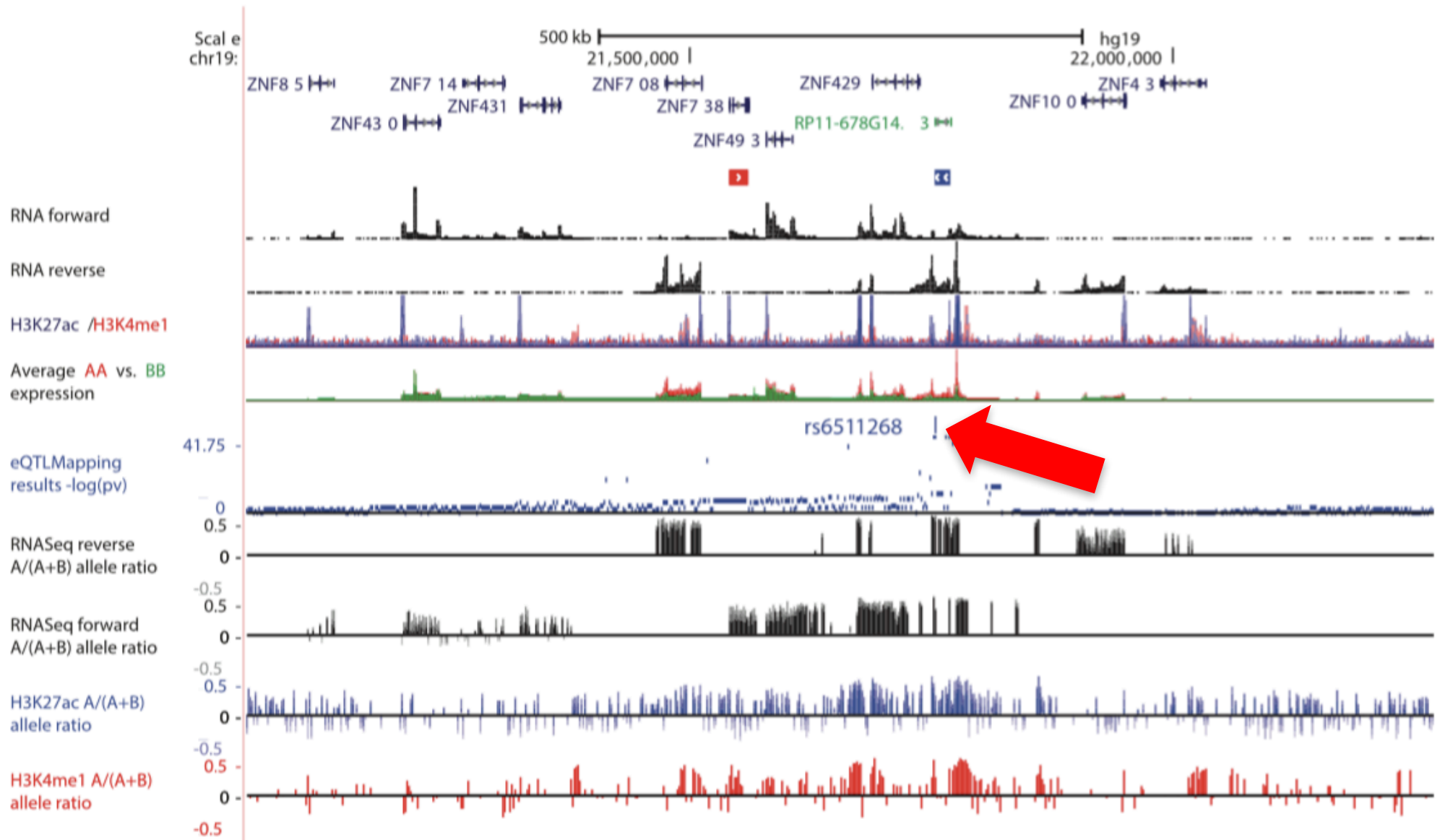
Shared QTLs between cell types



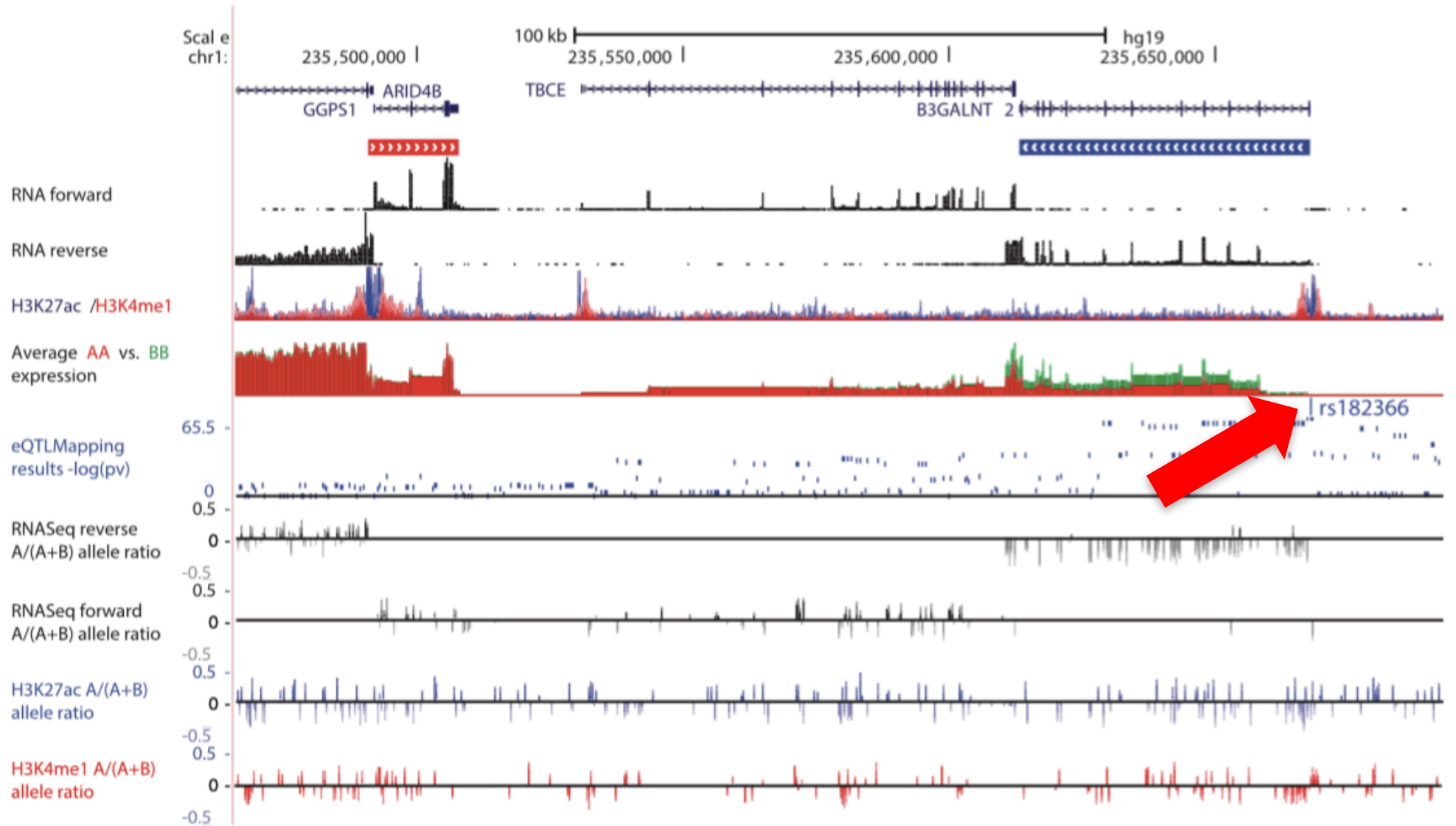
eSNP effects at a bidirectional promoter for *SLC39A6* and *ELP2*



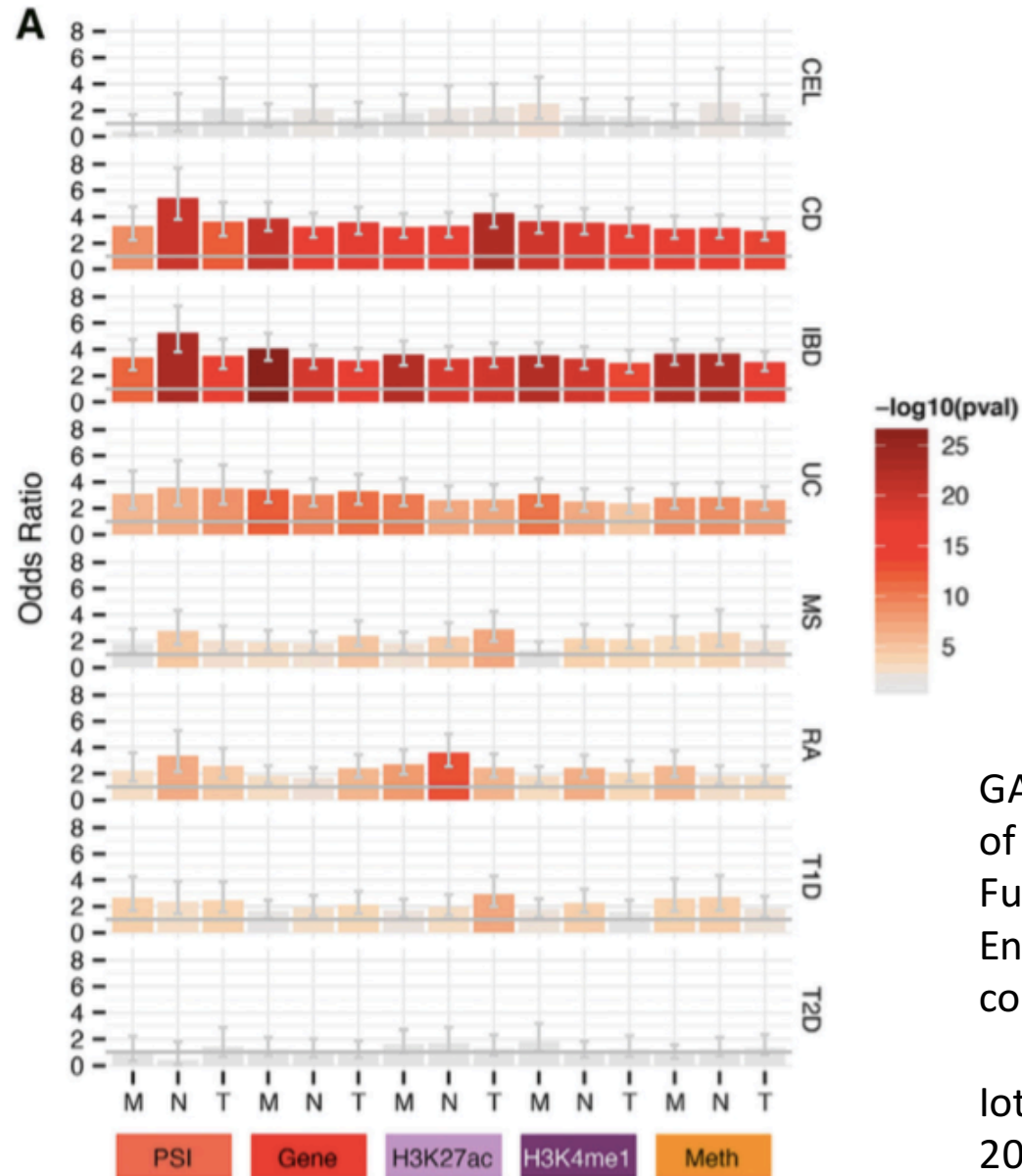
eSNP effects on chromatin and forward/reverse strand expression



eSNP effects *B3GALNT* & *ARID4B* promoters but only *B3GALNT* expression



Enrichment of cell type specific QTLs at autoimmune loci



GARFIELD - GWAS Analysis of Regulatory or Functional Information Enrichment with LD correction.

lotchkova et al *BioRxiv* 2016

Integrative analysis of genomic, transcriptomic & metabolomic variation



DILGOM: 590 randomly sampled individuals



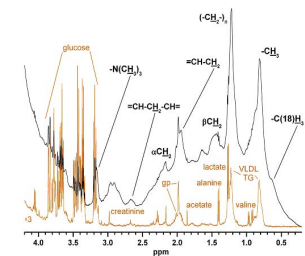
Fasting whole blood



Genome

Transcriptome

Metabolome



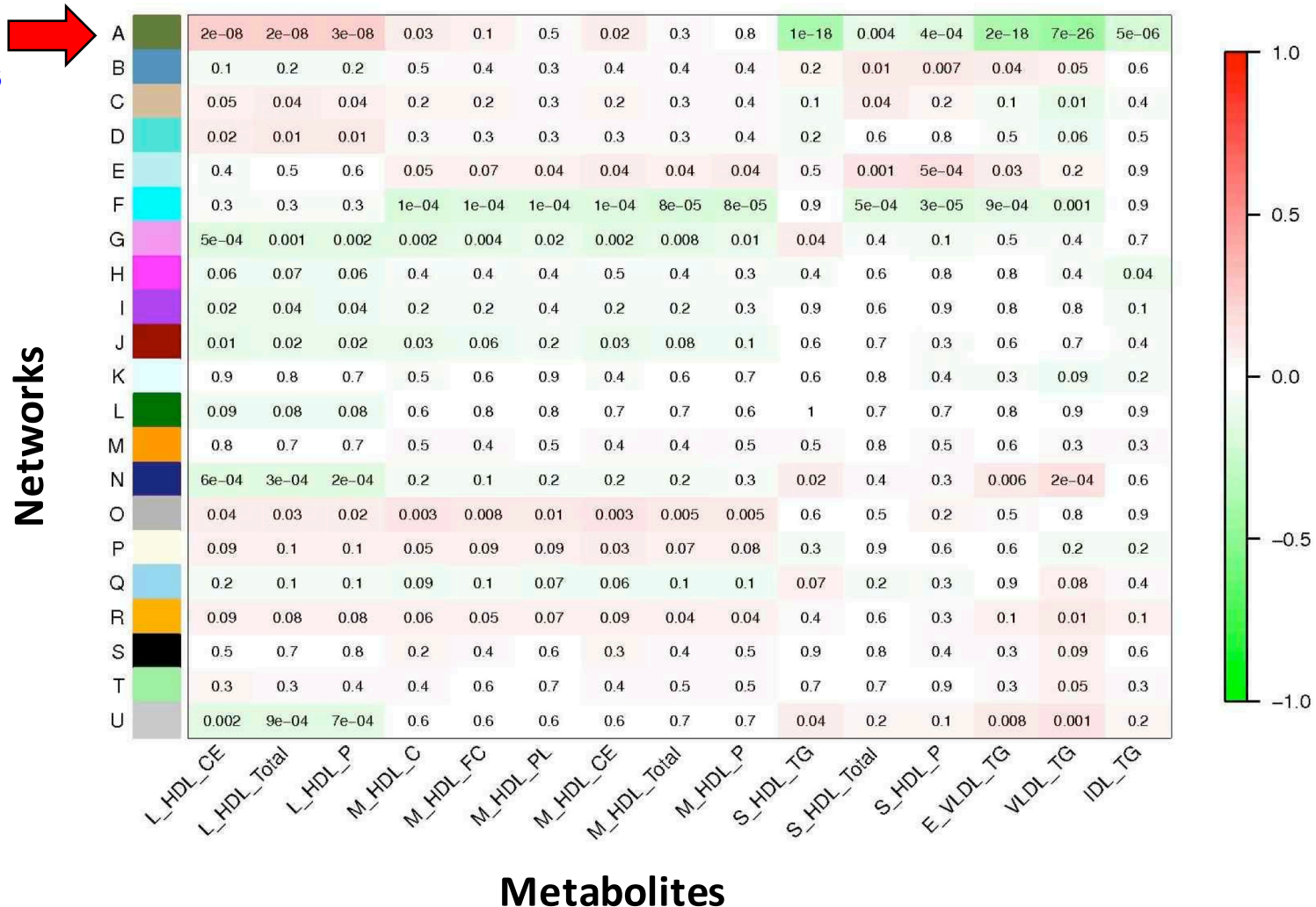
+ clinical data

Inouye *PLoS Genetics* 2010

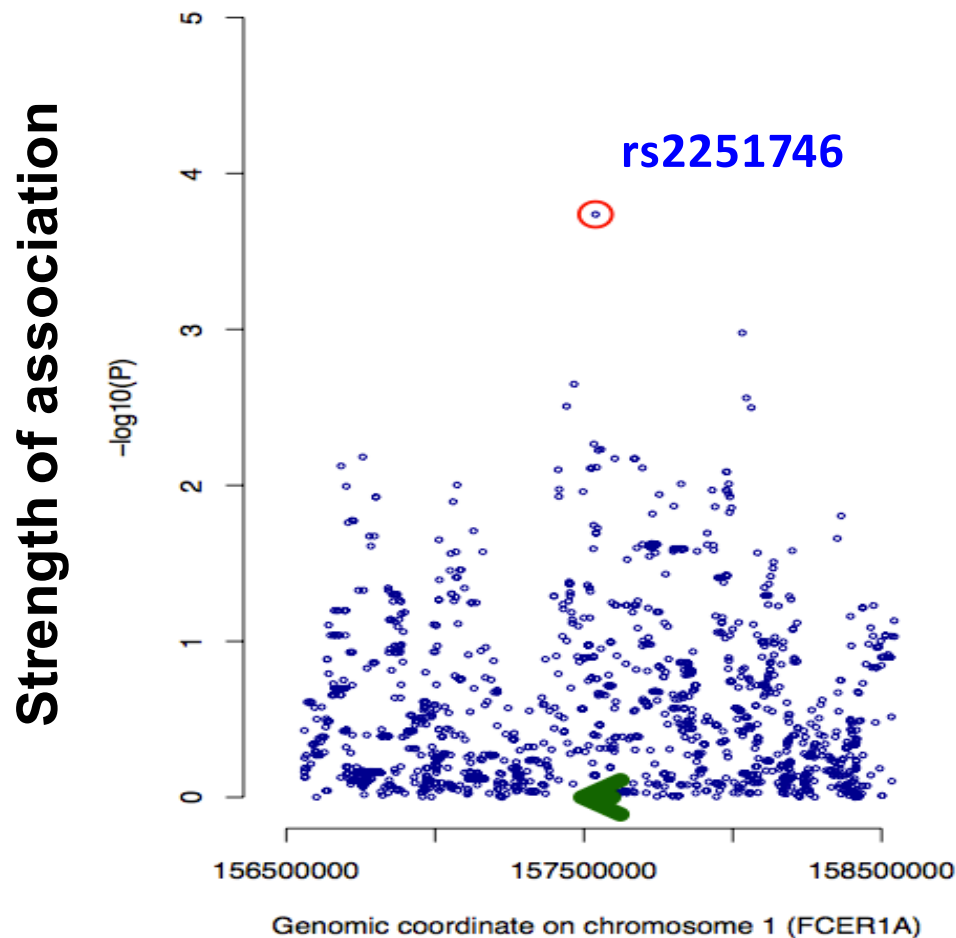


Relationships between gene networks and metabolome

83 / 134
metabolites



Does genetic variation influence LL module?



FCER1A $P = 1.83 \times 10^{-4}$
LL module $P = 4.28 \times 10^{-6}$

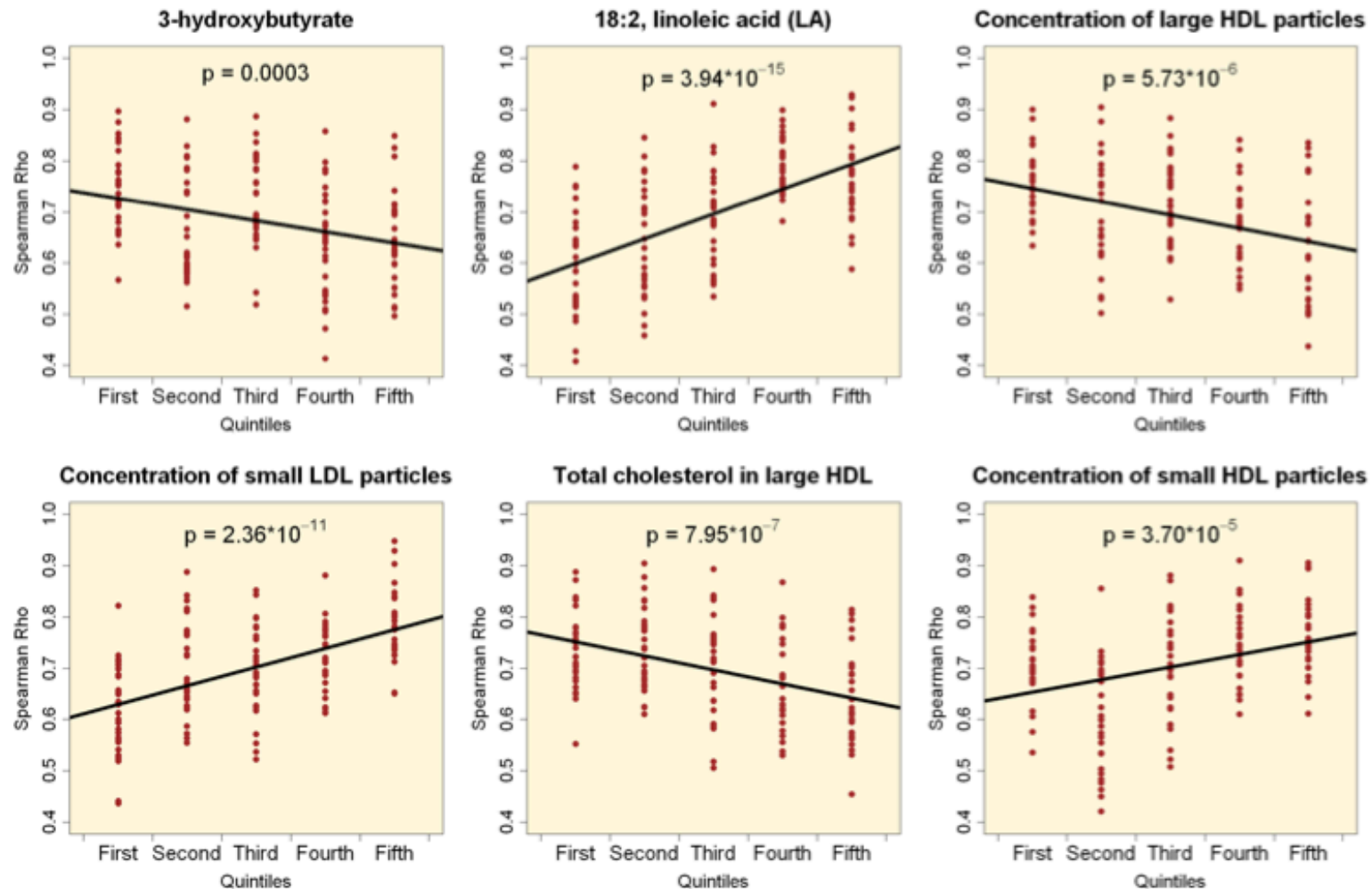
OPEN ACCESS Freely available online

PLoS GENETICS

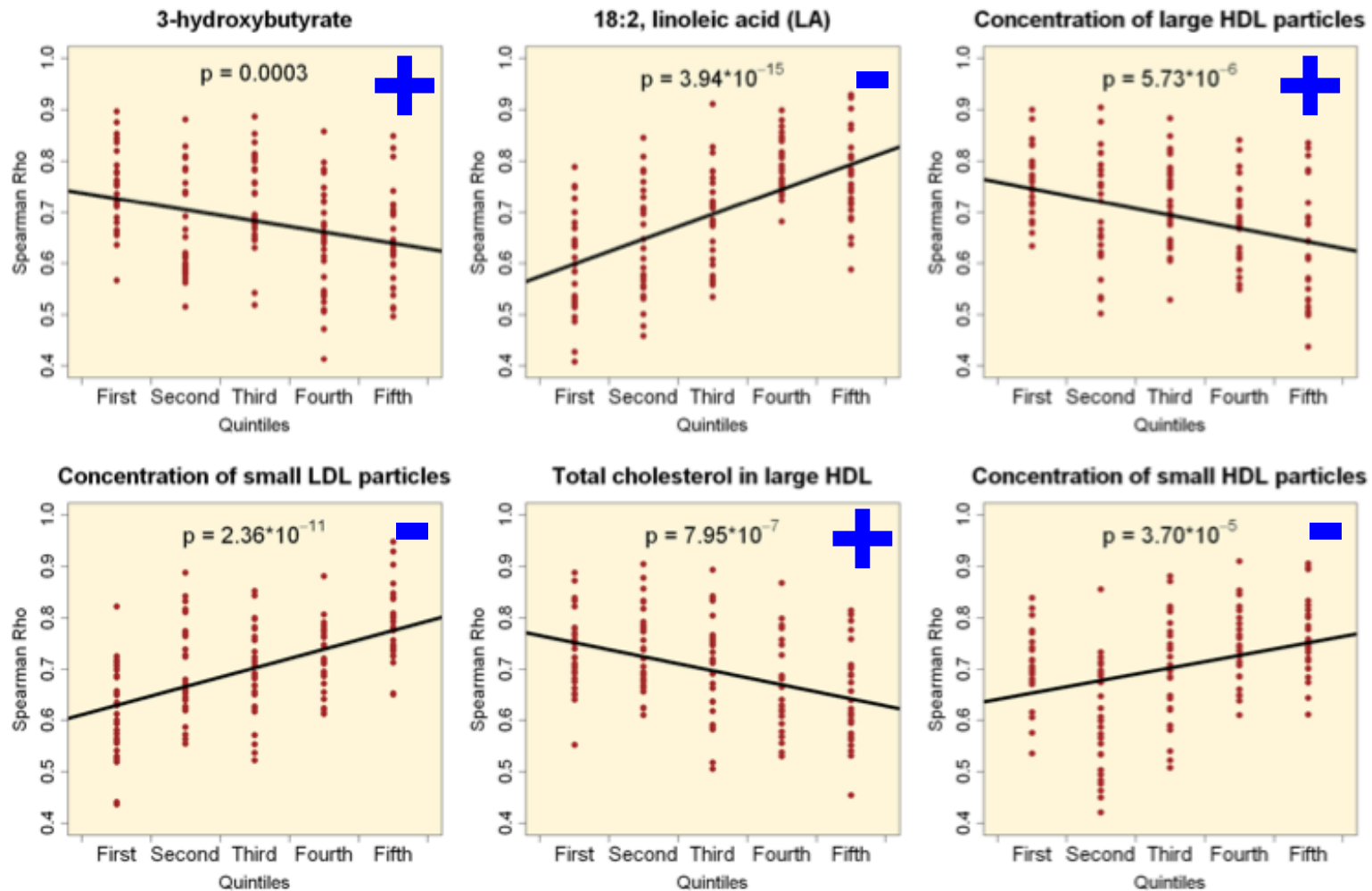
Genome-Wide Scan on Total Serum IgE Levels Identifies *FCER1A* as Novel Susceptibility Locus

Stephan Weidinger^{1,2,9,*}, Christian Gieger^{3,4,9}, Elke Rodriguez², Hansjörg Baurecht^{2,5}, Martin Mempel^{1,2}, Norman Klopp³, Henning Gohlke³, Stefan Wagenpfeil^{5,6}, Markus Ollert^{1,2}, Johannes Ring¹, Heidrun Behrendt², Joachim Heinrich³, Natalija Novak⁷, Thomas Bieber⁷, Ursula Krämer⁸, Dietrich Berdel⁹, Andrea von Berg⁹, Carl Peter Bauer¹⁰, Olf Herbarth¹¹, Sibylle Koletzko¹², Holger Prokisch^{13,14}, Divya Mehta^{13,14}, Thomas Meitinger^{13,14}, Martin Depner¹², Erika von Mutius¹², Liming Liang¹⁵, Miriam Moffatt¹⁶, William Cookson¹⁶, Michael Kabesch¹², H.-Erich Wichmann^{3,4}, Thomas Illig³

LL module appears reactive, do metabolites affect its connectivity?



Potential negative feedback loop

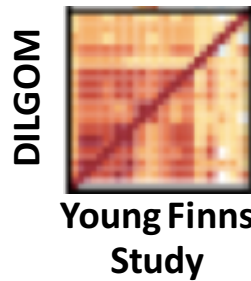


IgE signaling subnetwork at the transcriptome - metabolome interface

Independent replication of subnetwork and metabolite associations

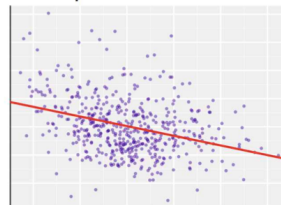
Natural human knockouts
36,000 exomes (SISu)

Gene-gene correlations



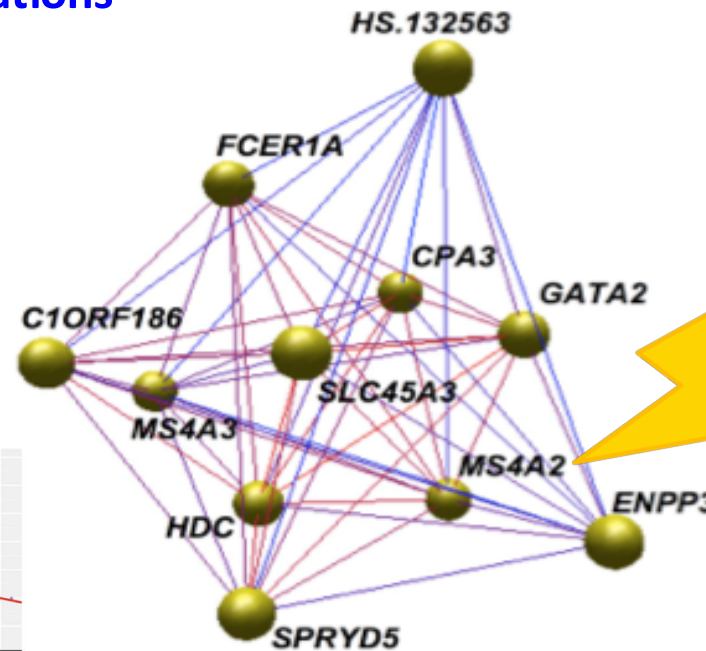
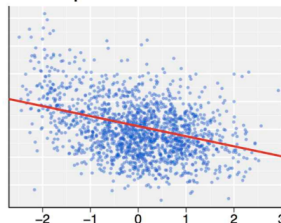
$p = 1.13 \times 10^{-15}$

DILGOM
N=518

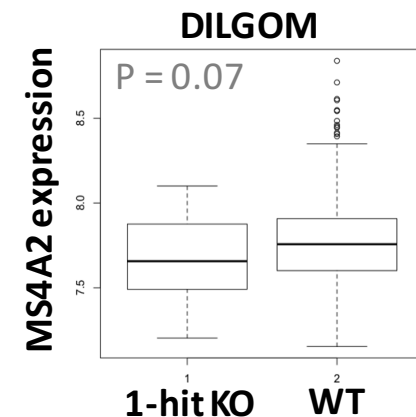


$p = 4.63 \times 10^{-51}$

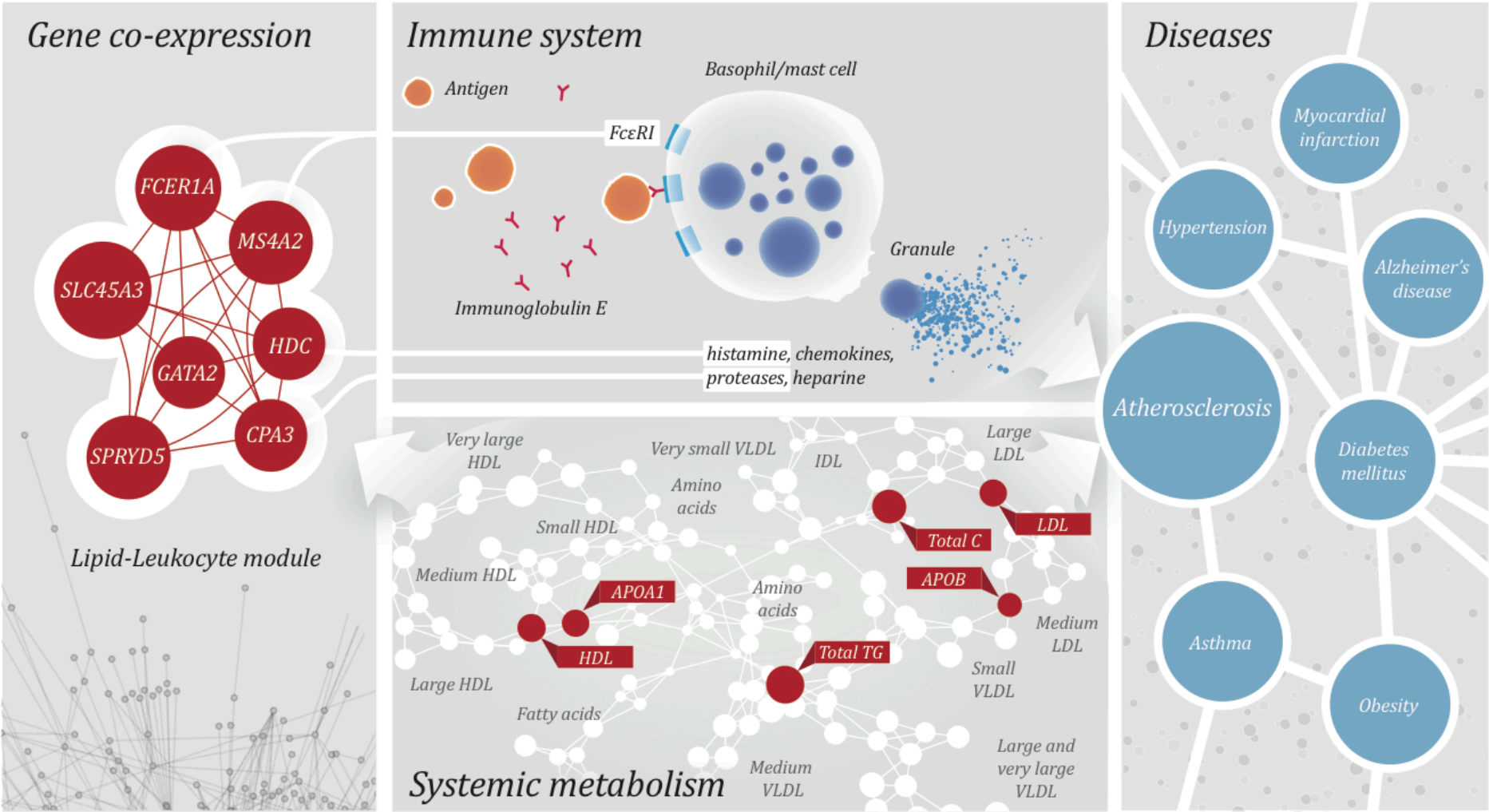
YFS
N=1,400



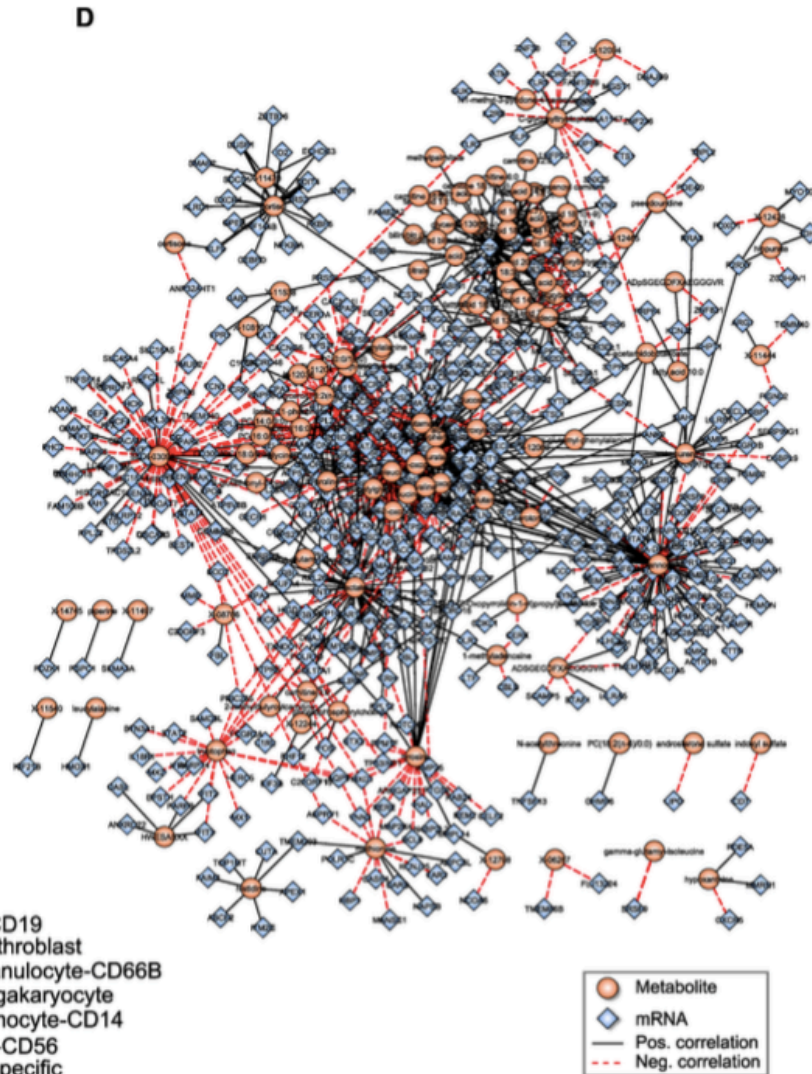
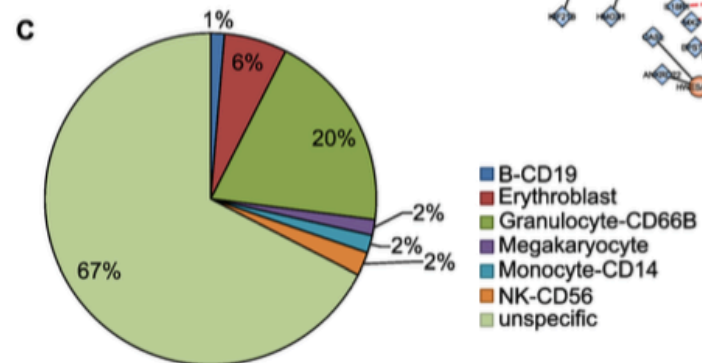
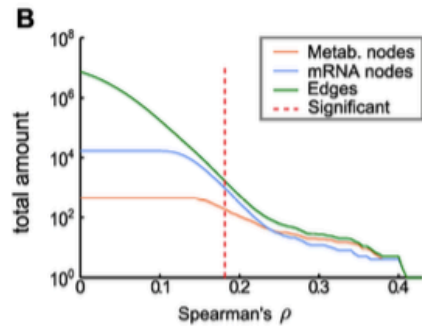
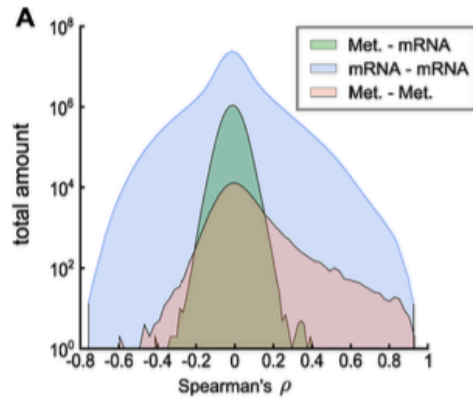
1-hit KO *MS4A2* → ↑ Circulating triglycerides



Constructing a working biological model

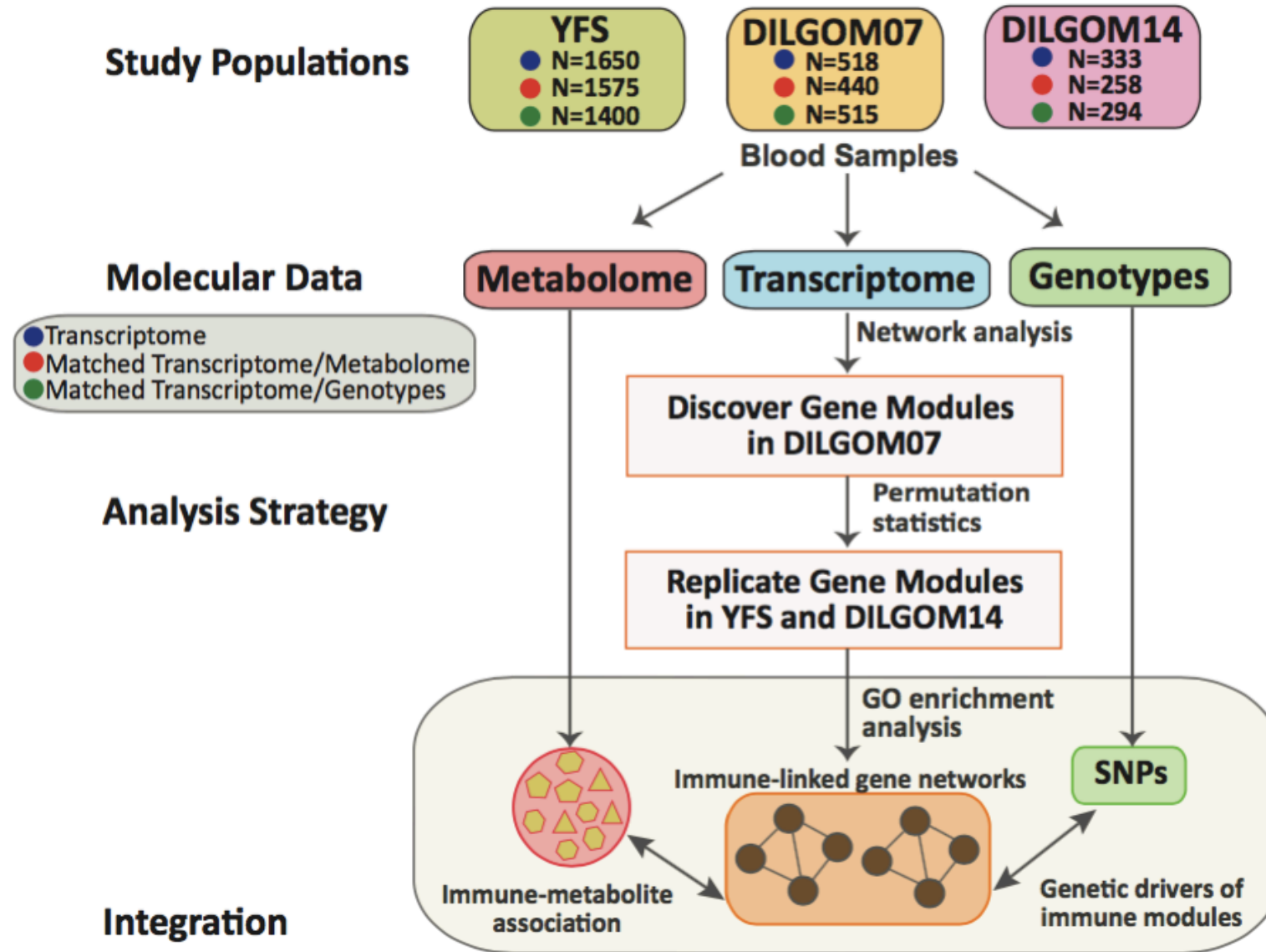


External validation

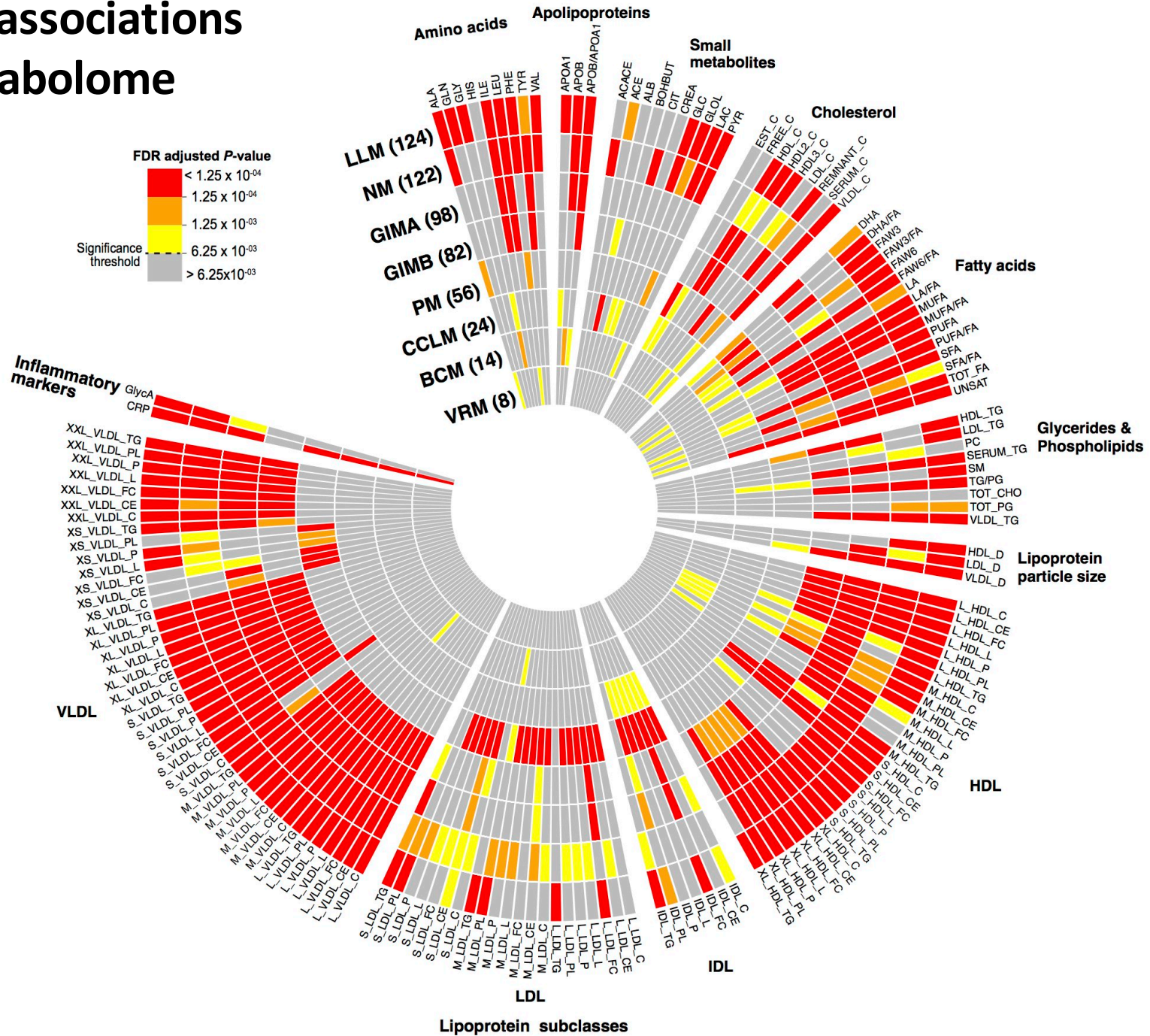


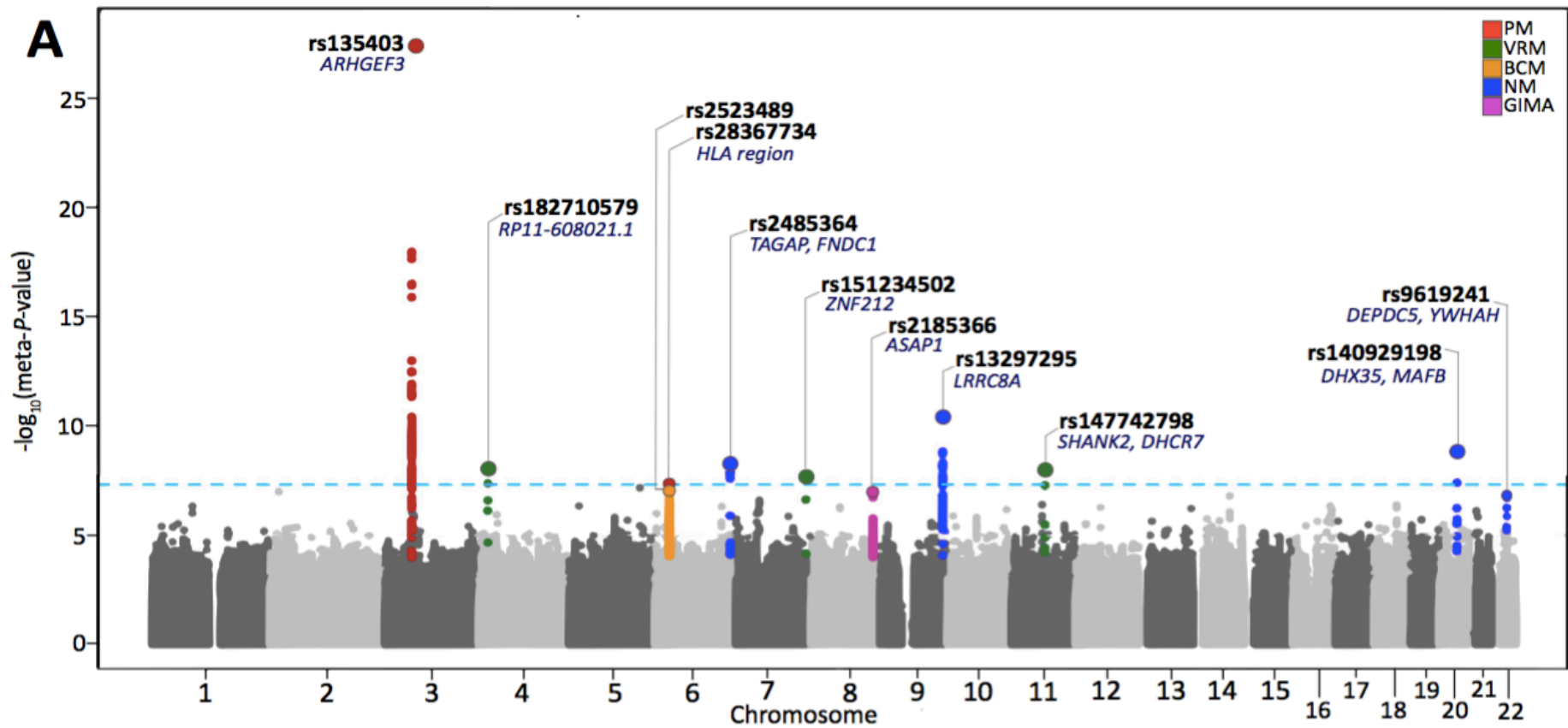
KORA cohort
N=700

N = 2,200



Blood transcriptional network associations with metabolome





Summary

- **Integrative omics is a highly promising and evolving field with many challenges to be addressed**
- **Transcriptome and scRNA-seq are rapidly advancing in size and scope**
- **Global patterns vs intriguing specific examples**
- **Transcriptome-metabolome (and microbiota-metabolome) interactions are extensive**

Accessible resources for integrative genomics

- SageBase (via Sage BioNetworks)
- UK BioBank
- ImmGen
- ImmVar
- ENCODE
- THL Biobank
- TwinsUK
- iHMP / HMP2
- GTEx
- Epigenomics Roadmap Project
- Collaborative Cross (~outbred mice)
- Coming Soon: Precision Medicine Initiative