

# **Evolutionary causes and clinical implications of genetic diversity**

Research Talk

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## Introduction

Research Project 1

Research Project 2

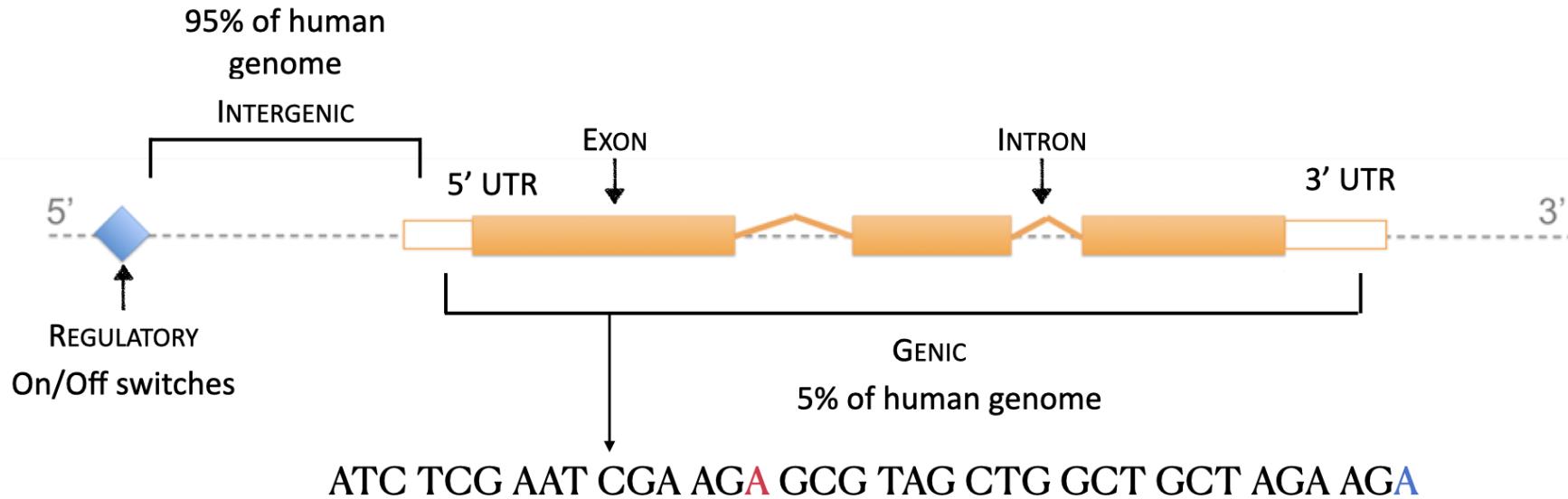
Research Project 3

Conclusions & Future Directions

# My research: an overview

# My research: zooming in

# Architecture of a genome



First Base	U	C	A	G	Third Base
U	UUU phe	UCU ser	UAU tyr	UGU cys	U
	UUC phe	UCC ser	UAC tyr	UGC cys	C
	UUA leu	UCA ser	UAA stop	UGA stop	A
	UUG leu	UCG ser	UAG stop	UGG trp	G
C	CUU leu	CCU pro	CAU his	CGU arg	U
	CUC leu	CCC pro	CAC his	CGC arg	C
	CUA leu	CCA pro	CAA gln	CGA arg	A
	CUG leu	CCG pro	CAG gln	CGG arg	G
A	AUU ile	ACU thr	AAU asn	AGU ser	U
	AUC ile	ACC thr	AAC asn	AGC ser	C
	AUA ile	ACA thr	AAA lys	AGA arg	A
	AUG met	ACG thr	AAG lys	AGG arg	G
G	GUU val	GCU ala	GAU asp	GGU gly	U
	GUC val	GCC ala	GAC asp	GGC gly	C
	GUA val	GCA ala	GAA glu	GGA gly	A
	GUG val	GCG ala	GAG glu	GGG gly	G

**Nonsynonymous:** changes the amino acid  
(A->C; arg-> ser)

**Synonymous:** no change of amino acid;  
silent (A->G; arg-> arg)

# Processes that shape genomic diversity in the absence of selective pressures

# Selective processes that shape genomic diversity

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**MHC molecules present antigens and unleash immune responses**

# MHC/HLA: an extreme instance of balancing selection

Is there support for the divergent allele advantage model?

# Is there support for the divergent allele advantage model?

**Hypothesis:** divergent allele advantage model (heterozygote advantage is greater for genotypes with more divergent alleles) explains selective patterns in the HLA genes

**Prediction:** increased signatures of balancing selection between pairs of HLA alleles that match different antigens

To answer these questions, I looked at the human class I HLA genes

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**How prevalent has balancing selection  
been throughout human evolution?**

**What are the instances beyond the MHC  
loci?**

## **Can we devise a statistical test specific for signatures of balancing selection?**

Approach: combine independent signatures into one statistic

## **If so, how prevalent has it been throughout human evolution?**

Approach: perform a genome-wide scan using a test specifically tailored for balancing selection

## **Are there common trends amongst the candidate regions/genes?**

Approach: Explore candidate regions/genes for common functions/patterns

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Can we devise a statistical test specific for signatures of balancing selection?

# A method to detect signatures of balancing selection

# Pervasiveness and targets of balancing selection in humans

Introduction

Research Project 1

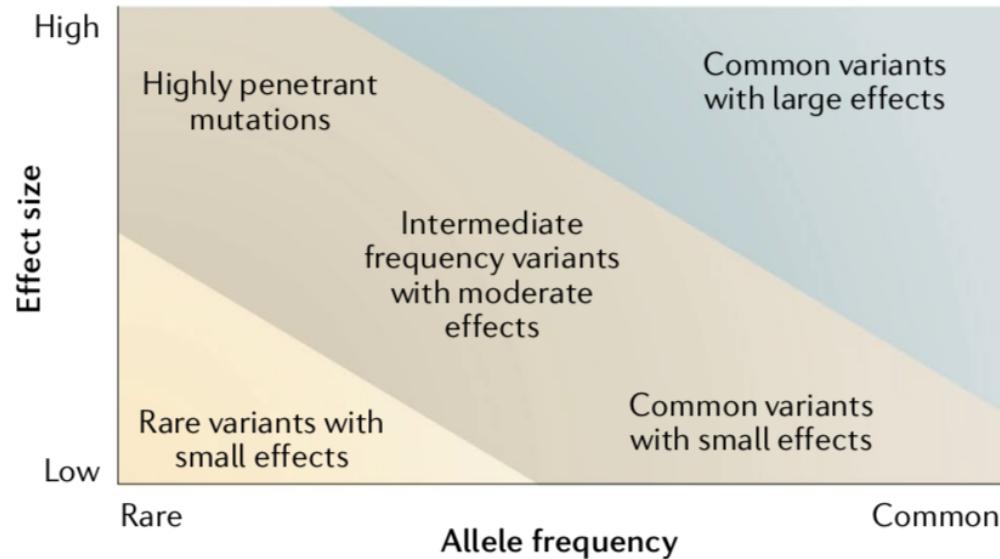
Research Project 2

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Conclusions & Future Directions

# Genome-wide association studies (GWAS)

# Many variants with small effect size



Tam et al. (2019) *Nat Rev Genet*

Rare, monogenic diseases/traits:

phenylketonuria, sickle-cell anemia, Duchenne muscular dystrophy

complex, common diseases/traits:

cardiovascular disease, T2 diabetes, cancers, **height**, BMI

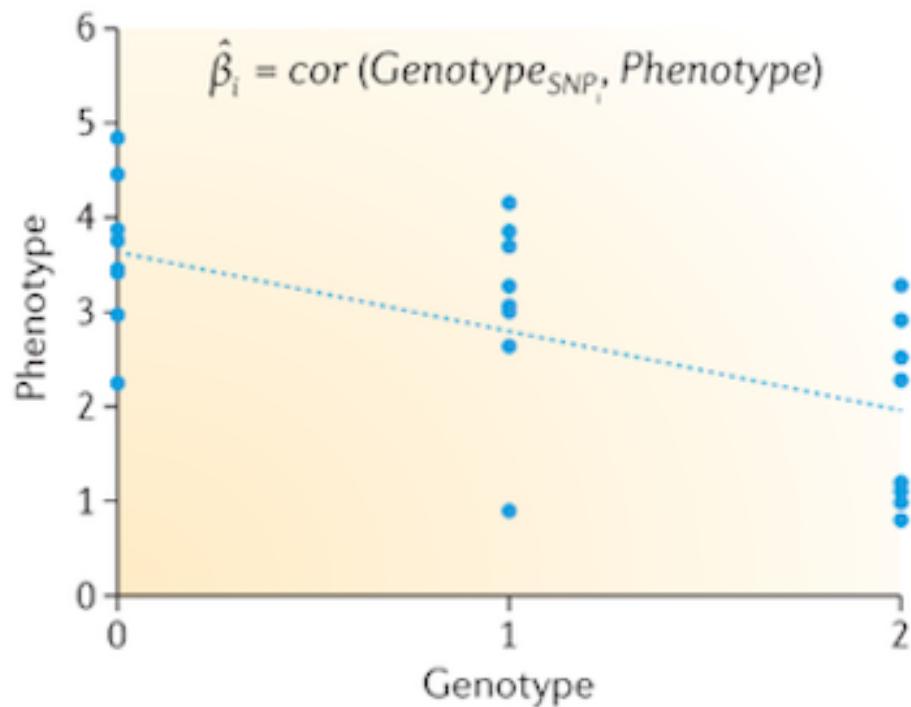


# Polygenic traits and their predictive power

Phenotype	Variance_Explained	Variants
height	25.0	3000
schizophrenia	7.0	100
ADHD	5.5	100

PS: for Europeans ancestry only...

# Polygenic risk scores combine all variants with an effect on the phenotype



$$PRS = \sum_{i=1}^m \hat{\beta}_i G_{j,i}$$

$\hat{\beta}$  : effect size (from GWAS)

$G$  : Effect allele dosage

$j$ : Individuals

$i$ : SNPs

independence

additive model

# PRSs are appealing

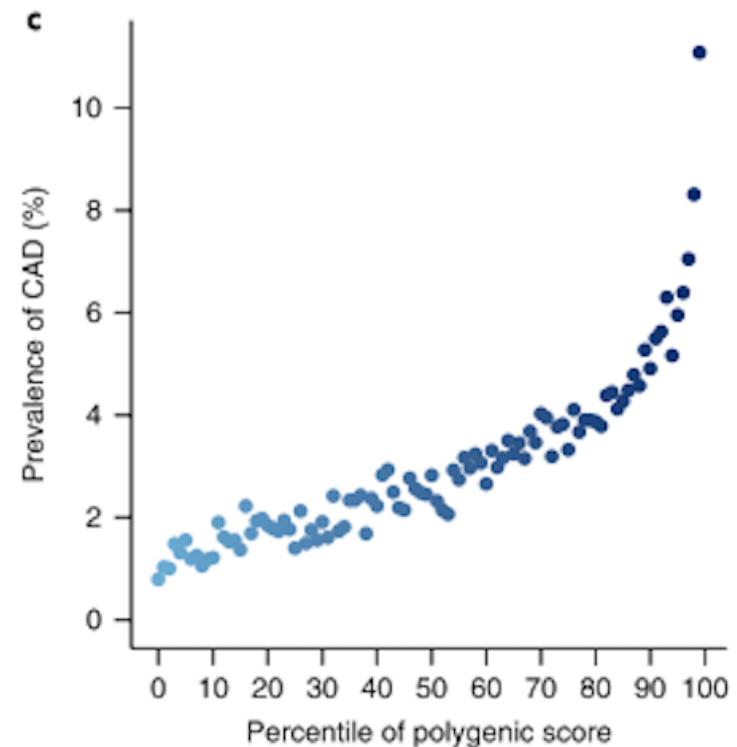
easy

promising

fast

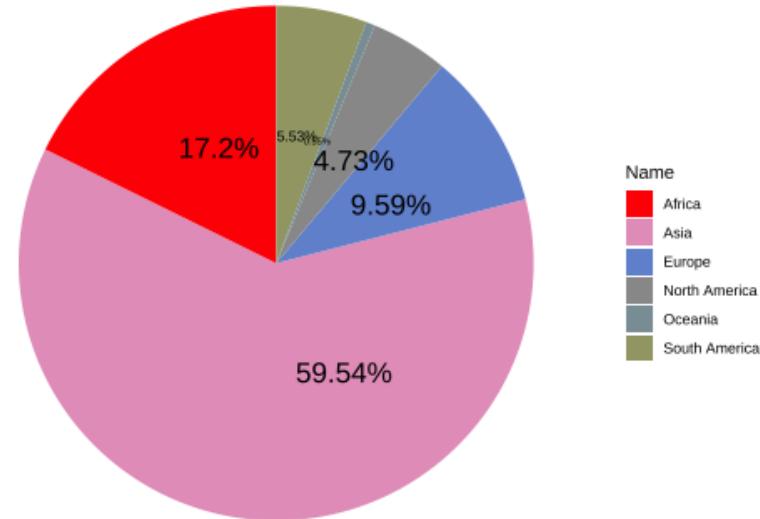
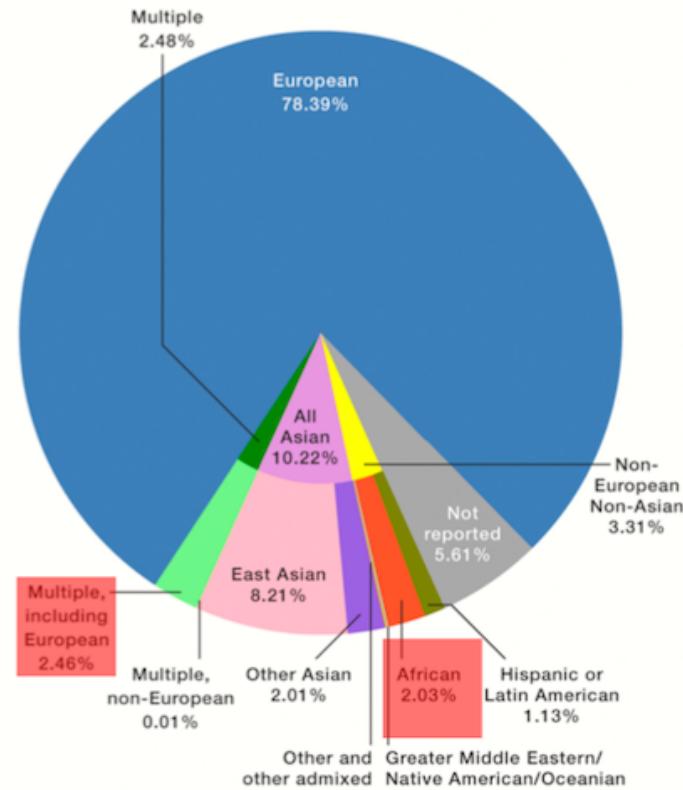
minimal requirements

Polygenic risk of cardiovascular disease





European ancestry  
represent almost 80% of  
GWAS participants...



[Data: <https://worldpopulationreview.com/>]

.. and <15% of the world's population

How much do polygenic scores predict phenotypes in other populations?

**How do these different factors affect prediction accuracy?**

**What can we do about it?**

## How do these different factors affect prediction accuracy?

**Approach:** examine how well we can predict a highly heritable trait in different populations, based on an European ancestry discovery cohort and explore the roles of different biological/statistical factors

## What can we do about it?

**Approach:** explore whether incorporating fine-scale ancestry information into these scores improves their performance

Let's look at height

Wow well can we predict a highly heritable trait?

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Wow well can we predict a highly heritable trait in different populations?

## **1. Introduction**

## **2. Research Theme 1: Balancing selection in humans**

## **3. Research Theme 2: Polygenic risk prediction for individuals with non-European ancestry**

## **4. Conclusions & Future Directions**

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**How has balancing selection shaped diversity in the HLA loci?**

**How prevalent has balancing selection been throughout evolution and what are the common trends?**

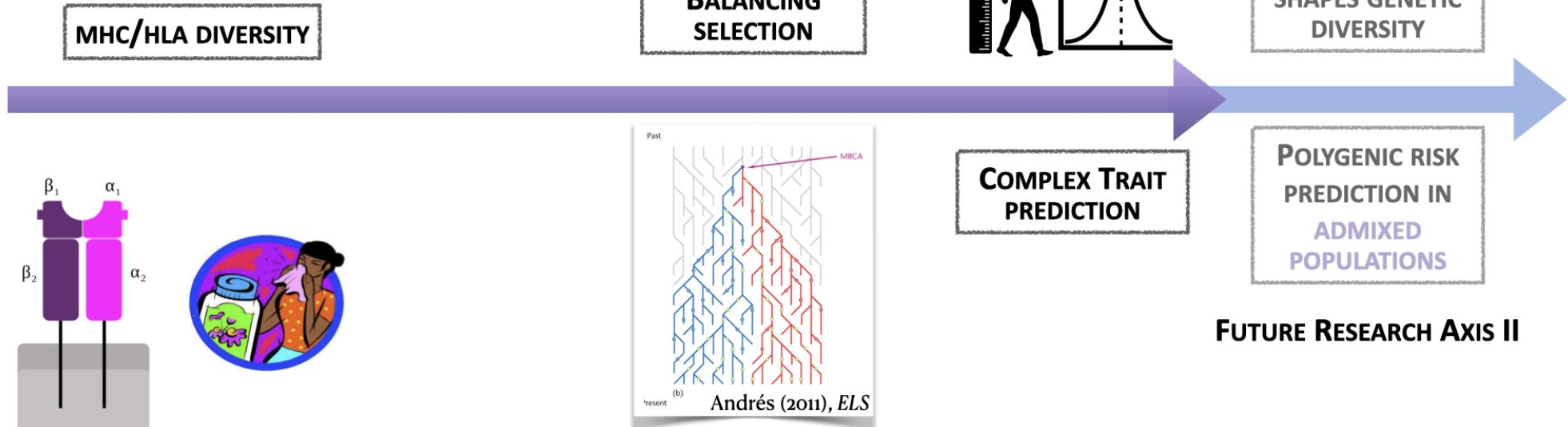
**How useful are polygenic risk predictors for individuals with non-European ancestries?**

- 1) There is support for the divergent allele advantage model in HLA evolution
- 2) A novel test, specific for balancing selection, revealed many new candidates, 1/3 of which are immune-related, and many others related to defense broadly and reproduction
- 3) At present, PRS approaches have little to no utility for individuals with non-European ancestry, many factors are responsible, need to diversify genetics studies at all stages

Francisco, (+2), Bitarello, França, (+2) (2015),  
*Immunogenet*  
Bitarello\*, Francisco & Meyer (2016), *J.Mol.Evol*  
Brandt, Aguiar, Bitarello (+3) (2015), *G3: Genes,  
Genomes, Genetics*

Bitarello\* et al. (2018), *GBE*  
Giner-Delgado (+6), Bitarello, (+12)  
(2019), *Nat. Comm.*  
Mathieson (+6), Bitarello, (+8)(2020),  
*BiorXiv*

## FUTURE RESEARCH AXIS I



Bitarello\* & Mathieson (2020),  
*G3: Genes, Genomes, Genetics*

# Research Axis I: Balancing selection as a force that shapes diversity

## Research Axis II: Polygenic risk prediction in admixed populations

# A final thought

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