Introduction to Genomics

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Outline

• Introduction to Genomics
• Ancestry, environmental factors and disease risk
• Psychosocial factors, genetics and asthma
Phenotypic variation in humans

Credit: © Giuseppe Porzani / Fotolia
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

Cost per Human Genome

Moore’s Law

NIH National Human Genome Research Institute

genome.gov/sequencingcosts
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.

Source: 23andme.com
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.

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.

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

Source: 23andme.com
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

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 variant 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
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

ATCCCGATTTGGCAAT
ATCCCGAATGGCAAT
Genetic Variation

Environmental exposures

Chromatin Accessibility
Transcription Factor binding
ATAC-seq/scATAC-seq

Gene expression
RNA processing
RNA-seq/scRNA-seq

Phenotype
(e.g. cardiovascular disease, asthma)

Validation by MPRA/EMSA-seq
Research Program Overview

GxE in Molecular Phenotypes and complex traits

- Gene expression
- Chromatin accessibility
- RNA processing (Bulk and single cell)
- Cardiovascular disease
- Asthma

Functional Genomics of host-microbiome interactions

- In human populations
- Across primate species

Functional and evolutionary characterization of non-coding variants

- MPRA
- EMSA-seq
- Neanderthal introgression

References:

- Moyerbrailean et al, 2015, Sci Rep
- Moyerbrailean et al, 2016, Genome Research
- Richards et al, 2017, PLOS Genet
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- 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

\[(\text{mRNA level}) \sim \text{genotype}, \ y_n = \mu + \beta G_n + \varepsilon\]
Cis-eQTLs and Trans-eQTLs

a  Cis (local)

b  Trans (distal)
Genetic regulation of gene expression is variable across environmental and cellular contexts.

No genetic effect on expression

The A allele is associated with higher expression following treatment

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
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Transcriptional responses vary between populations and ancestry groups

- 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

*Nedelec et al., 2016*
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

\[ y = \beta_i,0 + \beta_i,\text{trt} + \beta_i,\text{batch} + \beta_i,\text{individual} \]

Down-regulated
Up-regulated

DEGs

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

Dubaisi et al, in prep
How does ancestry impact gene expression in treated PBMCs?

Ancestry-related differences in gene expression

Expression in EA > AA

\[ y = \beta_{i,0} + \beta_{i,\text{trt}} \times \beta_{i,\text{ethnicity}} + \beta_{i,\text{batch}} + \beta_{i,\text{individual}} \]
How does ancestry impact host transcriptional response to caffeine, vitamin A, and zinc?

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

\[ y = \beta_{i,0} + \beta_{i,\text{trt - control}} \ast \beta_{i,Af} + \beta_{i,\text{batch}} + \beta_{i,\text{individual}} \]

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

- Signaling by Interleukins
- Interleukin-10 signaling
- Regulation of Cell Cycle Genes by TP53
- Transcriptional Regulation by TP53
- Interleukin-4 and Interleukin-13 signaling
- Senescence-Associated Secretory Phenotype
- Cellular responses to external stimuli
  - Cellular Senescence
  - Infectious disease
  - Neutrophil degranulation
  - Intron processing
  - MHC mediated antigen processing

Dubaisi et al, in prep
Are genes differentially responsive between ancestry groups associated with complex traits?

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)

TWAS data from Zhang et al, 2020

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.
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Psycosocial experiences modulate asthma-associated genes through gene-environment interactions

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

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This article is a preprint and has not been certified by peer review [what does this mean?].
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
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
ELISA
HC ctrl

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

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

Resztak et al, under review
A novel approach to de-noise and impute environmental effects on gene expression

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

Cross-validated correlation

N=119

N=251

Example model fit

rho≈0.7
Shared signatures of psychosocial environments and asthma symptoms
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)

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

Gene expression\(_i\) = genotype dosage\(_i\) + transcriptional signature + genotype dosage\(_i\)\,*\,transcriptional signature + \(\varepsilon\)

ATCCCGA\,TTGGCAAT
ATCCCGA\,ATGGCAAT
Genetic Variation

Social Relationships
Emotionality
Socioeconomic Status

Interaction eQTL
Risky environment
Allele A
Allele B
Healthy environment
Allele A
Allele B
Gene Expression

Resztak et al, under review
Genetic and psychosocial factors in asthma risk

Genetic risk of asthma is modified by interactions with psychosocial factors

Resztak et al, under review
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

Genetic risk for asthma and other allergic diseases is modulated by psychosocial factors
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Image: GxE by Gaia Sperone, 2016, 7yrs