Introduction to Genomics

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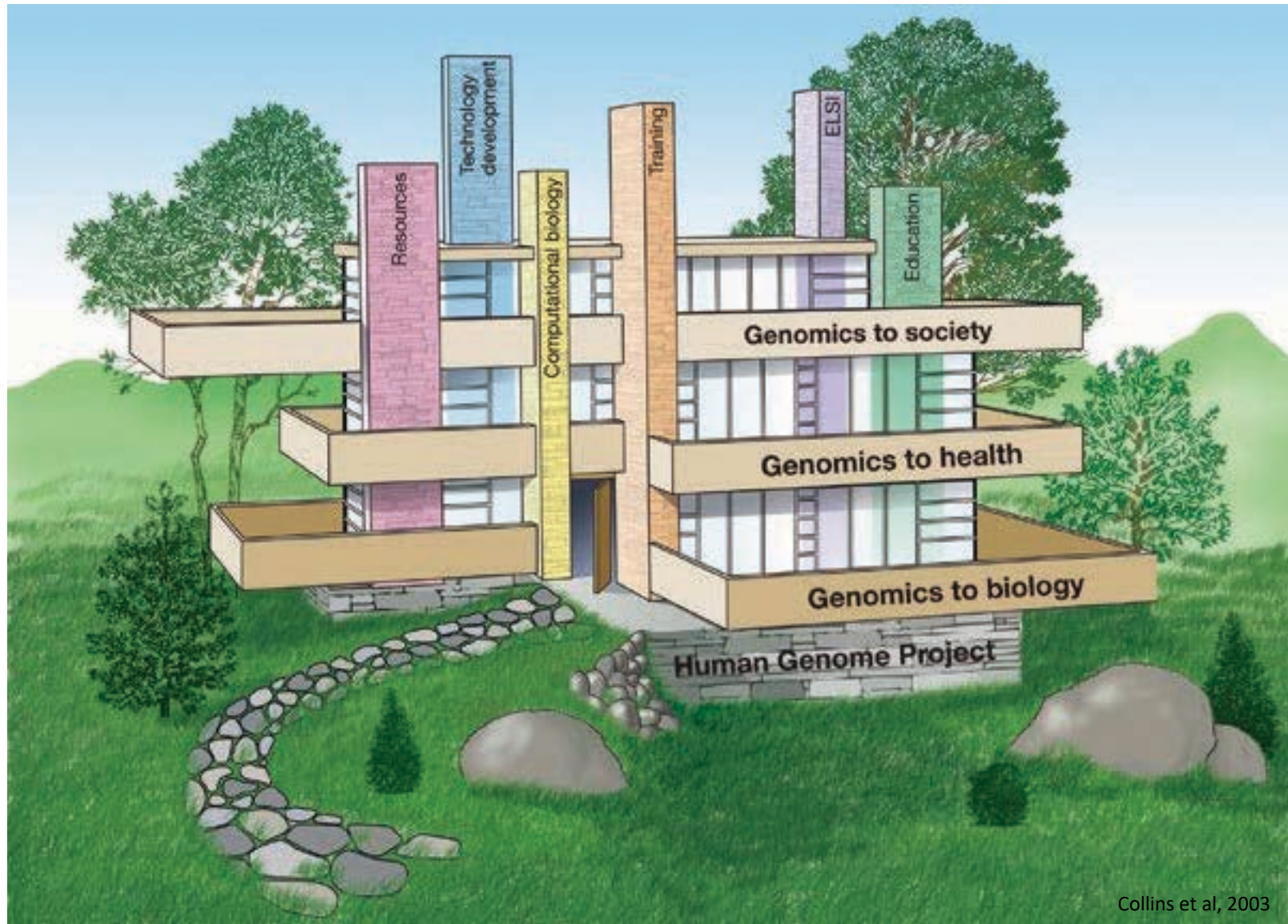www.lucalab.org

@fluca2406

Outline

- Introduction to Genomics
- Ancestry, environmental factors and disease risk
- Psychosocial factors, genetics and asthma

Phenotypic variation in humans

# From the Human Genome Project to Genomic Research

Collins et al, 2003

The essence of genomics

Genomics grew primarily out of human genetics and molecular biology.

- **Comprehensiveness.** Genomics aims to generate complete data sets.

- **Scale.** Large-scale efforts
  - large interdisciplinary consortia;
  - robust data standards
  - computational intensity

- **Technology development.** High-throughput, low-cost data production.

- **Rapid data release.** Large data catalogues and analytical tools are community resources.

- **Social and ethical implications.**

Whole genome sequencing becomes affordable enabling Genomic Research
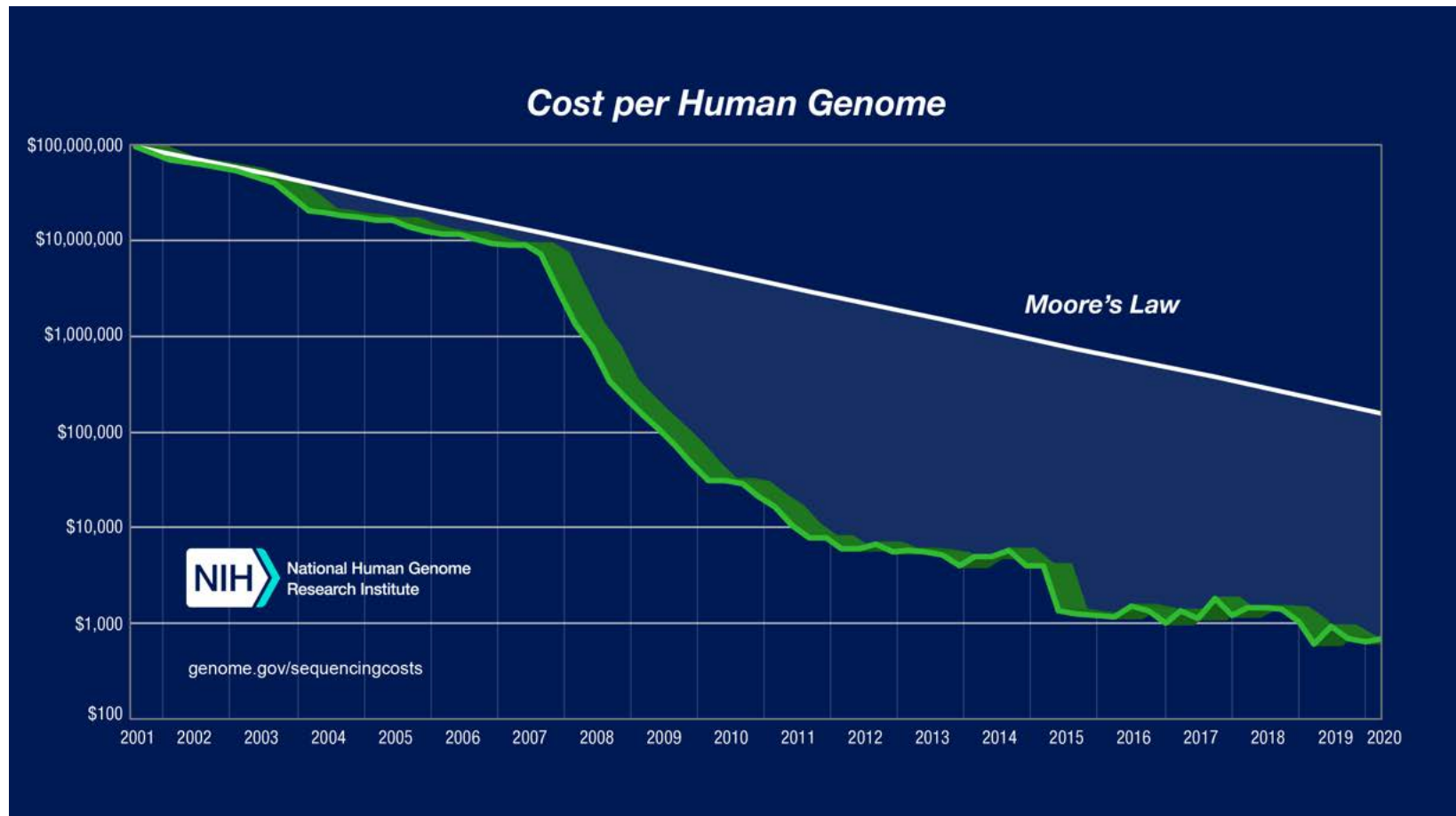
Genomics impact on Society

Many parts of our daily lives are influenced by genomic information and technologies
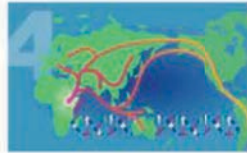

Social Context >

Direct-to-Consumer Genomic Testing >
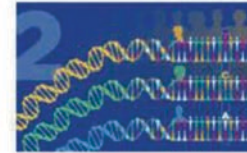
Pharmacogenomics >

Agriculture >

Human Origins and Ancestry >

Human Genomic Variation >

An individual's phenotype can be accurately predicted from their genotype only for a limited set of rare conditions
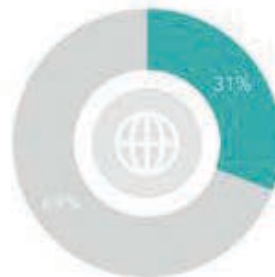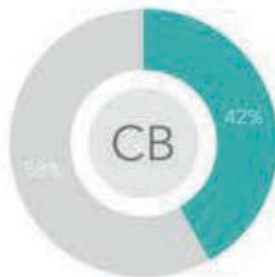
Photic Sneeze

Do you sneeze after going from a dark room out into bright sunlight? Even if you don't, chances are you have a friend who does. This unusual "photic sneeze reflex" is at least partly genetic.

Photic Sneeze Reflex   What You Can Do

Cordell, you are not likely to sneeze when suddenly exposed to bright sunlight.

58% of customers who are genetically similar to you don't sneeze when exposed to bright sunlight.

CB   42%   31%

Your genetic likelihood		European ancestry customers	
Photic sneeze reflex	42%	31%	Photic sneeze reflex
No photic sneeze reflex	58%	69%	No photic sneeze reflex
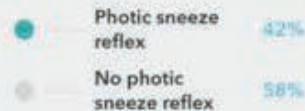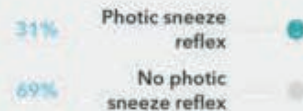
This prediction best applies to customers of European descent. We analyzed over 110,000 customers who consented to research to identify genetic markers associated with the photic sneeze reflex. Our prediction is based on your results at 54 genetic markers, as well as your age and sex.

Source: 23andme.com

For most human traits we can only predict risk and with very limited accuracy

Why is it difficult to predict complex traits from genetic sequences?

1. Each genetic variants associated with a complex trait has a very small effect on the phenotype and many are necessary to modify the phenotype.

Finding the genetic basis of complex traits: Genome Wide Association Studies (GWAS)
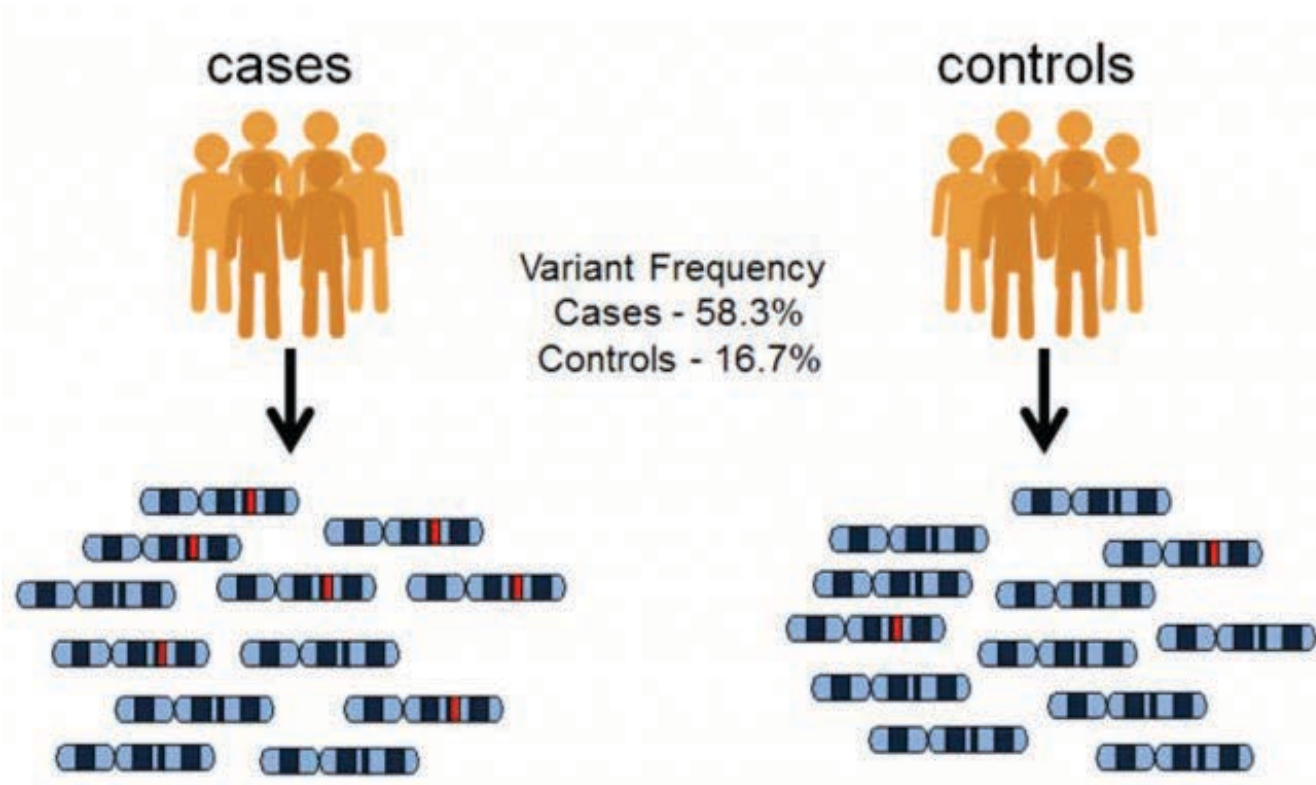
Finding the genetic basis of complex traits: Genome Wide Association Studies (GWAS)

Genome-wide association studies (GWAS) are discovering thousands of genetic variants associated with human phenotypic variation

Controls

Cases

Compare differences to discover SNPs associated with trait

SNPs associated with Cardiovascular Disease in the GWAS catalog
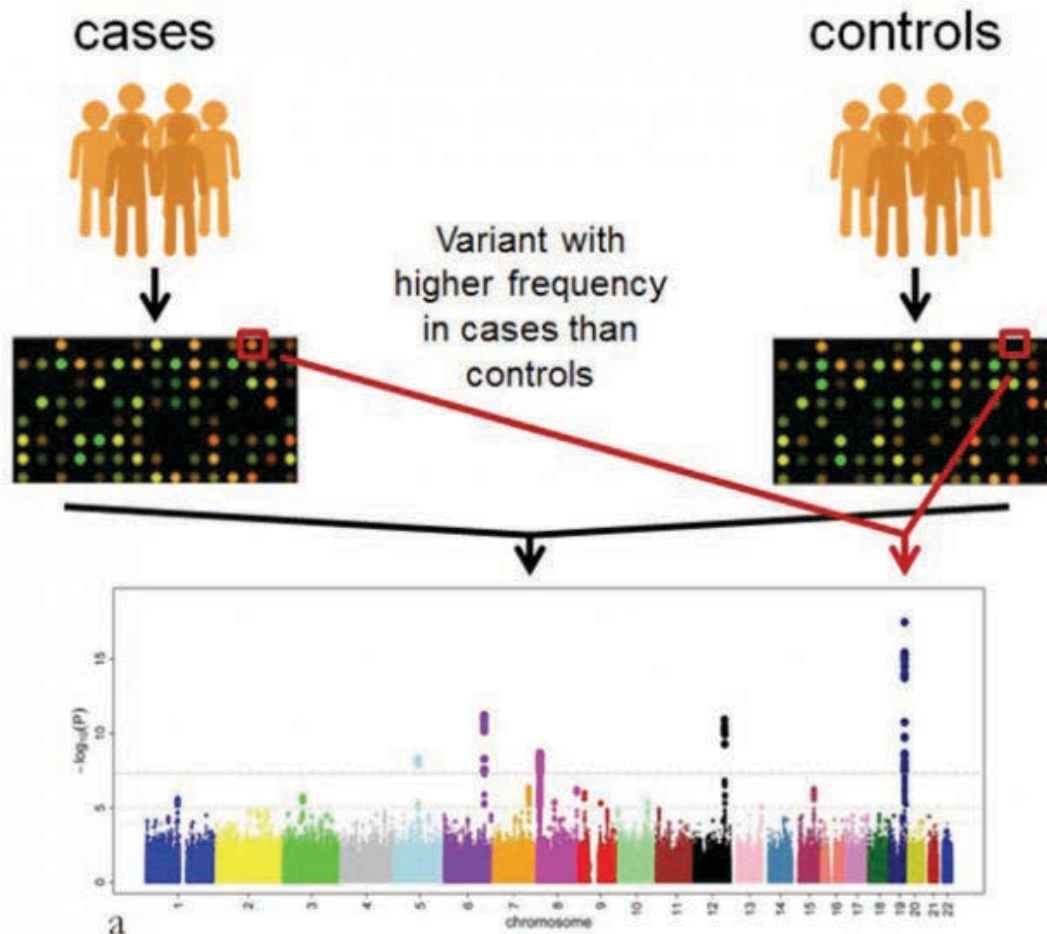
GWAS catalog, 2020

Why is it difficult to predict complex traits from genetic sequences?

1. Each genetic variants associated with a complex trait has a very small effect on the phenotype and many are necessary to modify the phenotype.

2. Genetic variants associated with complex traits tend to occur in regulatory non-coding regions and their molecular function is often unknown.

Much of the key phenotypic variation likely due to changes in gene regulation

GWAS hit for adult onset asthma

Pividori, 2019

Why is it difficult to predict complex traits from genetic sequences?

1. Each genetic variants associated with a complex trait has a very small effect on the phenotype and many are necessary to modify the phenotype.
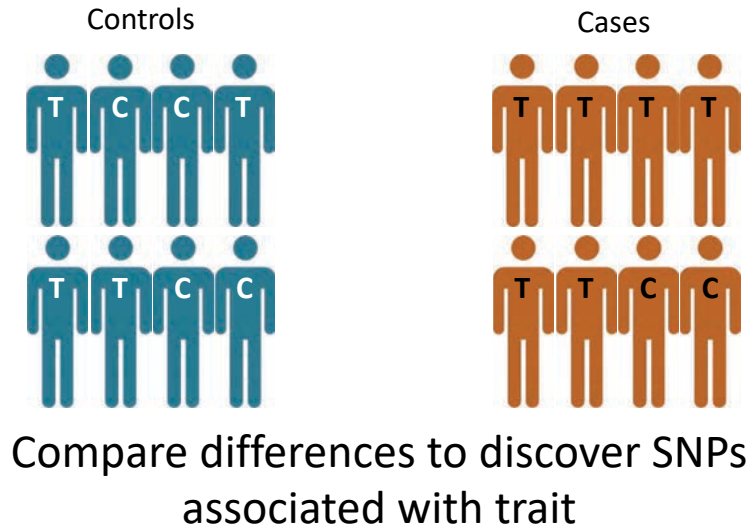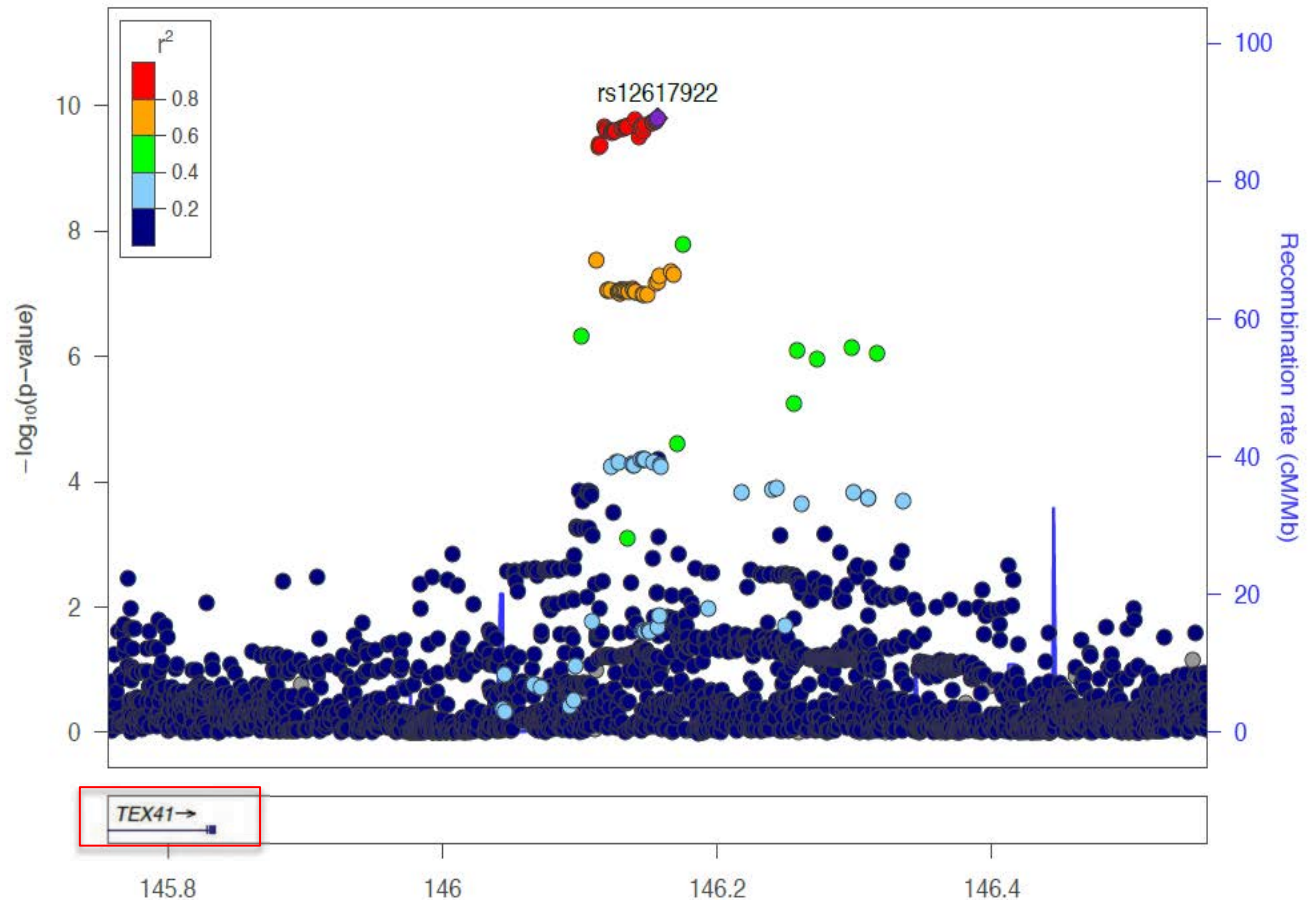
2. Genetic variants associated with complex traits tend to occur in regulatory non-coding regions and their molecular function is often unknown.

3. Complex traits are the results of both genetic and environmental factors.

Genetic, Environmental and GxE factors determine human phenotypic variation

ATCCCGA**T**TGGCAAT
ATCCCGA**A**TGGCAAT

Genetic Variation

Environmental exposures
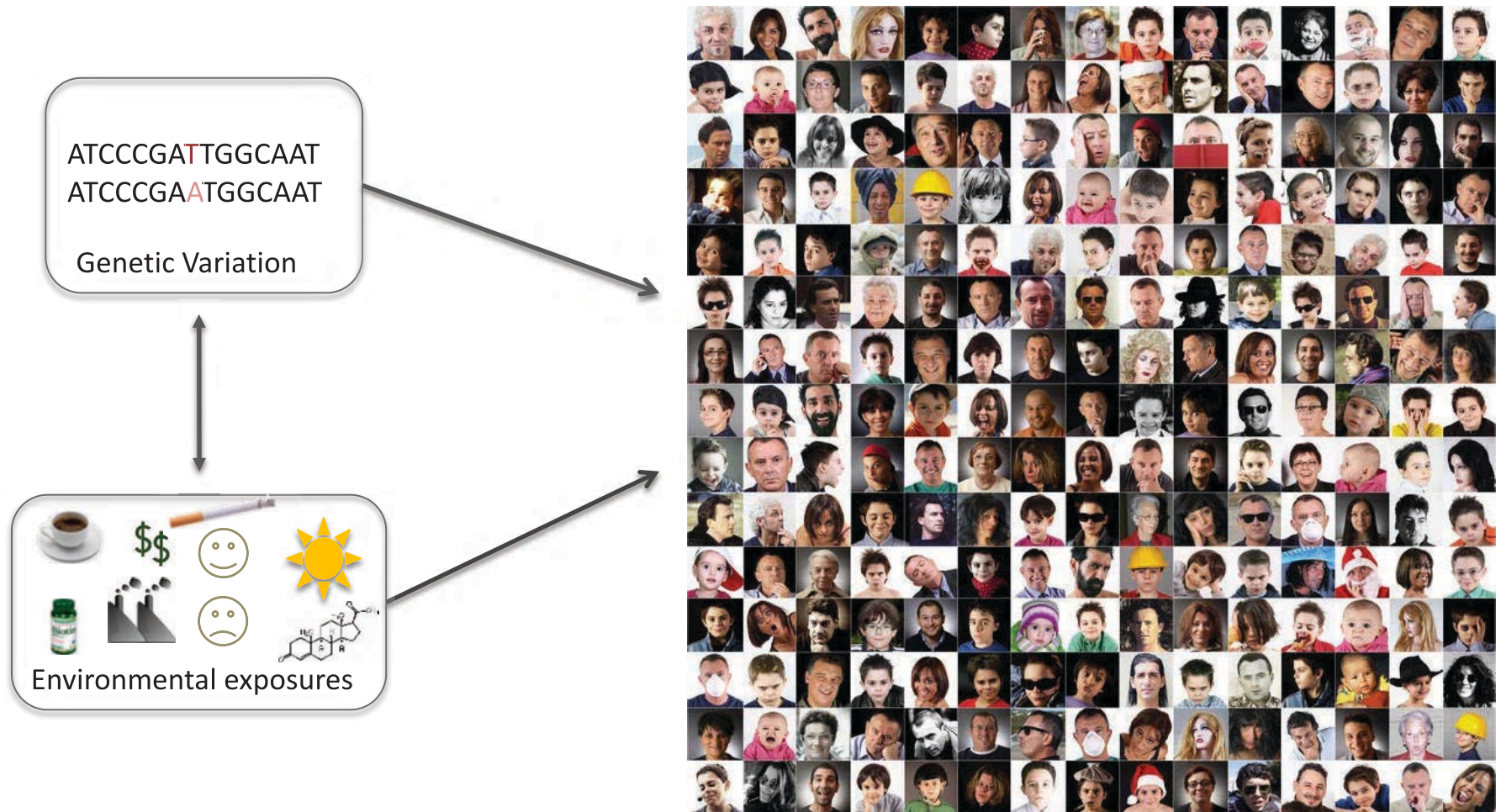
Functional Genomics: beyond the DNA sequence

Ecker et al, 2012
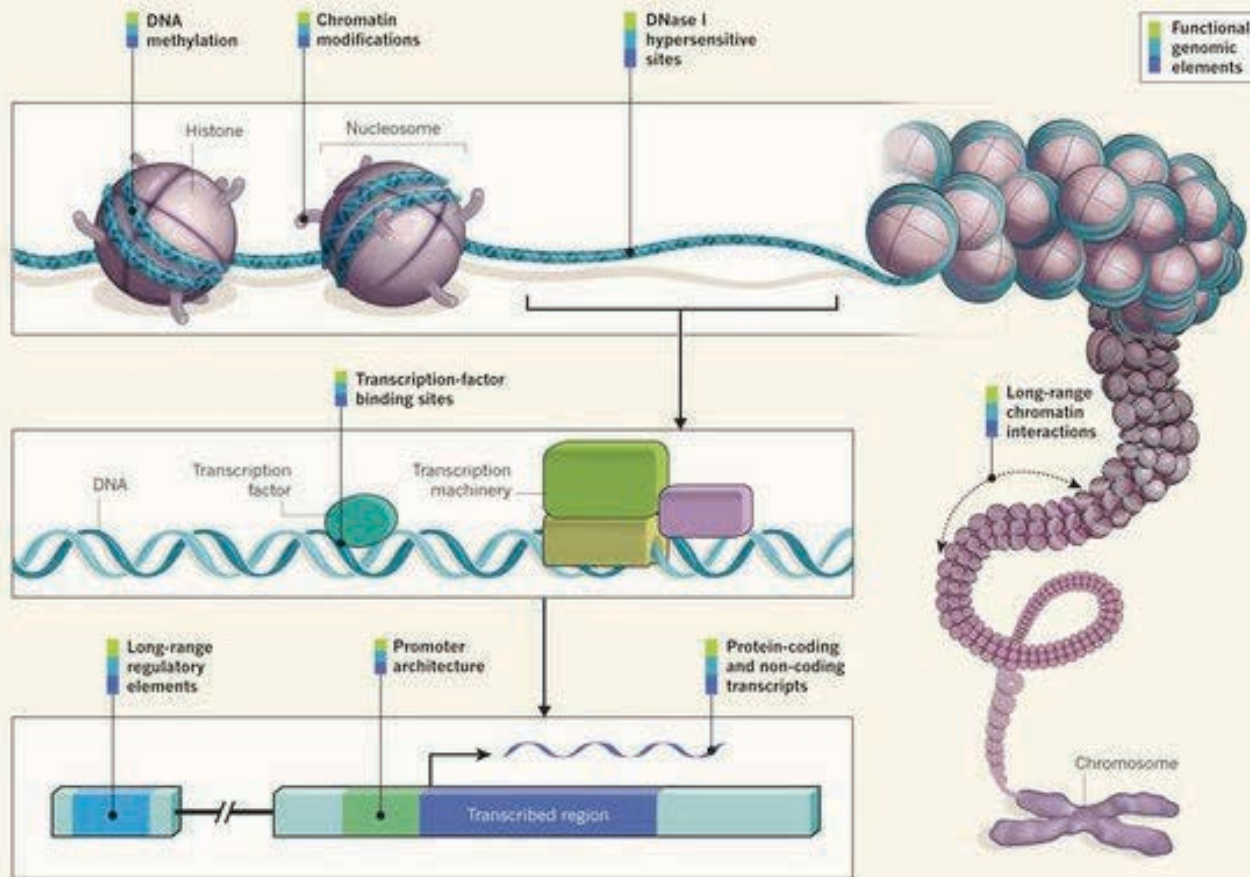
Functional genomics assays

ENCODE, Roadmap Epigenome and others. Image credit: ENCODE
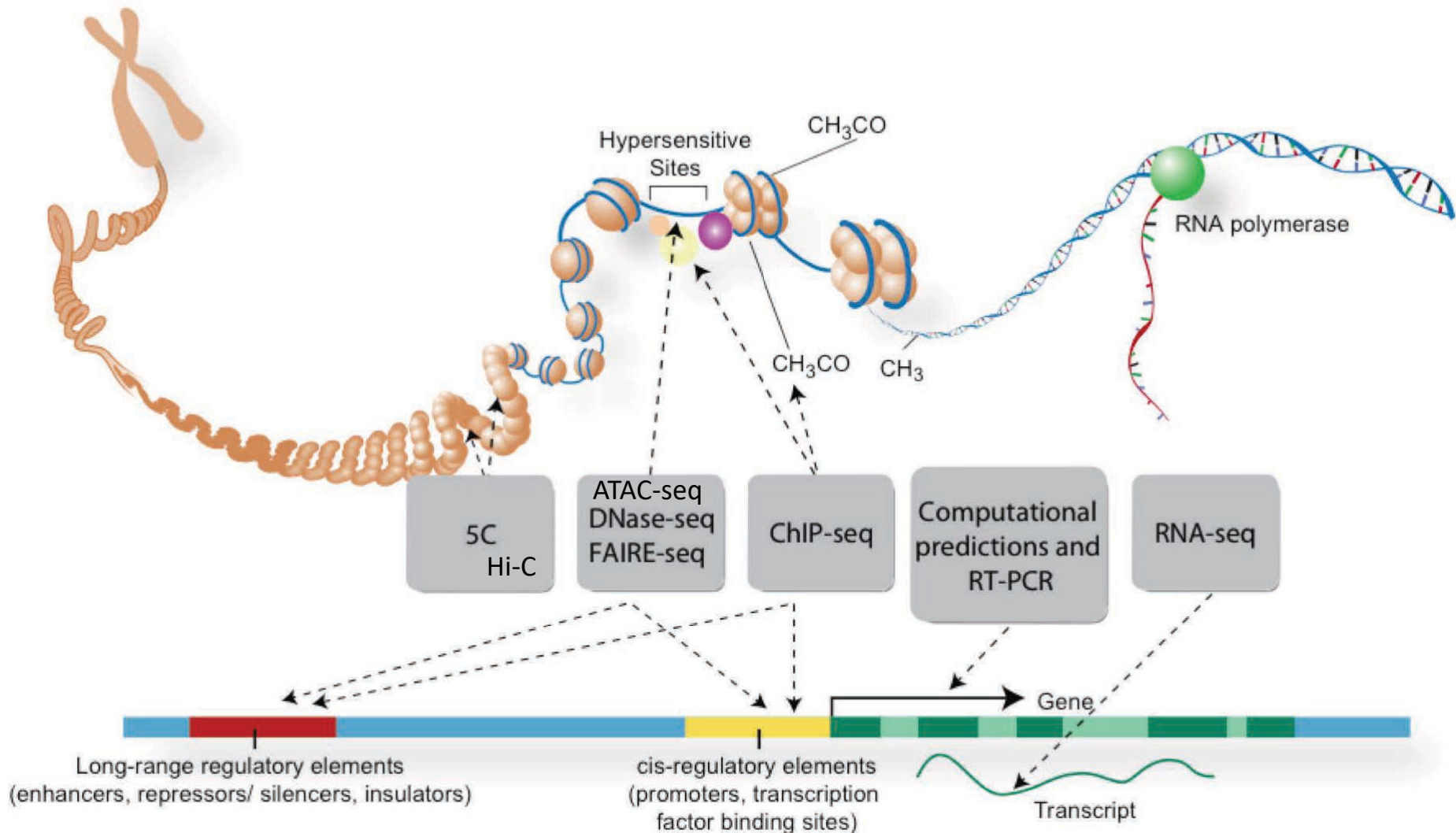
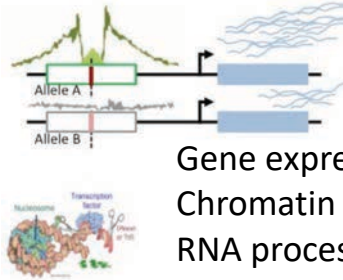# Understanding genetic, environmental and GxE regulation of molecular and organismal phenotypes
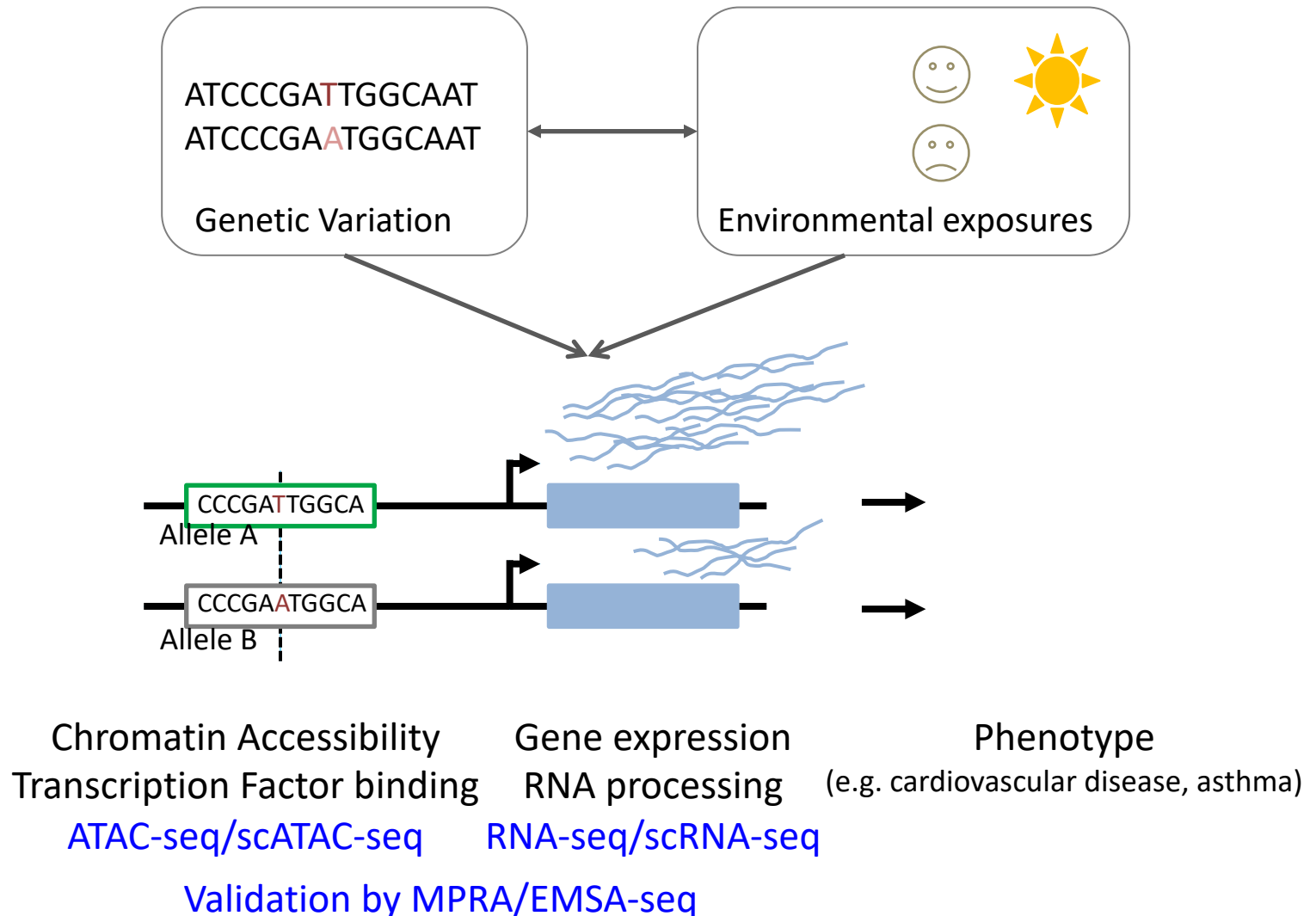
Research Program Overview

GxE in Molecular Phenotypes and complex traits

Gene expression
Chromatin accessibility
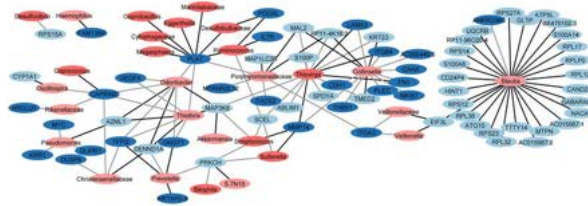RNA processing
(Bulk and single cell)

Cardiovascular disease

Asthma

Moyerbrailean et al, 2015, Sci Rep
Moyerbrailean et al, 2016, Genome Research
Richards et al, 2017, PLOS Genet
Findley et al, 2019, Genetics

Functional Genomics of host-microbiome interactions

Richards et al, 2016, mSystems
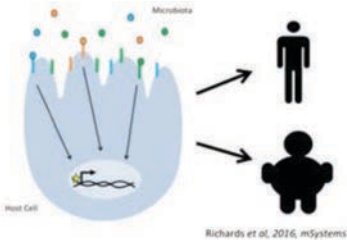
In human populations
Across primate species

Richards et al, 2016, mSystems
Richards et al 2019, mSystems
Luca et al, 2018, TIG

Functional and evolutionary characterization of non-coding variants

Run EMSA

DNA
P50

Bound

Unbound

Cut out bands and sequence

Counts

Unbound Bound

RNA-seq

ASE
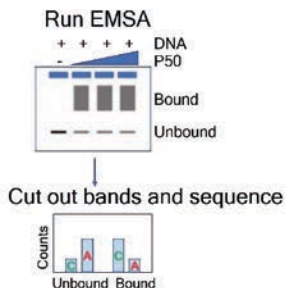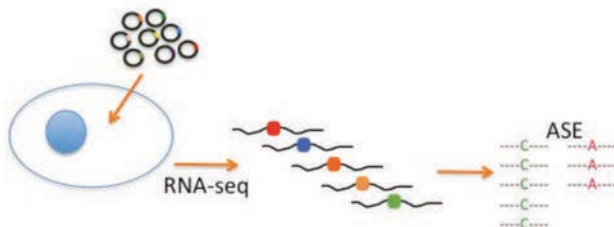
MPRA
EMSA-seq
Neanderthal introgression

Harvey et al, 2014 Bioinf
Moyerbrailean et al, 2016, PLOS Genet
Kalita et al, 2018, Bioinf
Kalita et al, 2018, Genome Res

Many studies identify regulatory variation by eQTL (expression Quantitative Trait Loci) mapping

No genetic effect on expression
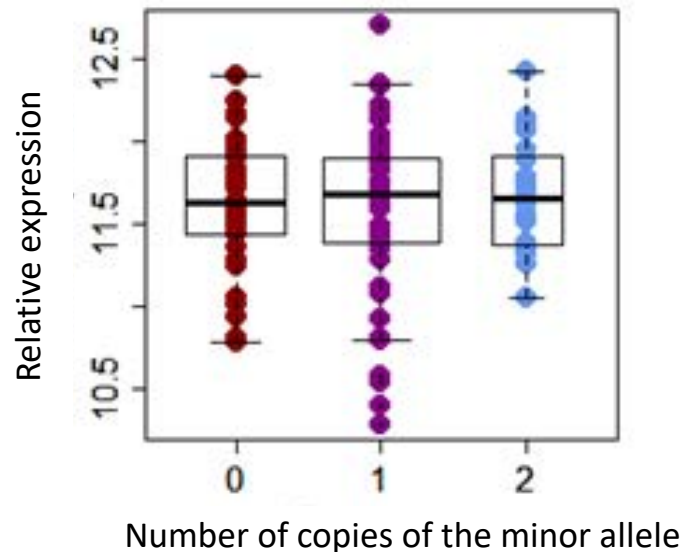
The minor allele is associated with higher expression

(mRNA level)~ genotype, $y_n = \mu + \beta G_n + \varepsilon$

Cis-eQTLs and Trans-eQTLs

Nature Reviews | Genetics
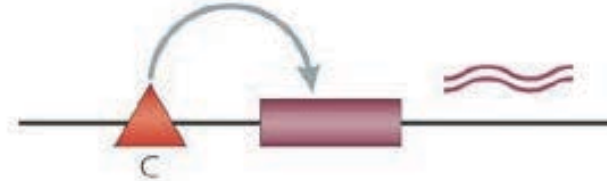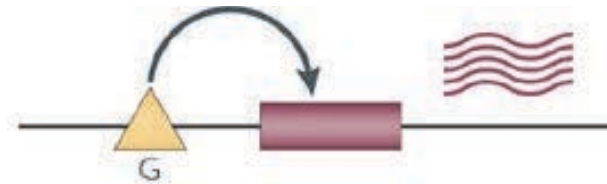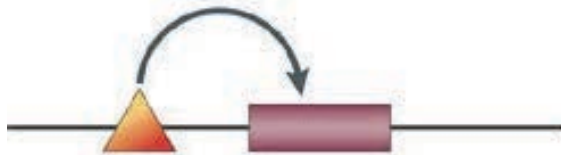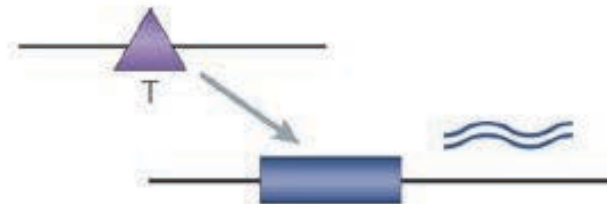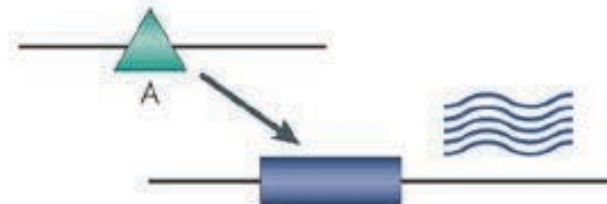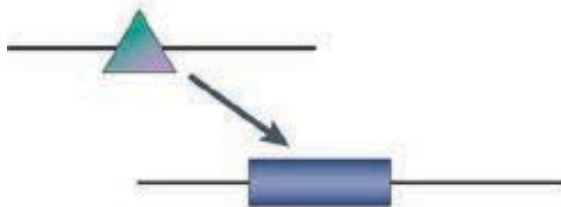
Genetic regulation of gene expression is variable across environmental and cellular contexts

Treatment

A/B

No genetic effect on expression

Control

Relative expression

Number of copies of the A allele
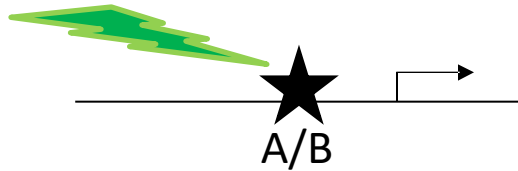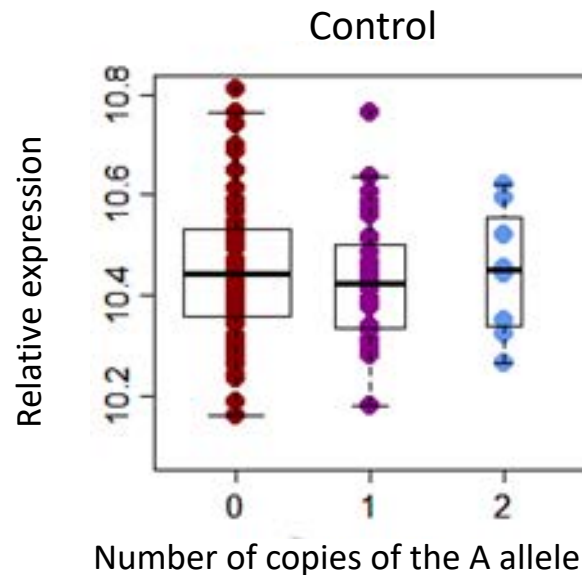
The A allele is associated with higher expression following treatment

Treatment

Relative expression

Number of copies of the A allele

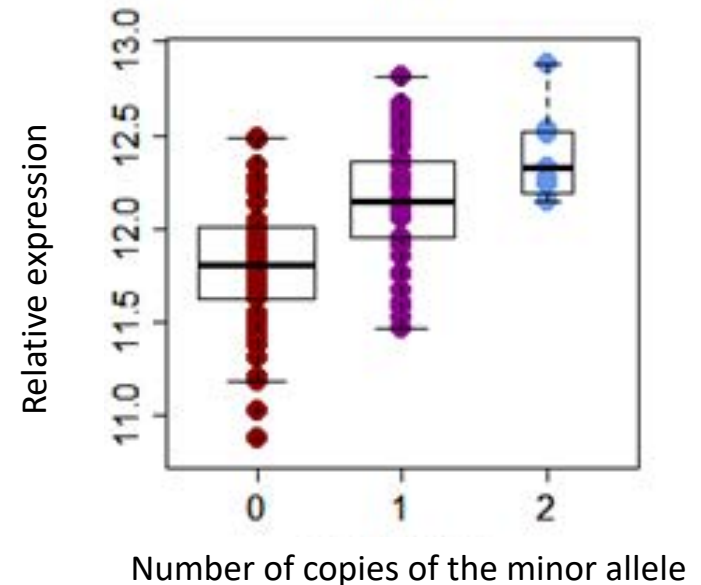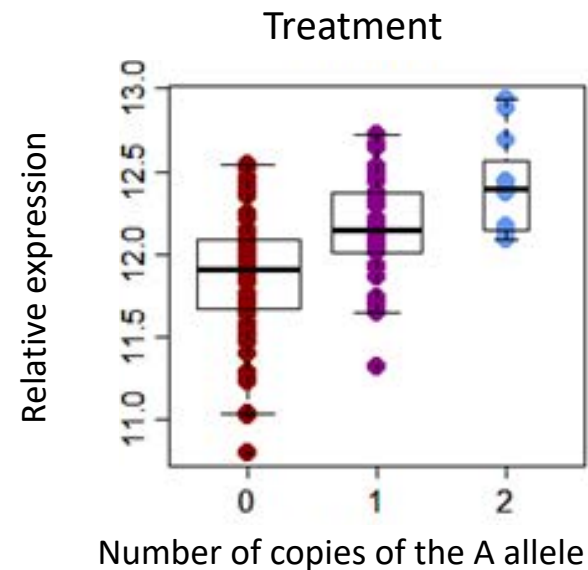See also work by Smith & Kruglyak 2008; Smirnov et al. 2009, Barreiro et al. 2011, Fairfax et al. 2014, Mangravite et al. 2013, Caliskan et al, 2015, GTEx and others

Maranville , Luca et al. 2011

Outline

- Introduction to Genomics

- Ancestry, environmental factors and disease risk

- Psychosocial factors, genetics and asthma

Transcriptional responses vary between populations and ancestry groups
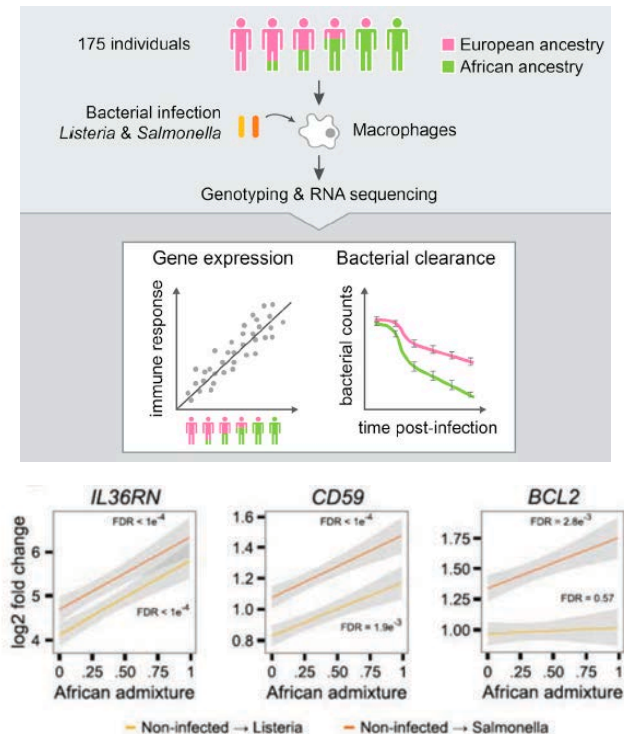
Nedelec et al., 2016

- Markedly stronger response to infection induced in macrophages from African Americans (AA) compared to European Americans (EA).
- 9.3% of macrophage-expressed genes show ancestry-associated differences in the gene regulatory response to infection
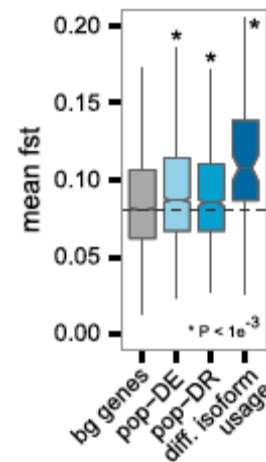
- Natural selection has contributed to present-day inter-population differences in innate immune responses to infection

See for example: Quach et al., 2016; Maranville et al., 2013

Transcriptional response to caffeine, vitamin A, and zinc

Study Design

EA (n=8)   AA (n=10)

PBMCs

Treatment
Caffeine
Vitamin A
Zinc

RNA-seq

Differentially expressed genes

$$y = \beta_{i,\,0} + \beta_{i,\,\text{trt}} + \beta_{i,batch} + \beta_{i,individual}$$

☐ Down-regulated
■ Up-regulated

DEGs

Caffeine   Vitamin A   Zinc

Reactome pathways enriched for up-regulated genes

Immuno-regulatory interactions
Neutrophil degranulation
Cell surface interactions
Integrin cell surface interactions
Class A/1 (Rhodopsin-like receptors)
Signaling by Interleukins
Cilium Assembly
Response to metal ions
Metallothioneins bind metals
Interleukin-10 signaling
Cellular responses to external stimuli
Infectious disease
Transcriptional Regulation by TP53
Intron processing
MHC mediated antigen processing

Vitamin A   Caffeine   Zinc   background

GeneRatio
● 0.04
● 0.08
● 0.12
● 0.16

p.adjust
0.025
0.050
0.075

How does ancestry impact gene expression in treated PBMCs?

Ancestry-related differences in gene expression

EA

AA

Expression in EA > AA
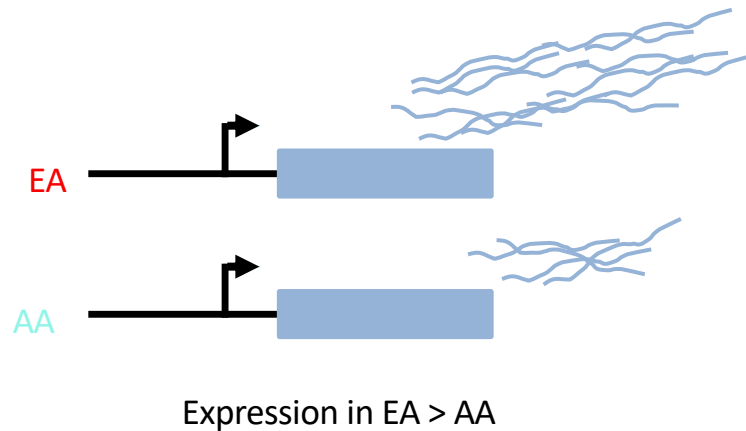
$$y = \beta_{i,0} + \beta_{i,trt} * \beta_{i,Ethnicity} + \beta_{i,batch} + \beta_{i,individual}$$

Ancestry-related differentially expressed genes (Anc-DEGs) FDR<10%

Expression in AA > EA
Expression in EA > AA

Anc-DEGs

1500
1000
500
0

Caffeine (N=18) Vitamin A (N=18) Zinc (N=18) Control 1 (N=39) Control 2 (N=39)

Dubaisi et al, in prep
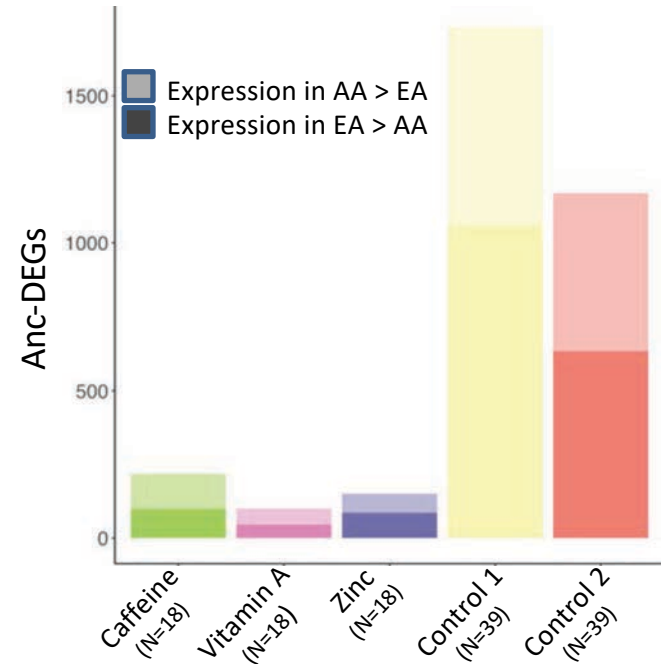
How does ancestry impact host transcriptional response to caffeine, vitamin A, and zinc?

Ancestry-related differentially responsive genes (Anc-DRGs), FDR<10%

$y = \beta_{i,0} + \beta_{i,\text{trt}-\text{control}} * \beta_{i,Af} + \beta_{i,batch} + \beta_{i,individual}$

775

- Expression in AA > EA
- Expression in EA > AA

66% of the Anc-DRGs exhibited stronger response in individuals with higher ratio of African ancestry
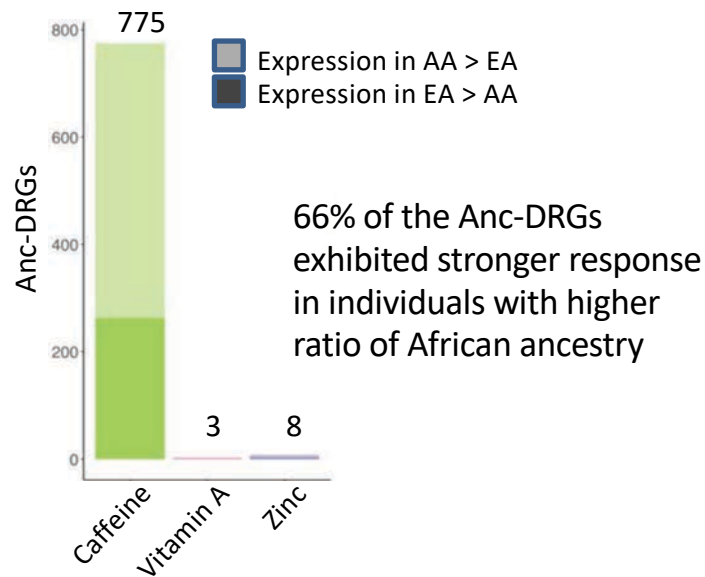
Reactome pathways enriched for Anc-DRGs are primarily involved in regulating immune or stress response
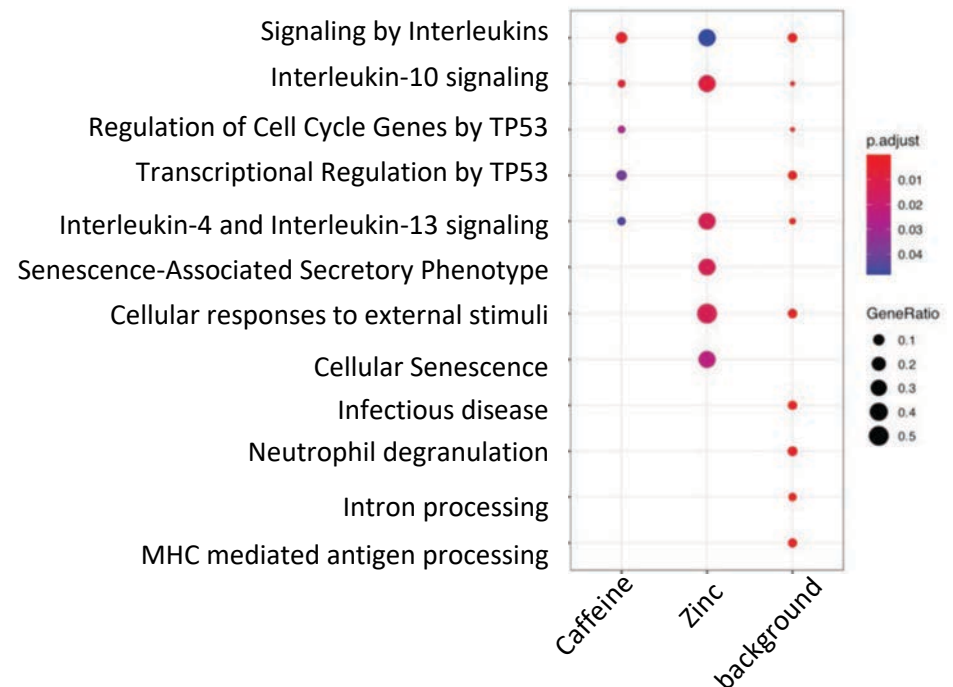
Are genes differentially responsive between ancestry groups associated with complex traits?

Control

AA

EA

Caffeine

AA

EA

TWAS data from Zhang *et al,* 2020

Caffeine Anc-DRGs
No-DRGs

Platelet count
Eczema
Inflammatory Bowel Disease
Methylene group ratio per a double bond
Rheumatoid Arthritis
Body mass index
Hayfever, allergic, rhinitis, and eczema

0.0   0.1   0.2
Proportion
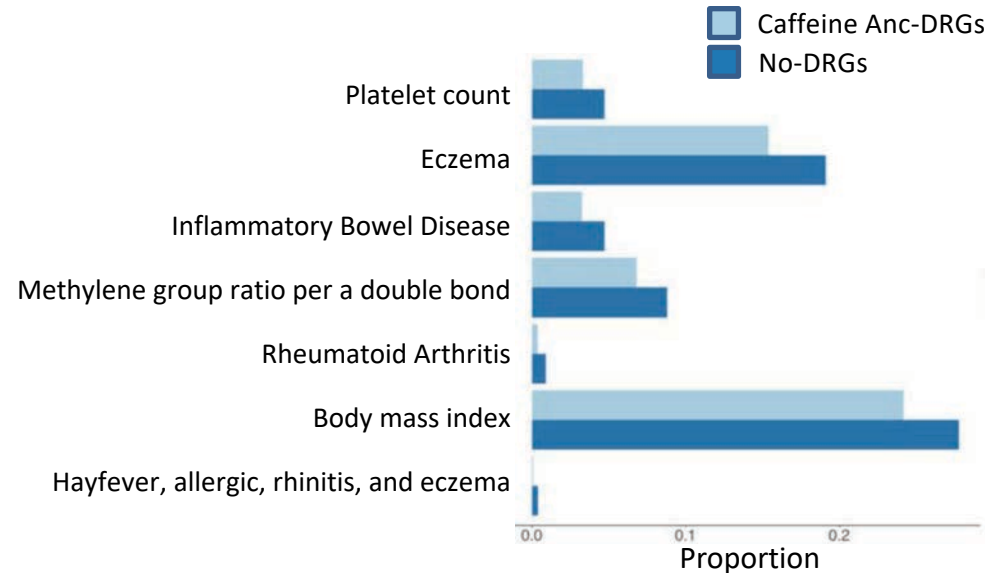
The proportion of genes associated with complex traits (TWAS) is greater for ancestry-related differentially responsive genes (DRGs) to caffeine compared to No-DRGs (81% compared to 76%, respectively)

Dubaisi et al, in prep

Summary 1

- Exposure to caffeine, vitamin A, and zinc can modify the host transcriptional profile by altering the expression of genes that are involved in regulating stress response and immune functions
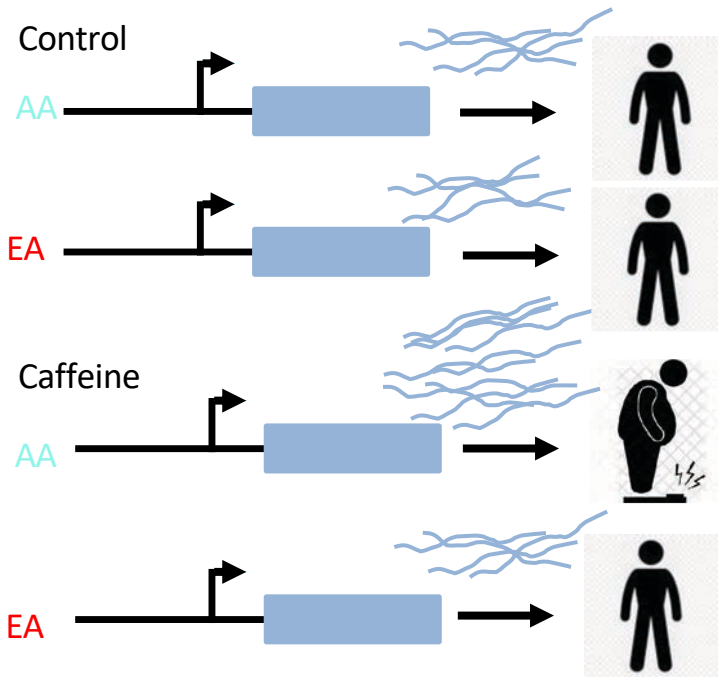
- Ancestry impacts the host transcriptional response to caffeine, zinc, and vitamin A

- 81% of the ancestry-related DRGs overlapped with genes whose expression was found to be correlated immune-related traits and diseases

Outline

- Introduction to Genomics
- Ancestry, environmental factors and disease risk
- **Psychosocial factors, genetics and asthma**
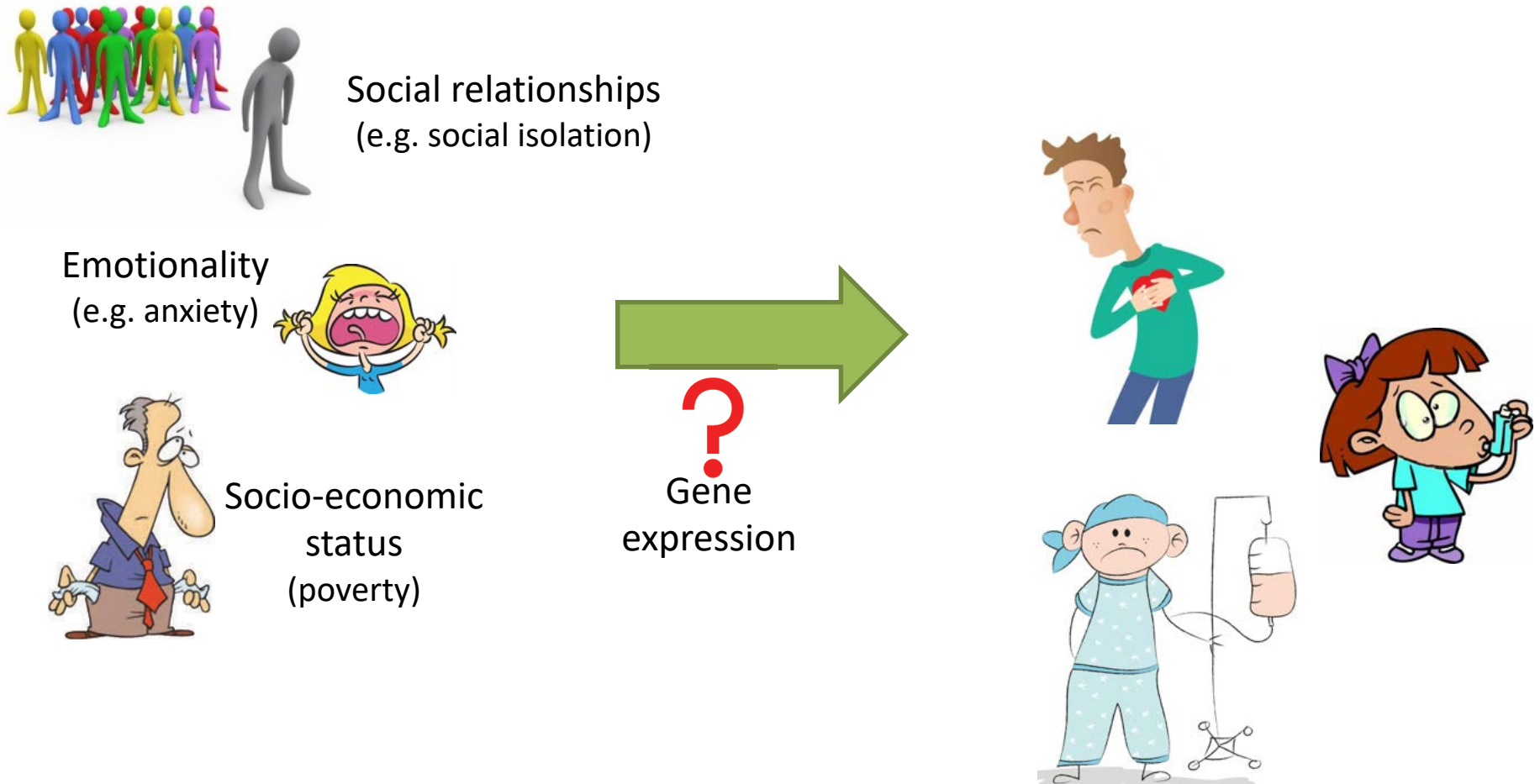
New Results

💬 **Comment on this paper**

Psychosocial experiences modulate asthma-associated genes through gene-environment interactions

Justyna A. Resztak, Allison K. Farrell, Henriette E. Mair-Meijers, Adnan Alazizi, Xiaoquan Wen, Derek E. Wildman, Samuele Zilioli, Richard B. Slatcher, 🆔 Roger Pique-Regi, 🆔 Francesca Luca

Psychosocial experiences affect health

Social relationships
(e.g. social isolation)

Emotionality
(e.g. anxiety)

Socio-economic
status
(poverty)

?

Gene
expression

Snyder-Mackler et al, 2019
Gaye et al, 2017
Cole et al, 2014
Chiang et al, 2019

cdc.gov/asthma
Sandberg, 2000

ATCCCGATTGGCAAT
ATCCCGAATGGCAAT

Genetic Variation

Social Relationships

Emotionality

Socioeconomic Status

Healthy environment

Allele A

Allele B

Risky environment

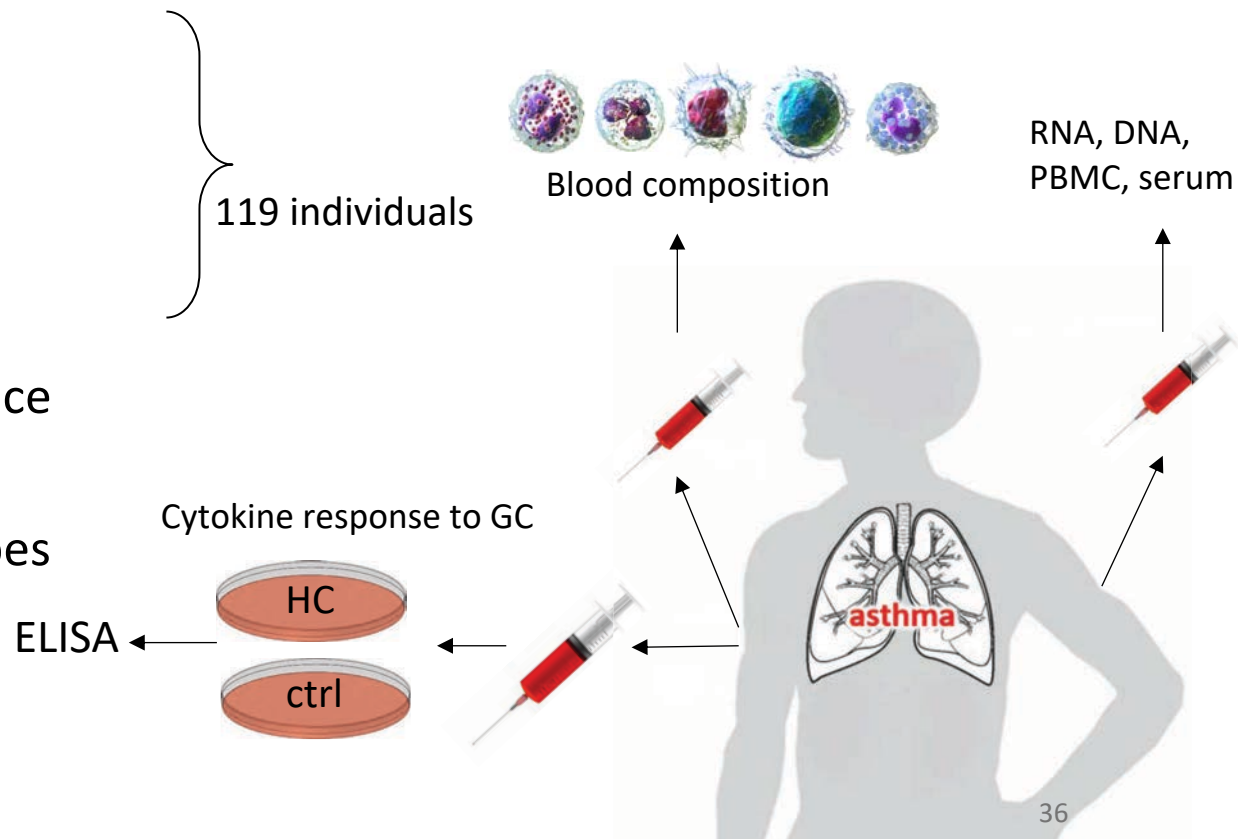Allele A

Allele B

Gene Expression
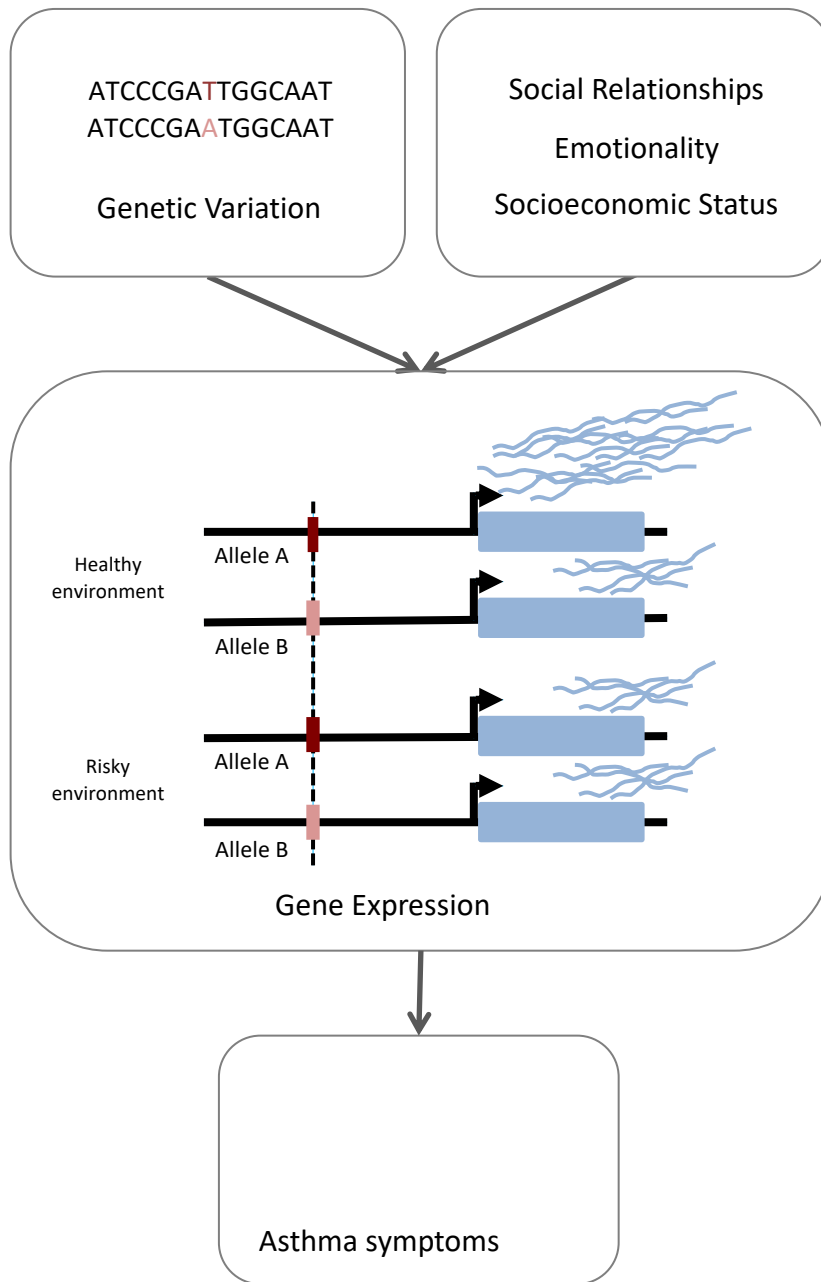
Asthma symptoms

What are the contributions of genetic variation and the psychosocial environment to inter-individual variation in asthma symptoms and severity?

ALOFT
Asthma in the Lives Of Families Today

- 250+ asthmatic children aged 10-17 living in Detroit Metro

- Extensive **medical and psychological** information
    - Emotionality
    - Social interactions
    - Socio-economic status
    - Blood composition
    - Asthma
    - Glucocorticoid resistance
    - Gene expression
    - Genome-wide genotypes

119 individuals

Blood composition

RNA, DNA, PBMC, serum

Cytokine response to GC
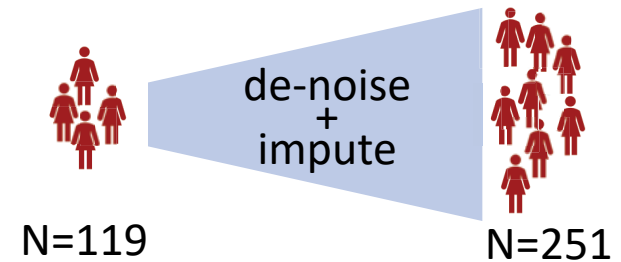
HC

ctrl

ELISA

asthma

Resztak et al, under review

Do psychosocial experiences alter gene expression in immune cells?

Does asthma alter gene expression in immune cells?

Do these transcriptional changes affect the same genes? Do they share a molecular mechanism? What are the causal pathways?

A novel approach to de-noise and impute environmental effects on gene expression

Phenotype/Environment = $\mu + \beta_1 E(gene_1) + \beta_2 E(gene_2) + \ldots + \beta_n E(gene_n)$

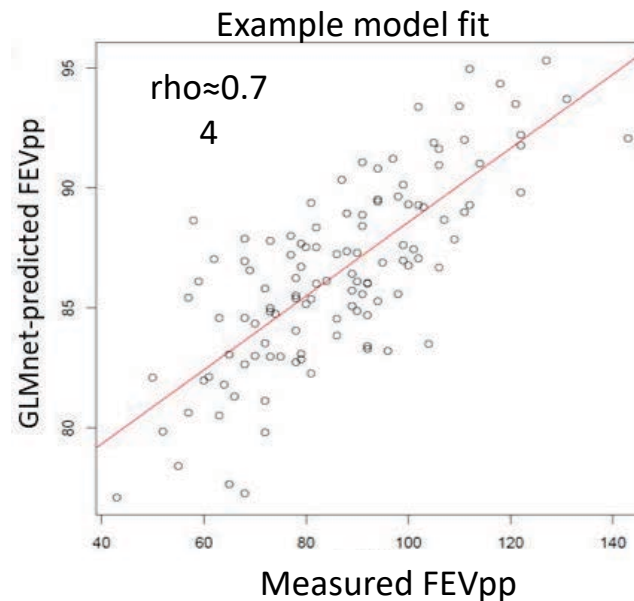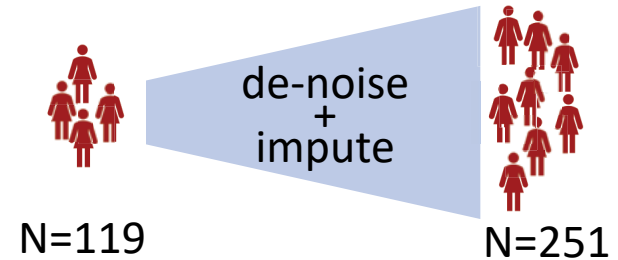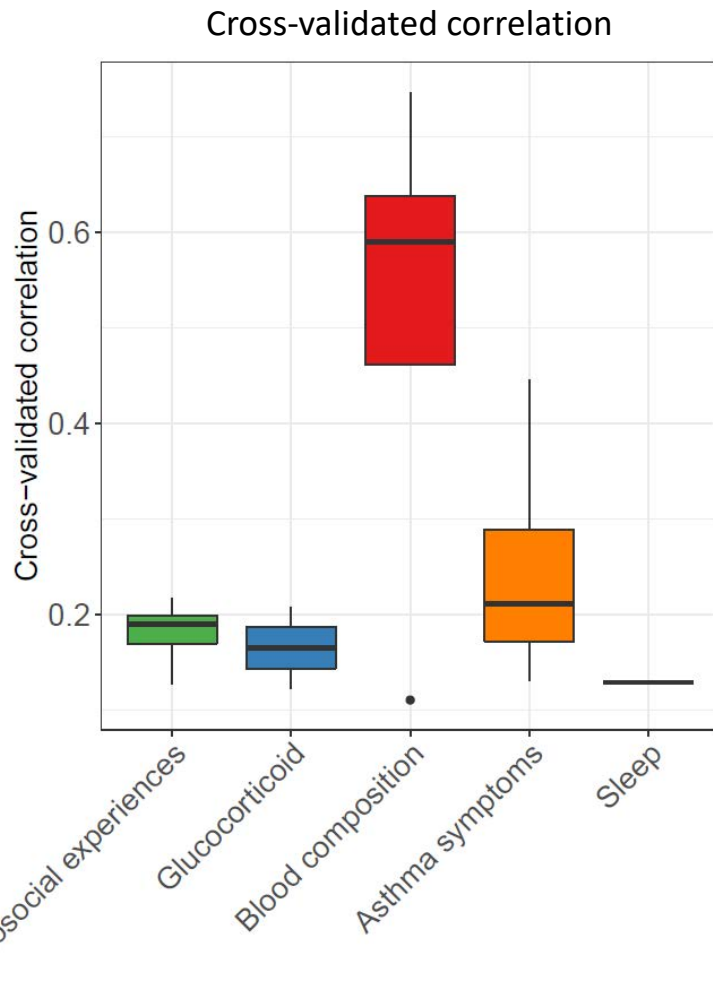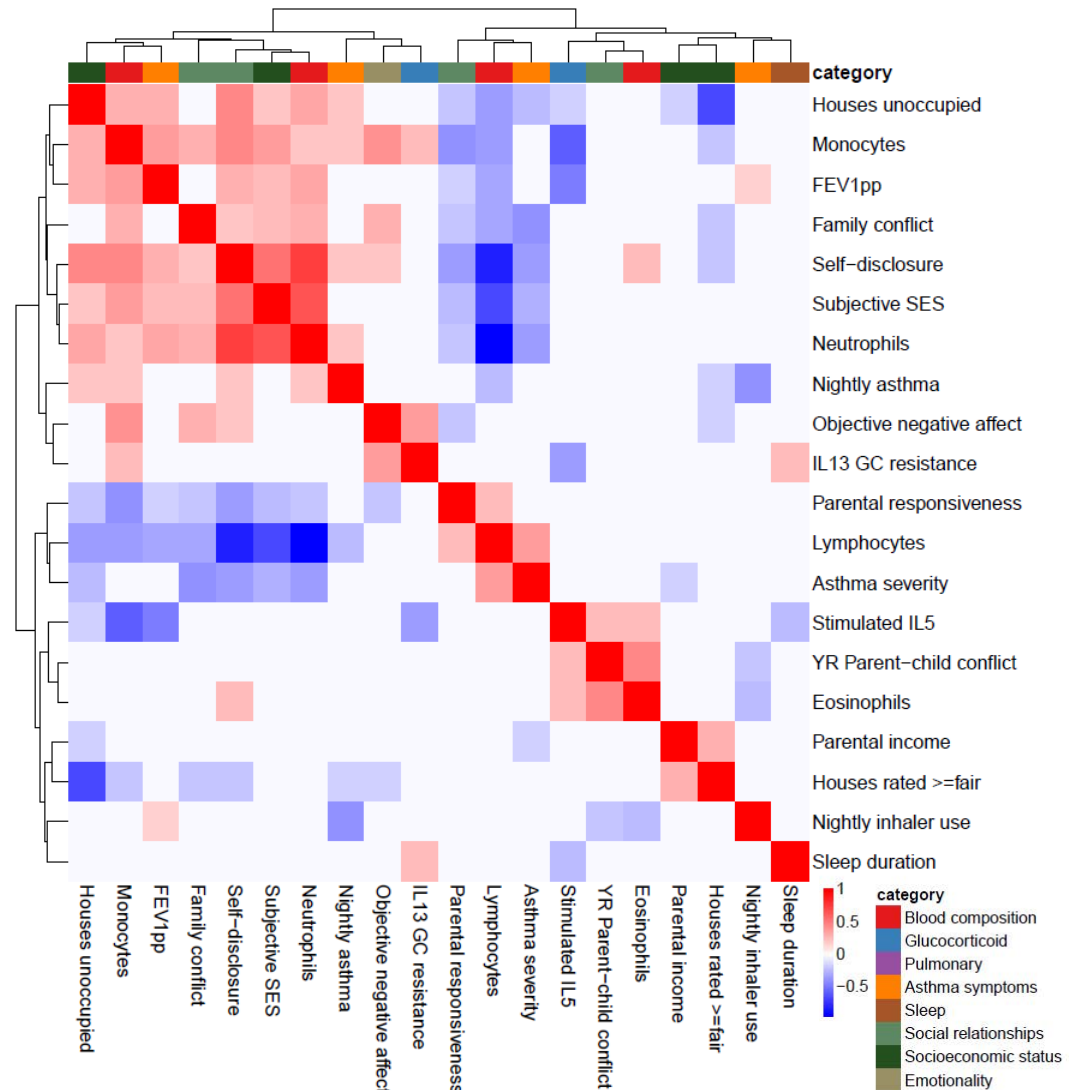N=119   de-noise + impute   N=251

A novel approach to de-noise and impute environmental effects on gene expression

$$\text{Phenotype/Environment} = \mu + \beta_1 E(\text{gene}_1) + \beta_2 E(\text{gene}_2) + \dots + \beta_n E(\text{gene}_n)$$
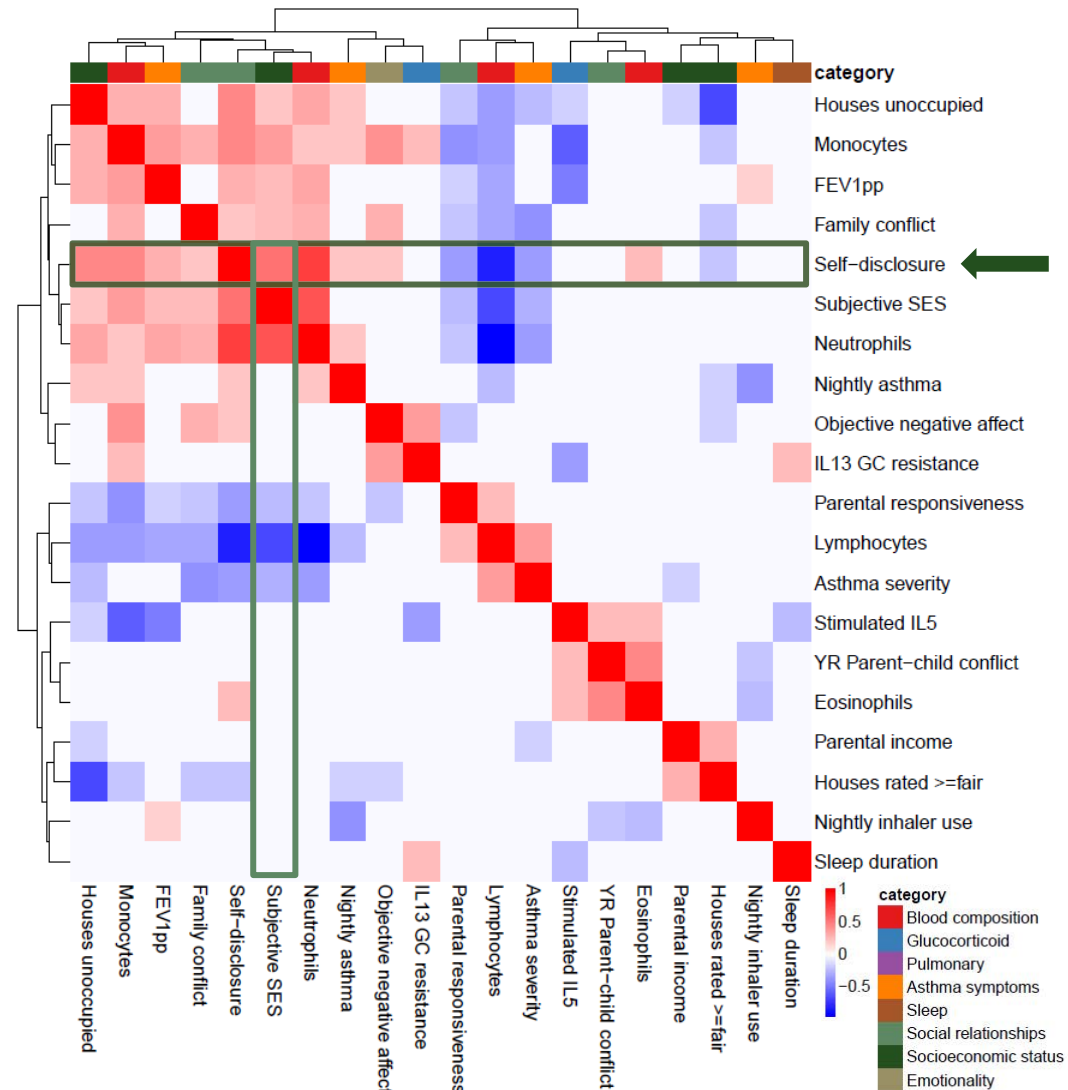

Cross-validated correlation

de-noise + impute

N=119   N=251

Example model fit

rho≈0.74

GLMnet-predicted FEVpp

Measured FEVpp

Resztak et al, under review

Shared signatures of psychosocial environments and asthma symptoms
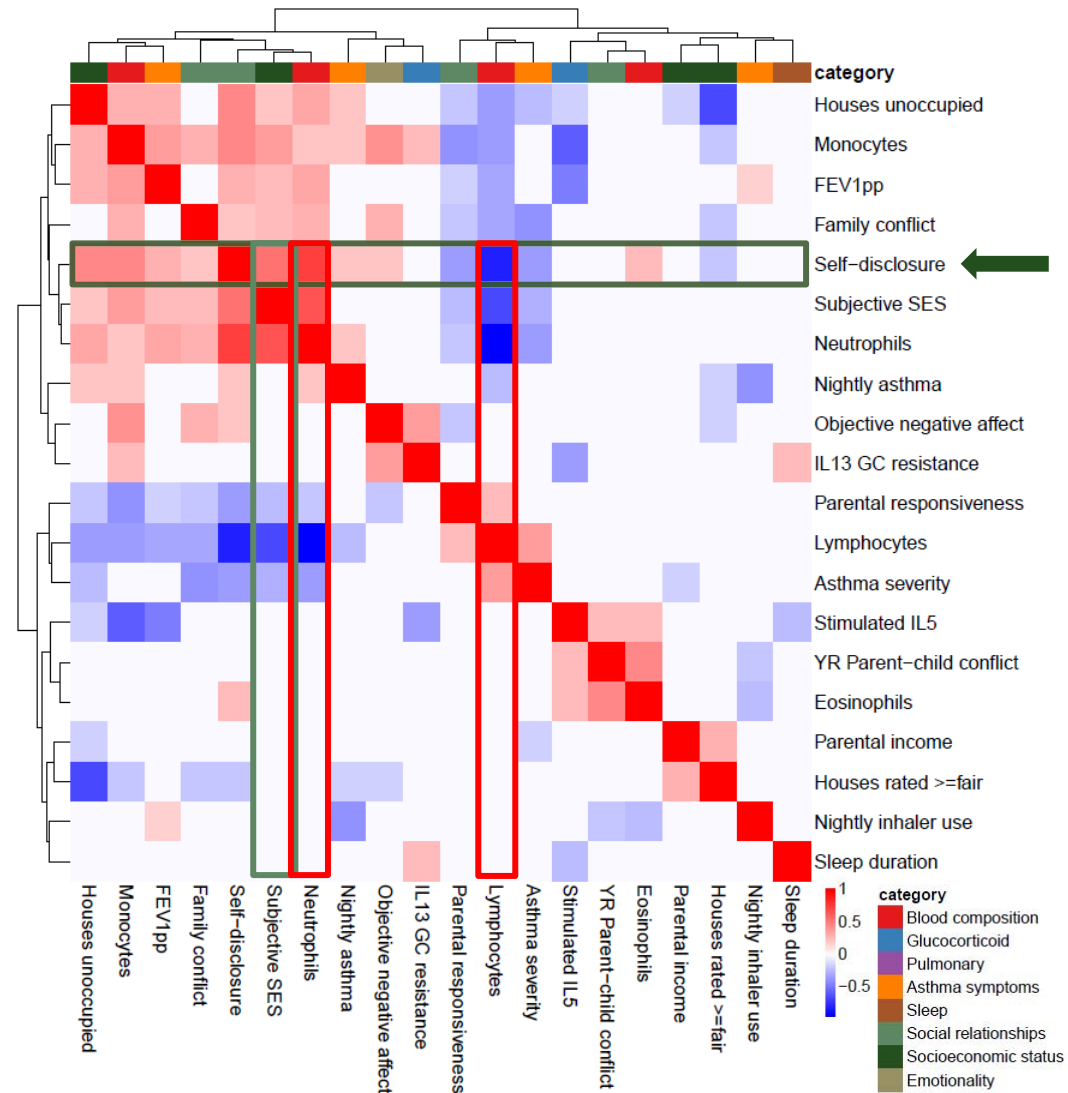

Resztak et al, under review

Shared signatures of psychosocial environments and asthma symptoms

- Self-disclosure:
  - Socio-economic status

Shared signatures of psychosocial environments and asthma symptoms

- Self-disclosure:
  - Socio-economic status
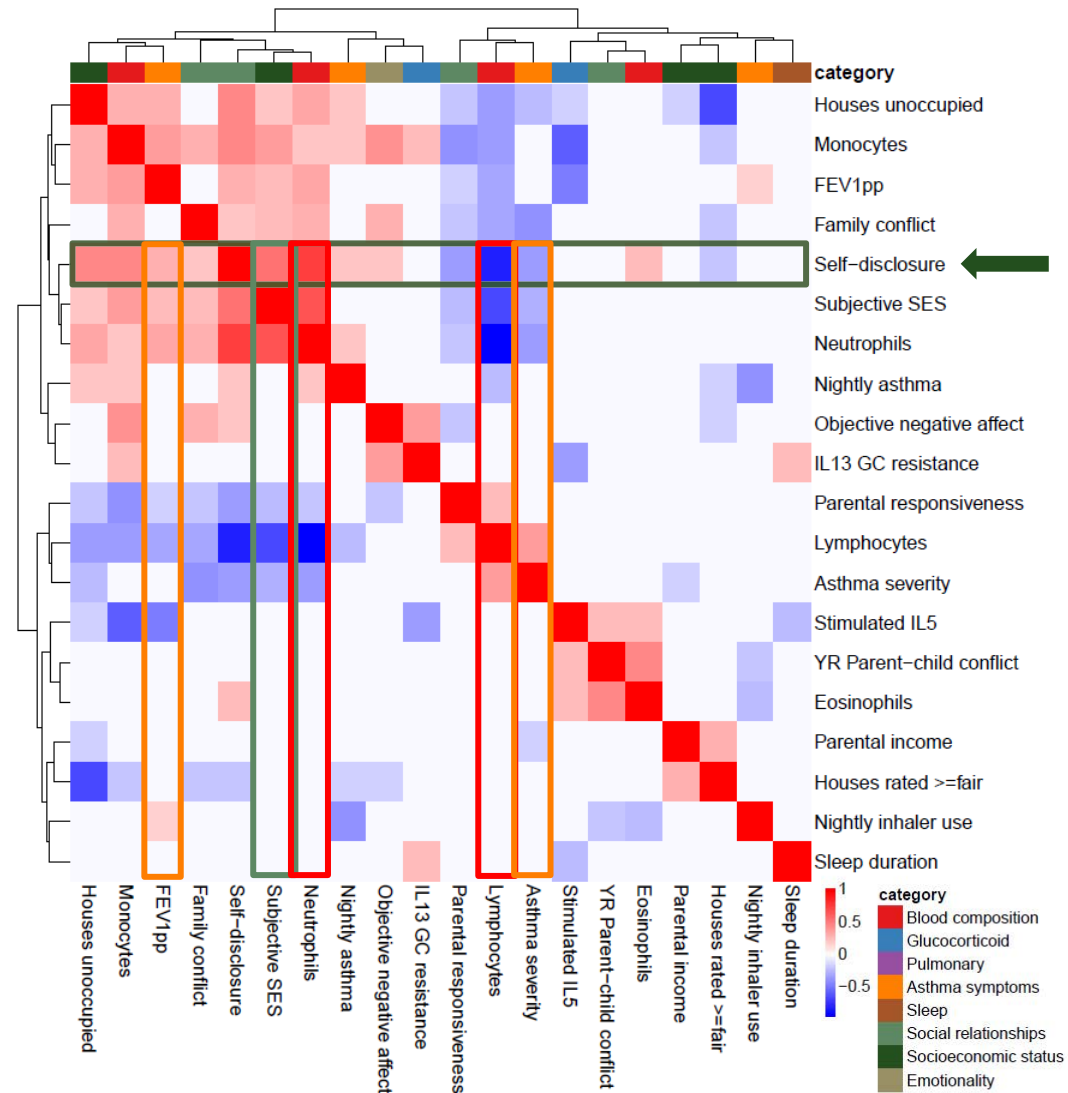 - neutrophils, lymphocytes
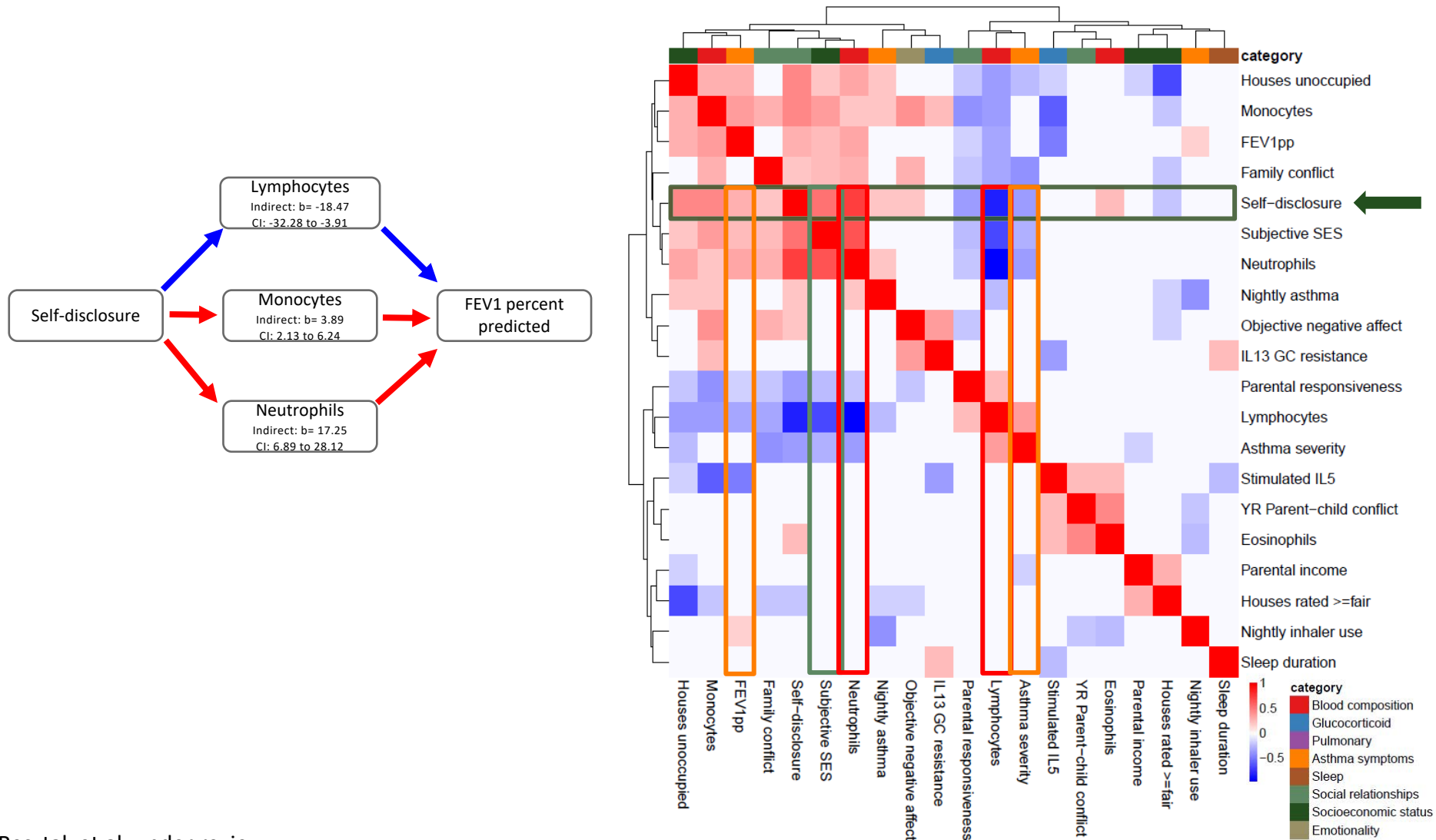

Resztak et al, under review

# Shared signatures of psychosocial environments and asthma symptoms

- Self-disclosure:
  - Socio-economic status
  - neutrophils, lymphocytes
  - asthma severity, pulmonary function (FEV1 percent predicted)

# Shared signatures of psychosocial environments and asthma symptoms

Resztak et al, under review

Expression of genes associated with complex traits is modulated by psychosocial experiences

Resztak et al, under review
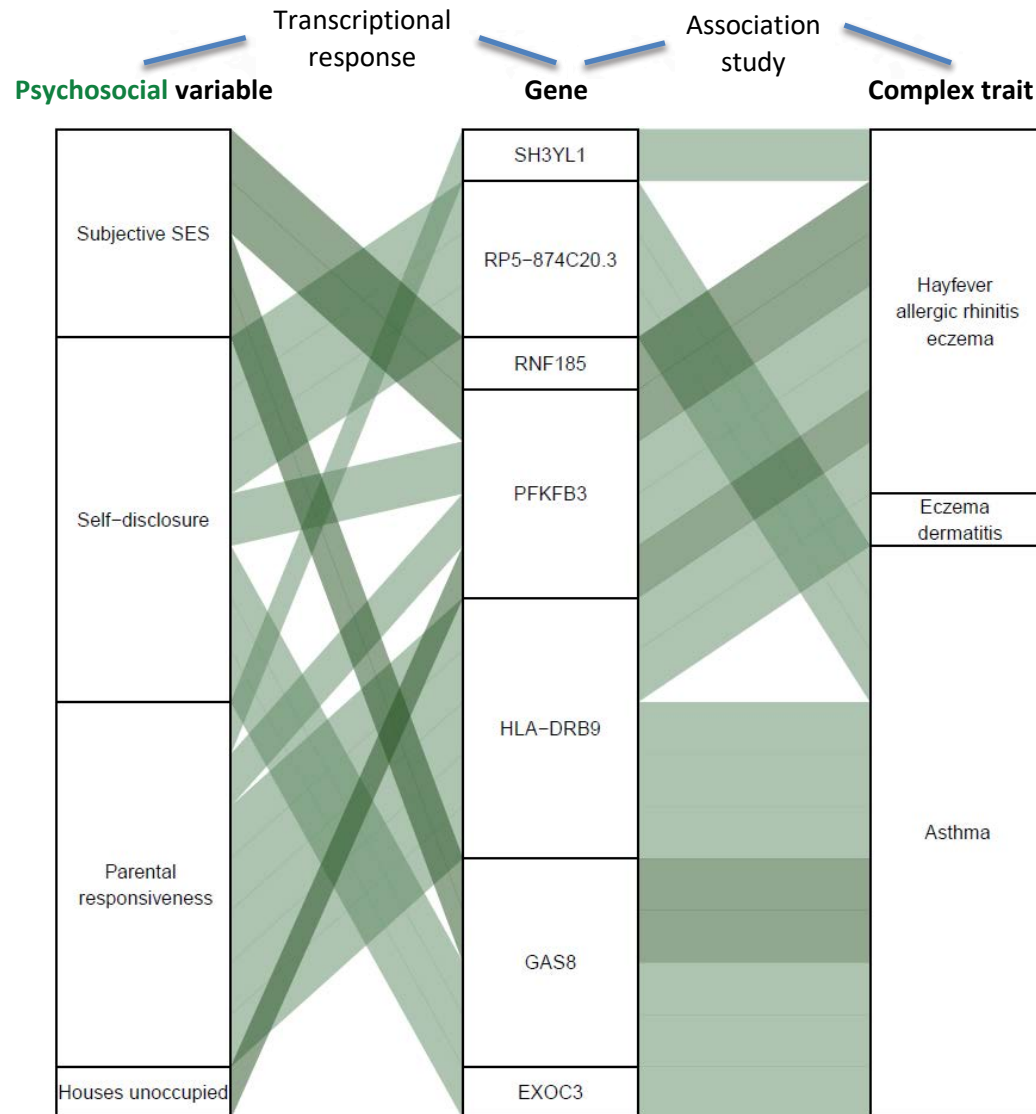
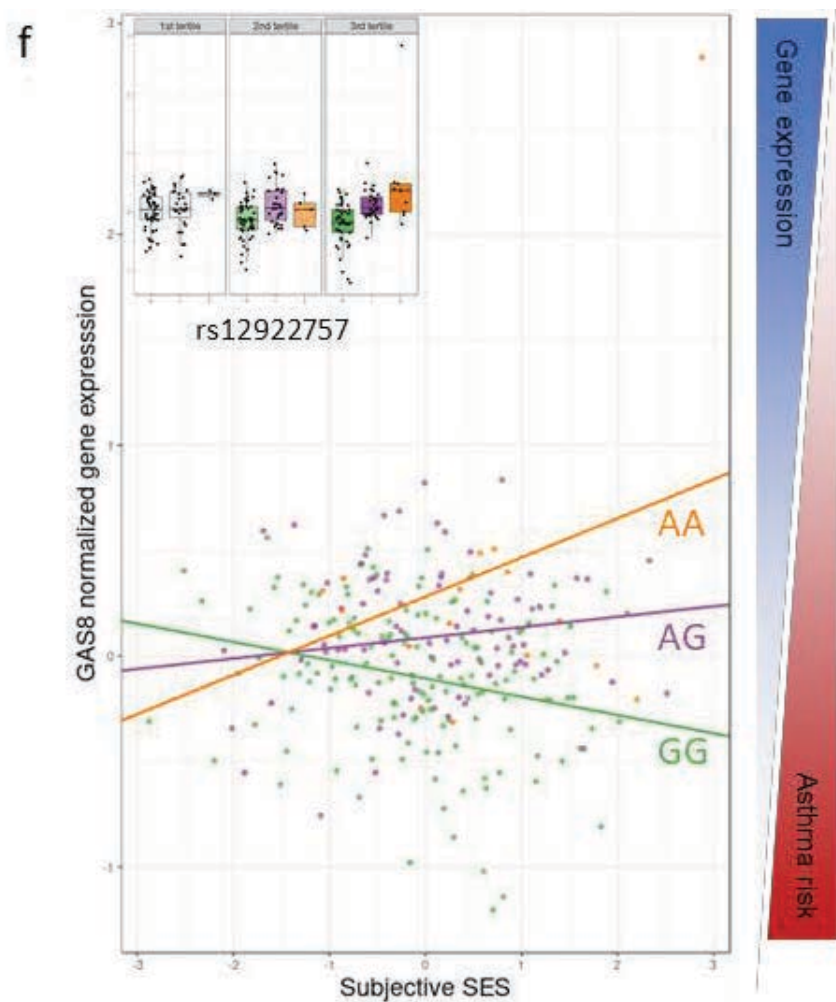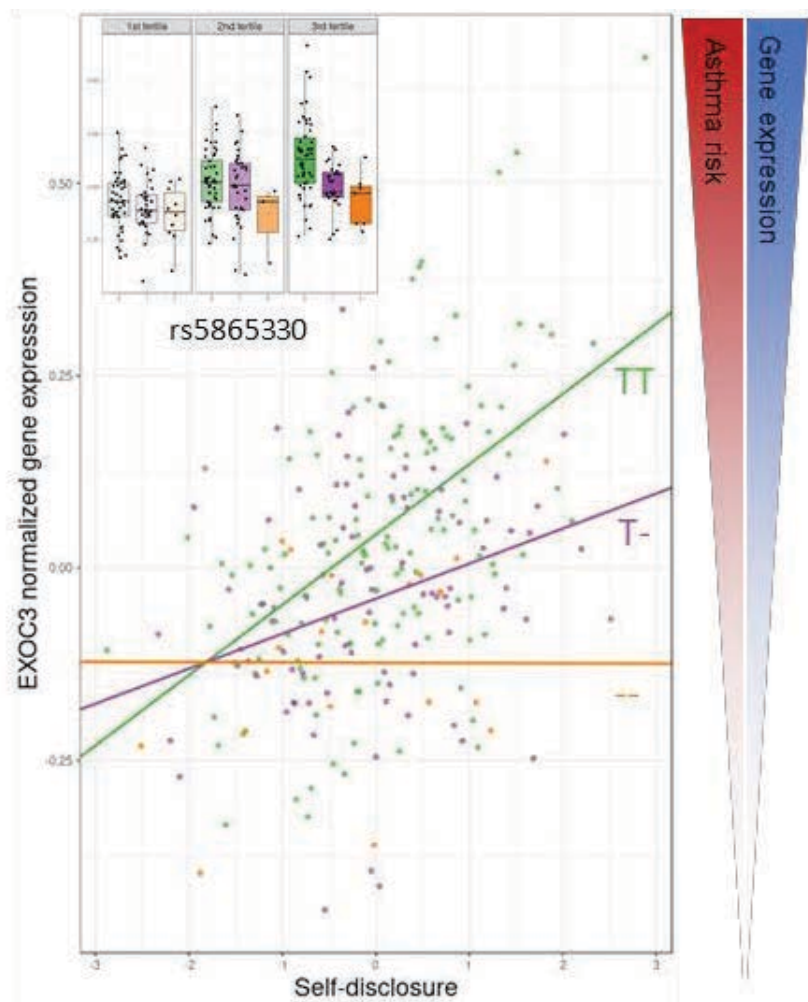# Psychosocial variables interact with genetic variants to regulate gene expression

Gene expression$_i$ = genotype dosage$_i$ + transcriptional signature + <u>genotype dosage$_i$*transcriptional signature</u> + ε
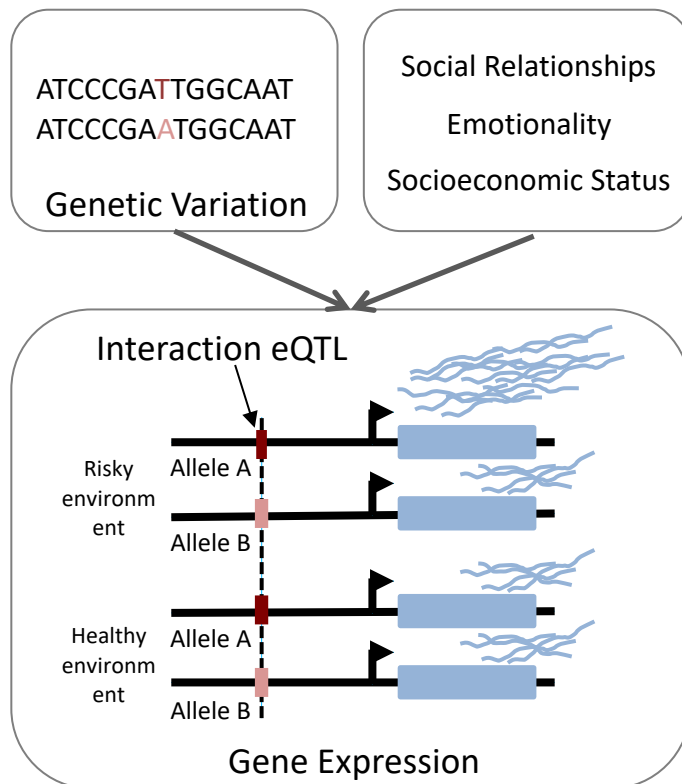
Genetic risk of asthma is modified by interactions with psychosocial factors

Resztak et al, under review

Summary 2

Social genomics approaches in humans can uncover potential molecular mechanisms underlying differences in disease risk

- Psychosocial experiences and asthma symptoms are reflected in blood gene expression

- Sharing of transcriptional signatures between psychosocial and asthma traits

- Genetic risk for asthma and other allergic diseases is modulated by psychosocial factors

Conclusion

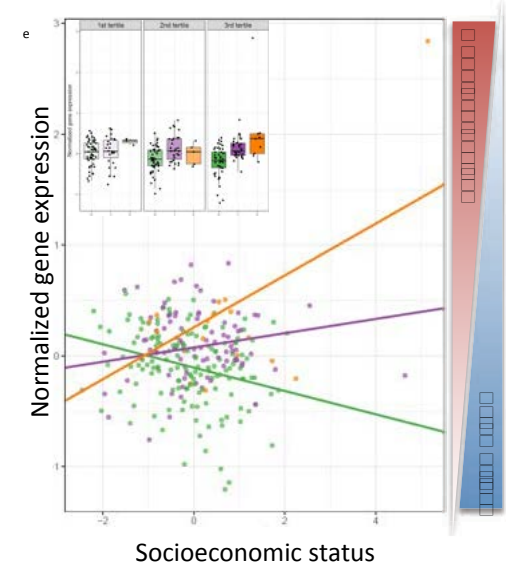Genomics is present in several aspect of our daily life

The transcriptional response to treatments varies between ancestry groups
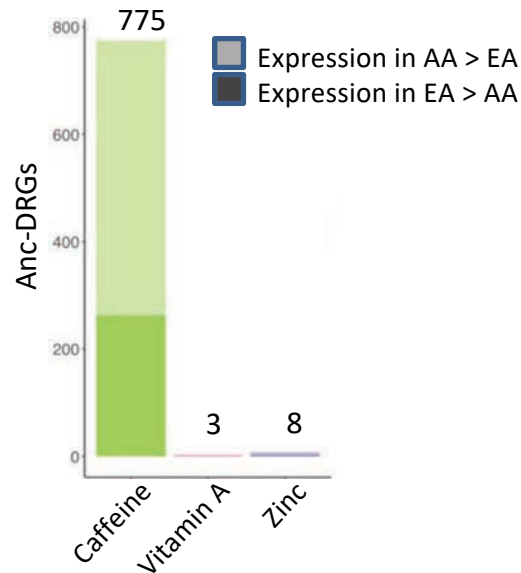
Legend: Expression in AA > EA; Expression in EA > AA

Genetic risk for asthma and other allergic diseases is modulated by psychosocial factors

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Image: GxE by Gaia Sperone, 2016, 7yrs