Genome-Wide Association Study of Immune Response to Twelve Common Pathogens

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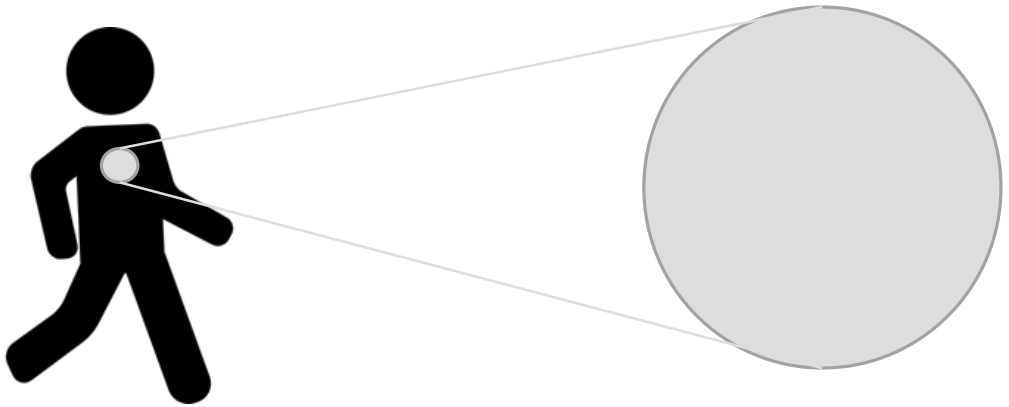
Summer Research Training Program 2019

UCSF Department of Epidemiology & Biostatistics

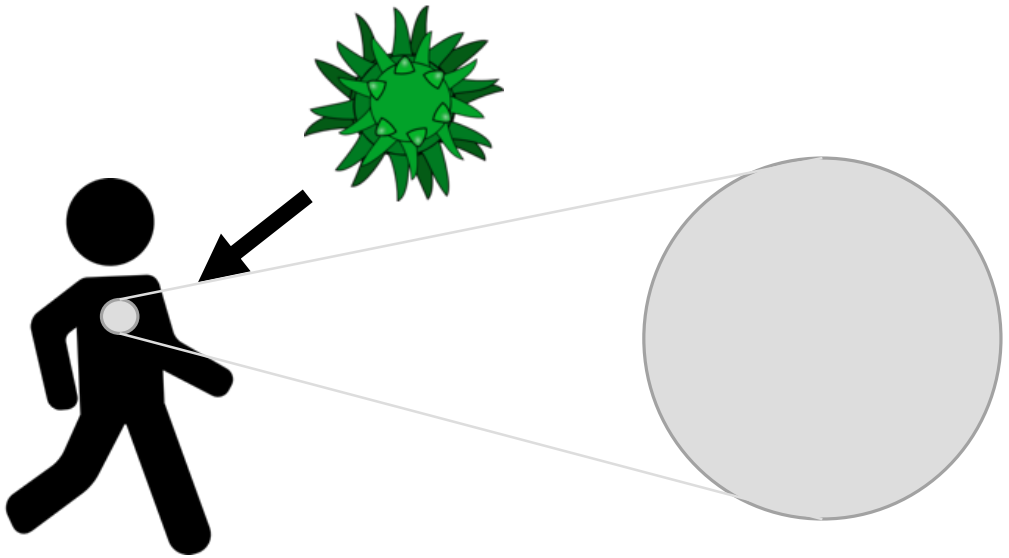
AMGEN Foundation

Amgen Scholars Program

TEXAS The University of Texas at Austin



Immune response varies between individuals.



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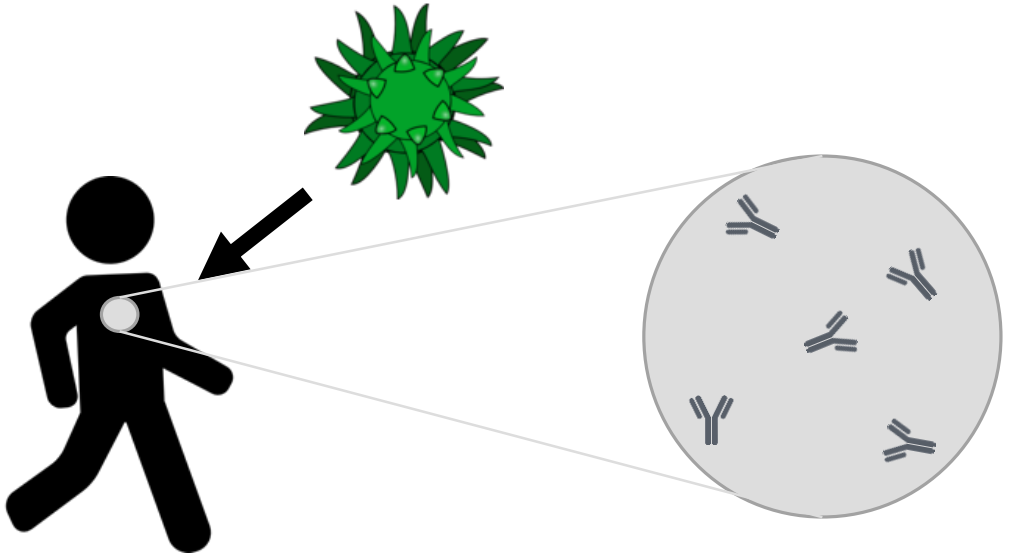

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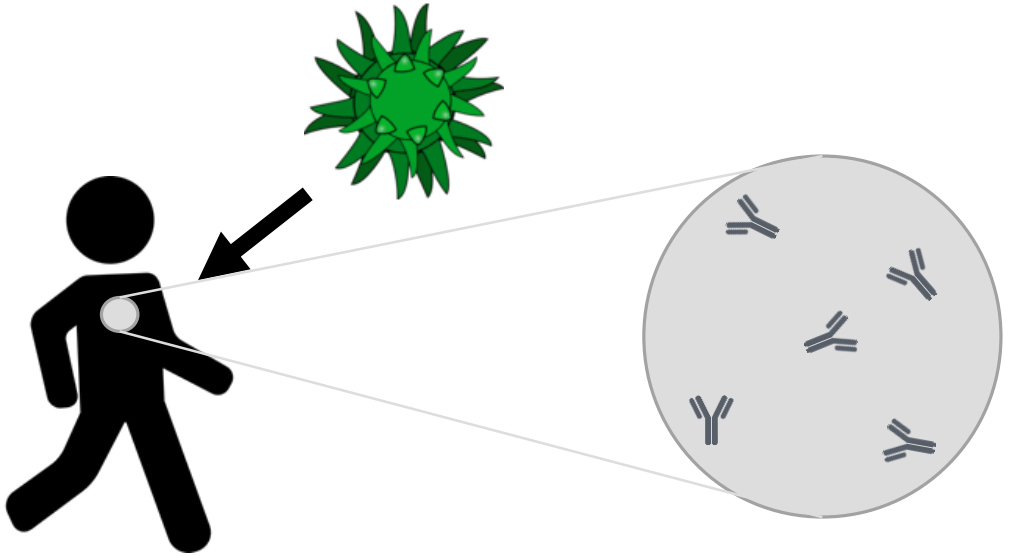

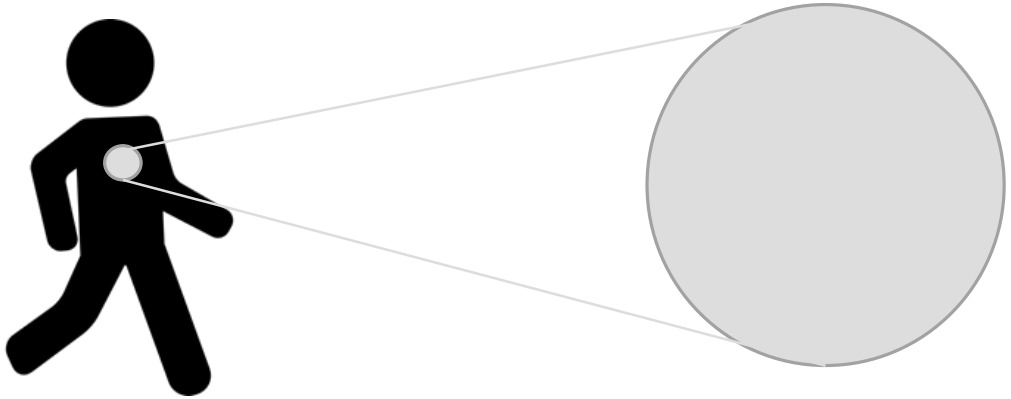

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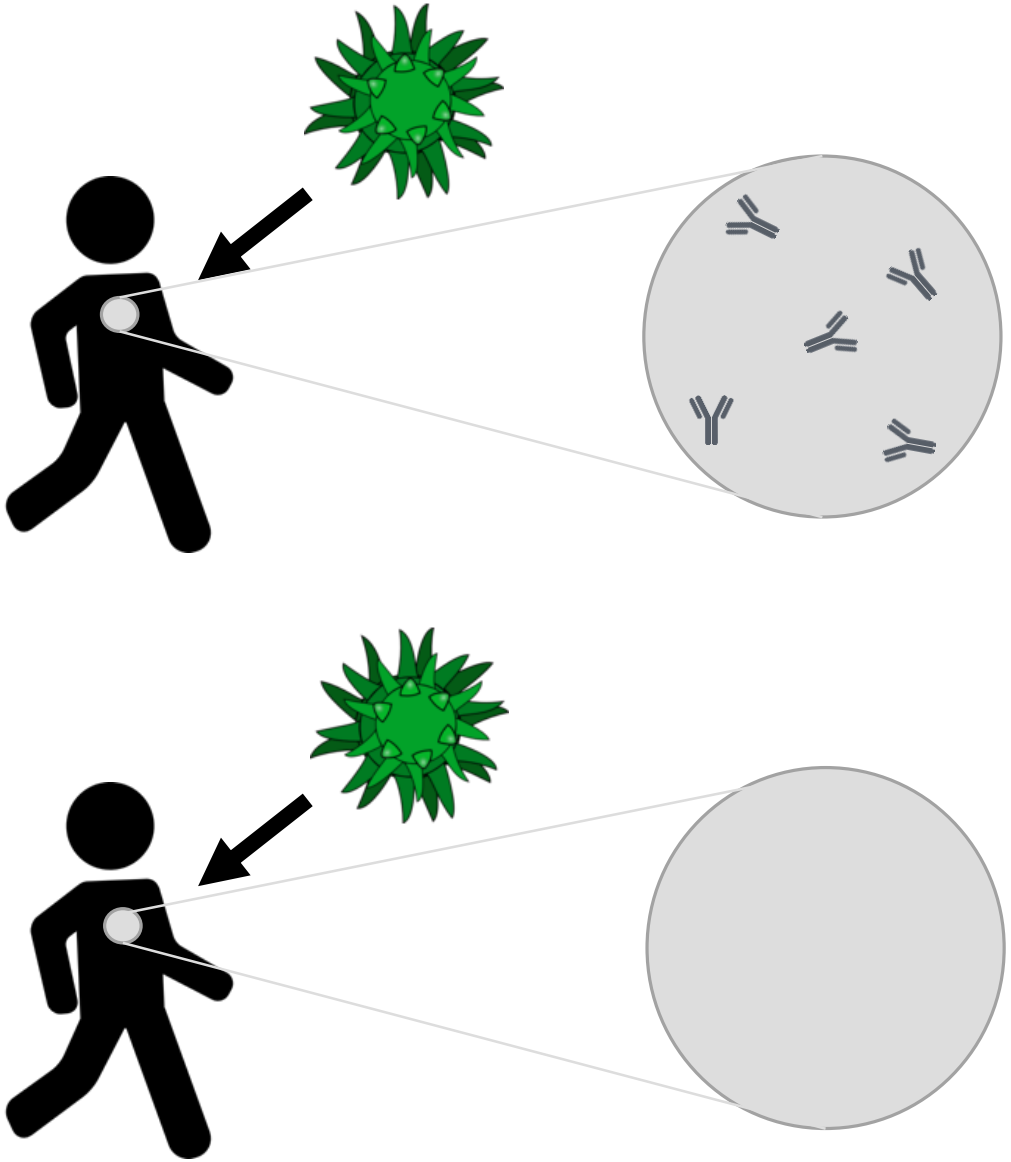

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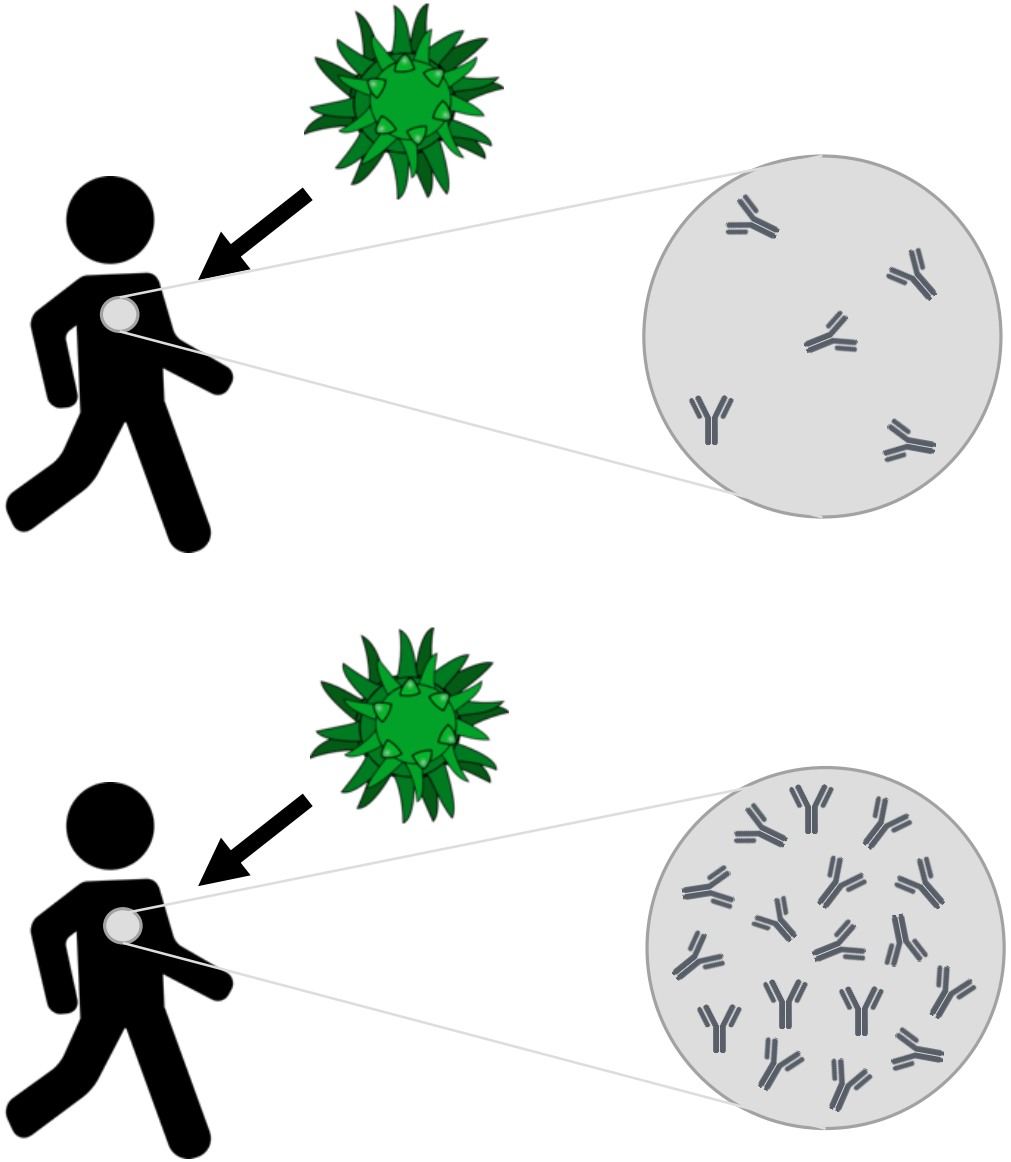

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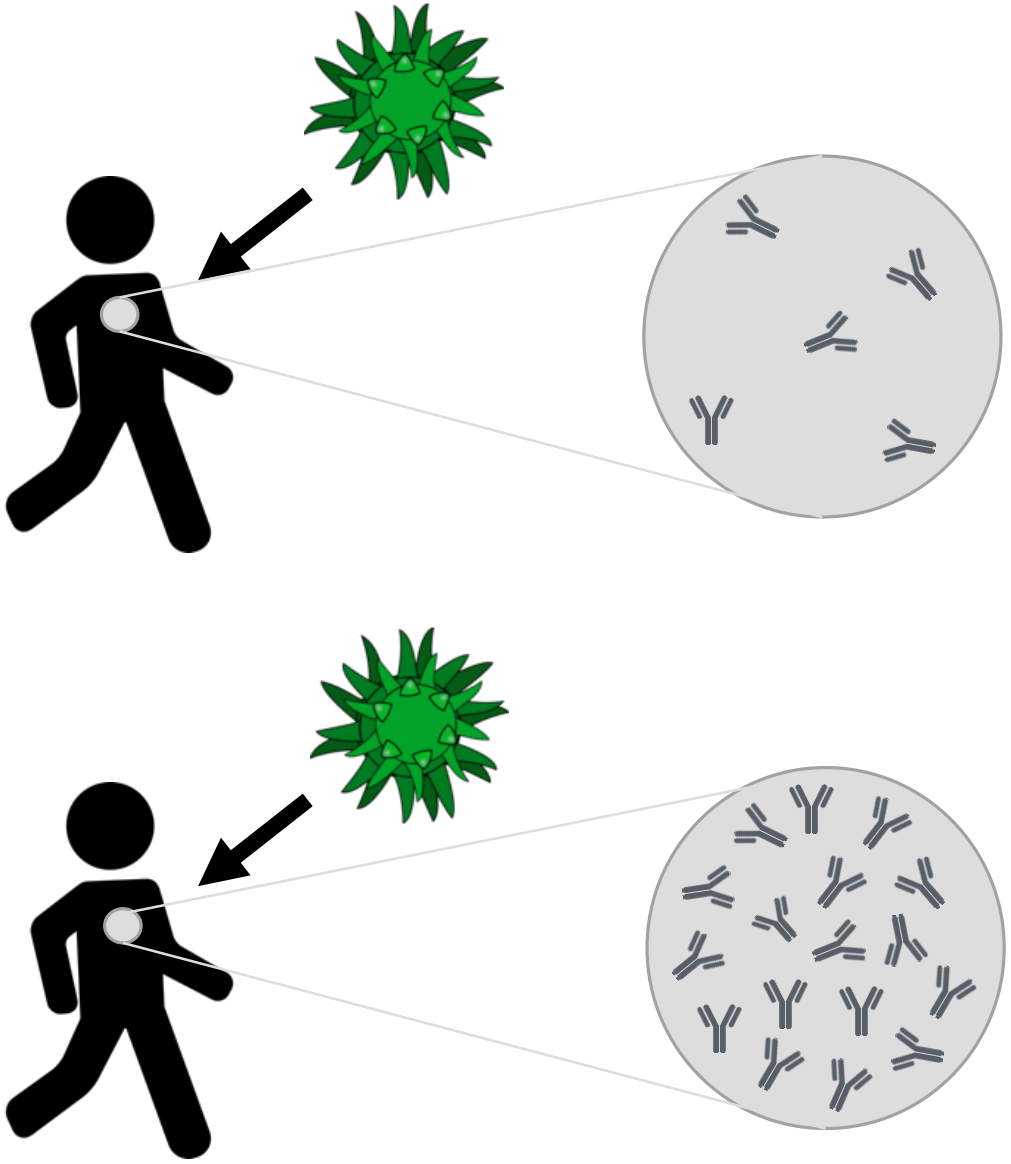
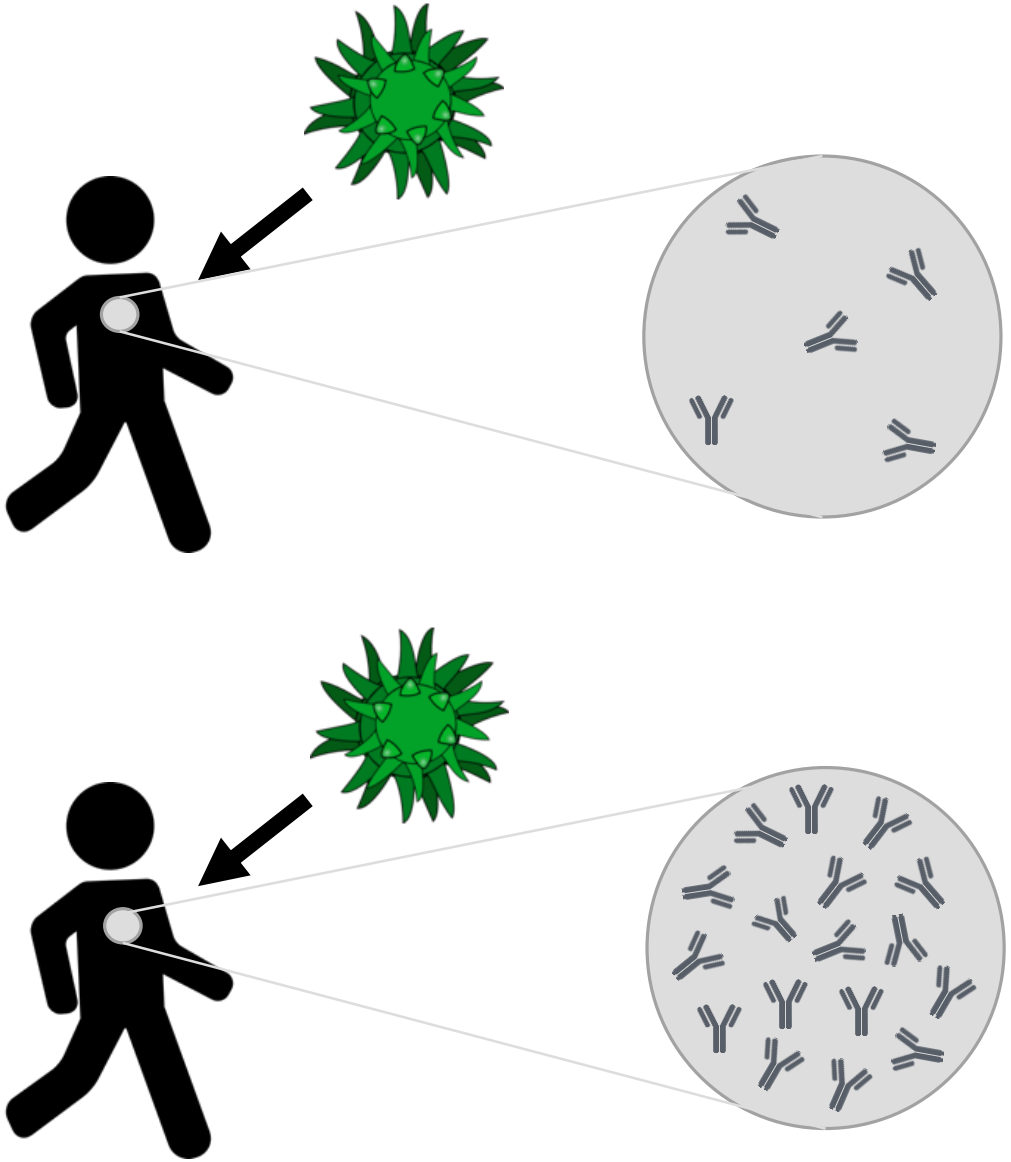


“Strength of Immune Response”

Immune response varies between individuals.



- Vaccine efficacy
- Pathogen-induced disease etiology
- Biological mechanisms of immune response
- Potential drug targets
- Immune-related cancer therapies

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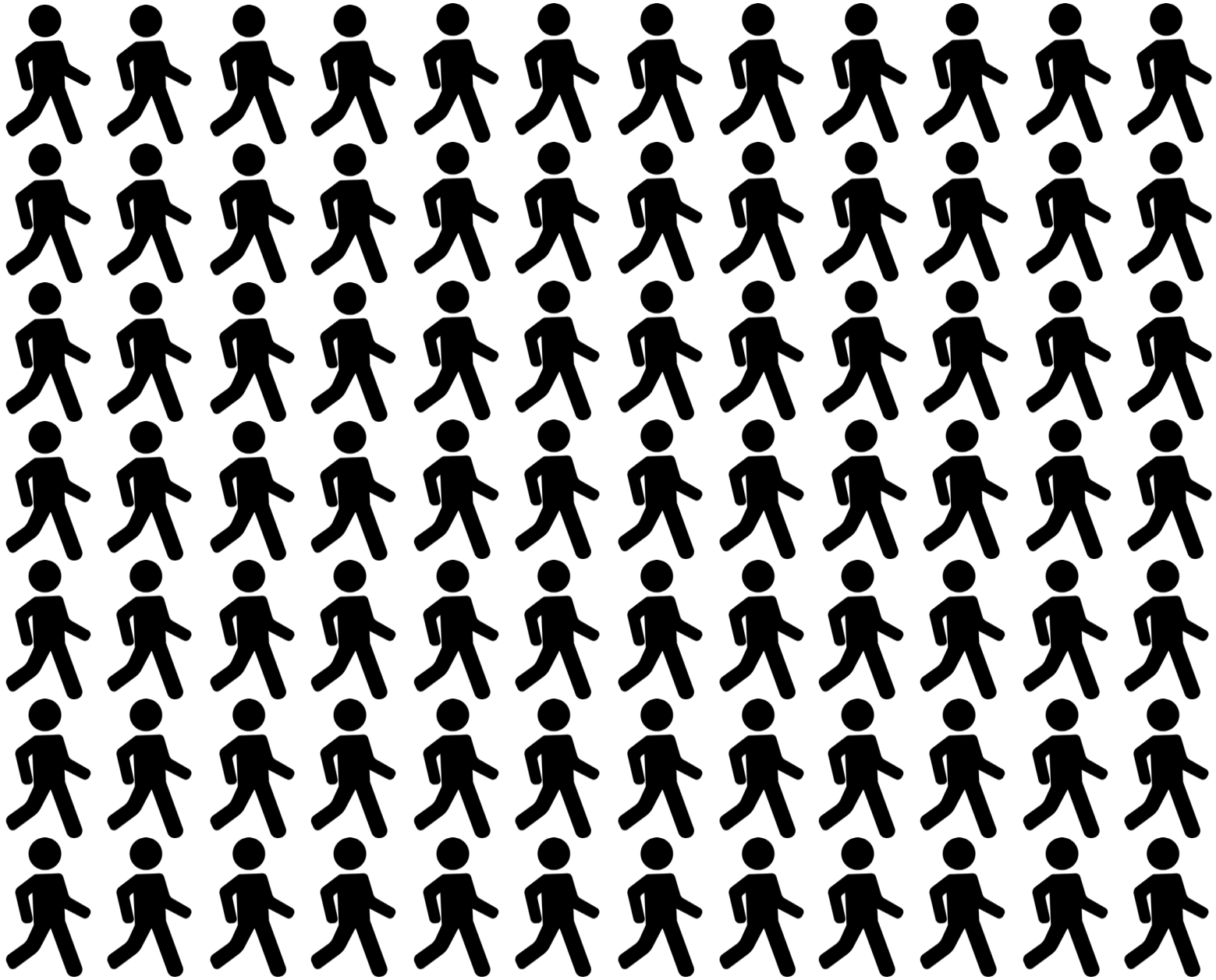
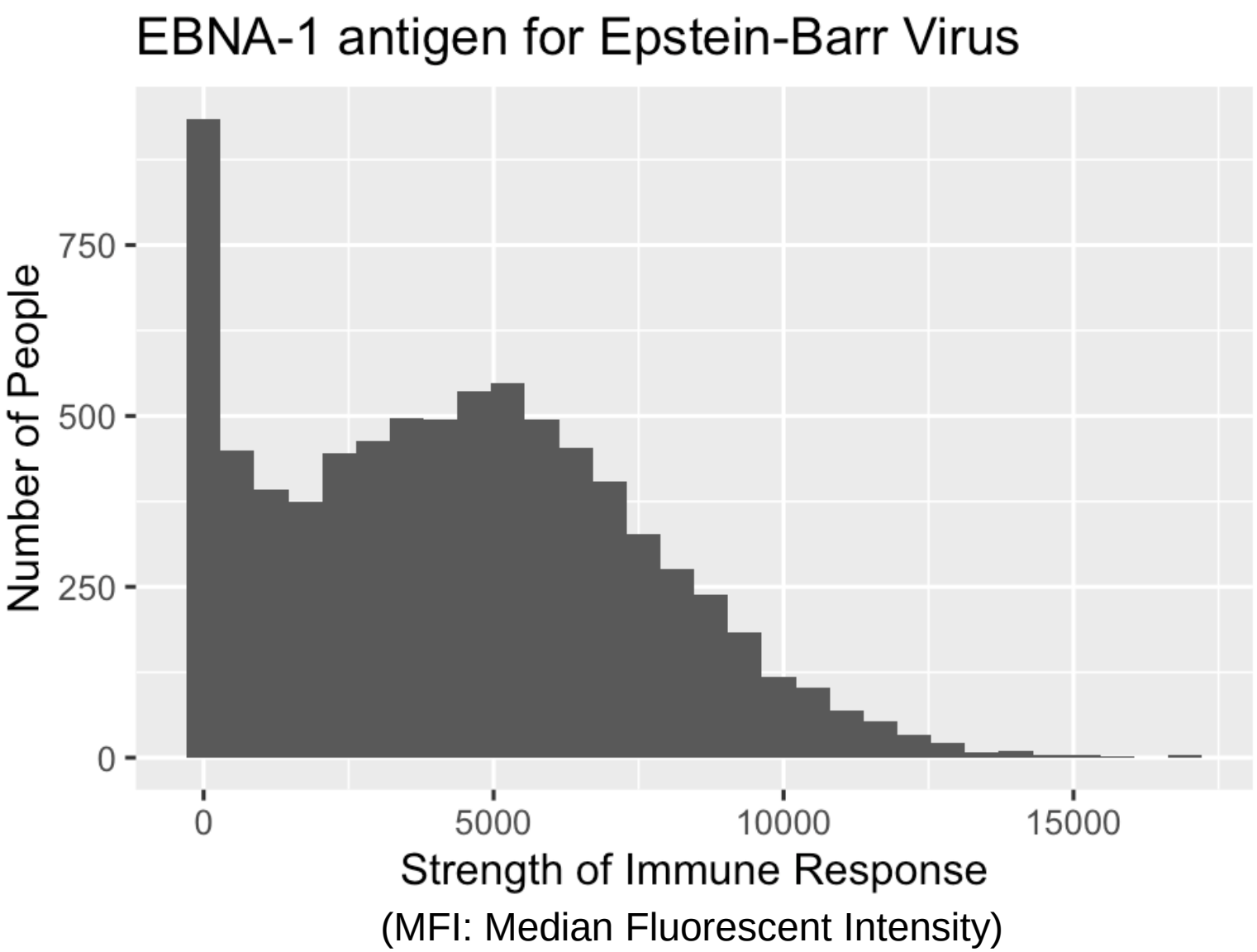


$N \approx 8{,}000$


EBNA-1 antigen for Epstein-Barr Virus
Number of People
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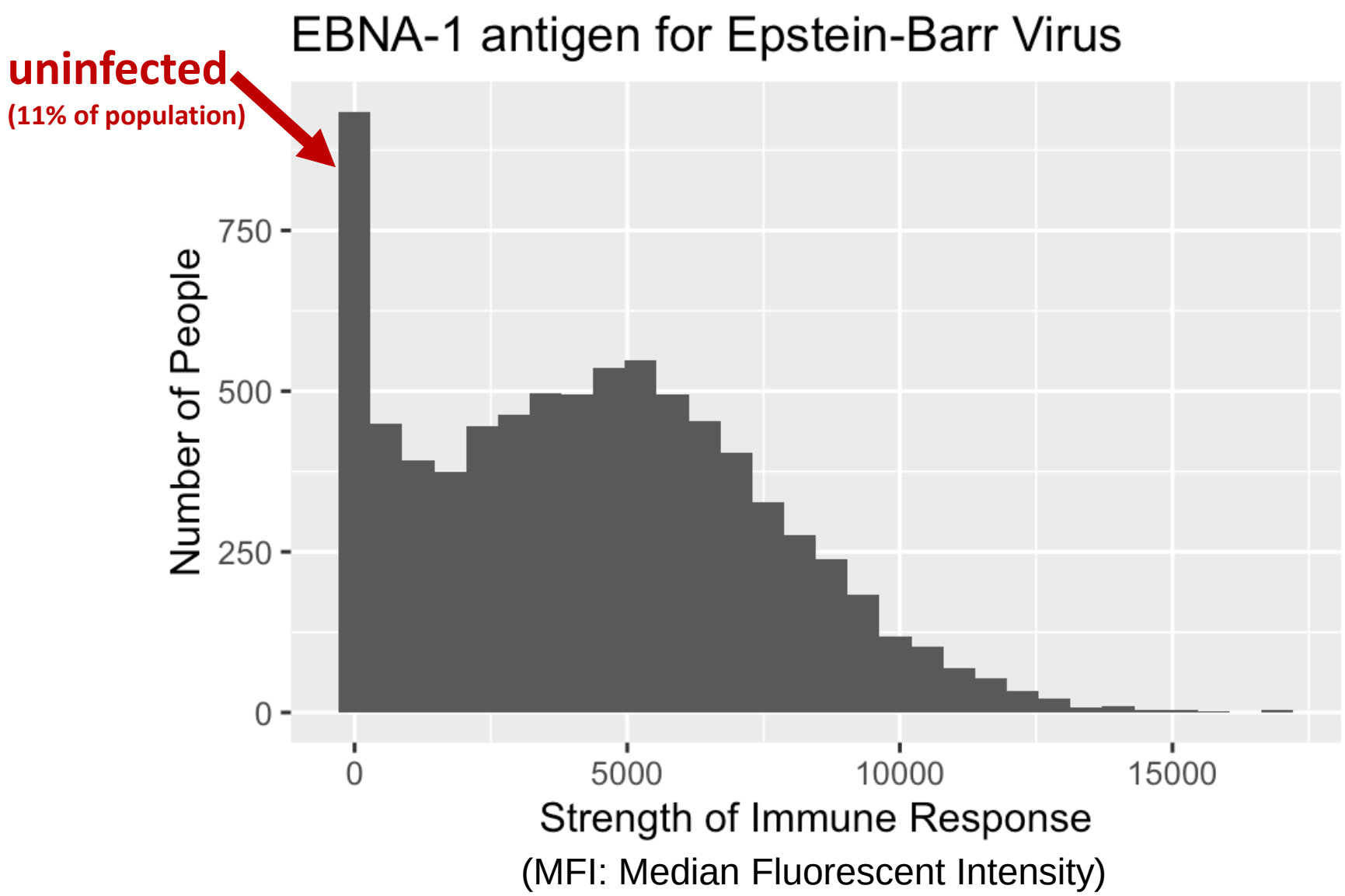
Strength of Immune Response
(MFI: Median Fluorescent Intensity)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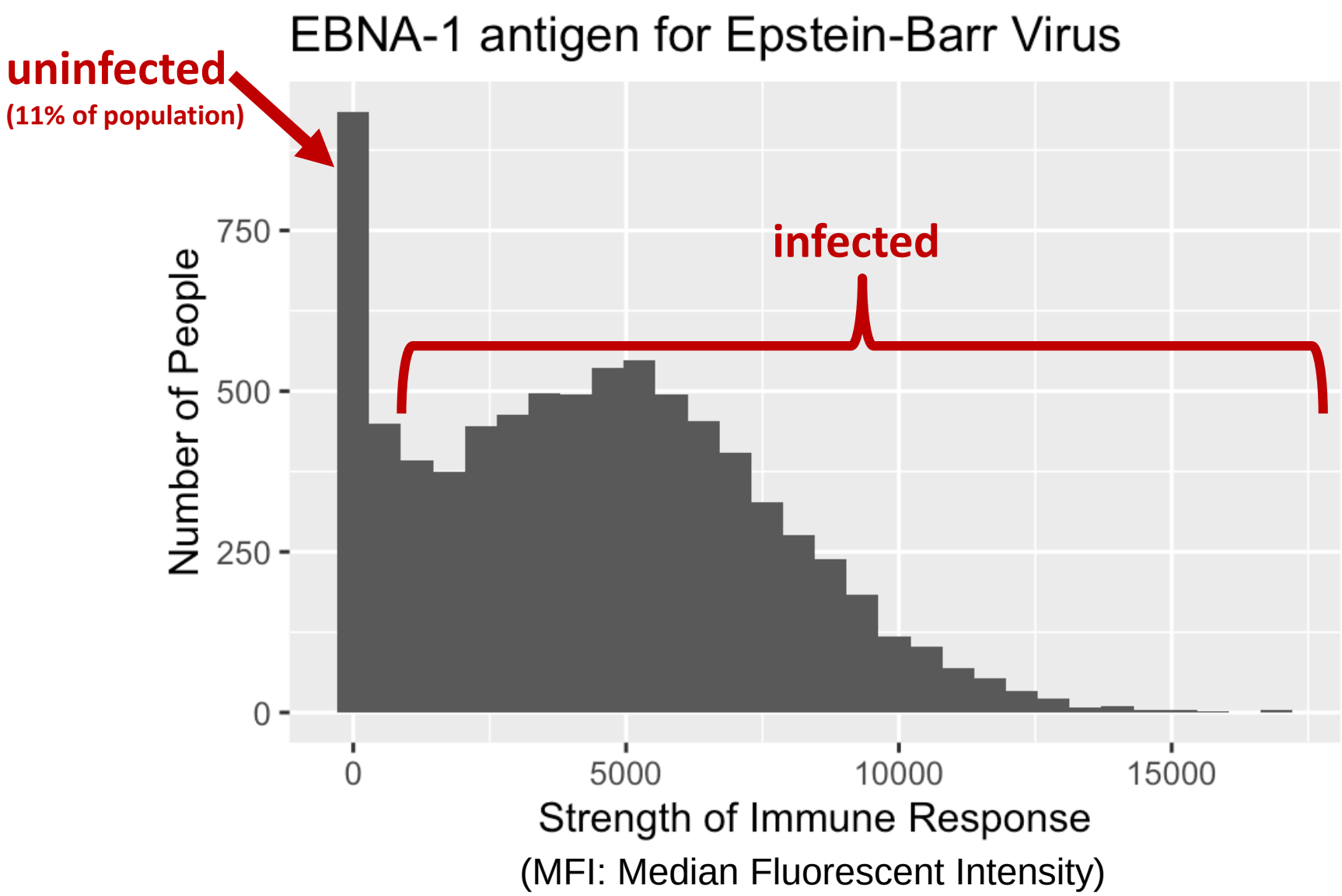
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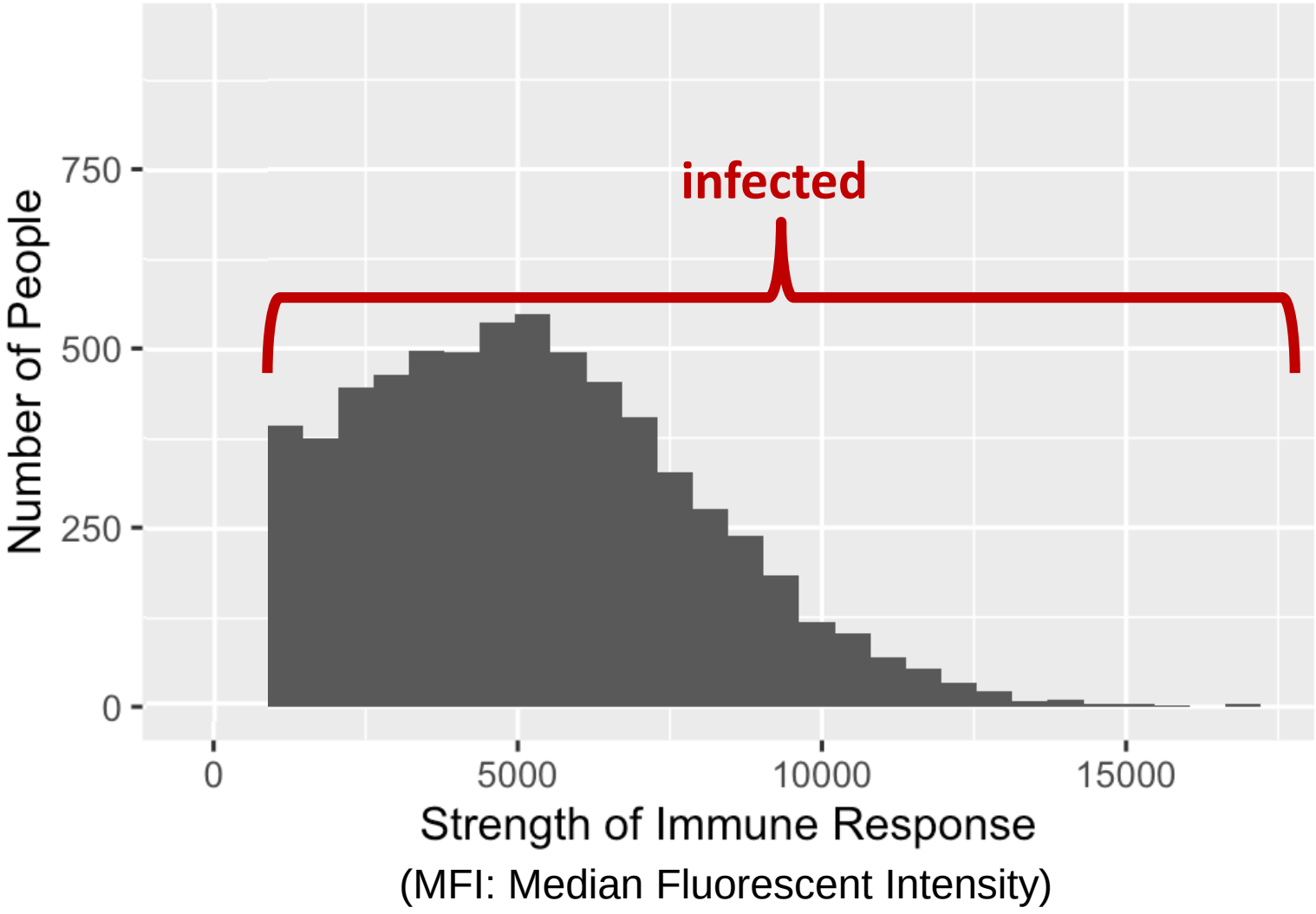
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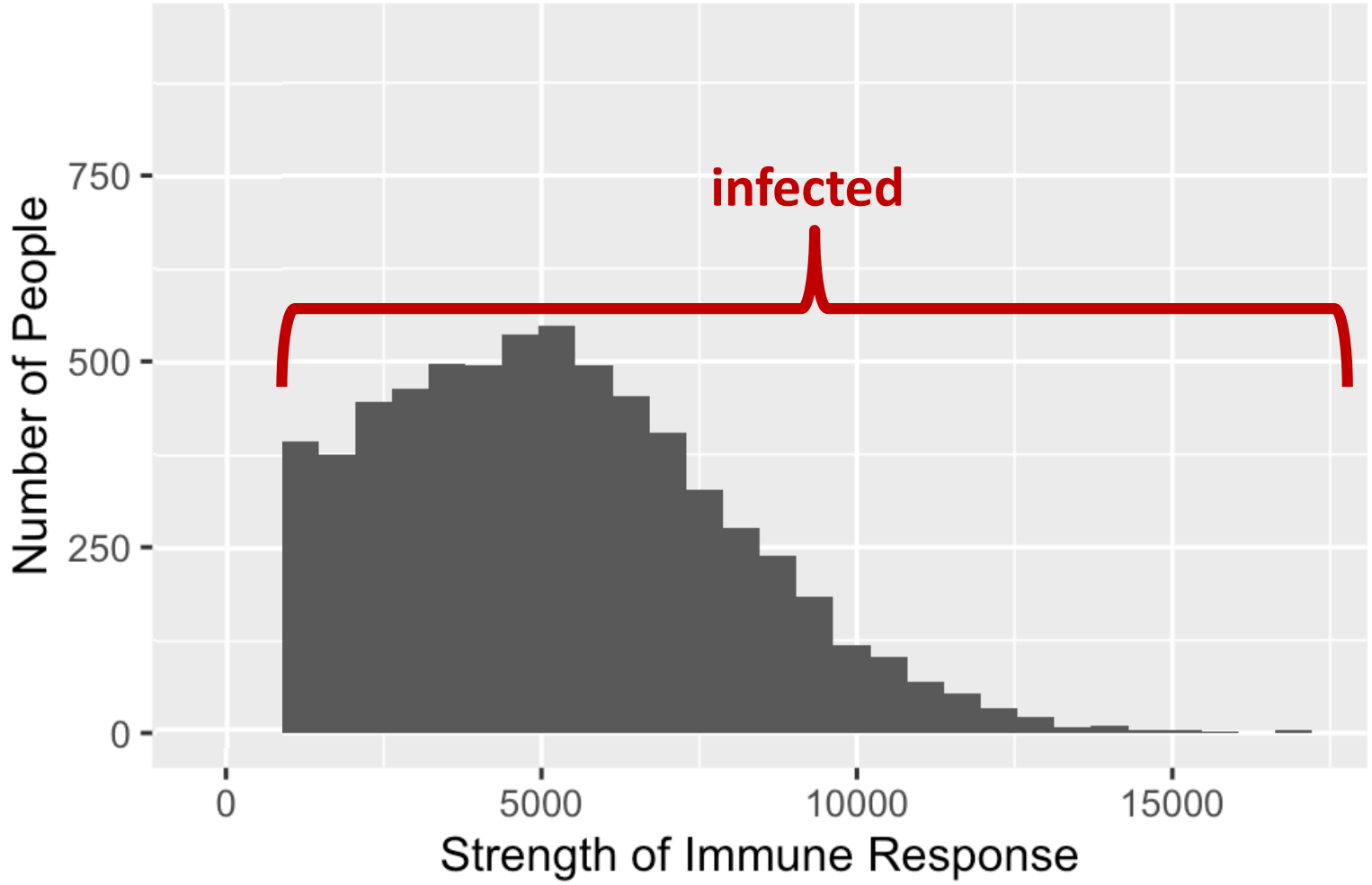
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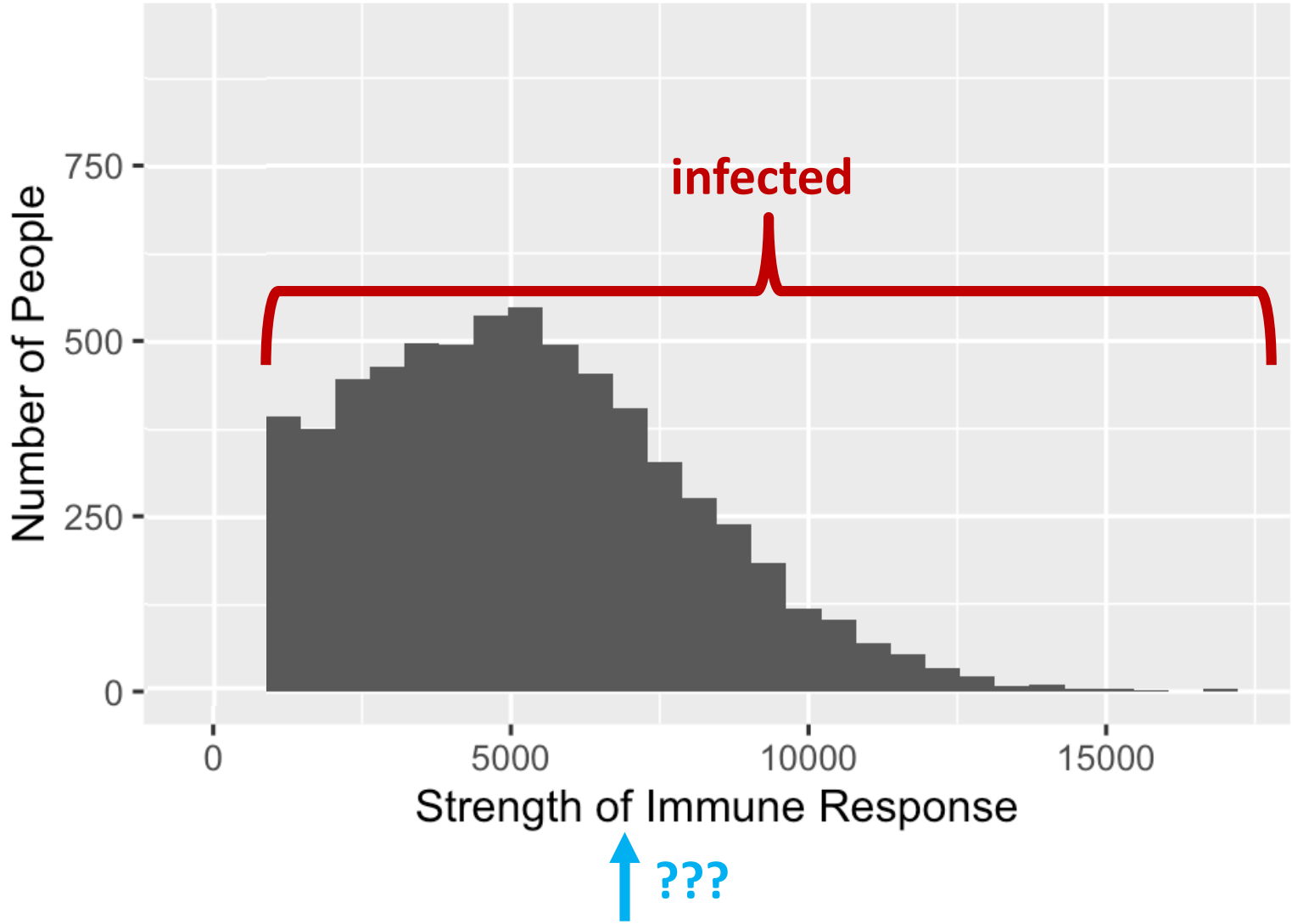

Genome-Wide Association Study

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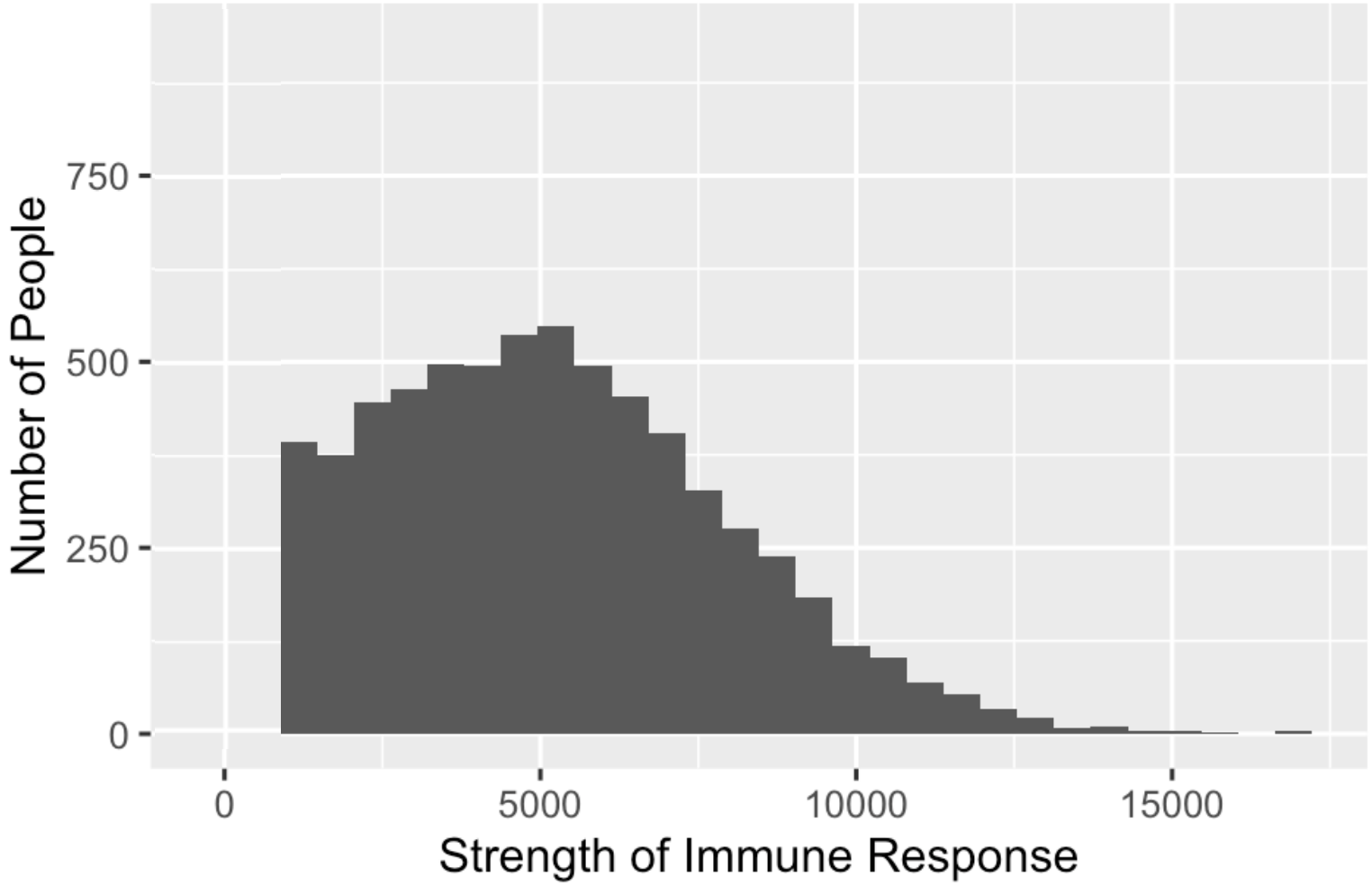
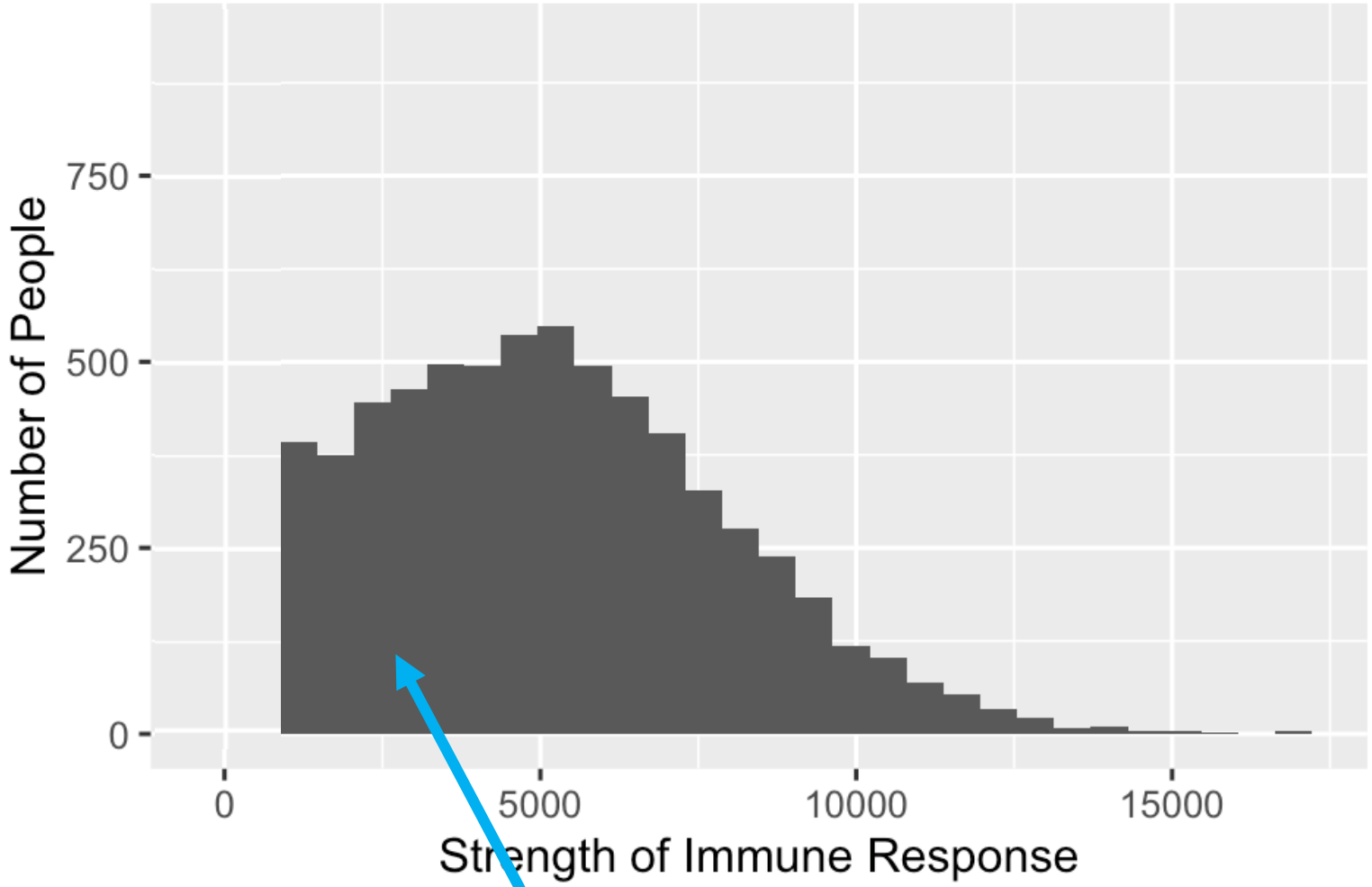


Single-Nucleotide Polymorphism (“SNP”)

AA



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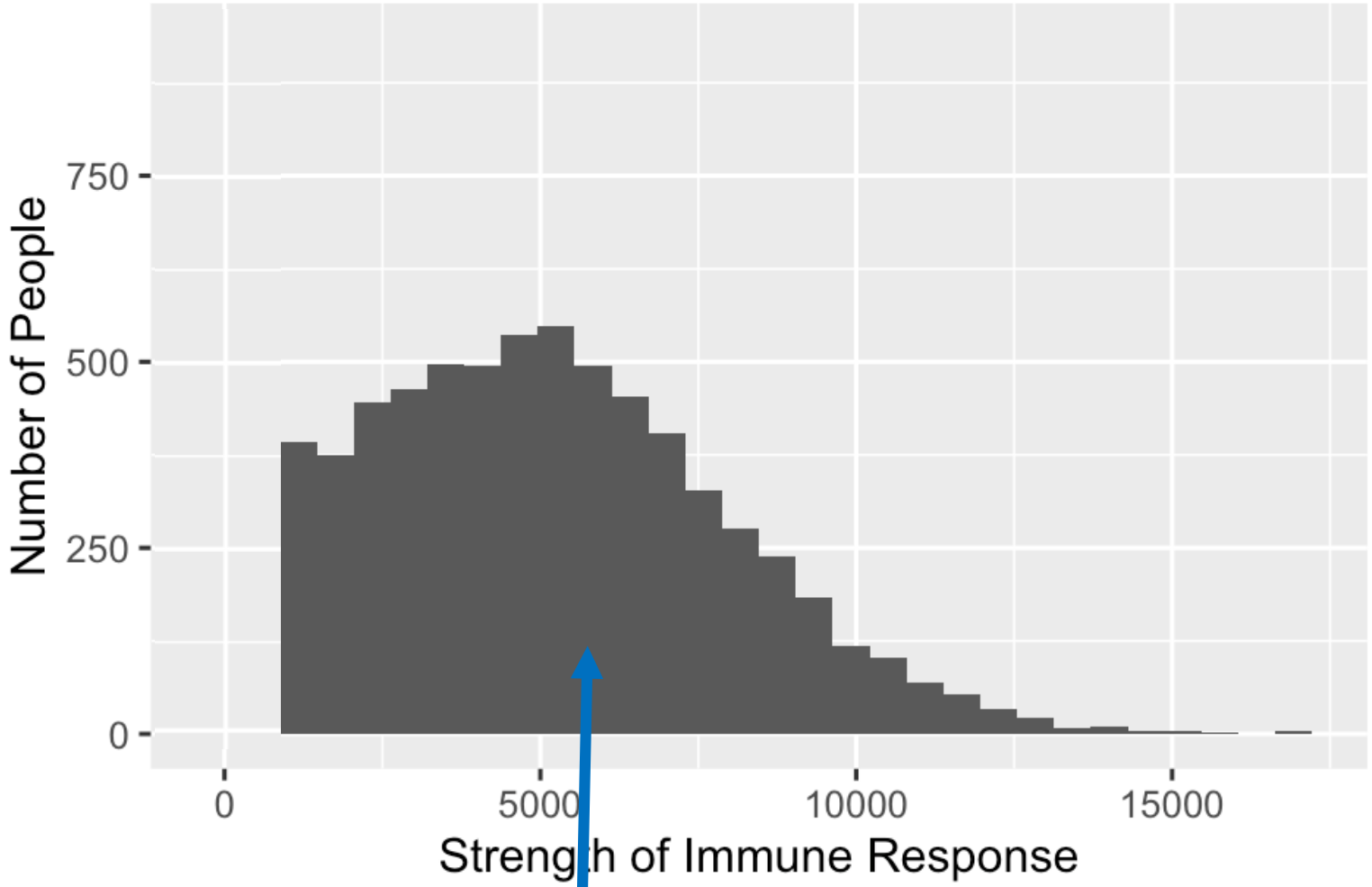

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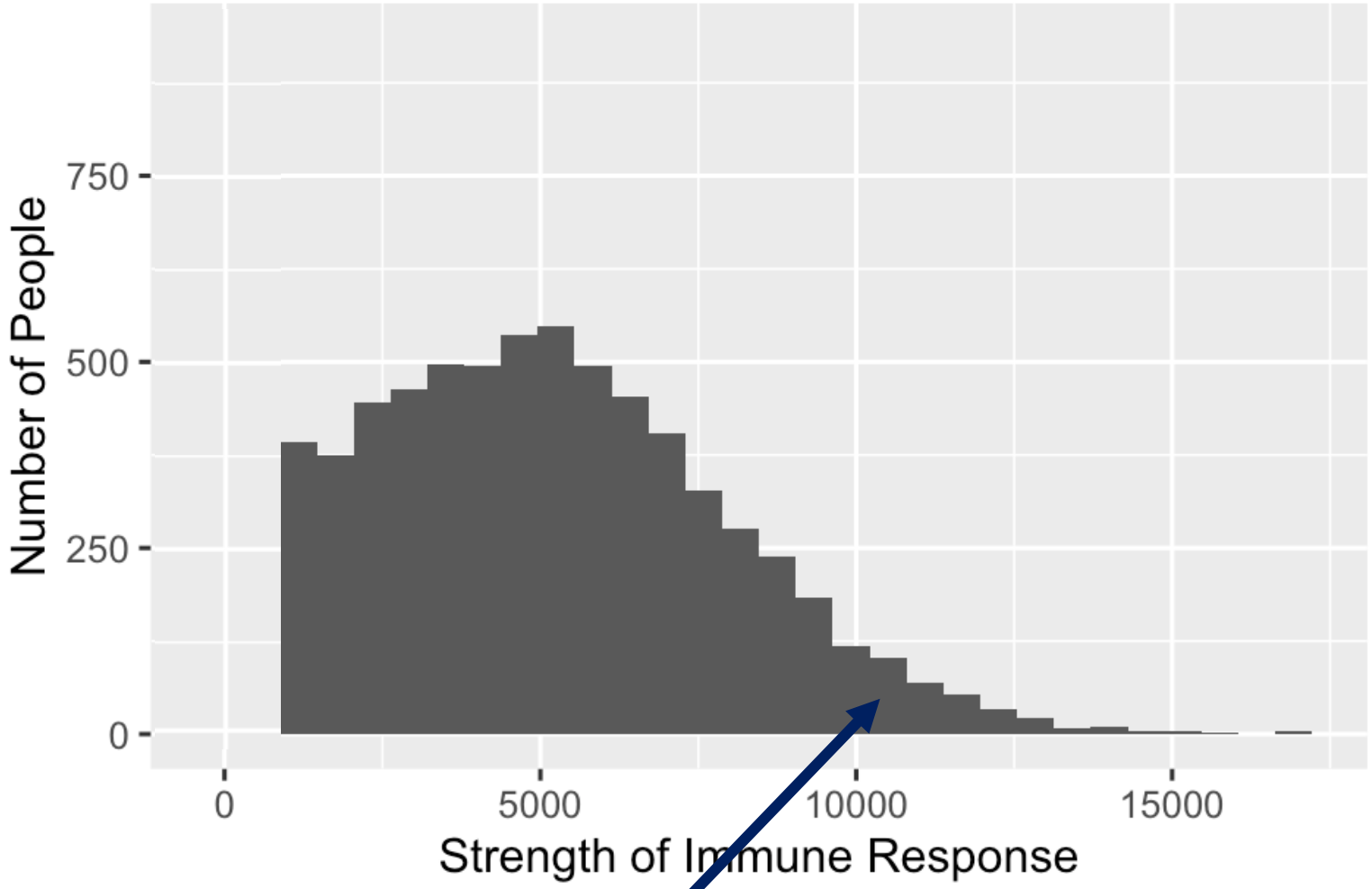

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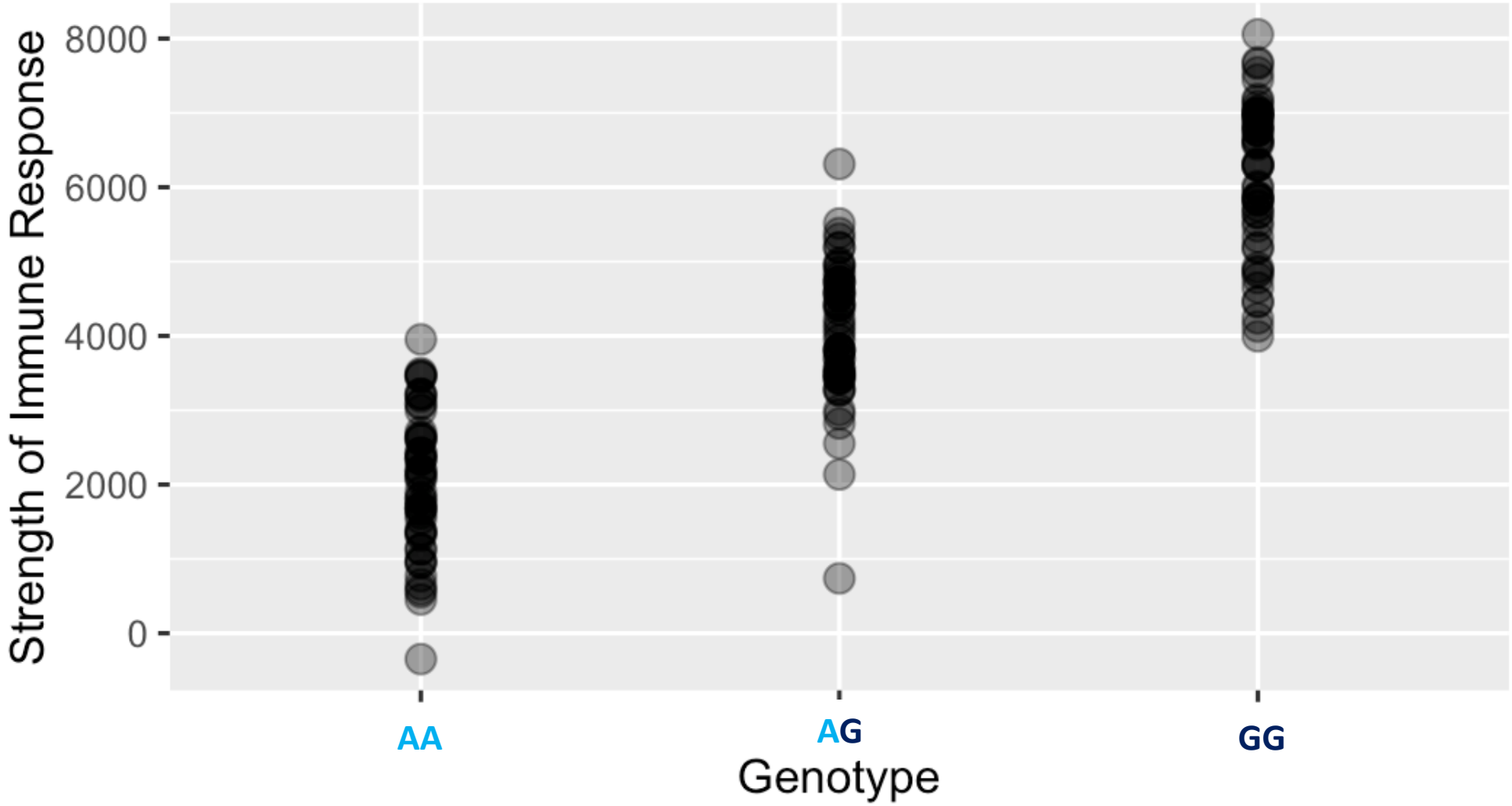
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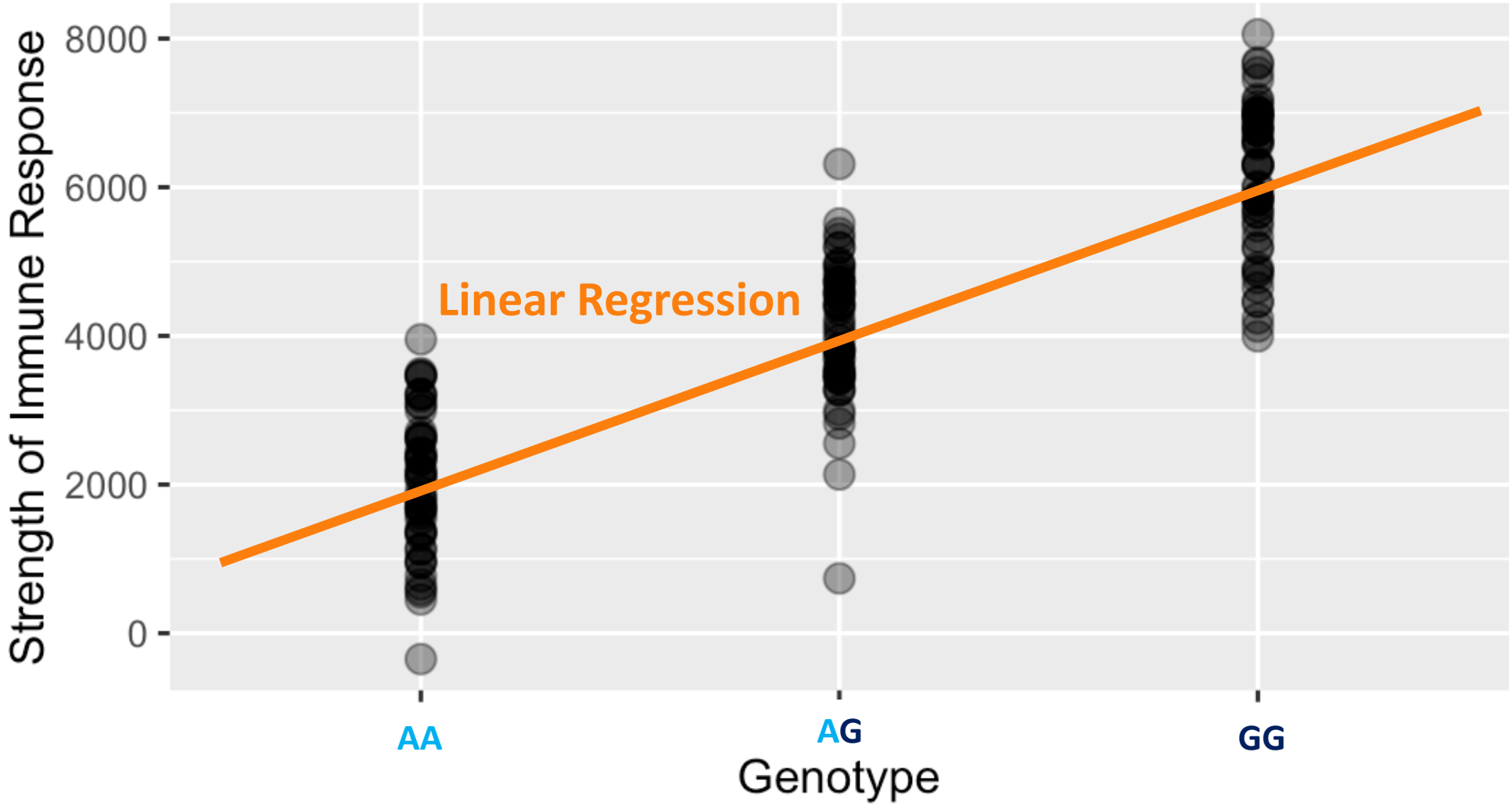
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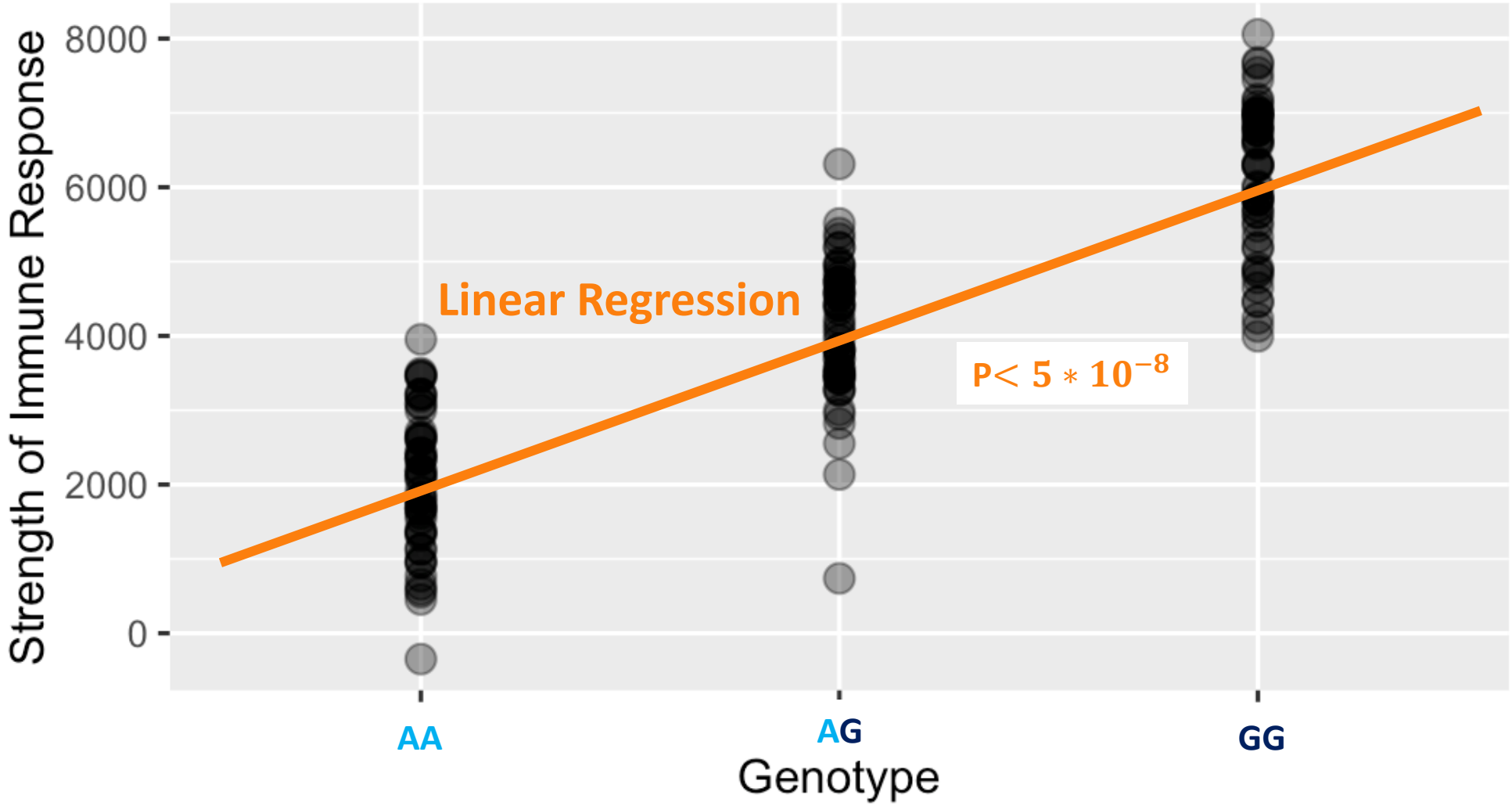
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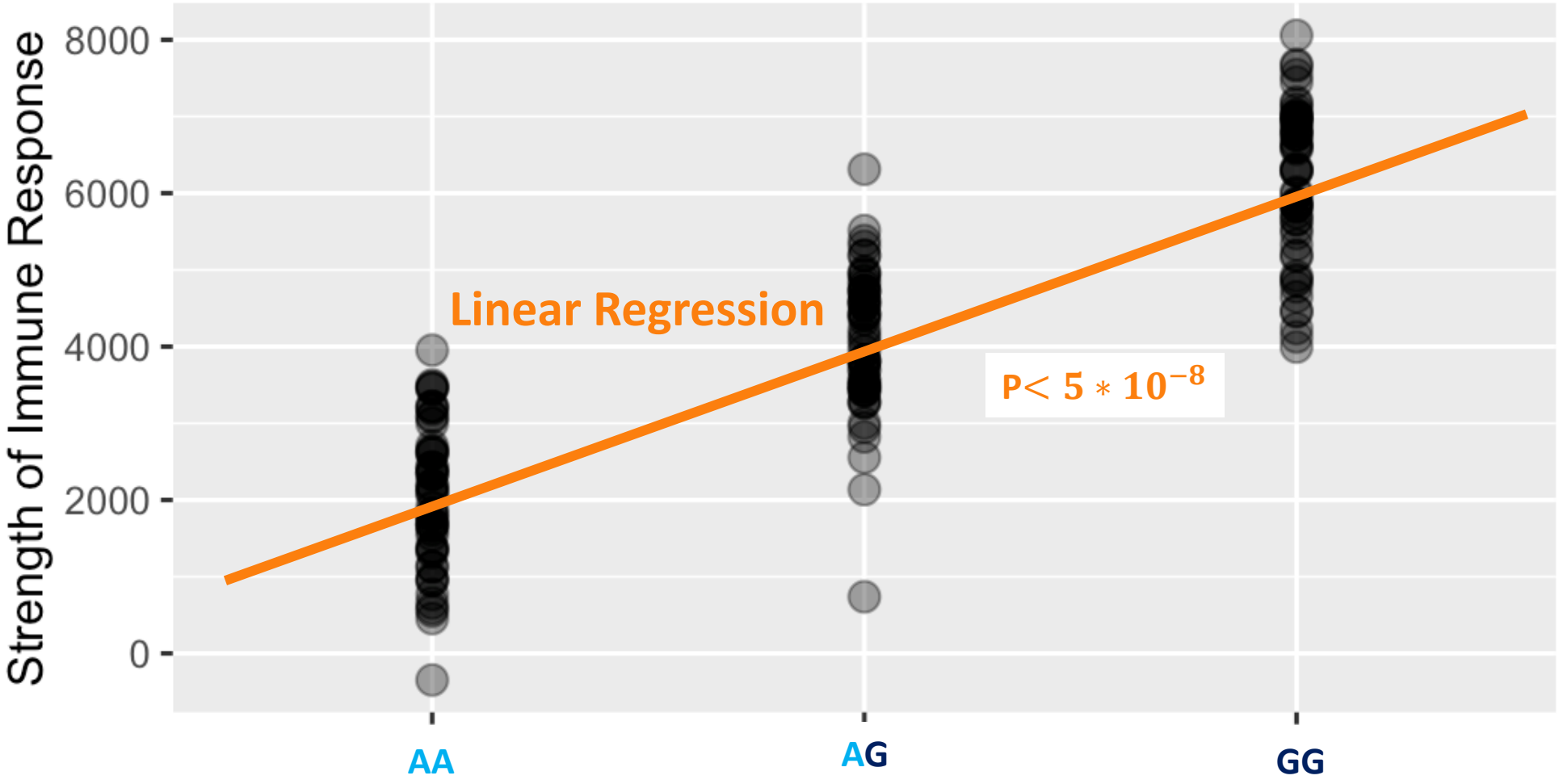

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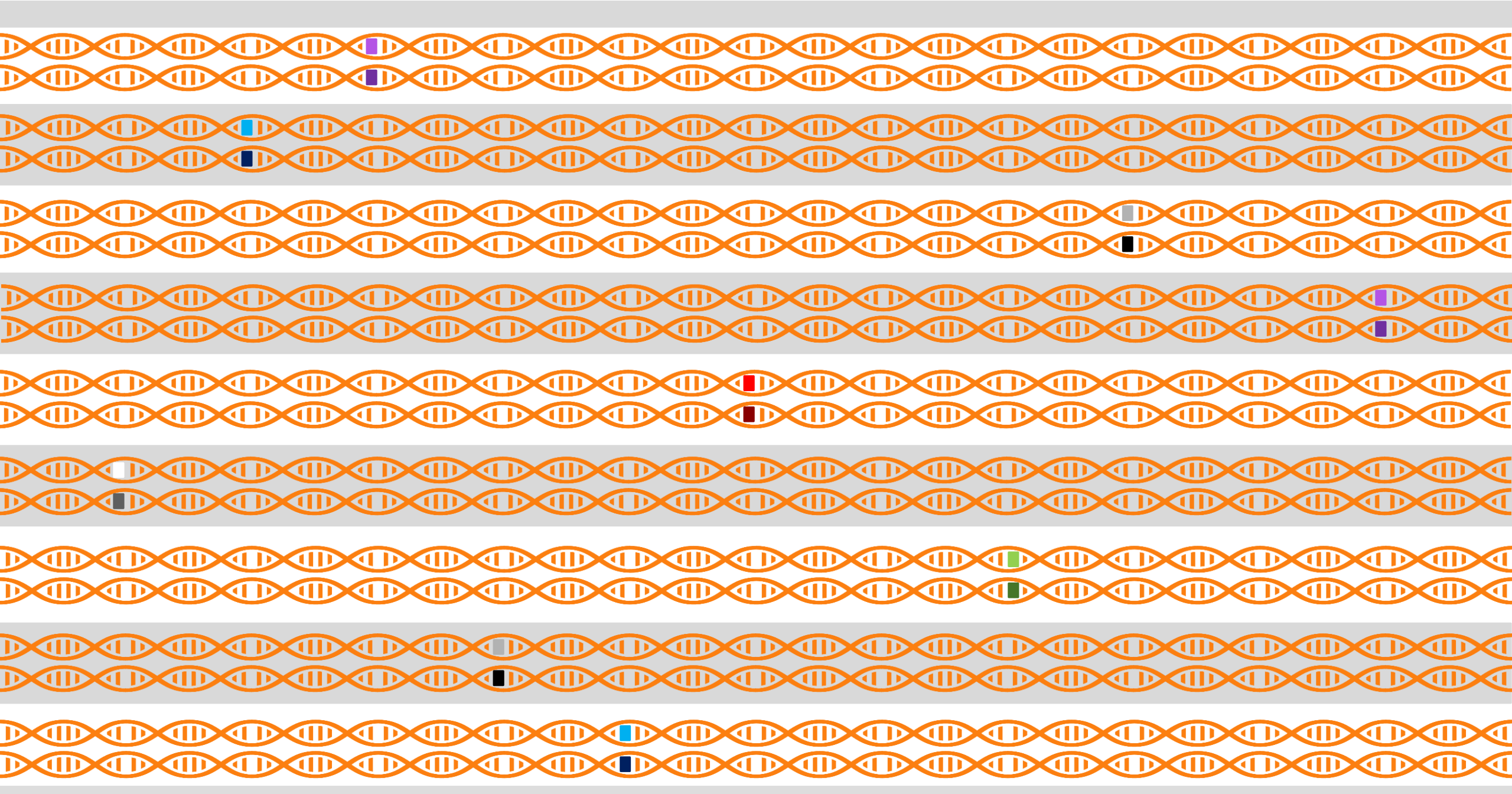
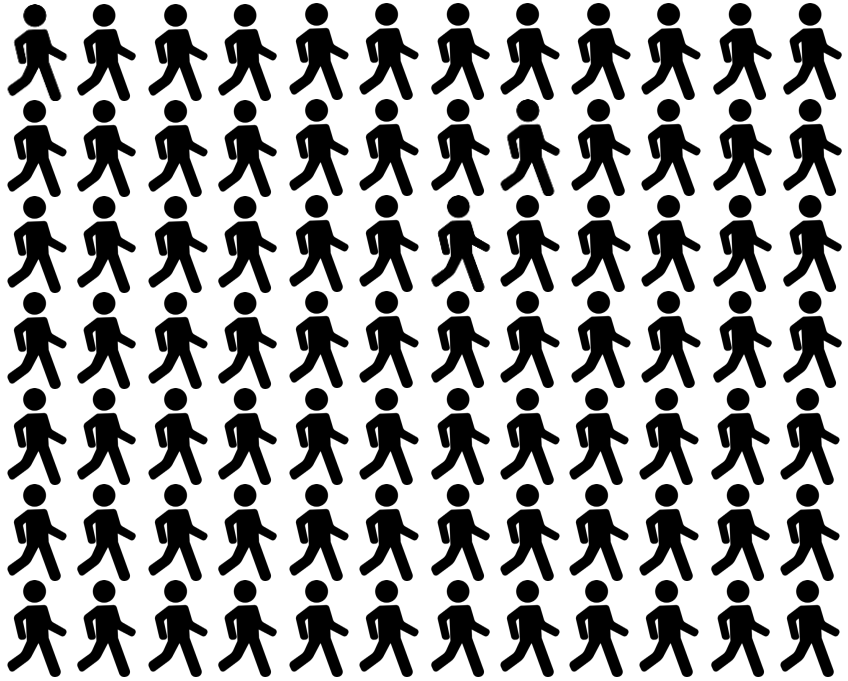


We analyzed many different SNPs throughout the genome.

Data

UK Biobank:

- ~500,000 individuals recruited (2006-2010)
- Aged 40-69 at time of recruitment



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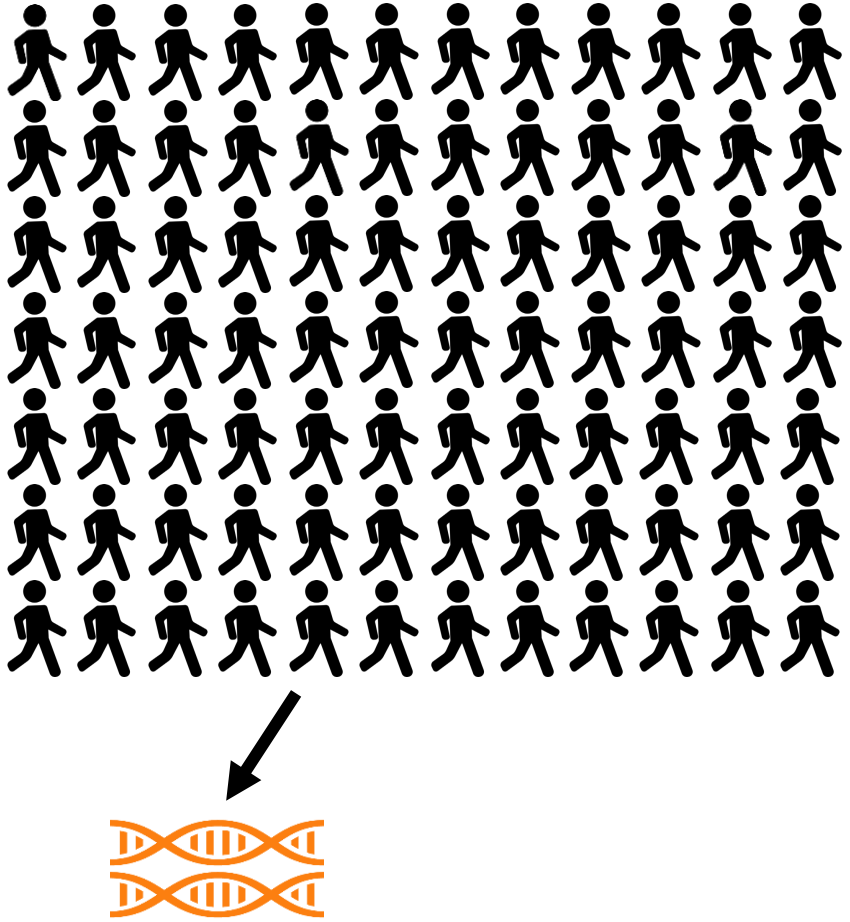

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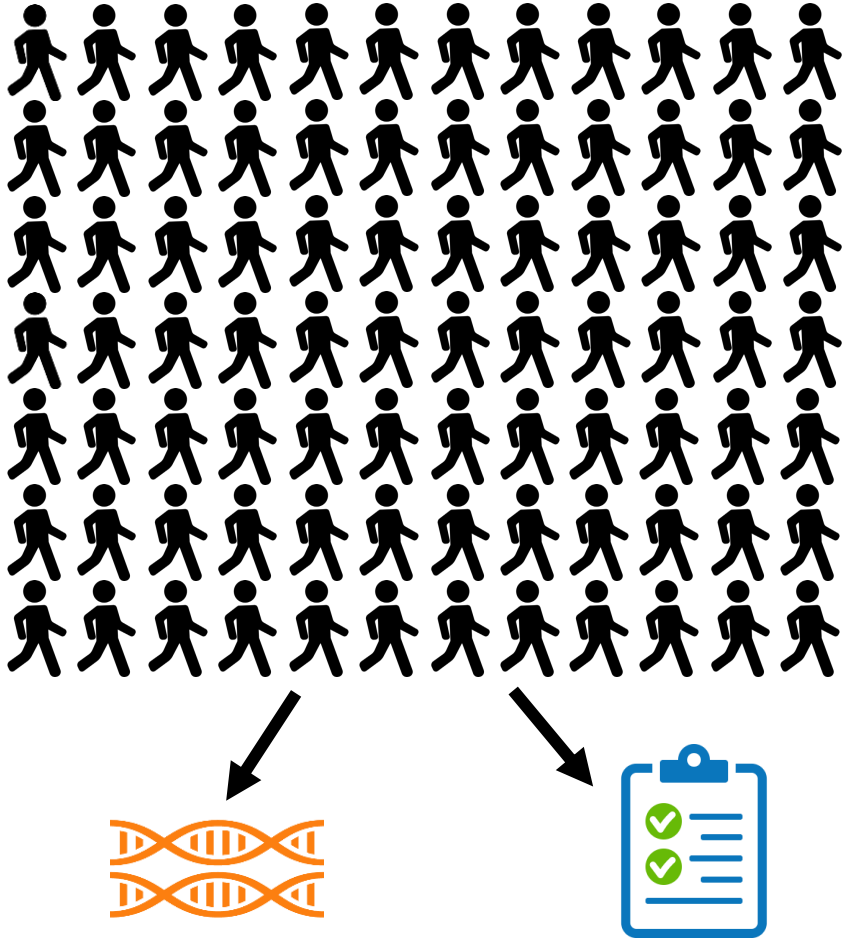

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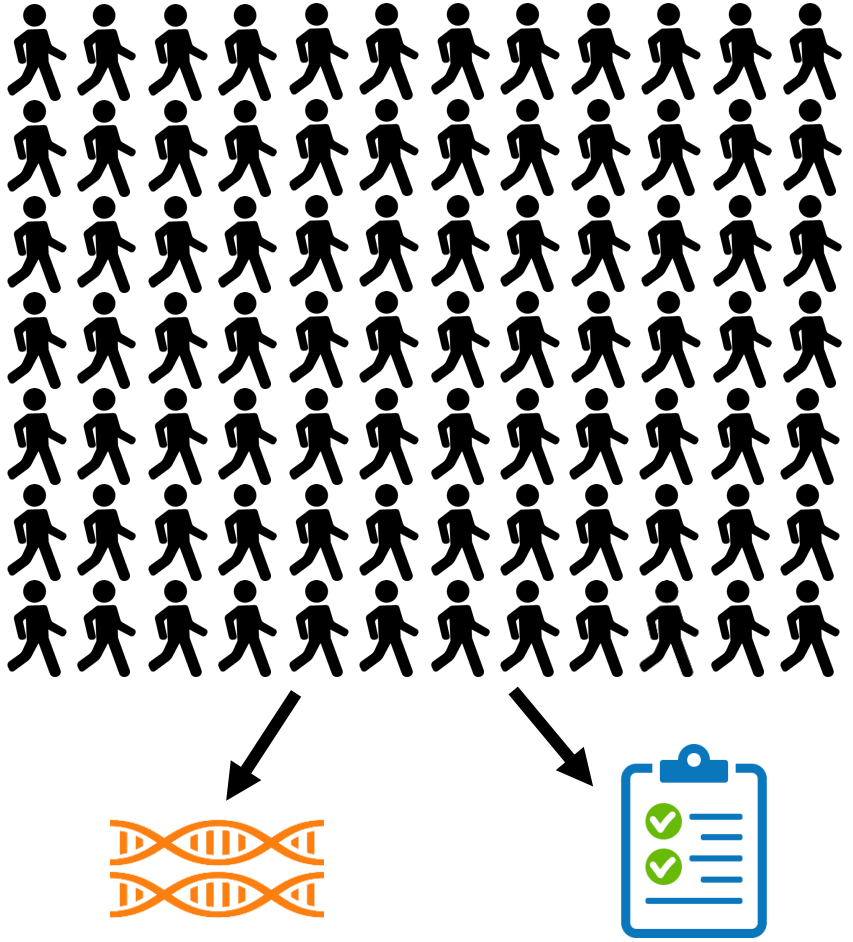
- ~8,000 individuals of European ancestry



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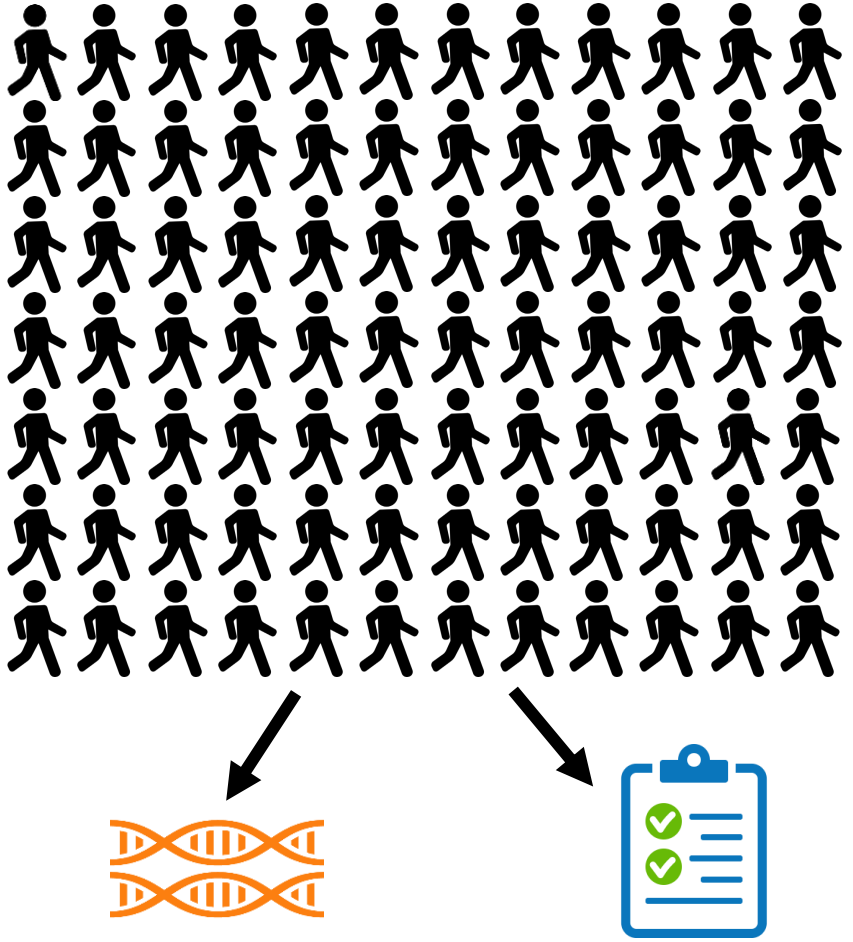
- Hundreds of biomarkers
  - Includes 44 antibodies
  - 22 antibodies with seroprevalence >20%



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12 Pathogens:

- Herpes Simplex virus-1
- Varicella Zoster Virus (Chickenpox)
- Epstein-Barr Virus
- Human Cytomegalovirus
- Human Herpesvirus-6
- Human Herpesvirus-7
- Human Polyomavirus BKV
- Human Polyomavirus JCV
- Merkel Cell Polyomavirus
- *Chlamydia trachomatis*
- *Helicobacter pylori*
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Total of 22 antibodies against these pathogens
Each antigen's seroprevalence >20%

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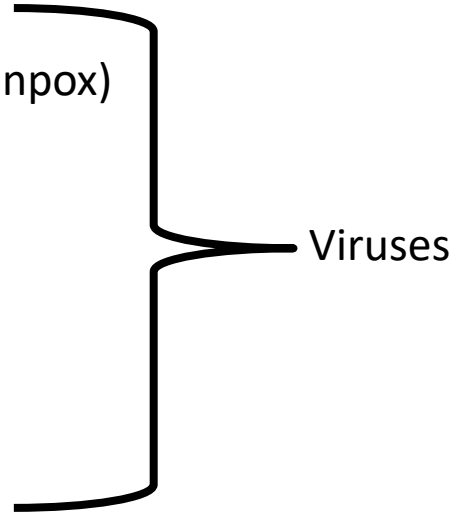

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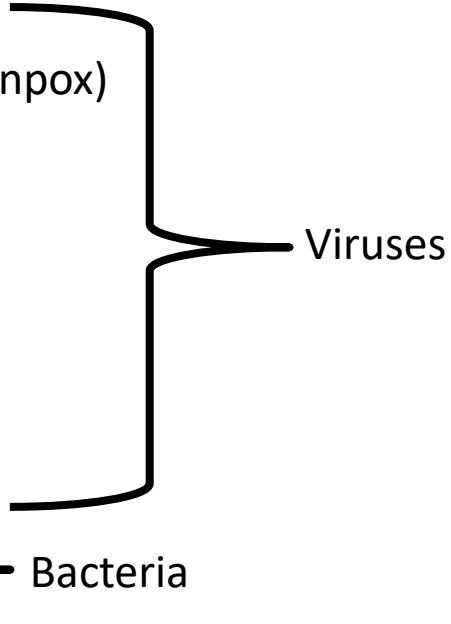

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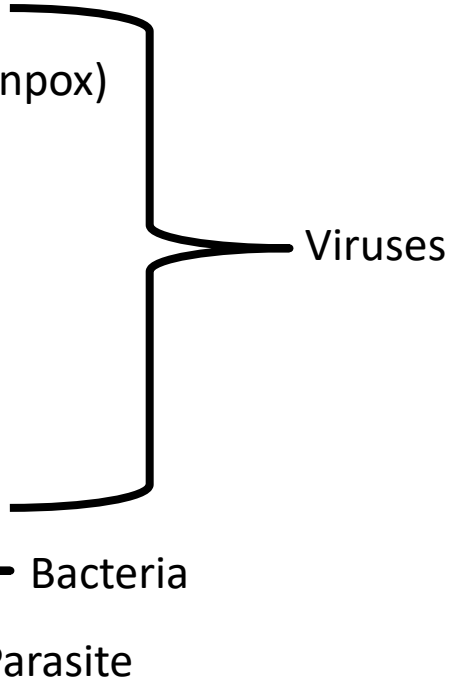

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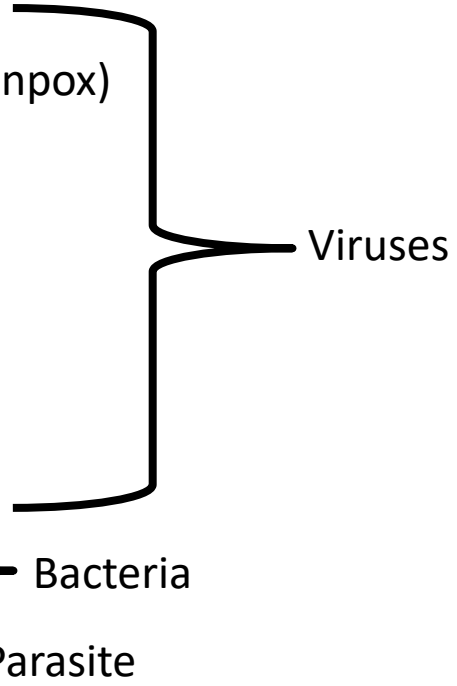

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These pathogens are risk factors for cancer and cardiovascular or neurodegenerative diseases.

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Covariates for all regression models:

- Age
- Sex
- Body mass index
- Genotyping array
- Antigen assay date
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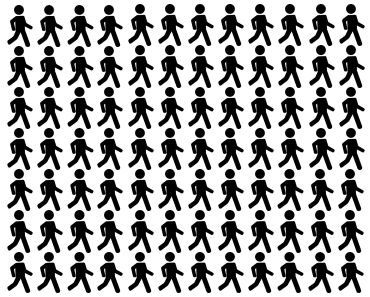
Methods - Summary

UK Biobank Data



N=8,000

22 common antibodies (12 pathogens)

Genome-Wide Association Study

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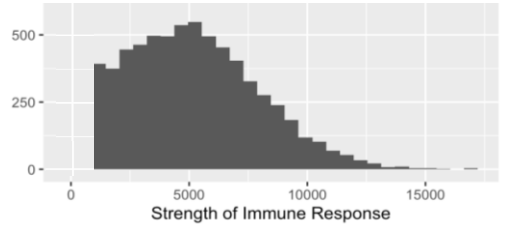

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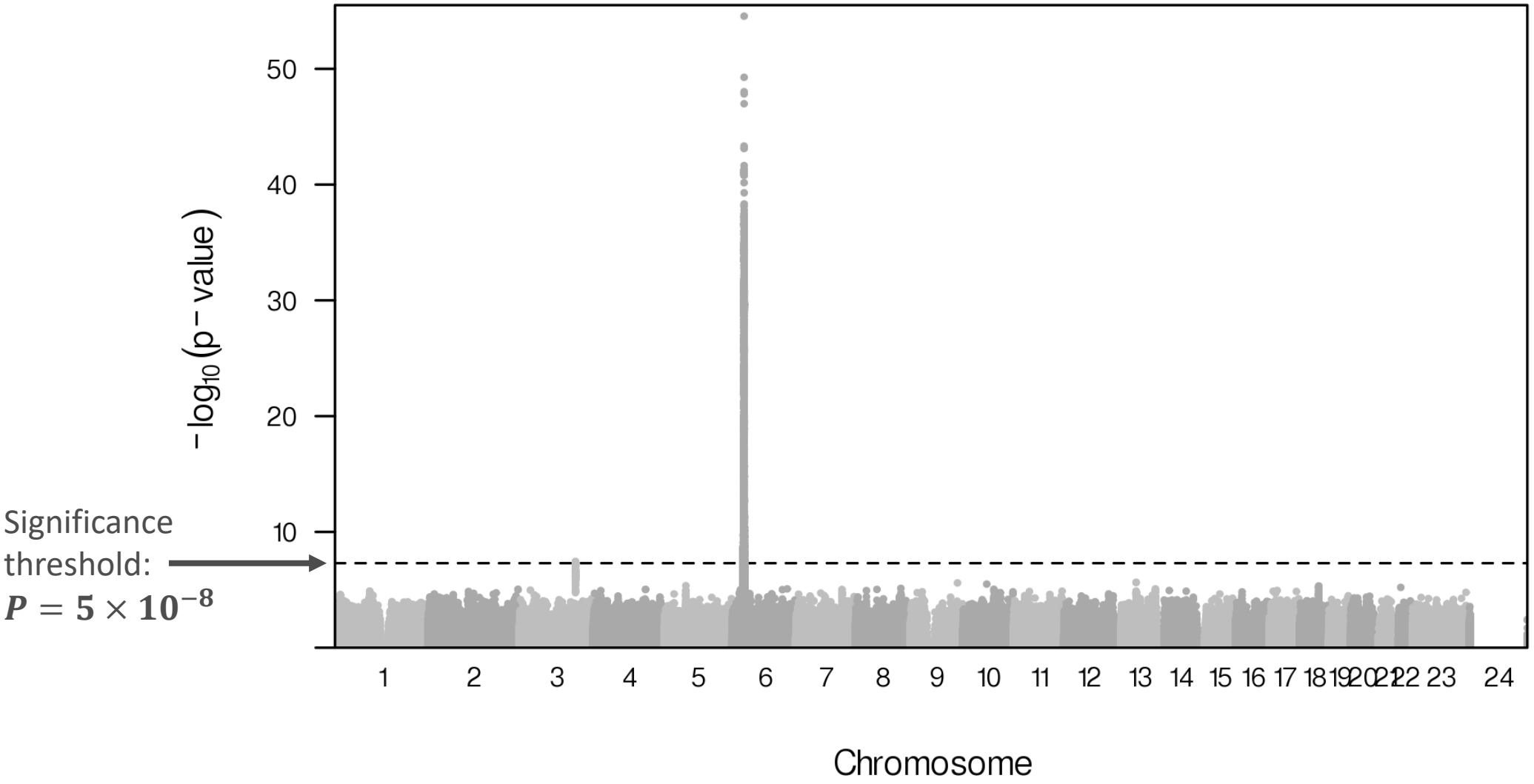
- **99** independent ($R^2 < 0.05$) SNPs ($P < 5 \times 10^{-8}$)
- **47** of these SNPs lie within genes (45 distinct genes)
  - Many genes associated with autoimmunity, inflammation, and vaccine response

EBNA-1 Antigen for **N = 6845**

Epstein-Barr Virus



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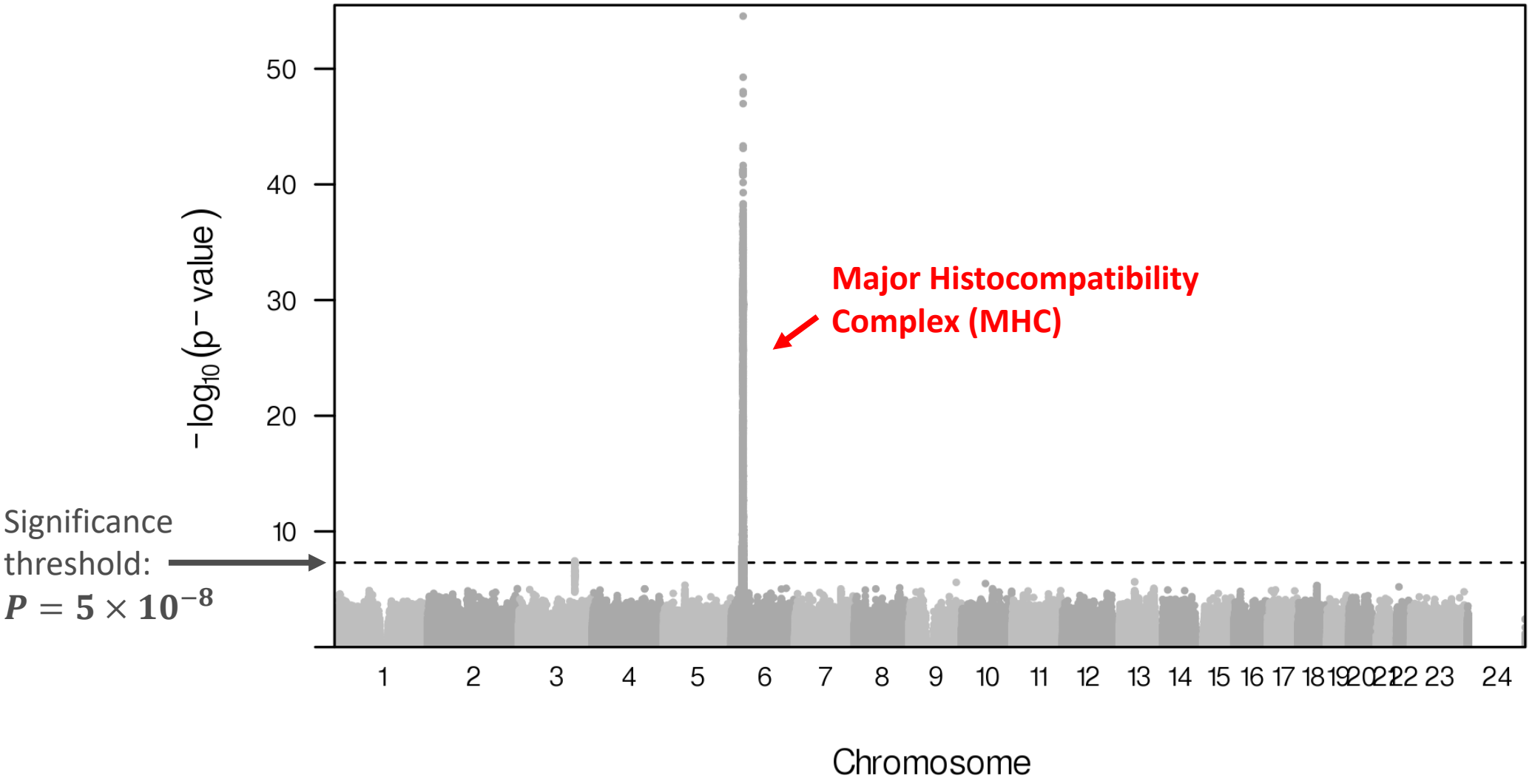
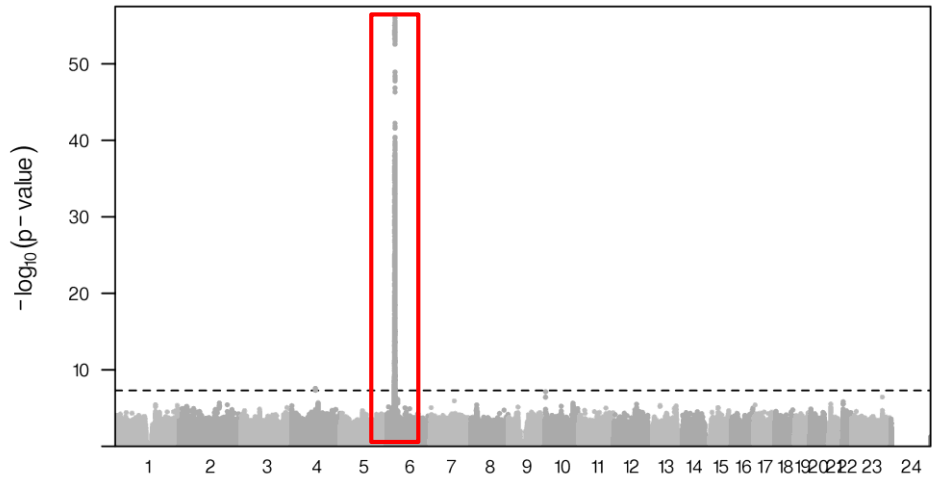
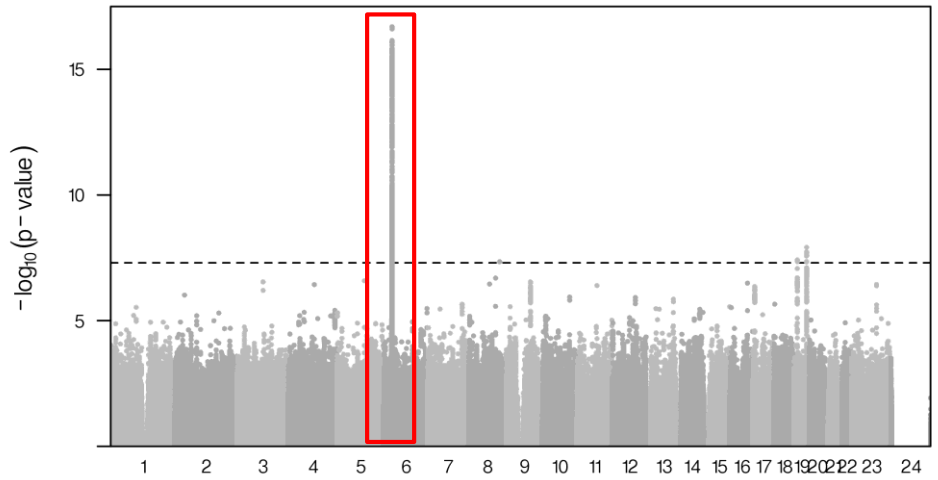


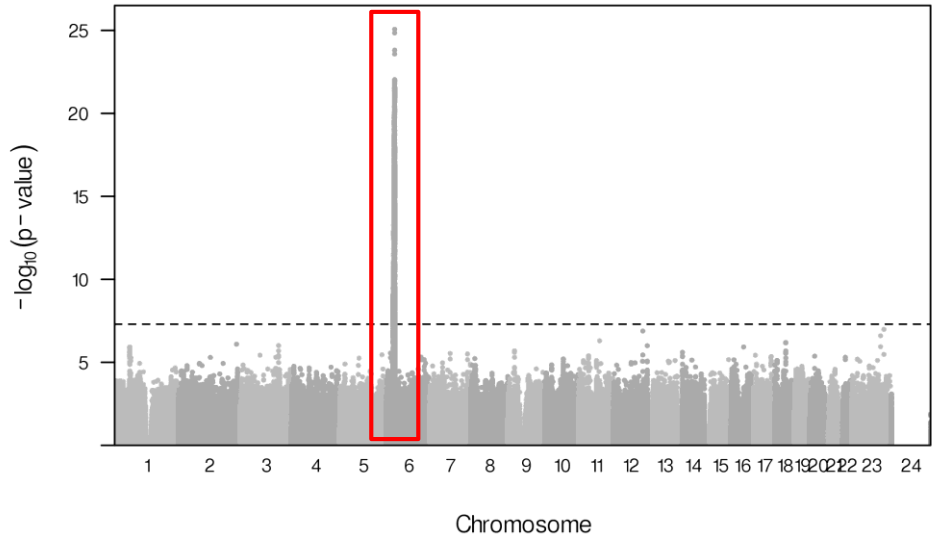
ZEBRA Antigen for **Epstein-Barr Virus** **N = 7033**



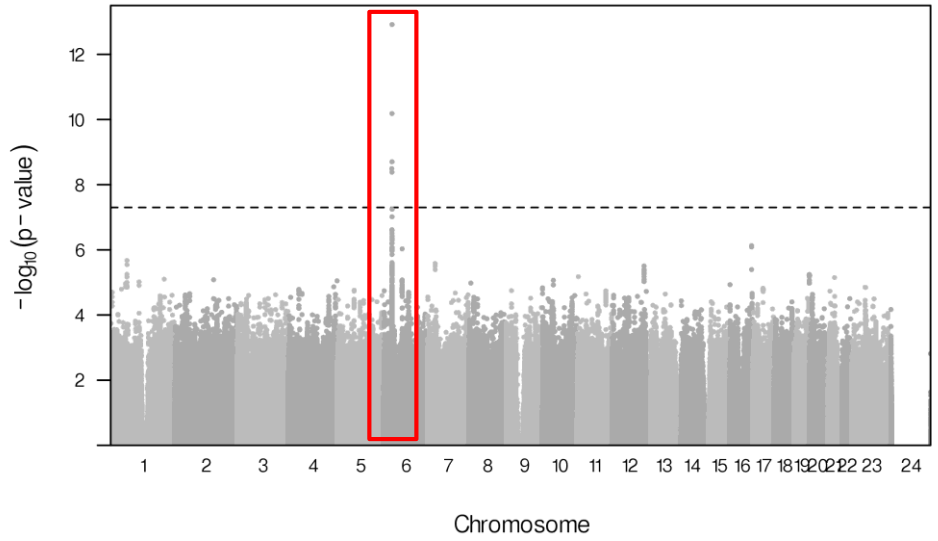
JC VP1 Antigen for **Human Polyomavirus JCV** **N = 4367**



gE/gI Antigen for **Varicella Zoster Virus** **N = 7124**



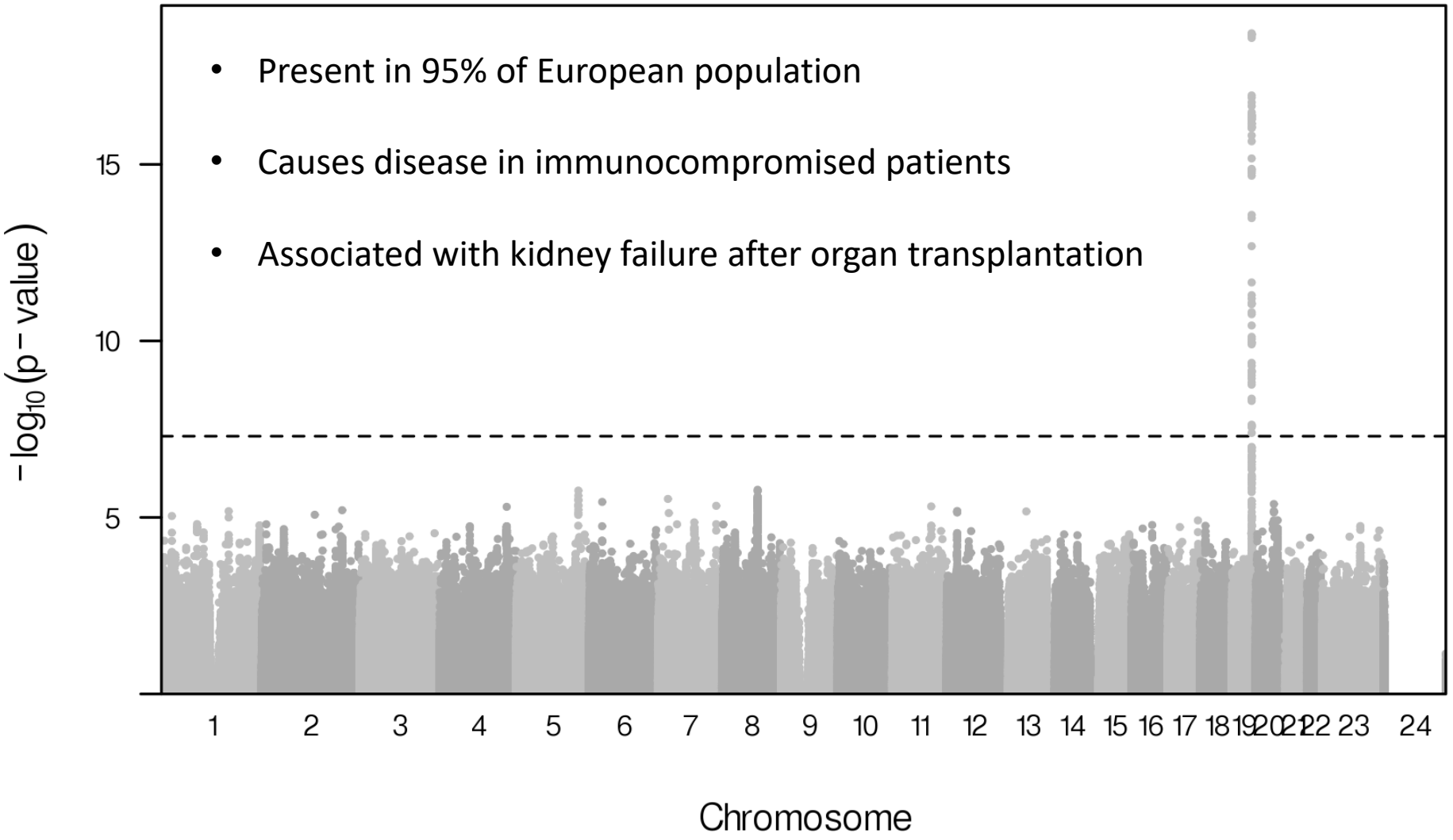
pp52 Antigen for **Human Cytomegalovirus** **N = 4881**



We identified **45** independent SNPs in the Major Histocompatibility Complex

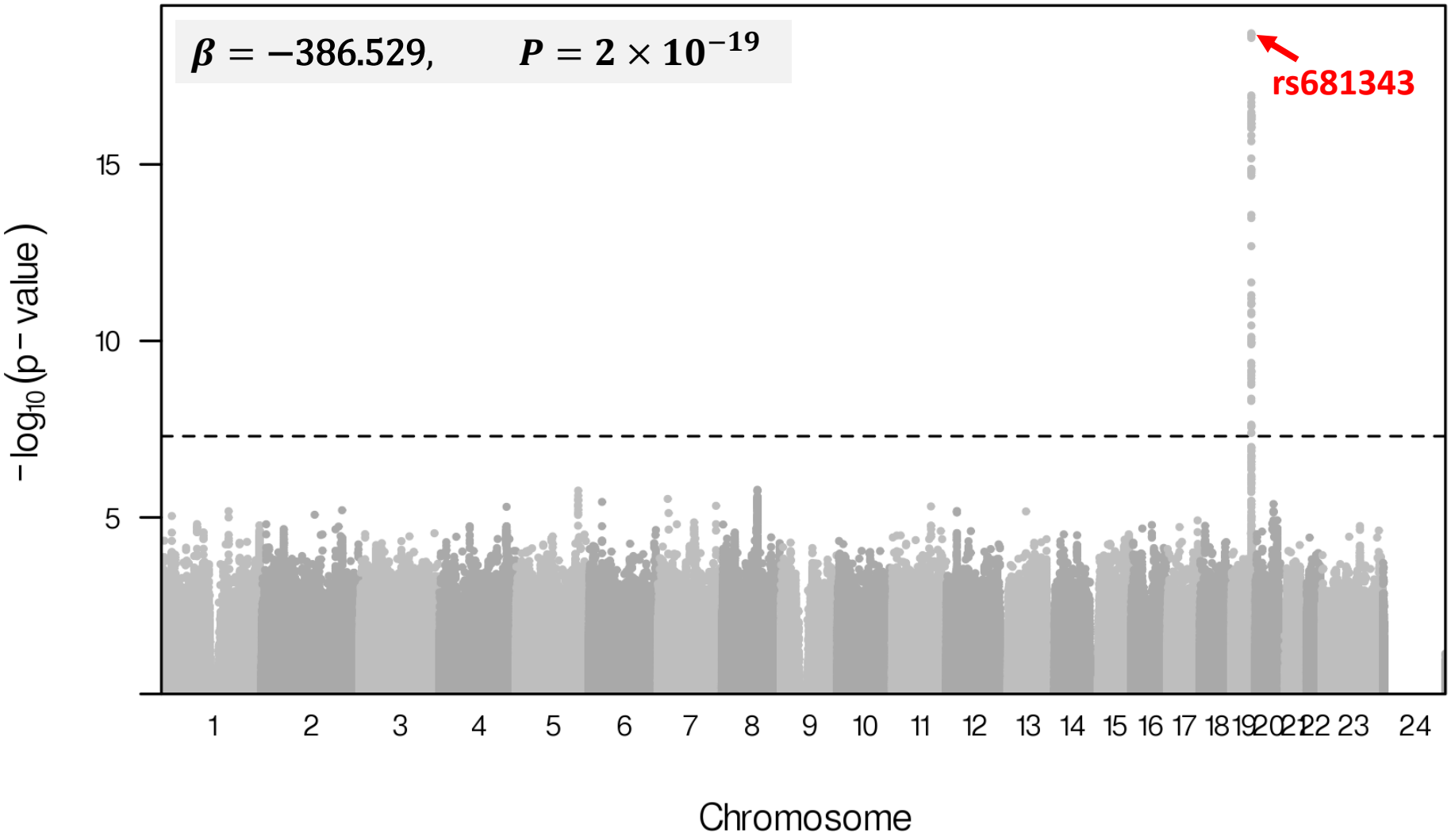
BK VP1 Antigen for **N = 7349**

Human Polyomavirus BKV (PBKV)



BK VP1 Antigen for **N = 7349**

Human Polyomavirus BKV (PBKV)



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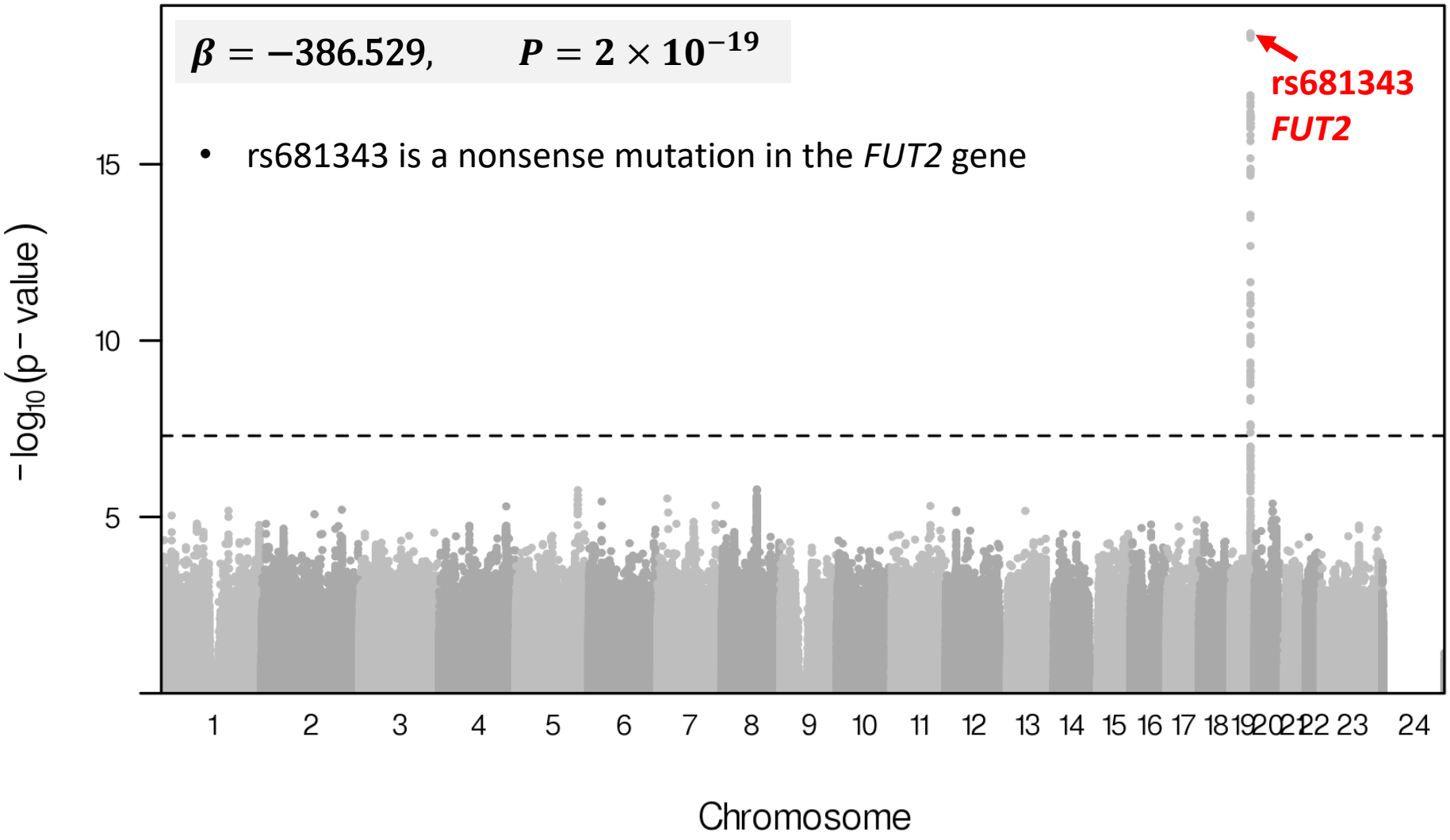

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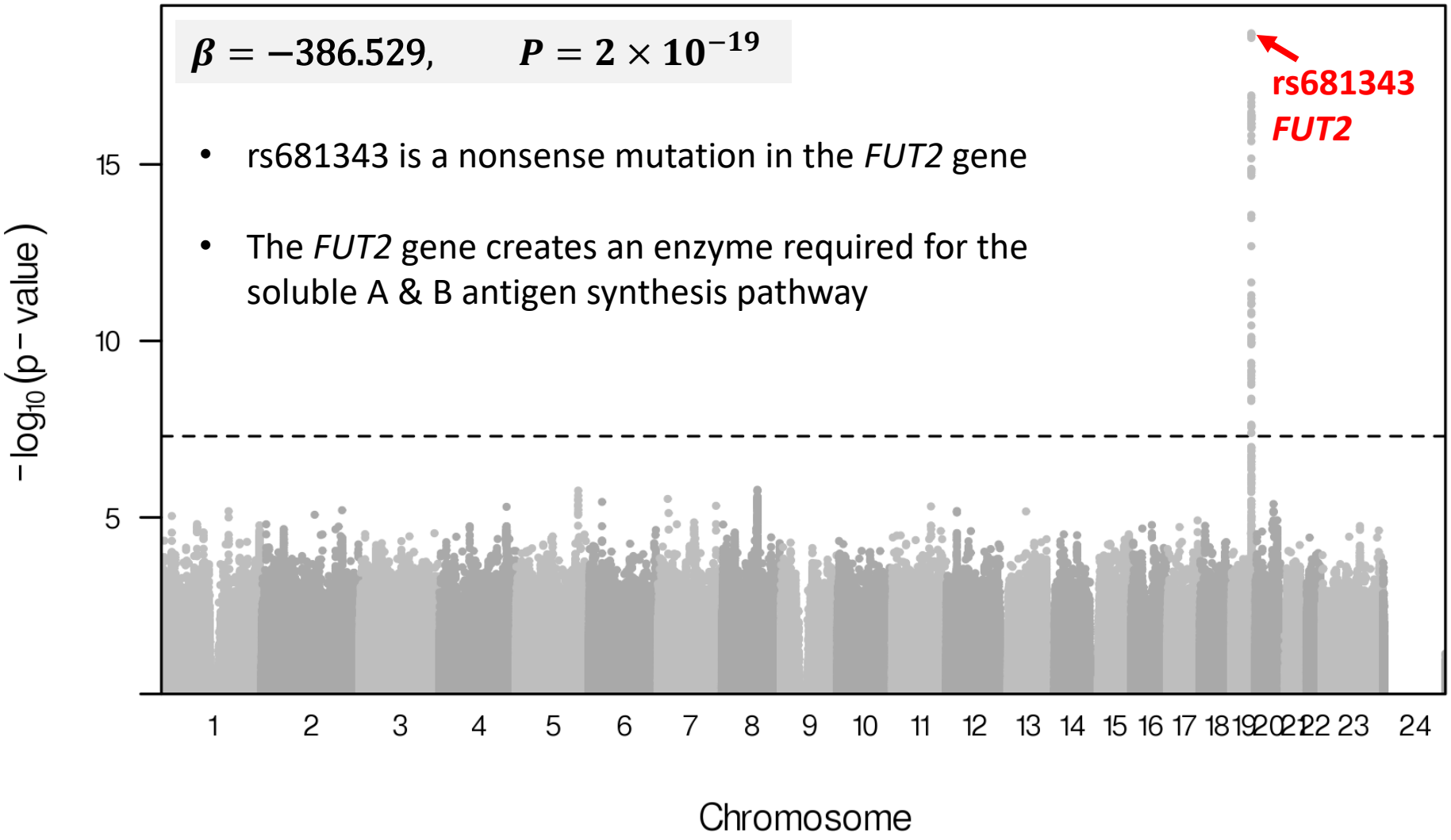
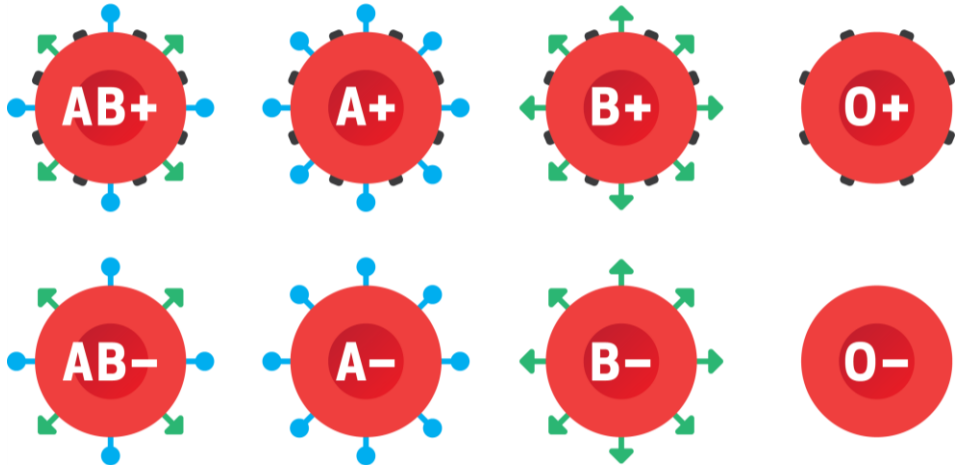
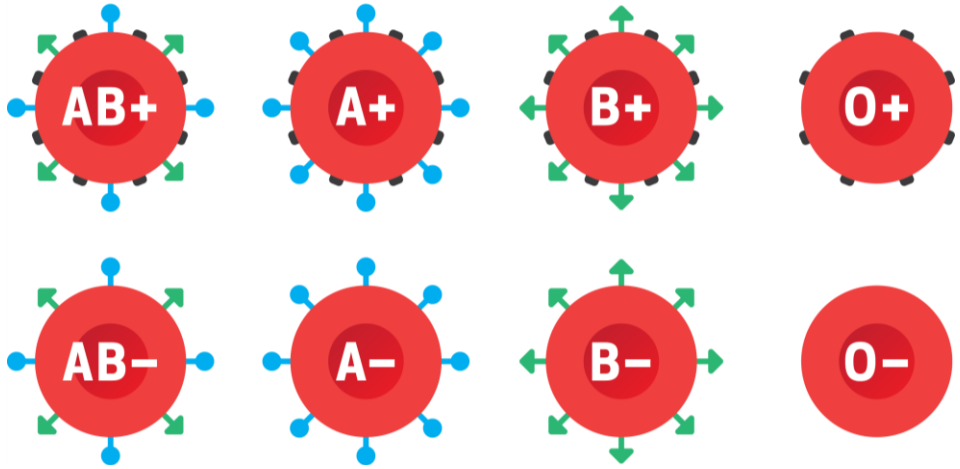
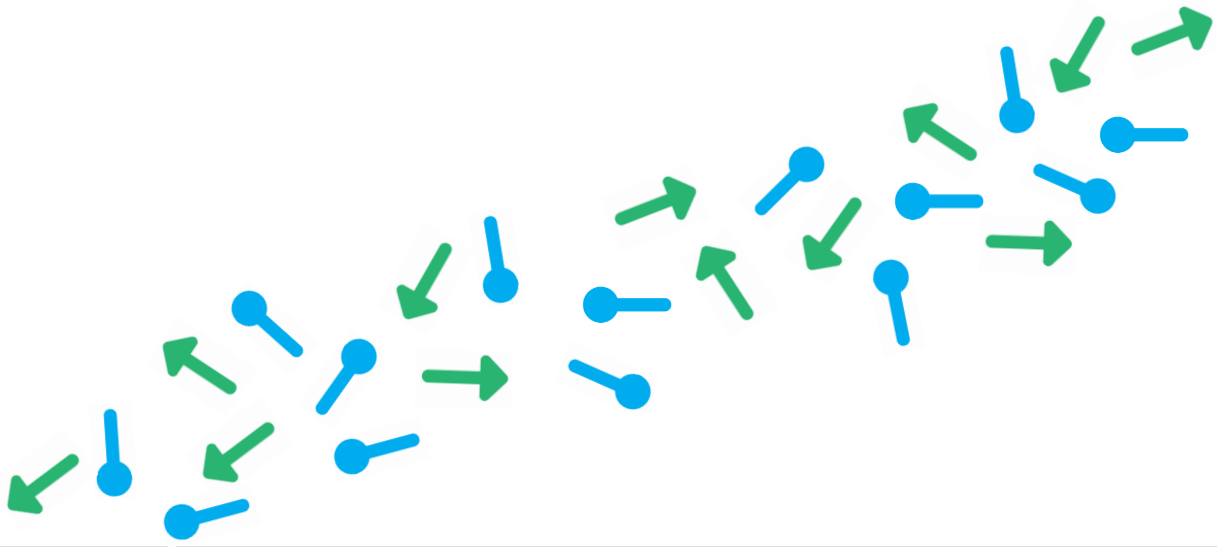




Graphics adapted from blood.ca





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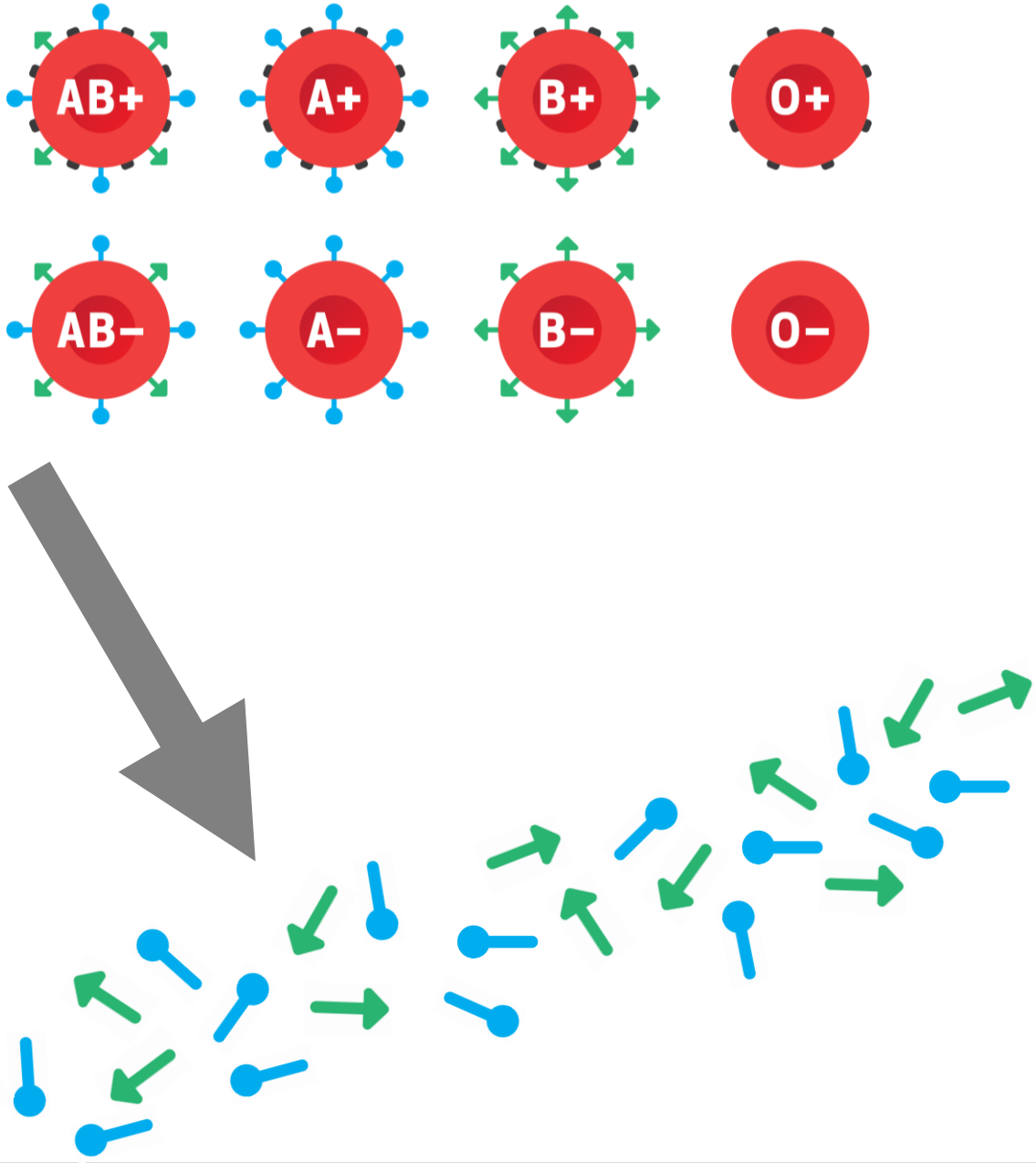
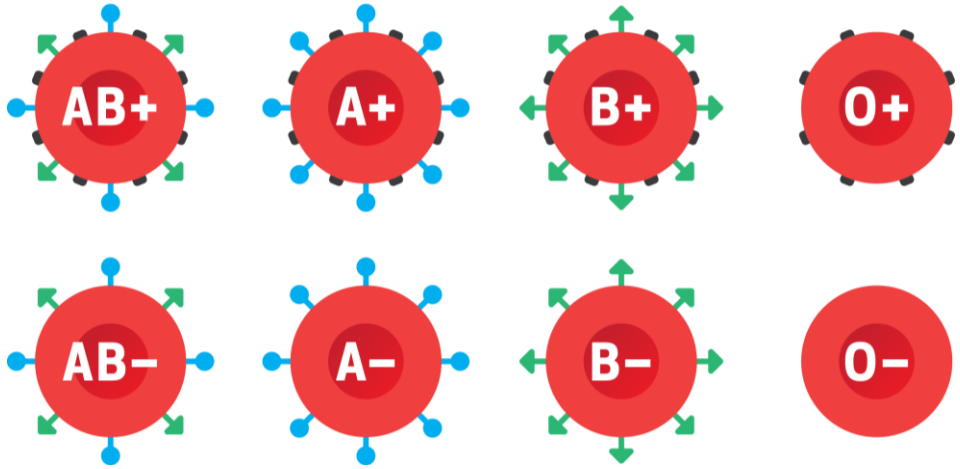
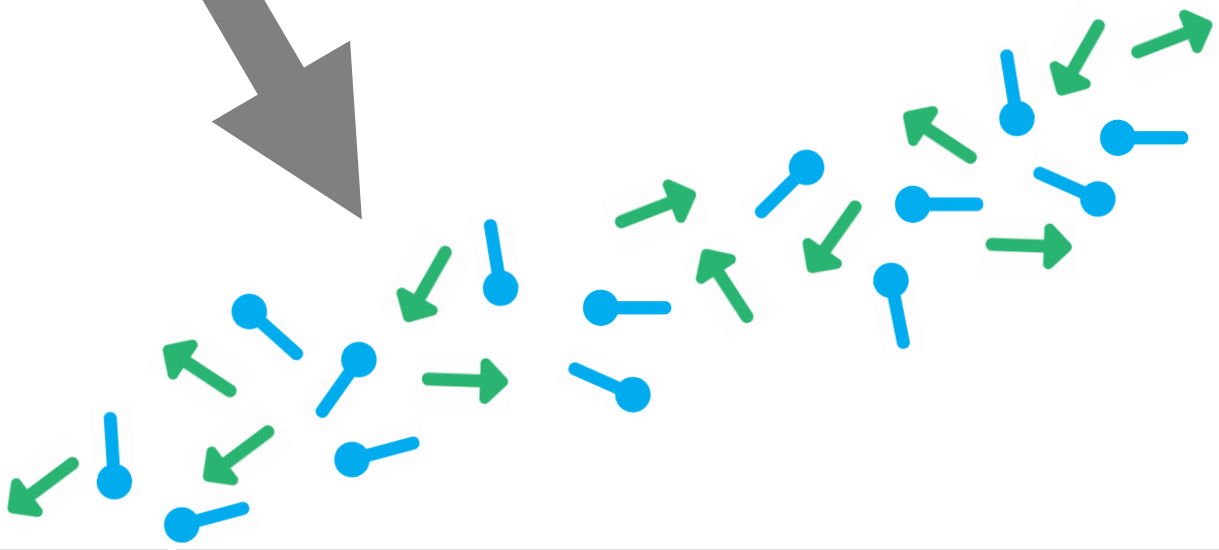


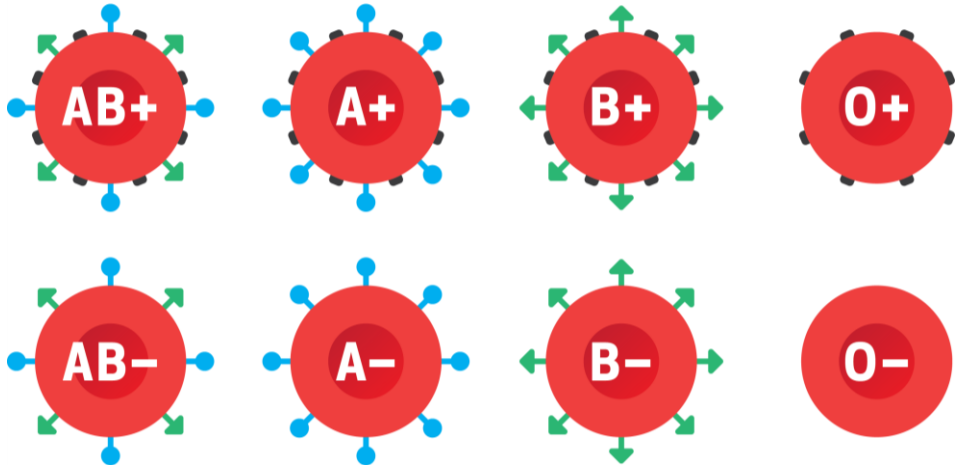
Graphics adapted from blood.ca



FUT2 (α1,2fucosyltransferase)



Graphics adapted from blood.ca



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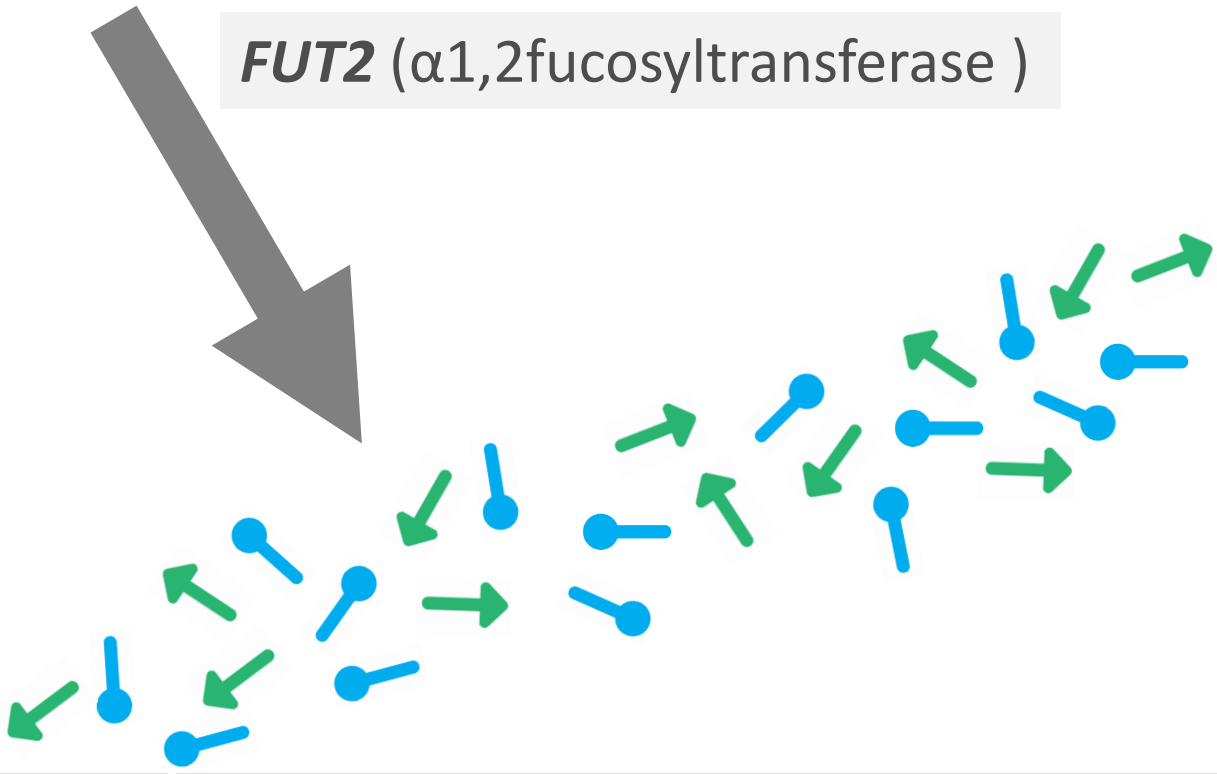
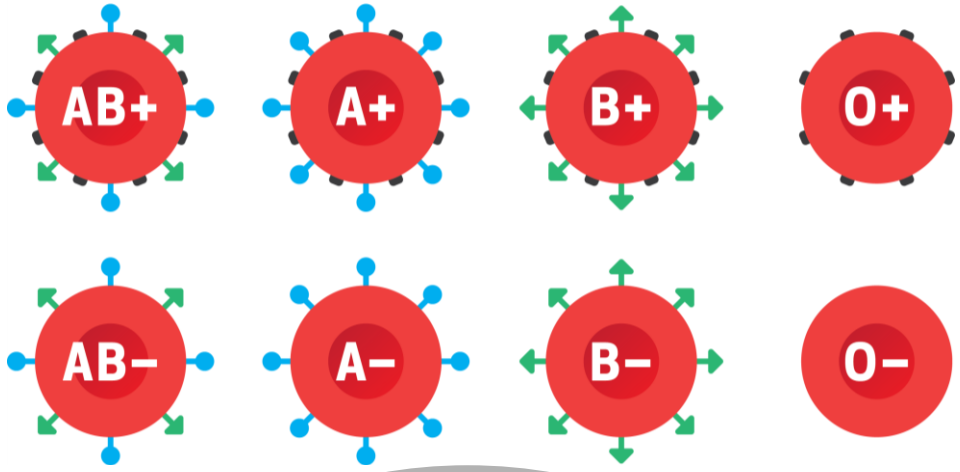


20% of Europeans are homozygous for a **recessive nonsense mutation** (FUT2-/-) which results in a **nonfunctional enzyme.**

PMID:7876235

Graphics adapted from blood.ca



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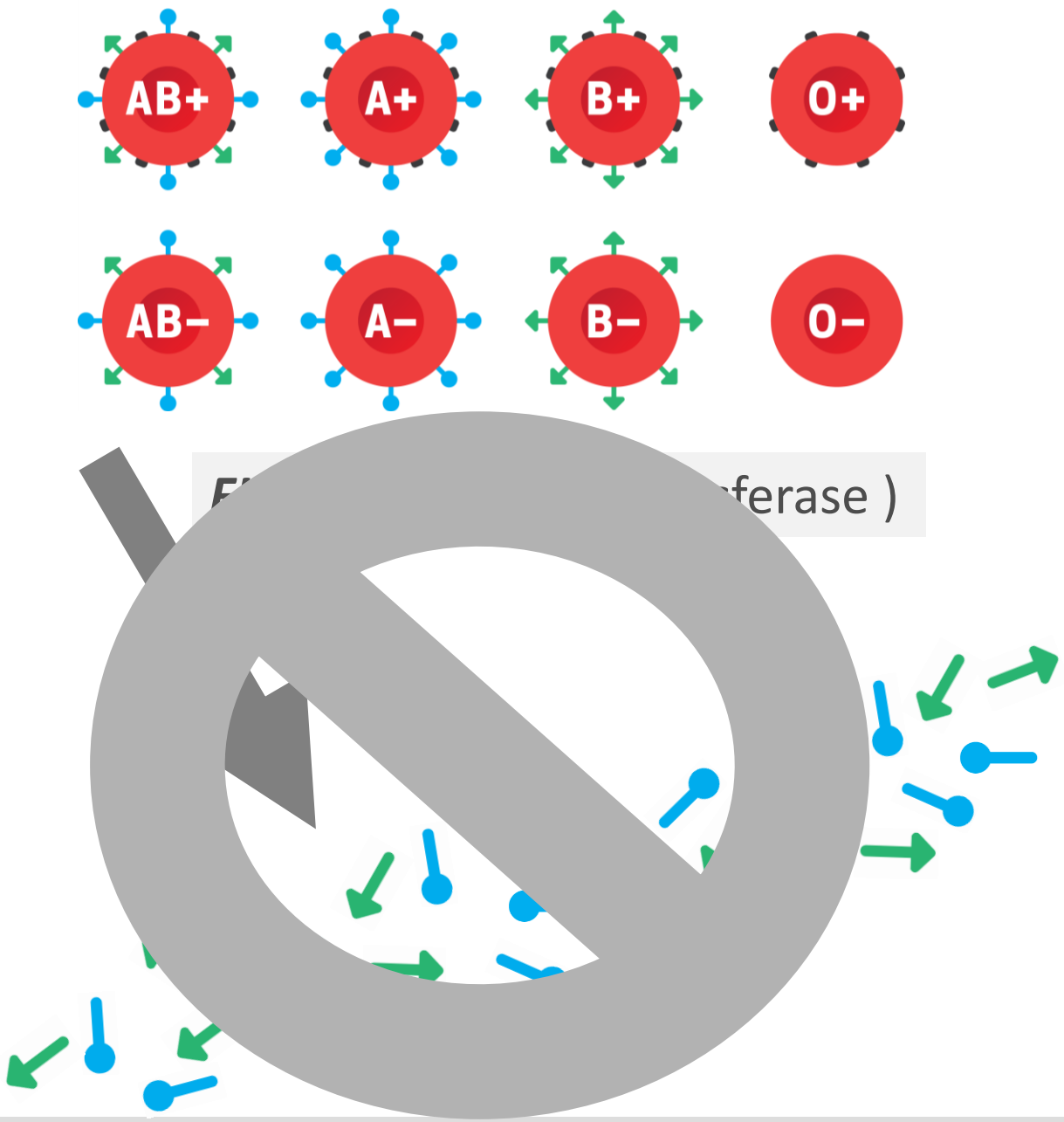

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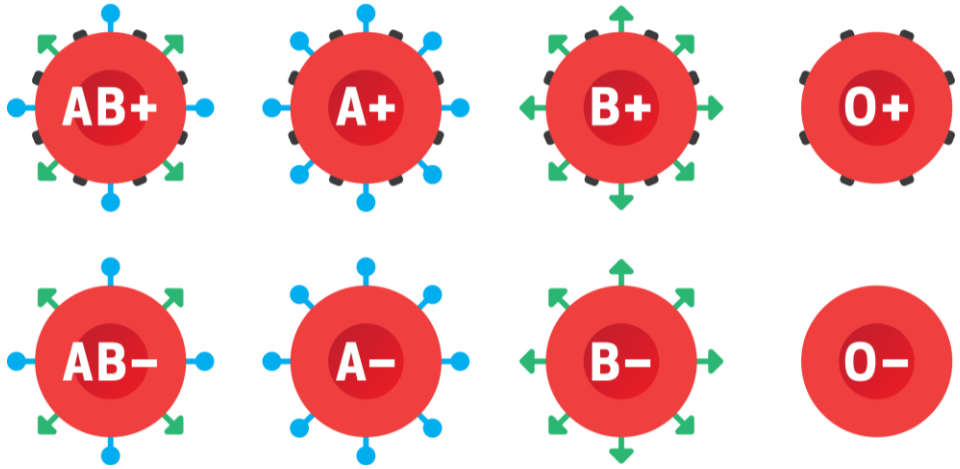
These individuals are **highly resistant** to **norovirus** infection.

PMID: 16306606, 16973373

Graphics adapted from blood.ca



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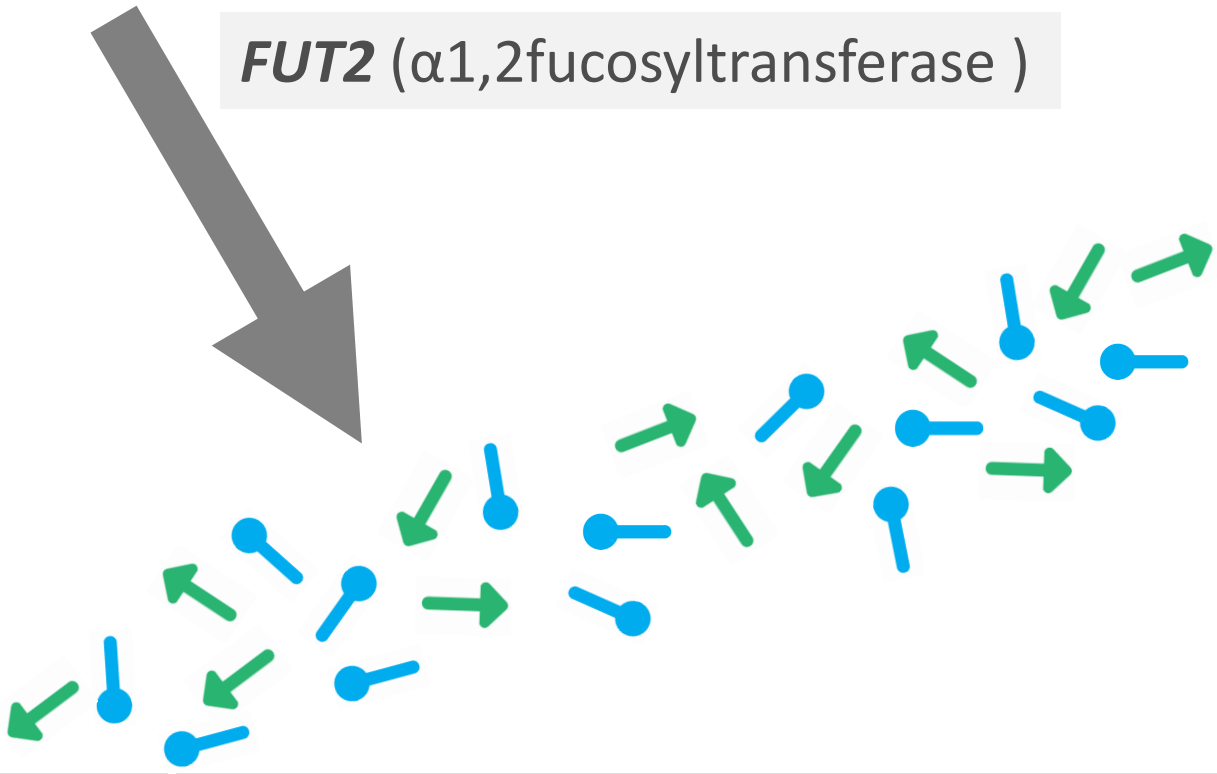

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The association of *FUT2* with Polyomavirus BKV suggests that **secreted histo-blood group antigens could play a role in polyomavirus response.**

Graphics adapted from blood.ca

Conclusions

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Some of these genes could elucidate how the immune system interacts with specific pathogens.

Future Directions

Genetic basis of pathogen-induced cancers & immune response

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Biological function of immune-response-associated genes

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Personalized prevention (vaccines) & intervention (drug targets)

Thank you!

- Dr. Linda Kachuri & Dr. Sara Rashkin
- Dr. John Witte & The Witte Lab
- UCSF SRTP: Julia Clark & Dr. D'Anne Duncan
- Amgen Foundation

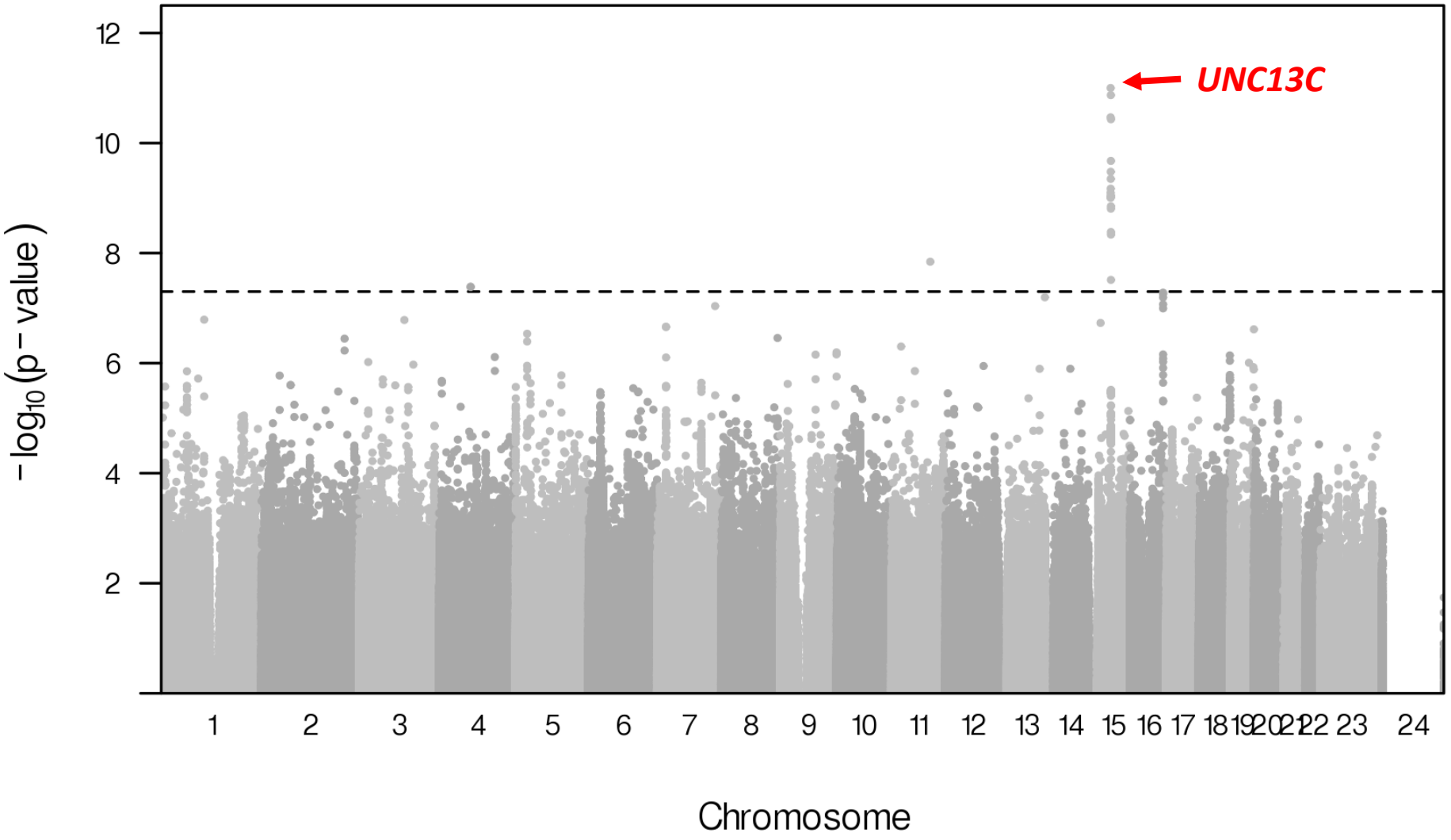
UCSF Department of Epidemiology & Biostatistics

AMGEN® Foundation

Amgen Scholars Program

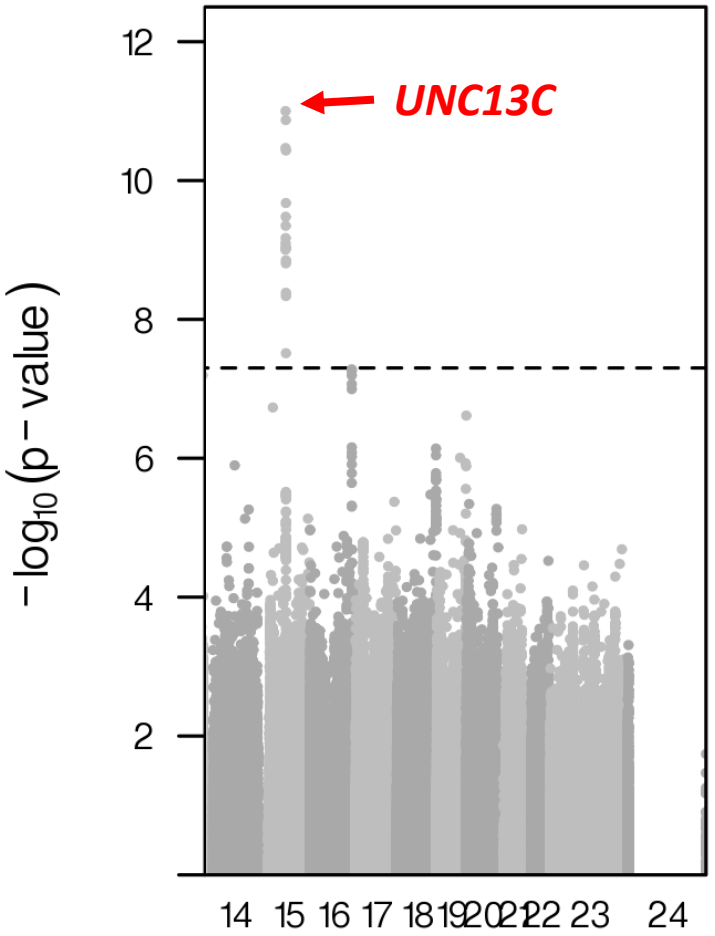
IE1B Antigen for **N = 6095**

Human Herpesvirus-6



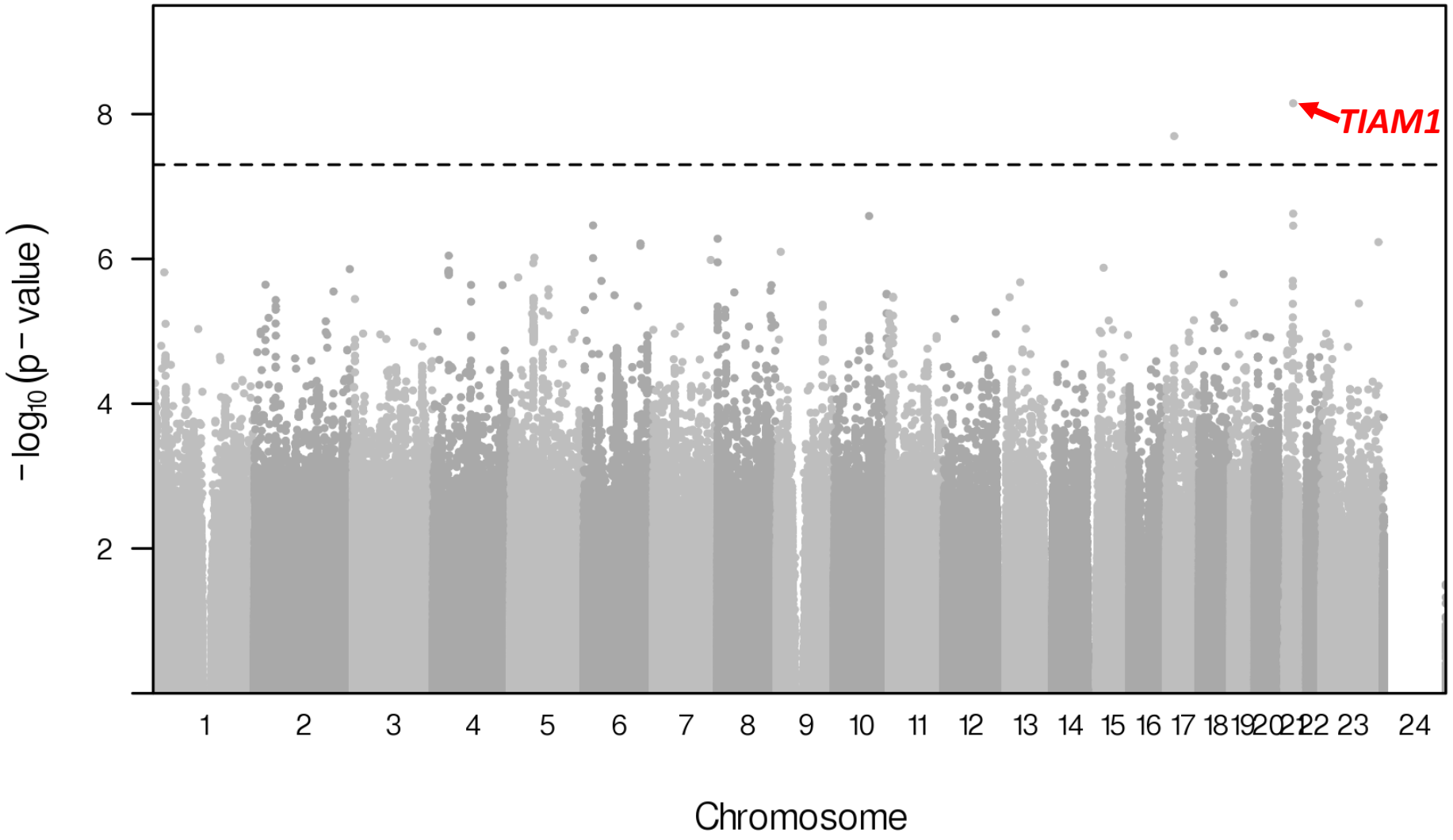
rs118162566 – *UNC13C* Gene

- Related to immune response to IE1B antigen for Human Herpesvirus-6 ($\beta = -506.2, P = 10^{-11}$)
- *UNC13C* may play a role in vesicle maturation during exocytosis
- Appeared in same GWAS of antibody response to the **smallpox vaccine** (PMID: 22542470, $P = 8 \times 10^{-7}$)



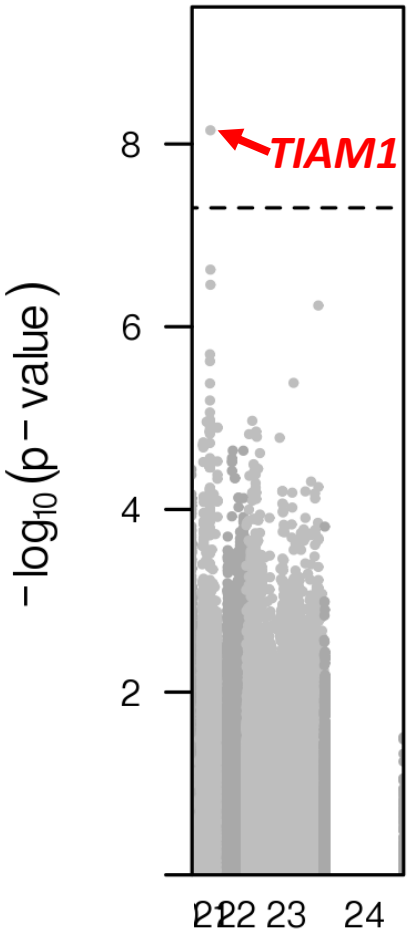
UreA Antigen for **N = 1891**

Helicobacter pylori



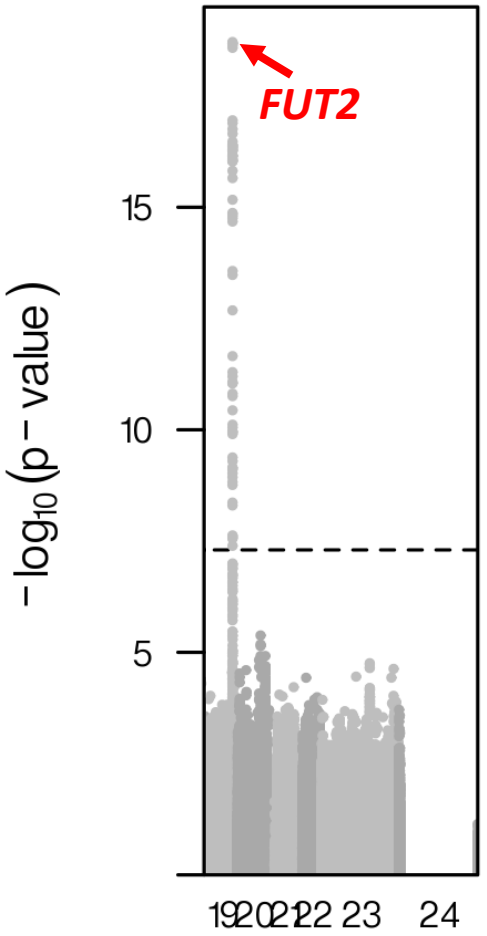
rs113552662 – *TIAM1* Gene

- Related to immune response to UreA antigen for *Helicobacter pylori* ($\beta = -2023, P = 7 \times 10^{-9}$)
- *TIAM1* (**T Cell Lymphoma Invasion and Metastasis 1**) plays a role in cell invasion, metastasis, and carcinogenesis
- Appeared in GWAS of **HIV-1 virologic failure** (PMID: 25461247, $P = 10^{-6}$)



rs681343 - Fucosyltransferase 2

- Related to immune response to BK VP1 antigen for Human Polyomavirus BKV ($\beta = -386.529, P = 2 \times 10^{-19}$)
- *FUT2* is an enzyme required for the soluble A & B antigen synthesis pathway

Also associated with:

- **Crohn Disease** (PMID: 26192919)
- Several **autoimmune diseases** (PMID: 26301688)
- **Infectious diseases** such as rotavirus, norovirus, and pneumonia (PMID: 24277741, 16306606, 2876155)