Science Webinar Series

Exploring evolutionary immunogenomics: Lessons from our ancestors and past pandemics

20 Apr 2022

Participating expert:

Luis Barreiro, Ph.D.
University of Chicago
Chicago, IL

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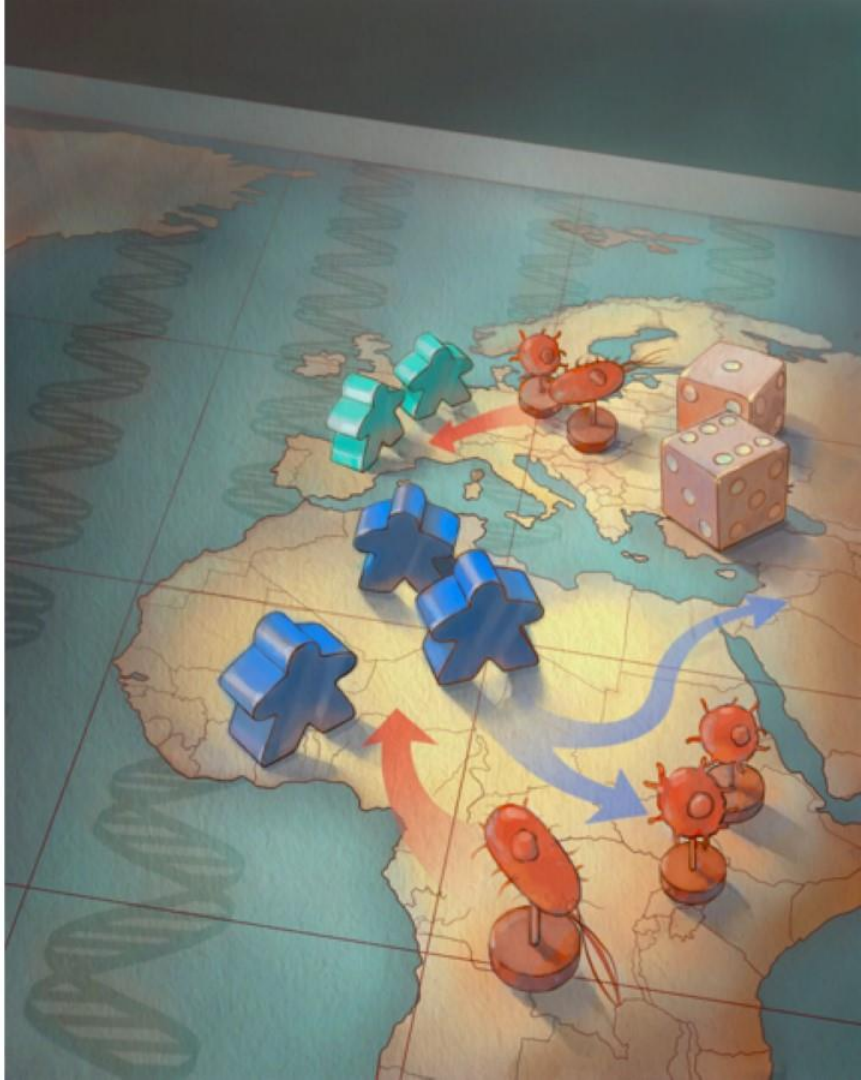
Exploring evolutionary immunogenomics: Lessons from our ancestors and past pandemics.

Luis Barreiro
University of Chicago
email: lbarreiro@uchicago.edu

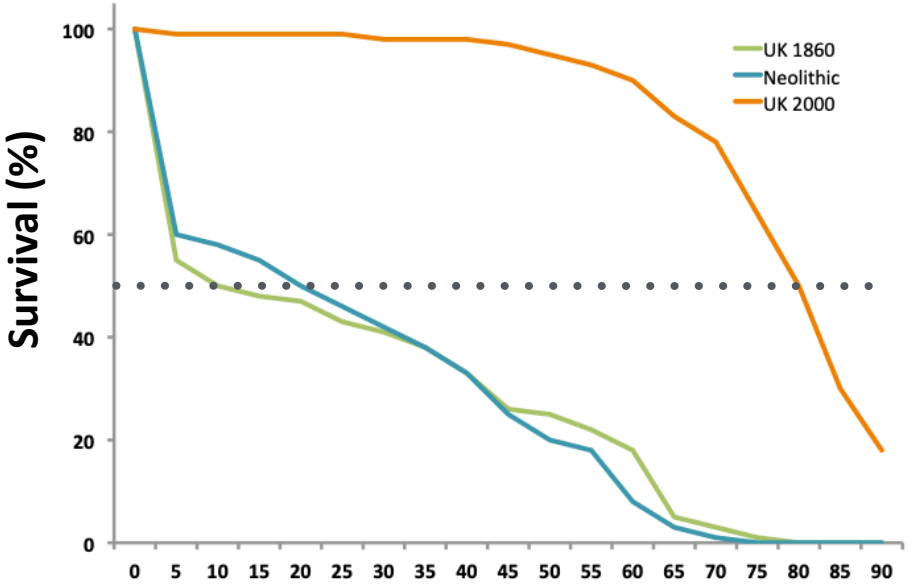
@LB_Barreiro



Pathogens have been the strongest selective pressure through human evolution

Alexander Fleming

1928: Discover of penicillin, the first natural antibiotic.

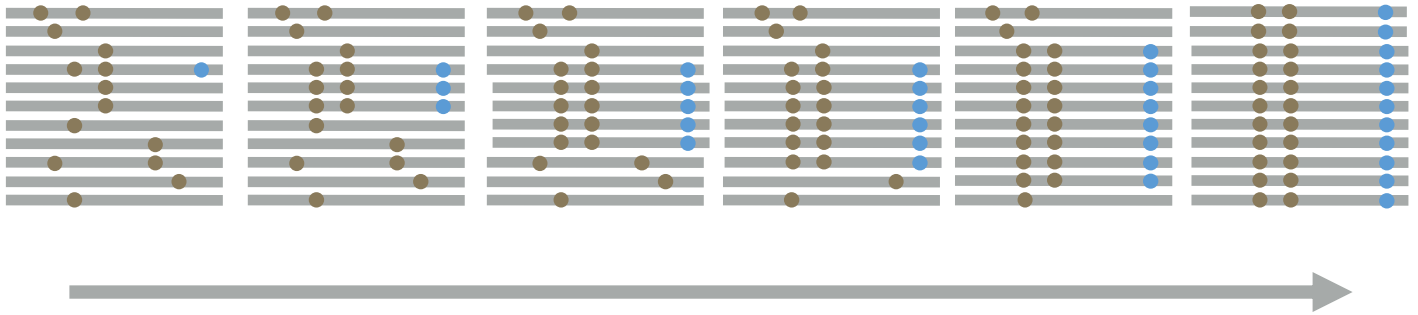


Louis Pasteur

1885: rabies vaccine.
Vaccines against diphtheria, tetanus, anthrax, cholera, plague, typhoid, tuberculosis, and more were developed through the 1930s.

Adapted from Casanova & Abel (2005) **JEM**

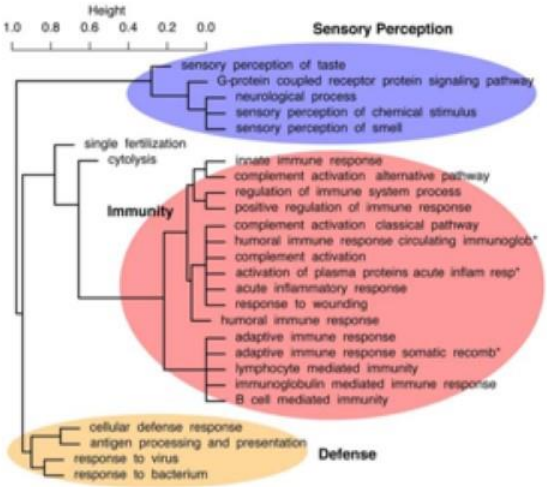
The molecular traces of natural selection in the human genome



Neutrality tests

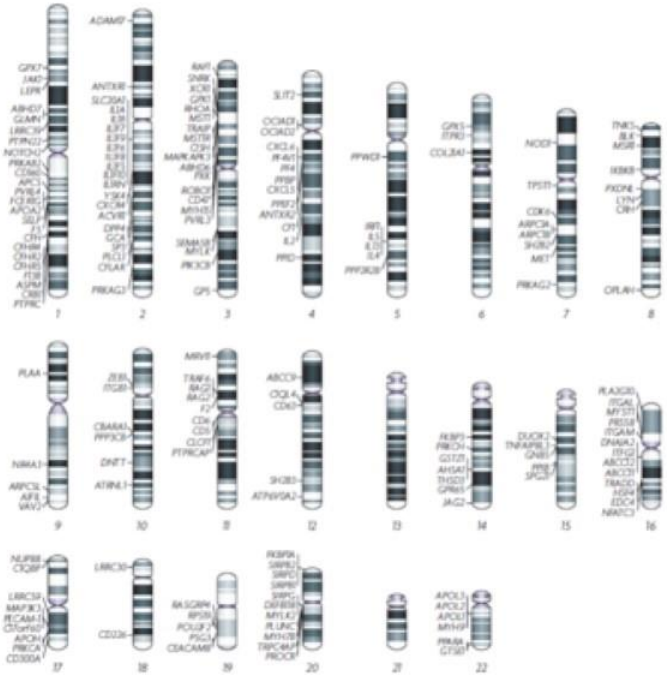
Natural selection on the immune system

Inter-species level



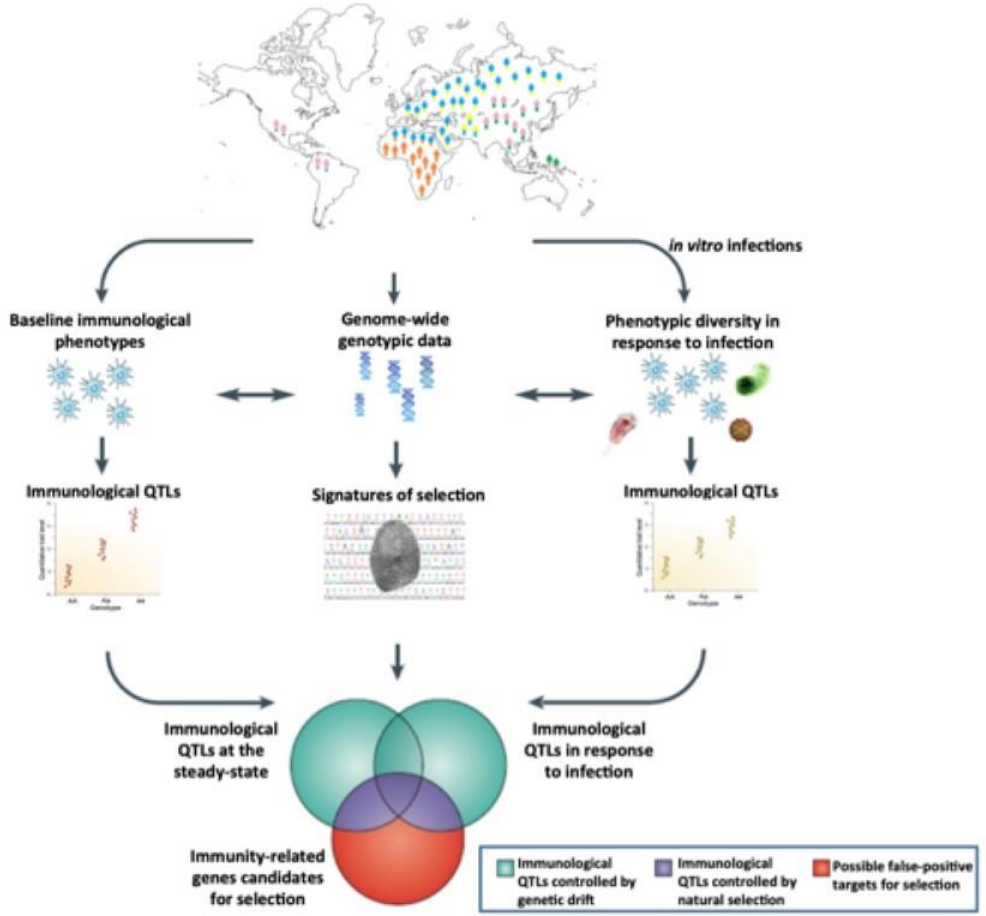
Kosiol et al. (2008) ***PLoS Genetics***

Within human populations



Barreiro & Quintana-Murci (2009) ***Nature Reviews Genetics***
Barreiro et al (2008) ***Nature Genetics***

Our approach to study selection on immune-related processes



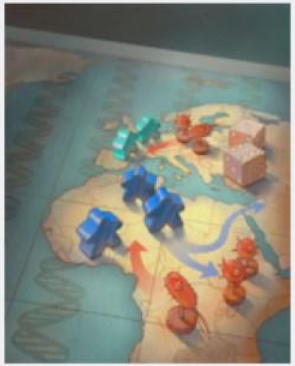
Outline

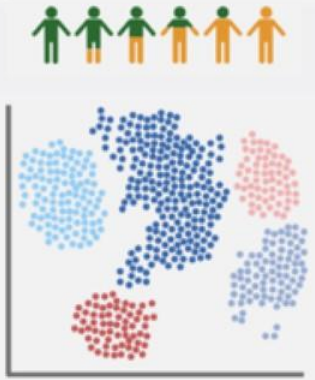
I. Ancestry-associated differences in immune responses

. Variation in immune responses to bacterial pathogens

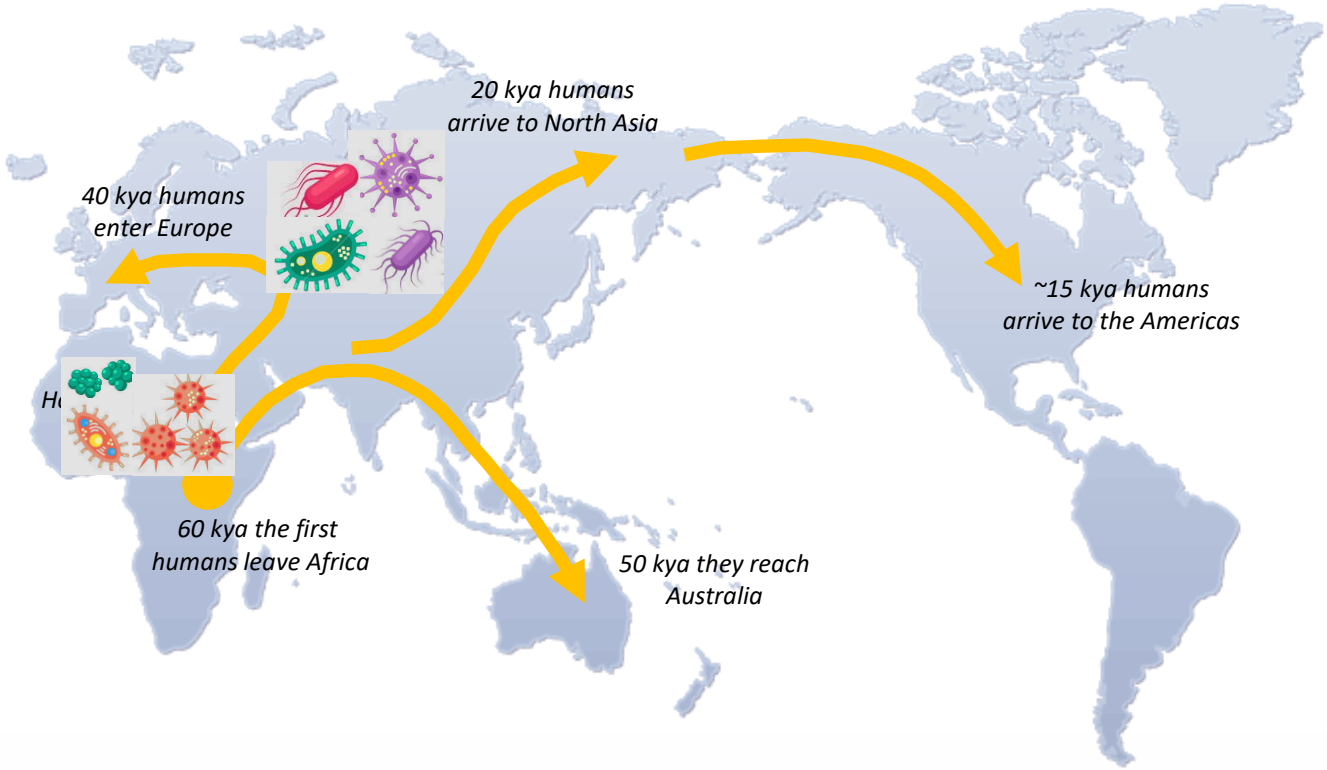
. Single cell resolution map of immune variation to flu infection

. The impact of past pandemics to the evolution of immune responses

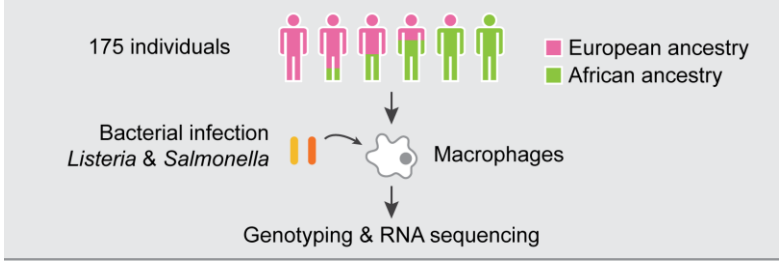


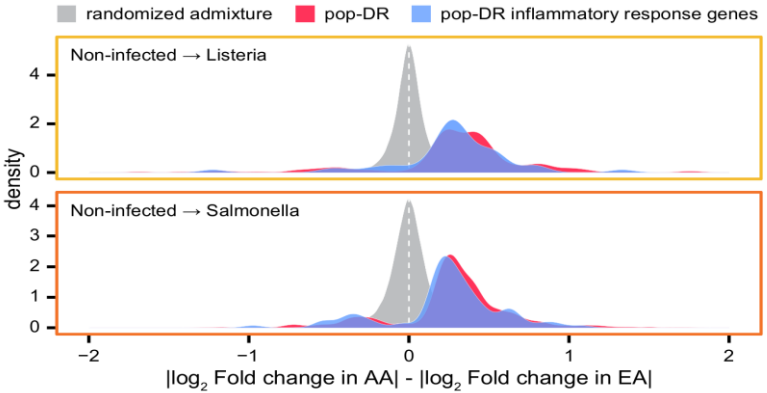


AFRICAN ORIGIN OF MODERN HUMANS

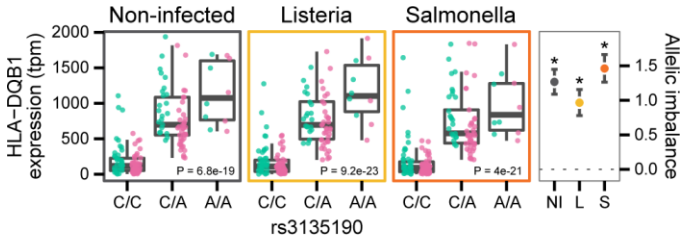


Genetic Ancestry Drives Population Differences in Immune Responses to Pathogens





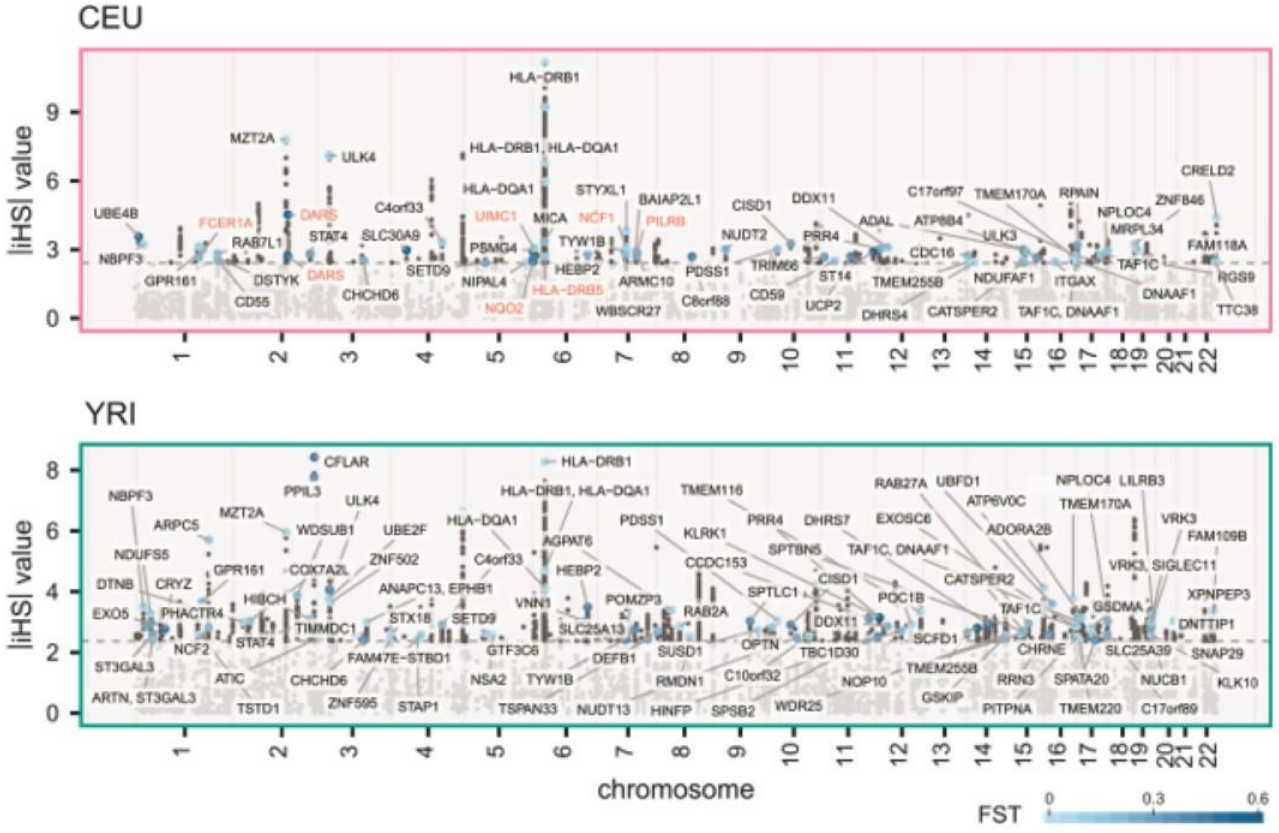
Over 20% of genes responding to either infection show a significant difference in the *intensity of the response* between European and African individuals. Increased African ancestry is associated with a stronger transcriptional response to infection.



~30% of population differences in immune regulation are explained by changes in allele frequencies of autosomal expression quantitative trait loci (eQTL)

Nedelec*, Sanz*, Baharian*, et al. (2016), ***Cell***

Natural Selection Contributed to Ancestry-Associated Differences in Immune response



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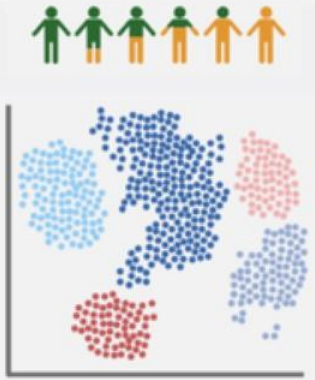
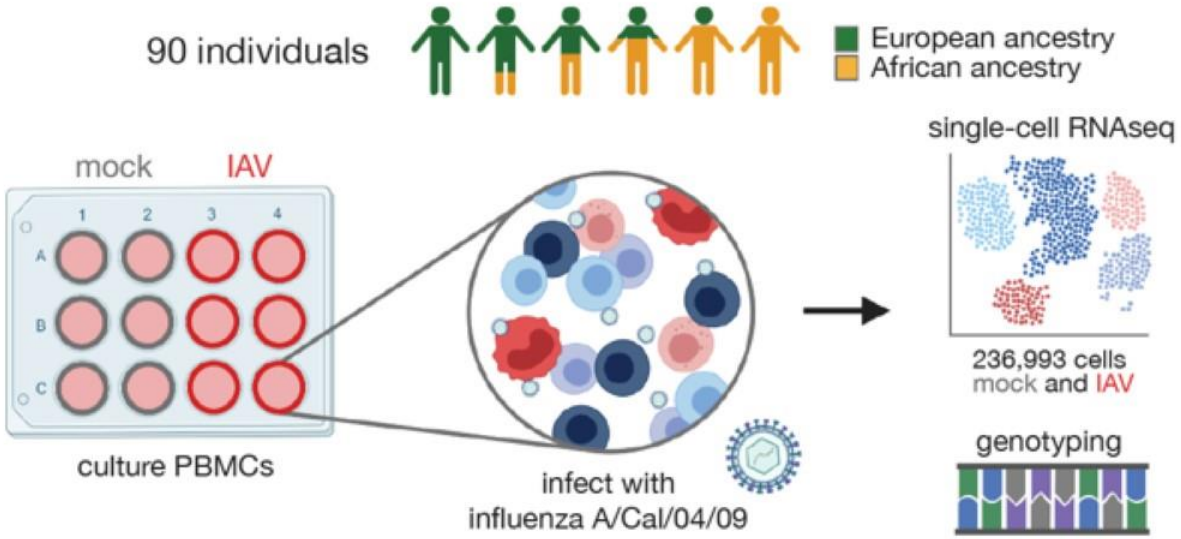


Ancestry differences in immune regulation at single cell resolution

Haley Randolph

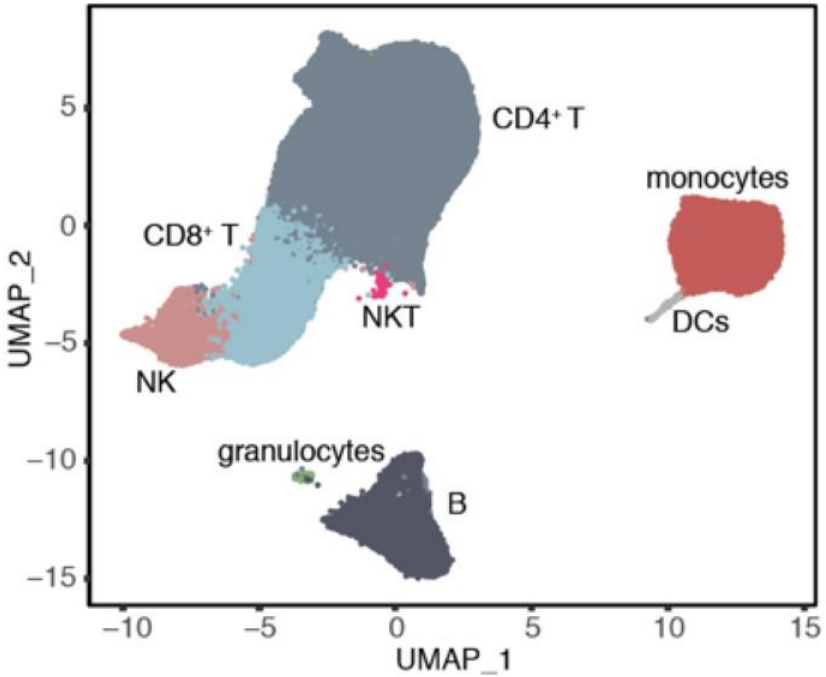


180 samples, paired mock-exposed and IAV-infected (MOI = 0.5) samples from each of 90 individuals

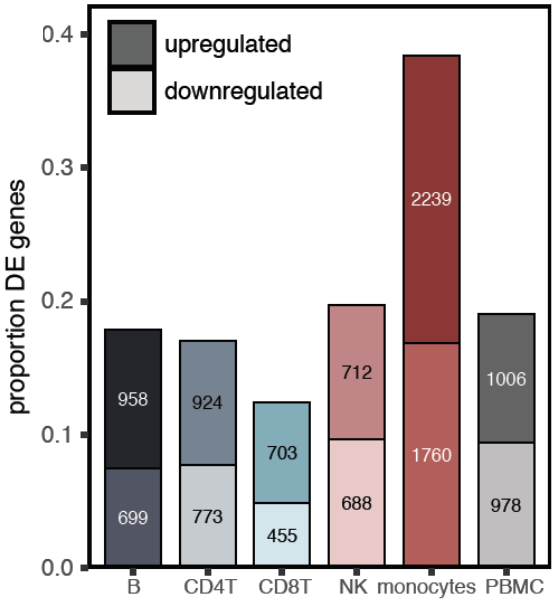
Randolph, et al. (2021) *Science*

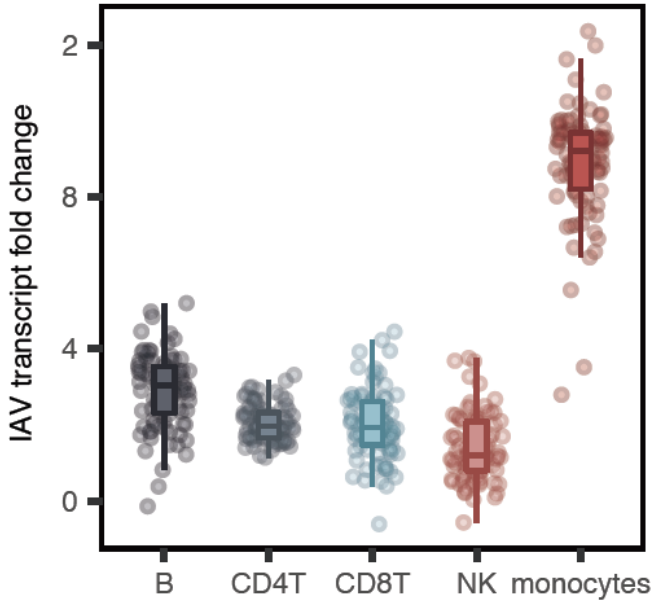
Clustering separates cells into five major populations

Dataset: 235,161 high-quality RNA-seq profiles retained after filtering



RESULTS | Monocytes are the most responsive to IAV infection

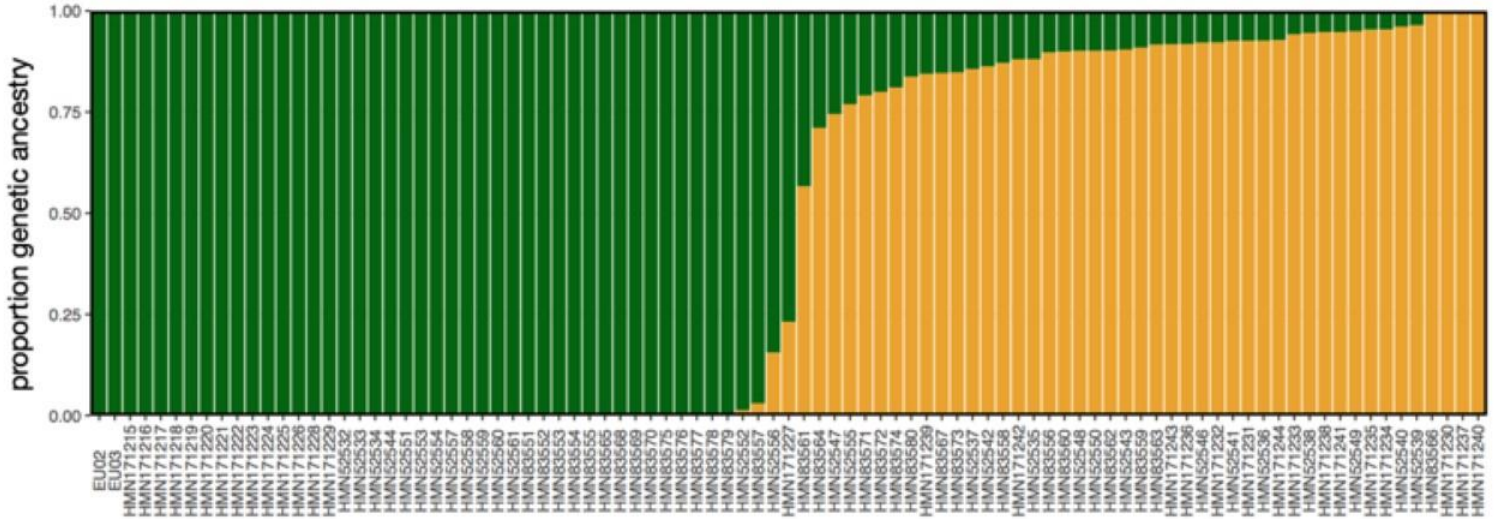




•38% of the monocyte transcriptome changes in response to IAV infection

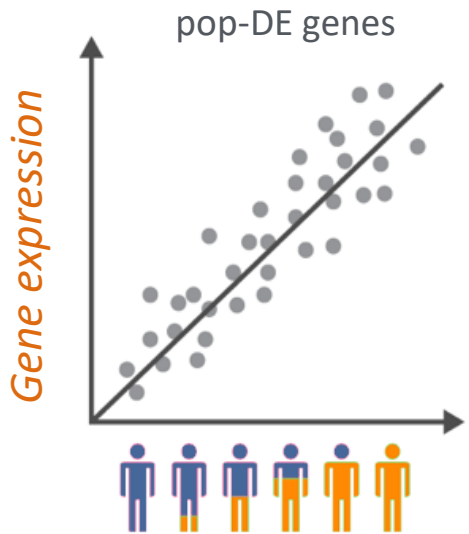
RESULTS | Differences in immune response between African- and European-ancestry individuals

- Collected low-pass (4X) whole-genome sequencing for the 90 individuals in the study.
- ***After imputation we obtained genotypes across >60 million SNPs per individual.***

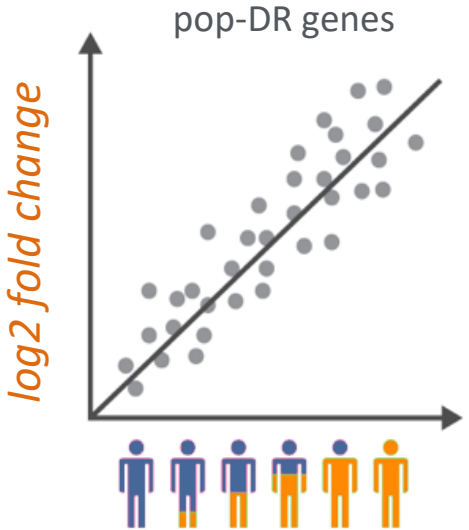


RESULTS | Differences in immune response between African- and European-ancestry individuals

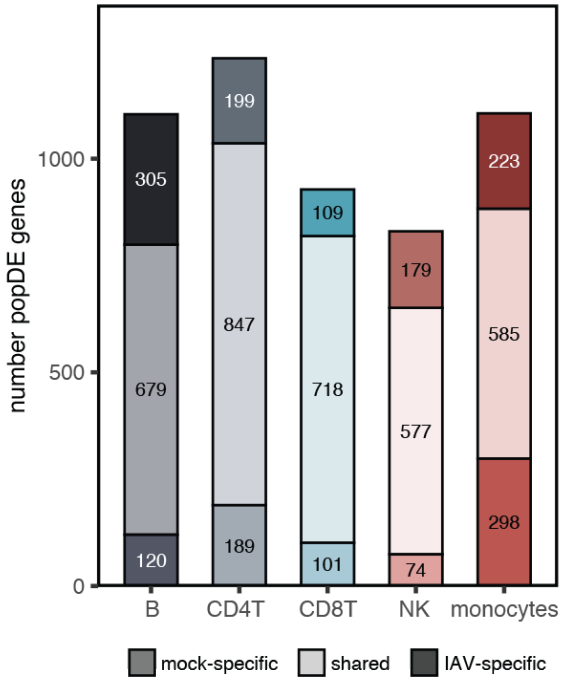
Population Differently *Expressed* genes

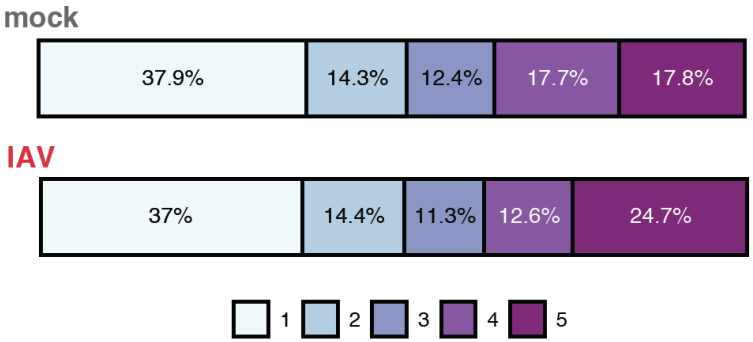


Population Differently *Responsive* genes



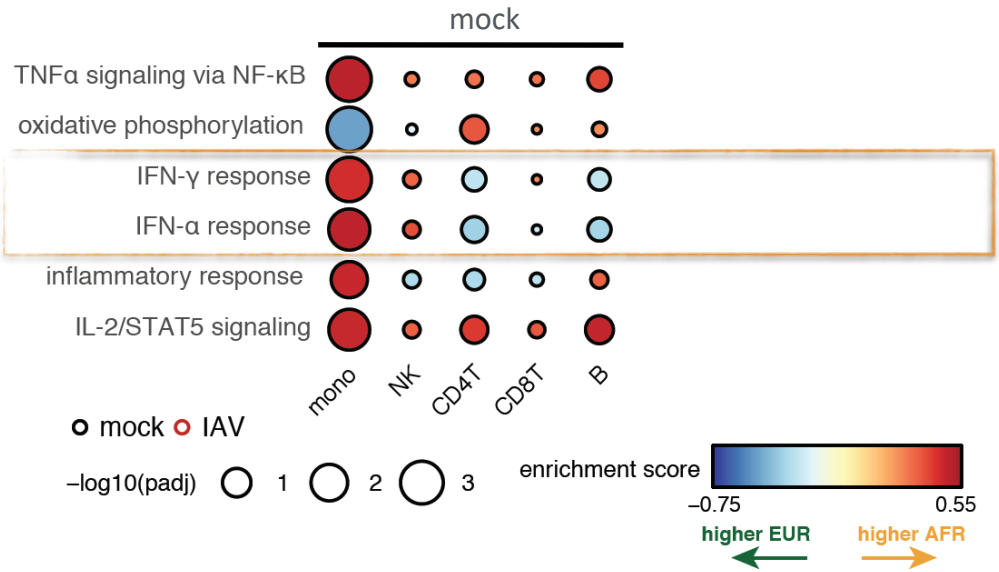
RESULTS | Most genetic ancestry effects are cell-type specific





~52% of popDE genes identified in only one or two cell types

RESULTS | Interferon pathways exhibit higher expression in individuals with increased European ancestry



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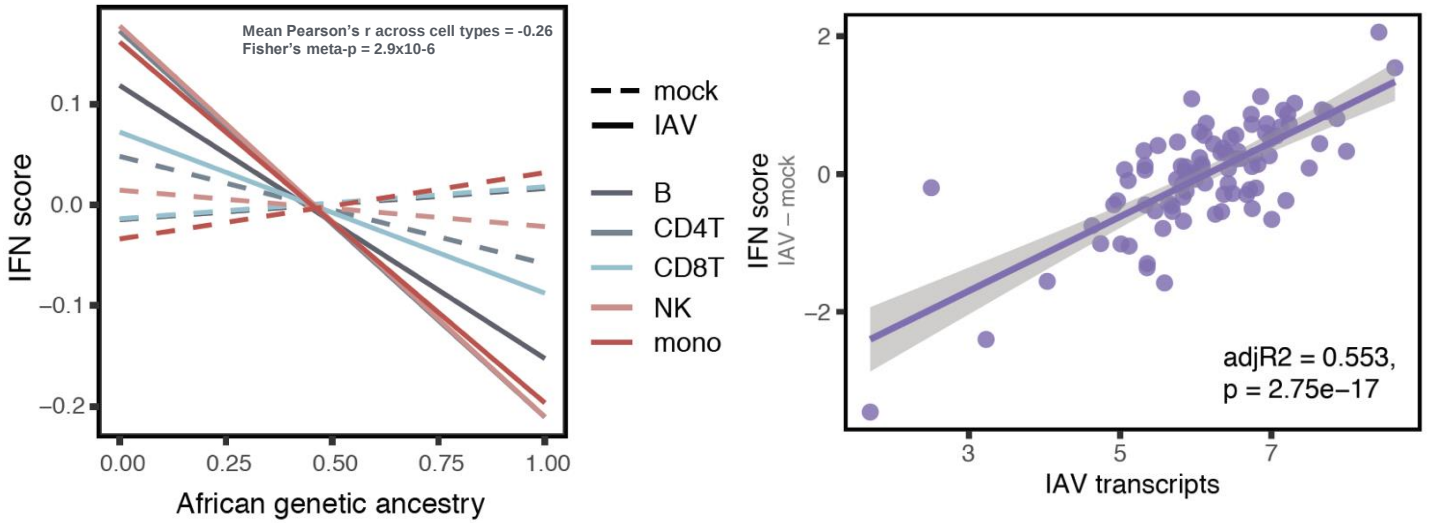
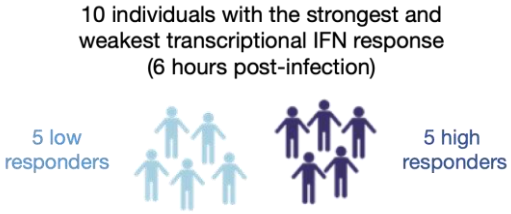
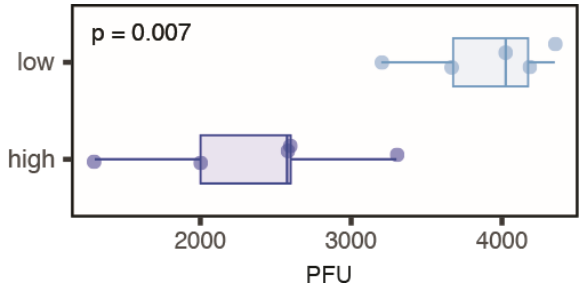
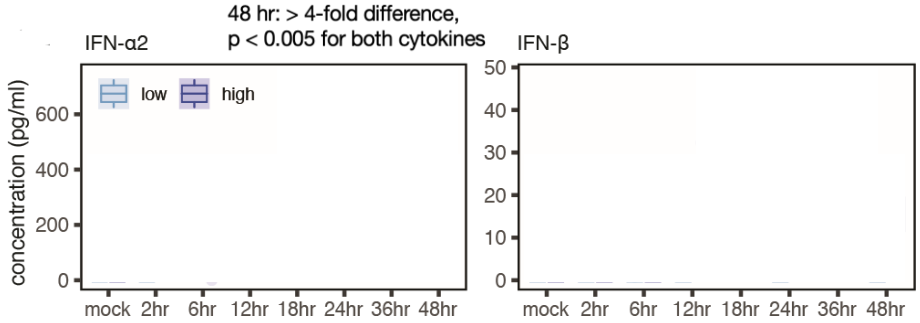


European-ancestry individuals engage a stronger interferon response to IAV infection

RESULTS | An early stronger interferon response is associated with better viral clearance at later time points





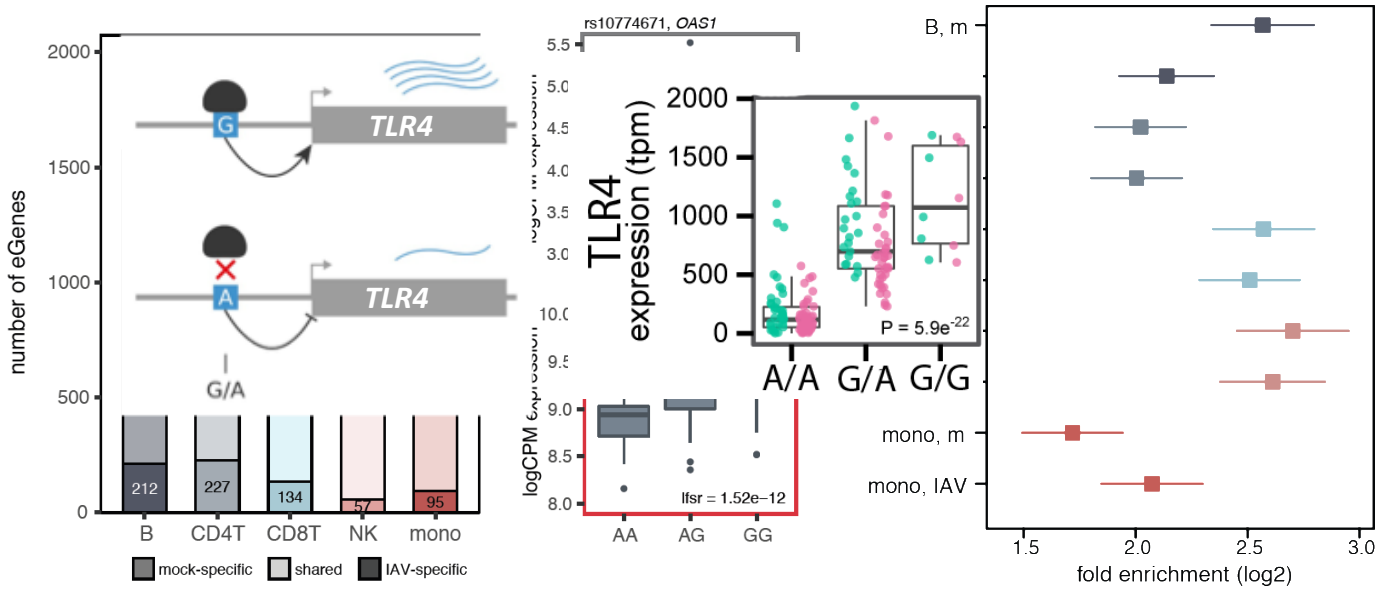


Individuals better able to mount type I IFN responses shortly after infection are also better able to limit viral replication at later time points.

RESULTS | Genetic drivers of population differences in immune response

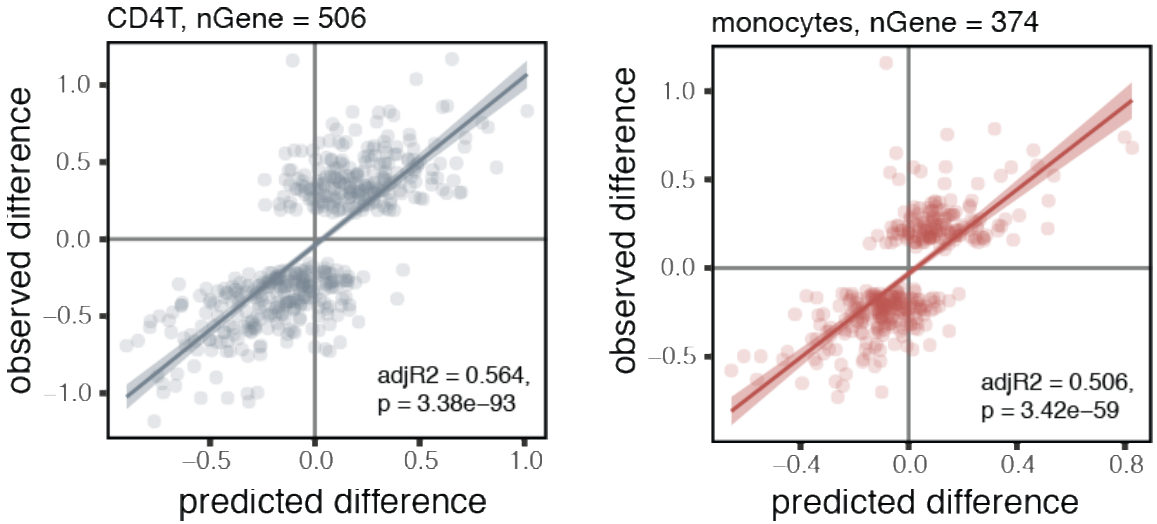
We identified 2,234 genes (eGenes) that are associated with at least one cis-eQTL

Cis-eQTL



eGenes were **3.2 to 6.5 X more likely be classified as popDE** than expected by chance

RESULTS | Genetic drivers of population differences in immune response



Among popDE genes in which we identify at least one cis-eQTL across cell types and conditions, we estimate that, on average, ***cis*-eQTLs explain approximately 53% of the variance in the observed population differences**

Do genetic ancestry-associated differences in immune responses partially underlie some of the observed variation in COVID-19 susceptibility?

- Association with **age, sex, race/ethnicity, and underlying comorbidities** and risk of COVID-19 hospitalization
- CDC estimates a **79% higher rate of influenza-related hospitalizations** for Black versus white Americans

Risk for COVID-19 infection, hospitalization, and death by race/ethnicity

Rate ratios compared to White, Non-Hispanic persons	American Indian or Alaska Native, Non-Hispanic persons	Asian, Non-Hispanic persons	Black or African American, Non-Hispanic persons	Hispanic or Latino persons
Cases[1]	1.6x	0.6x	1.0x	1.6x
Hospitalization[2]	3.3x	0.8x	2.6x	2.5x
Death[3]	2.2x	0.9x	1.9x	2.1x

Much of these differences in morbidity/mortality can be attributed to health disparities due to structural inequities, but **might immune response variation compound existing health disparities?**

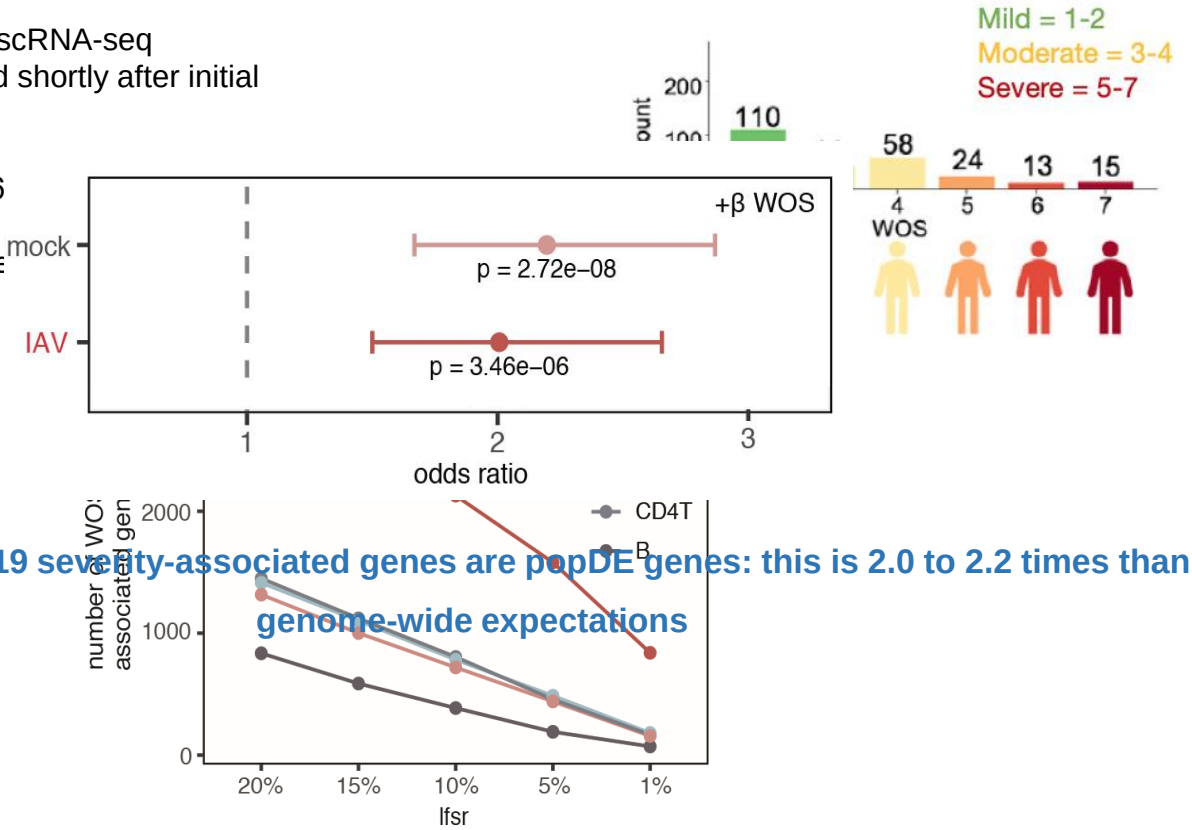
Data from the Centers for Disease Control and Prevention *(November 2021),* Ko et al., *Clinical Infectious Diseases (2021)*

RESULTS | Can ancestry-associated differences in immune response to viruses explain health disparities in COVID-19 outcomes?

- COVID-19 patients with scRNA-seq data on PBMCs collected shortly after initial diagnosis

- n = 127 patients, 505,616

- Disease severity measure ordinal scale (WOS)



23% of COVID-19 severity-associated genes are popDE genes: this is 2.0 to 2.2 times than genome-wide expectations

*Re-analysis of Su et al. dataset (*Cell*, 2020)

Some take home messages:

- **Genetic ancestry effects on the immune response to IAV are common but highly cell type specific**.
- **Increased European ancestry is associated with a stronger type I IFN response** shortly after influenza infection, which in turn predicts reduced viral titers at later time points.
- **cis-eQTLs explain approximately 53% of the variance in the observed population differences.**
- Genes differentially expressed by genetic ancestry are enriched among genes associated with COVID-19 disease severity. **Variation in the immune response may interact with or exacerbate environmentally driven health disparities in viral susceptibility**.

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I. Ancestry-associated differences in immune responses

. Variation in immune responses to bacterial pathogens

. Single cell resolution map of immune variation to flu infection

. The impact of past pandemics to the evolution of immune responses

COVID-19 susceptibility and past selective events

Article

The major genetic risk factor for severe COVID-19 is inherited from Neanderthals

nature medicine

ARTICLES

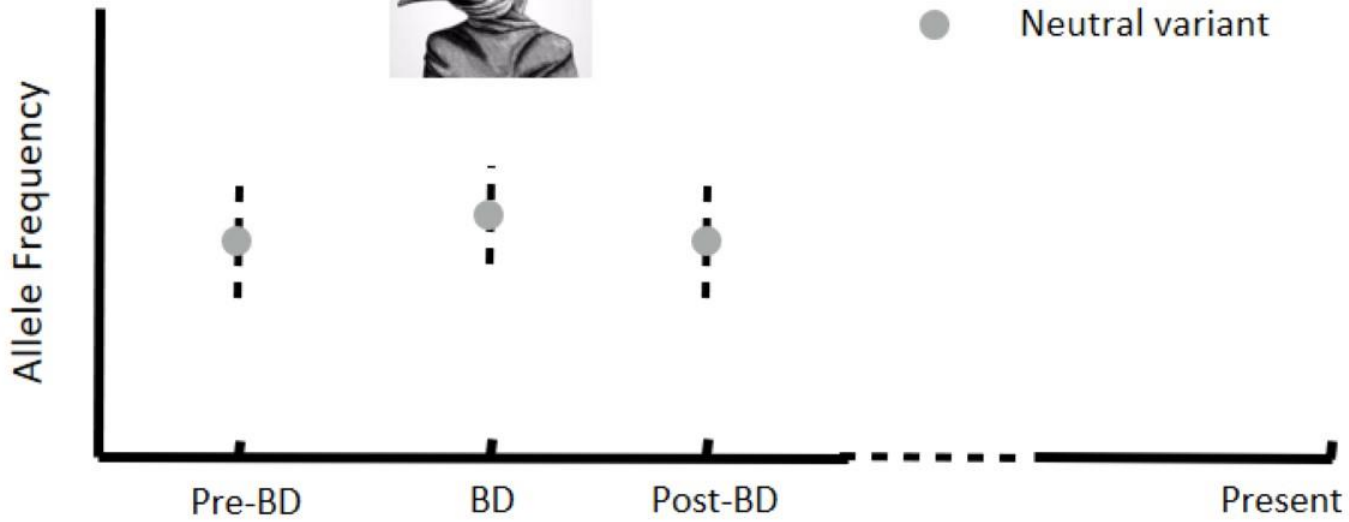
https://doi.org/10.1038/s41591-021-01281-1

Check for updates

A Neanderthal OAS1 isoform protects individuals of European ancestry against COVID-19 susceptibility and severity


Black Death (1346-1353 CE), which was caused by *Yersinia pestis*, devastated Europe, killing 30-50% of the population

Hypothesis



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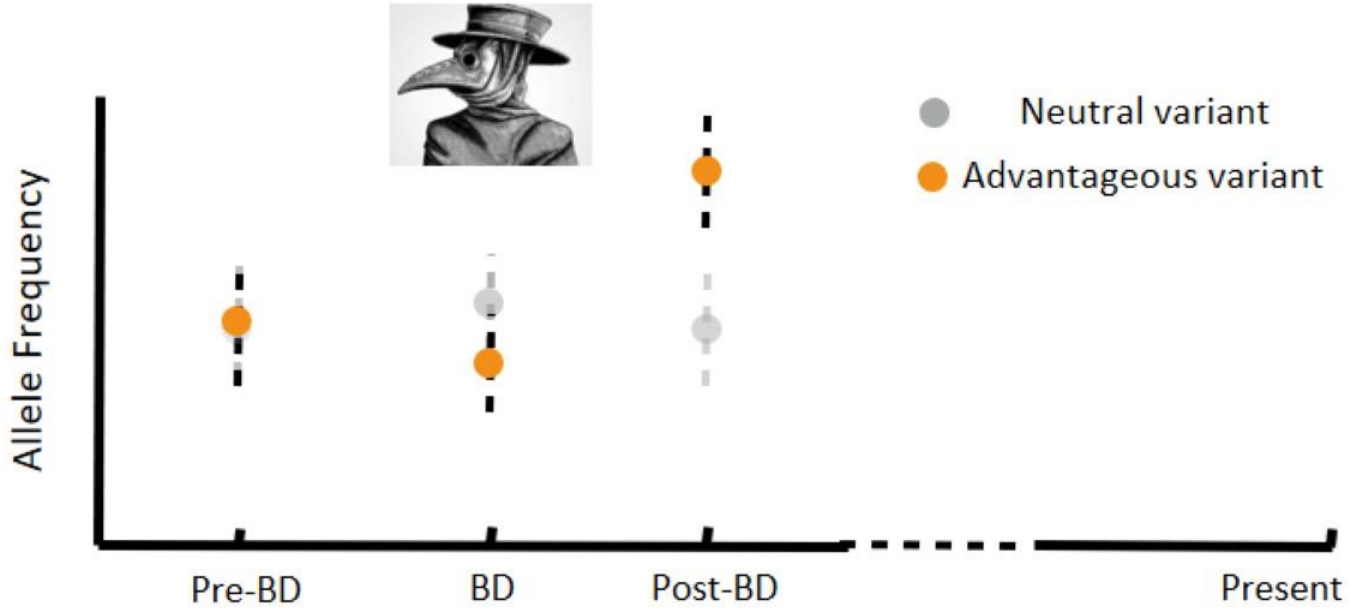

Neutral variant
Advantageous variant
Allele Frequency
Pre-BD
BD
Post-BD
Present

Tauras Vilgalys

Hendrik Poinar

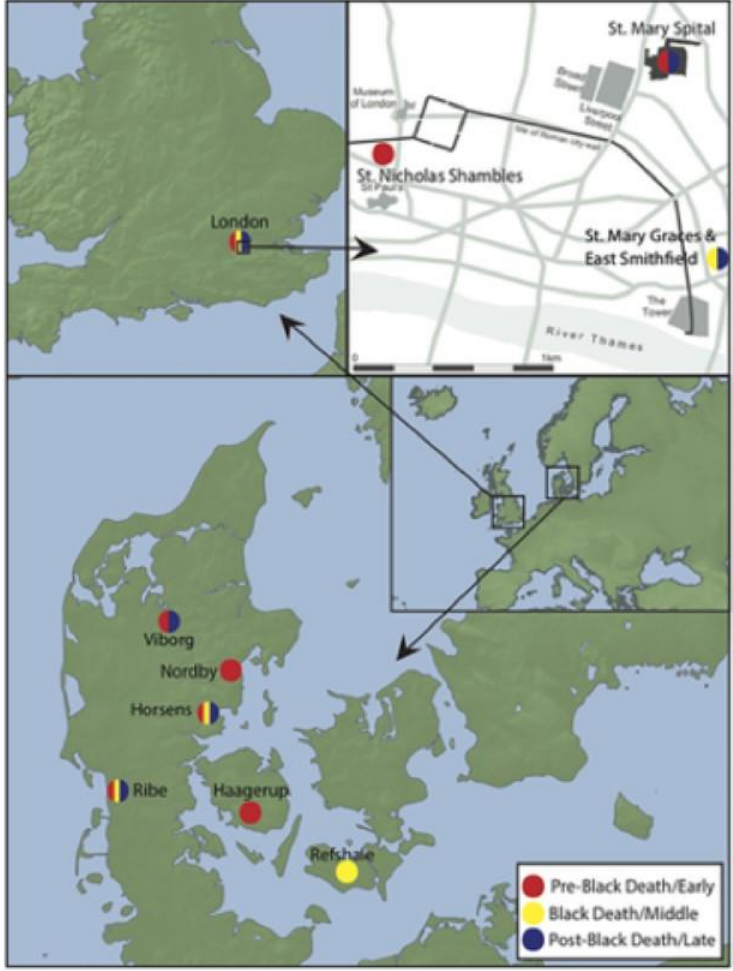
Jen Klunk

Study-design:

Studied genetic variation around immune-related genes from 321 ancient DNA samples from two European populations directly before, during, and after the Black Death

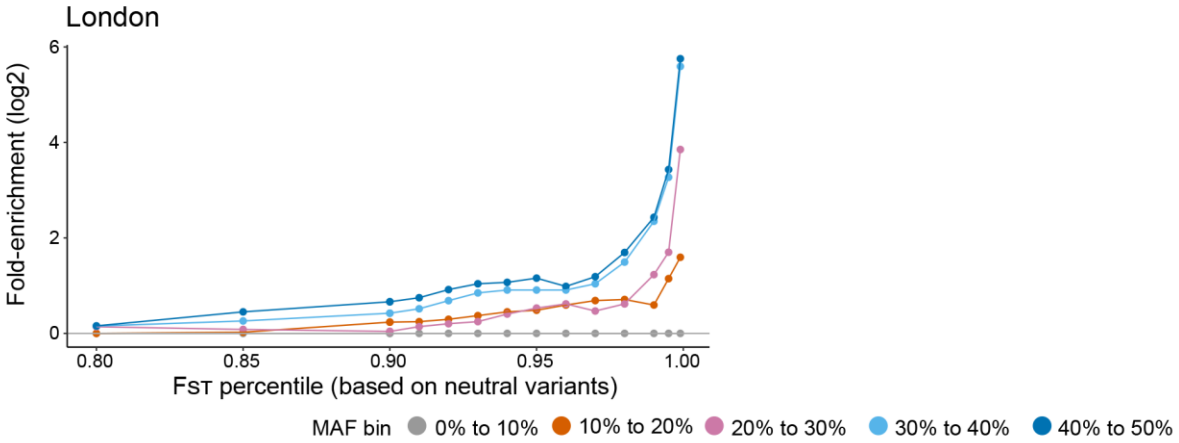
Targeted enrichment for:

- **Exons**: exons from 356 immune-related genes.
- **Neutral loci**: 200 regions of 1.5kb.
- **GWAS loci**: 446 SNPs associated with immune-related phenotypes.



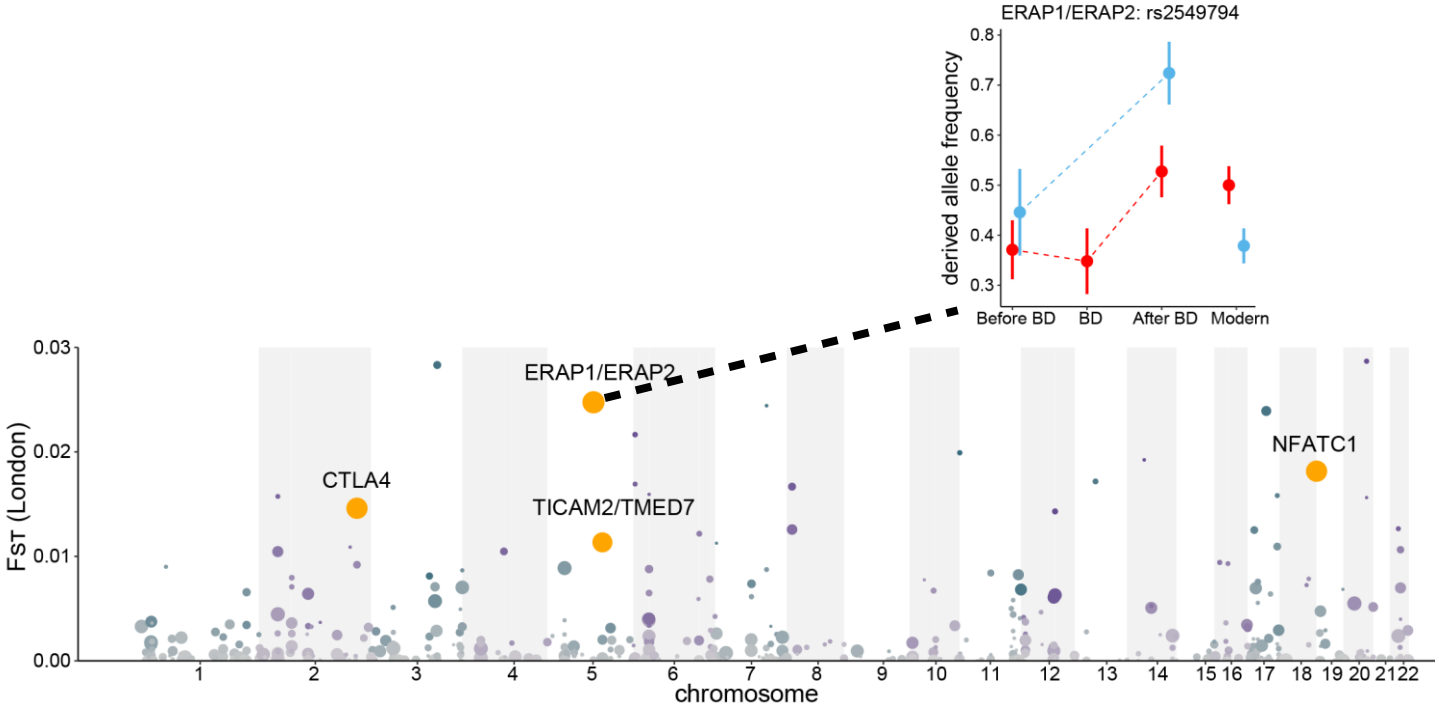
Klunk et al. 2019 (AJPA)

Immune loci are strongly enriched for highly differentiated sites



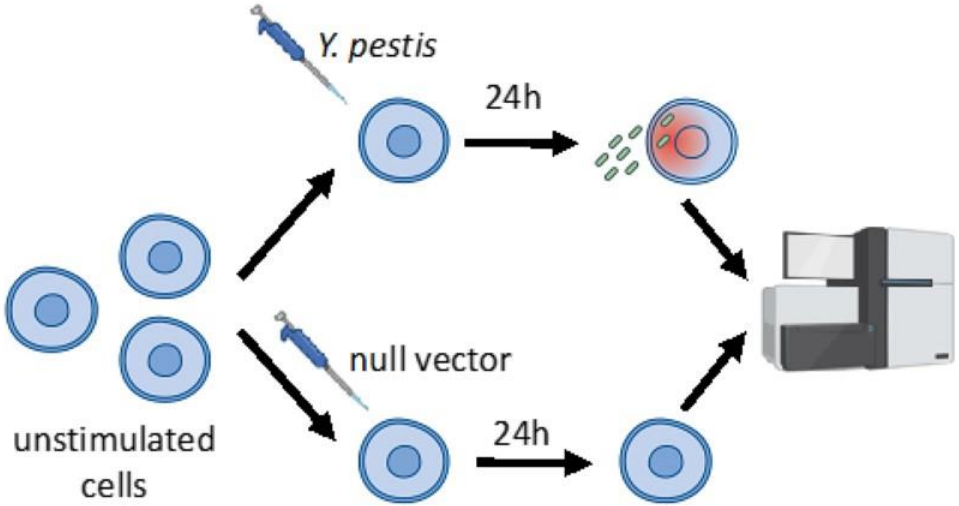
For variants with a MAF>30% highly-differentiated sites are found at **3.9x the rate expected by chance** (binomial test $p = 1.16 \times 10^{-14}$)

Immune loci are strongly enriched for highly differentiated sites



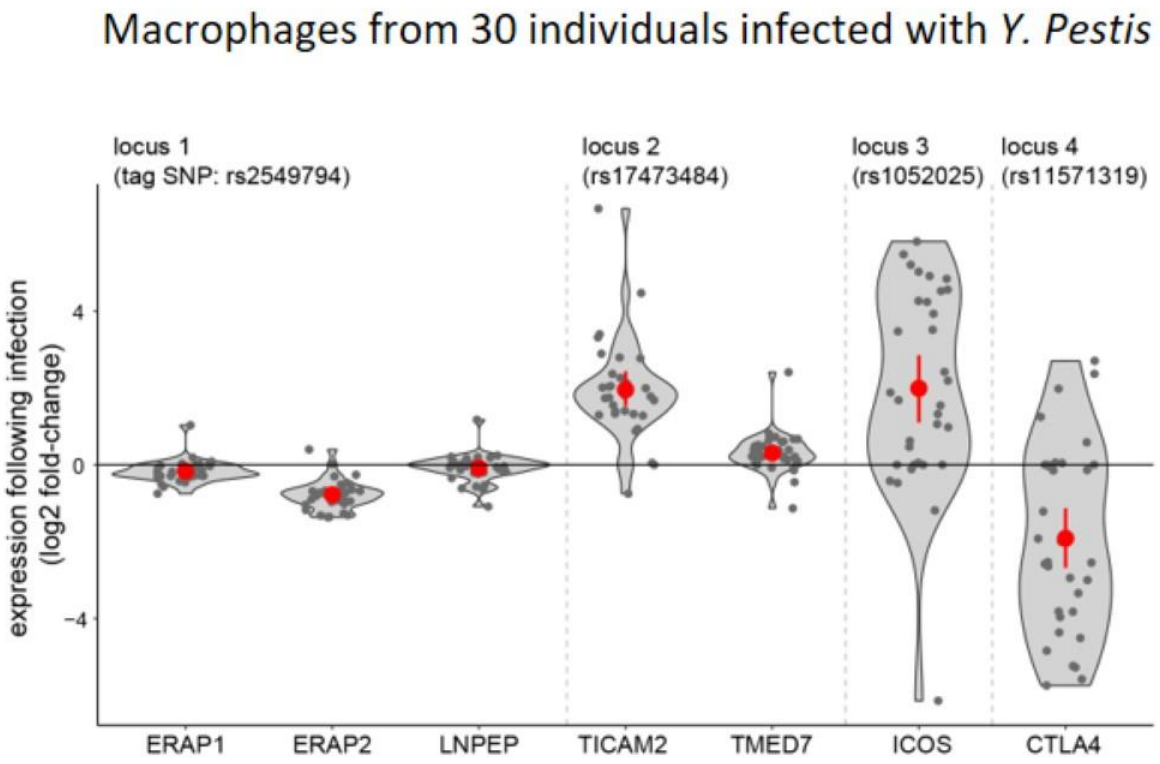
We identified 245 variants that are highly differentiated within London

Functional impact of putatively selected loci

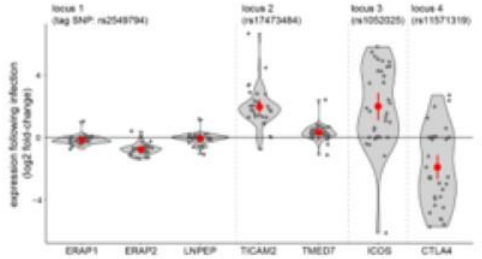


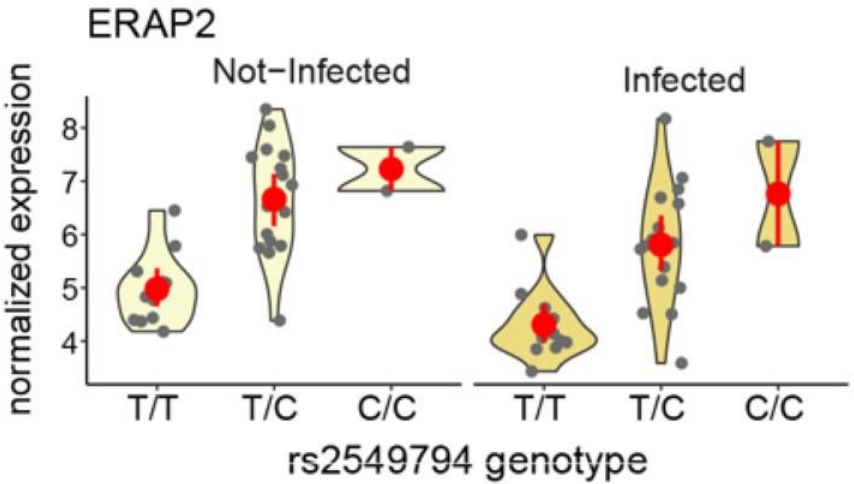
Mari Cobb & Anne Dumaine

Functional impact of putatively selected loci



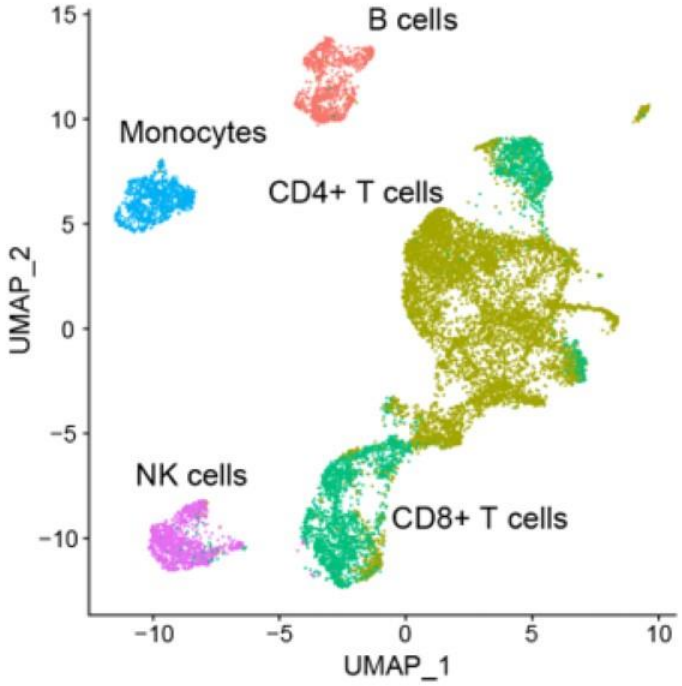
The protective allele is associated with increased levels of *ERAP2*





The protective allele is associated with increased levels of *ERAP2*

PBMCs using single-cell RNA sequencing, on a panel of 10 individuals, 5 of which were homozygous for the protective rs2549794 C allele and 5 of which are homozygous for the T allele



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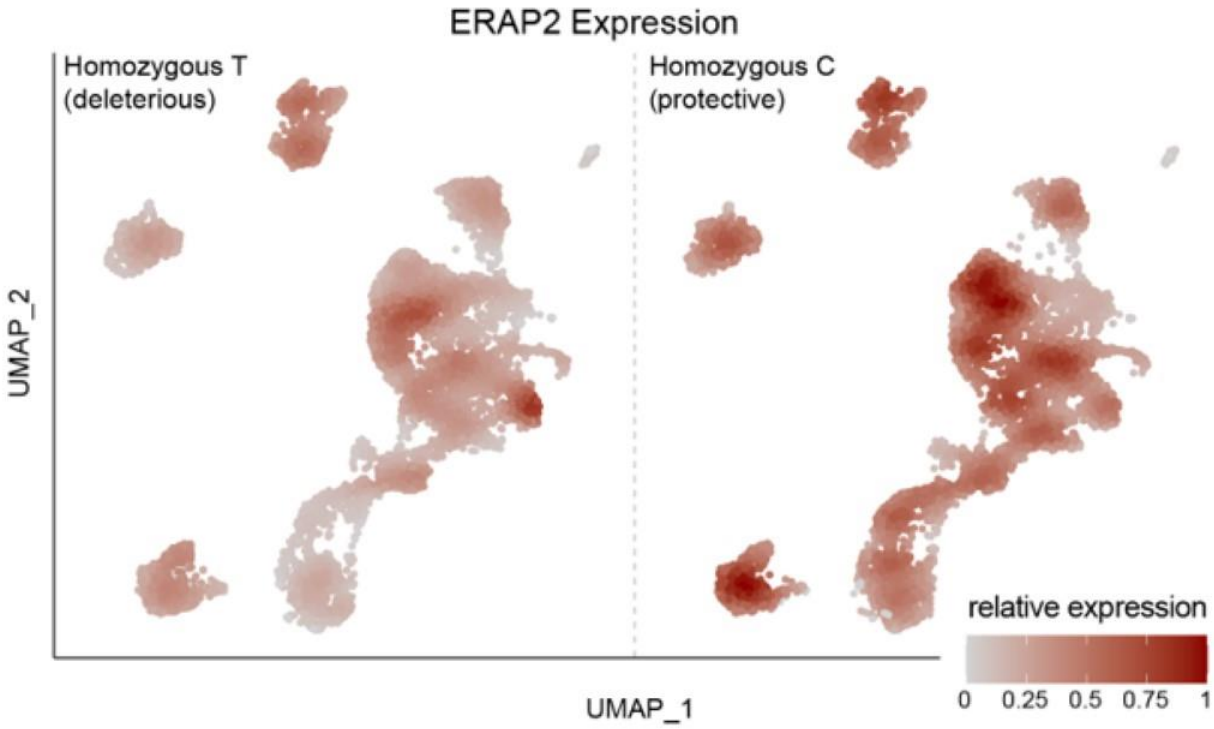

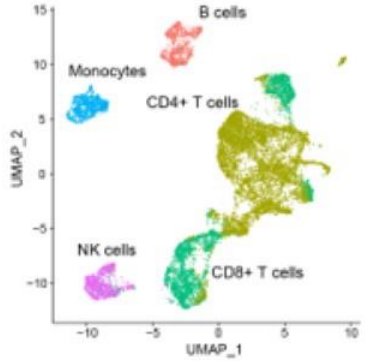

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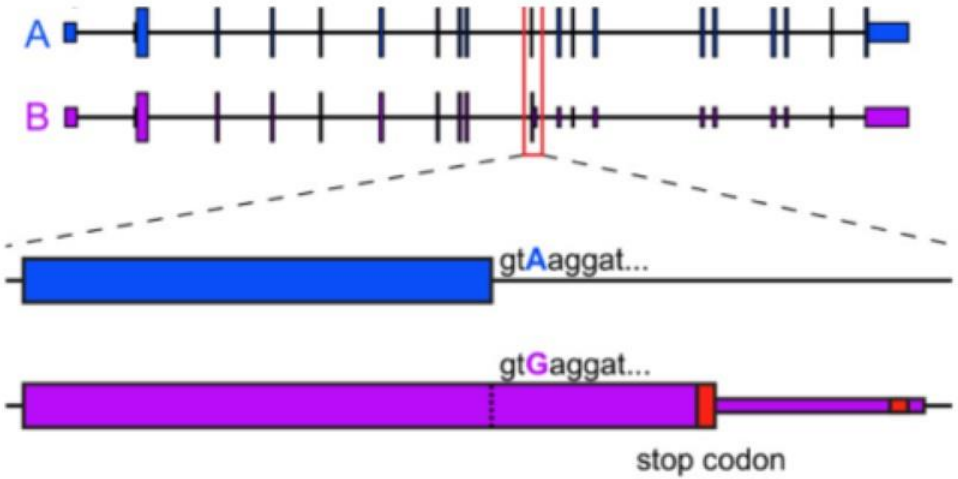
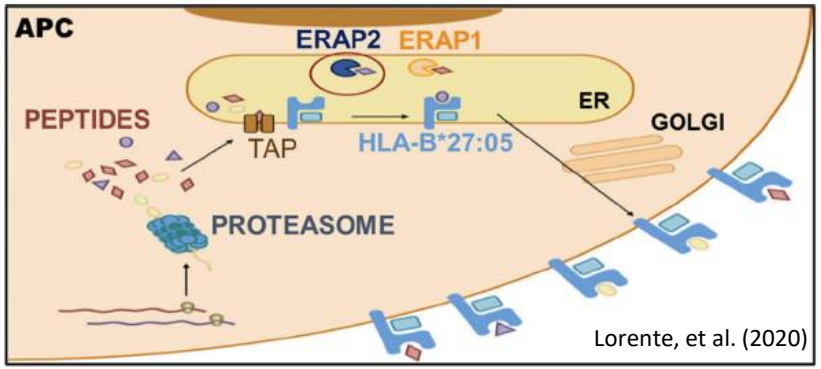


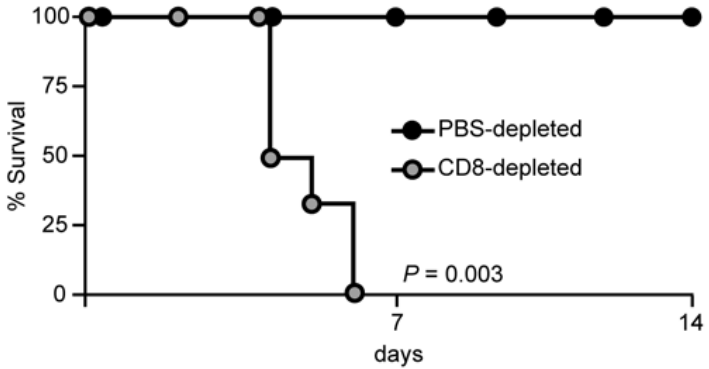
Andres et al. 2010 (PLoS Genetics)

Increased *ERAP2* seems to have been protective during Black Death

ERAP1 and *ERAP2* are aminopeptidases that work synergistically to trim peptides so that they can be presented to $CD8^+$ T cells by MHC class I



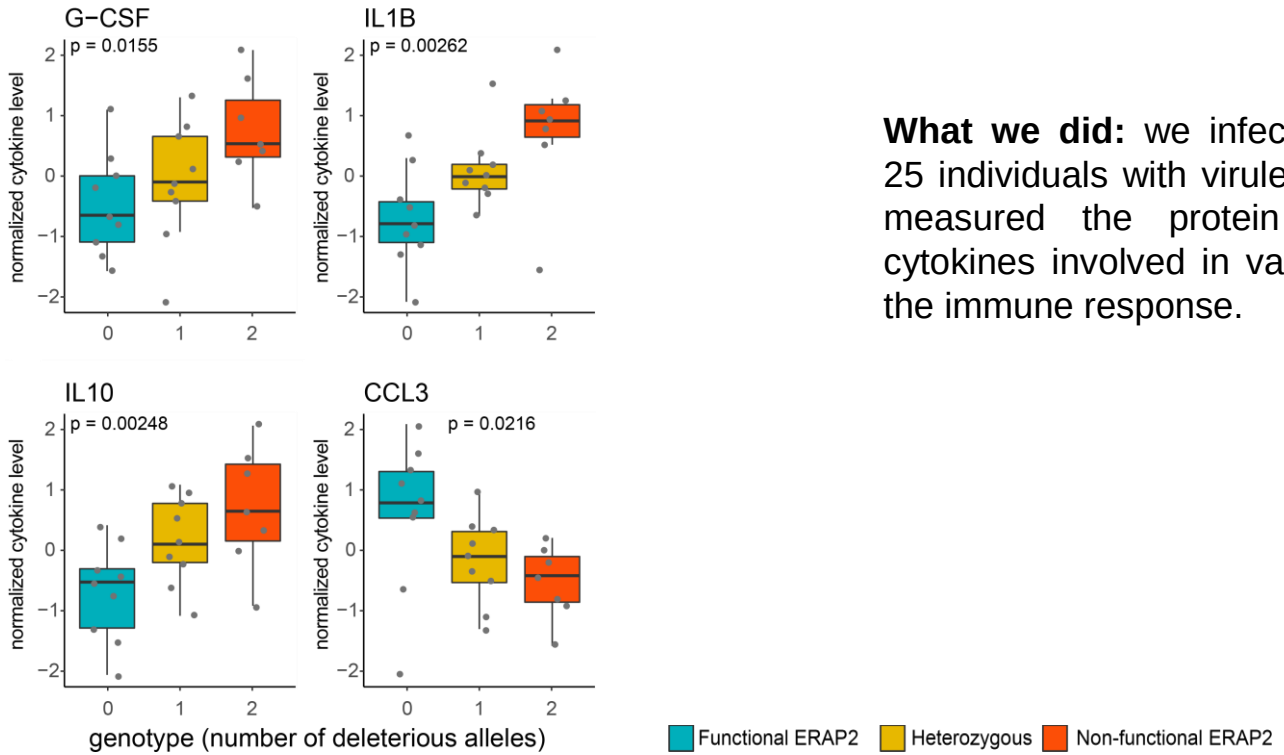
Lorente, et al. (2020)



Bergman, et al. (2009)

Functional depiction of *ERAP2* protective allele

Is the *ERAP2* genotype was associated with variation in the cytokine response to *Y. pestis* infection?



What we did: we infected MDMs from 25 individuals with virulent Y. pestis and measured the protein levels of 10 cytokines involved in various aspects of the immune response.

Some take home messages:

- **Black Death was an important selective force** that shaped genetic diversity around some immune loci.

- We speculate that the selective advantage provided by the ERAP2 variant stems from an **increased ability to present *Yersinia*-derived antigens to CD8$^+$ T cells and/or variation in the cytokine response upon infection**.

- Our results also highlight the **contribution of natural selection to present-day susceptibility towards chronic inflammatory and autoimmune diseases**: the *ERAP2* variant identified as protective against the plague, is a known risk factor for Crohn's disease. *Our data suggests that selection in response to plague is part of a recurring tradeoff between infectious and autoimmune disorders.*

Thanks to those who actually did the work…

Research Assistants


Anne Dumaine
Lab Manager

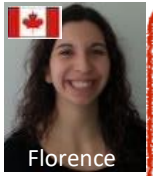

Vania Yotova
Lab Manager


Renata Sindeaux
R. Assistant


Mari Cobb
R. Assistant


Saideep Gonna
Bioinformatician

Graduate students



Mailhot-Leonard


Haley Randolph


Sarah Sun


Mohamed Fahmy


Katie Aracena


Bridget Chak

Post-doctoral fellows


Joao Batista


Paul Maurizio

Onta


Tauras


Raul

Key Collaborators:

Flu project
Ryan Langlois (U Minnesota)

Pestis
Hendrik Poinar (McMaster U)
Javier Pizarro-Cerda (Pasteur)
Christian Demeure (Pasteur)

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Luis Barreiro, Ph.D.
University of Chicago
Chicago, IL

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