

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

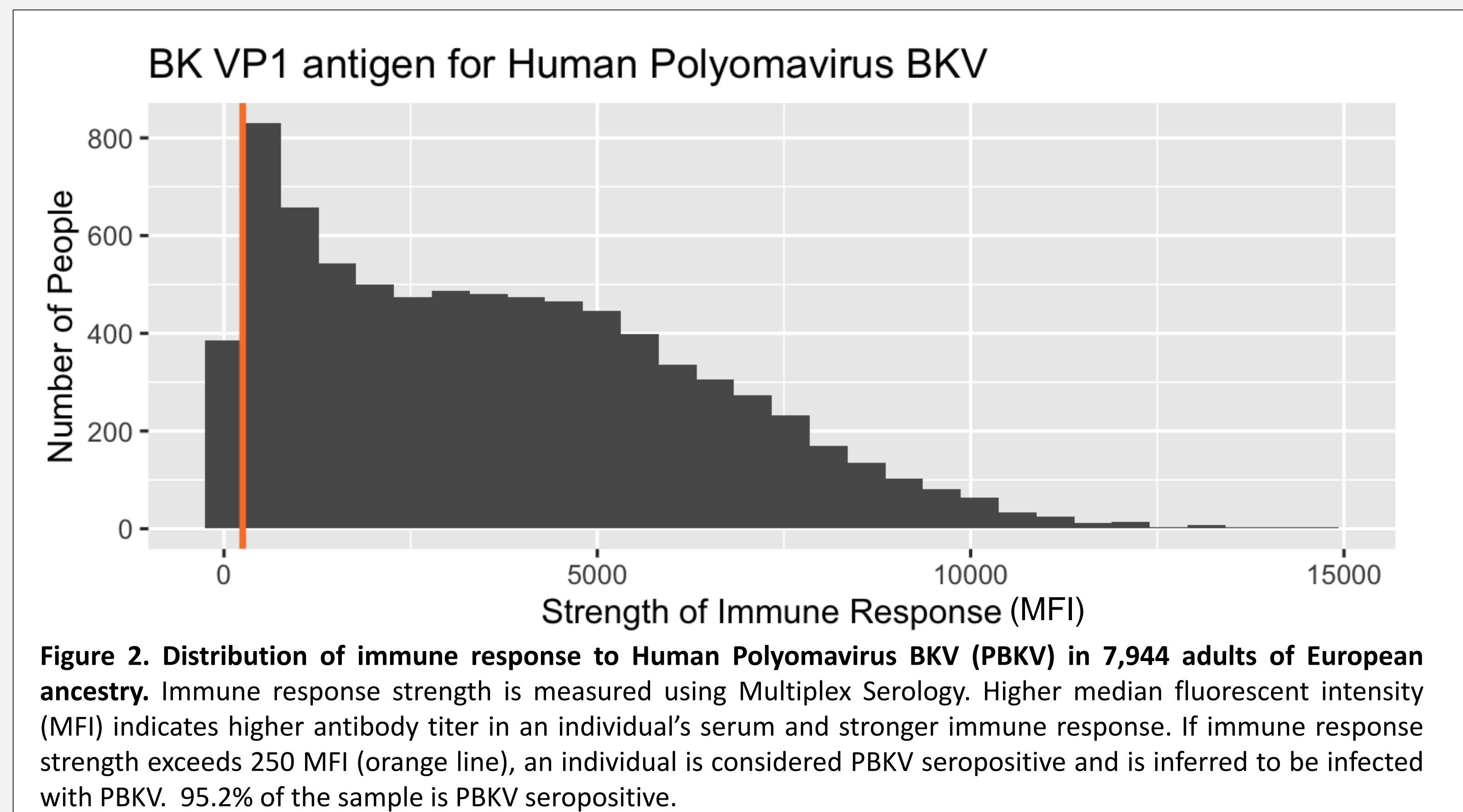
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## Background

- Immune response strength (amount of antibody produced in response to infection) varies between individuals (Figure 2).
- Understanding the genetics of variability in immune response strength can yield insights into pathogen-induced disease etiology, potential drug targets, and the biological mechanisms of immune response.



## Data & Methods

**UK Biobank Data**  
 N=7,944

- ~9 million SNPs (maf >0.01)
- Covariates:** Age (40-69 years), sex, body mass index, etc.
- Antibody Levels:** 22 antibodies for which >20% of study was seropositive

- The 22 antigens we analyzed target 12 viral, bacterial, and parasitic pathogens that are established risk factors for cancer and cardiovascular or neurodegenerative diseases.

## What is a GWAS?

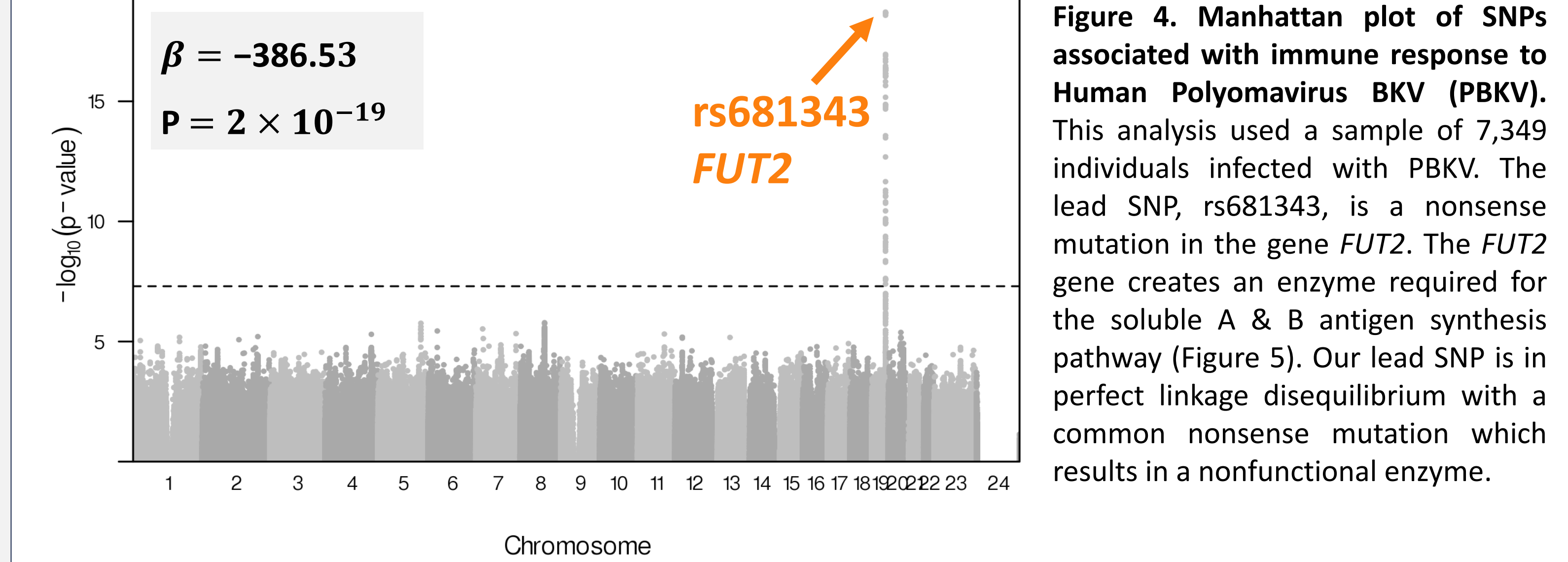
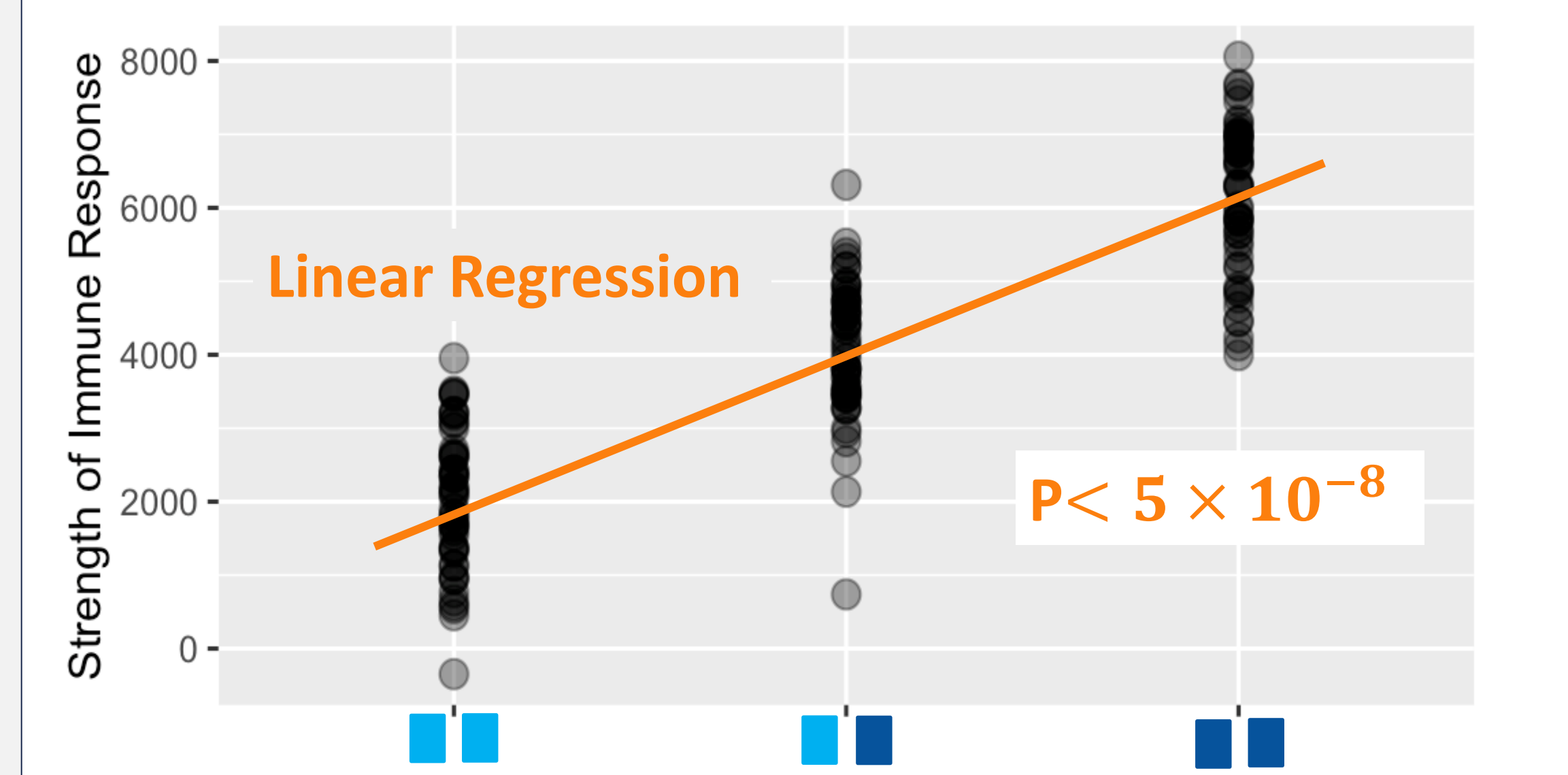
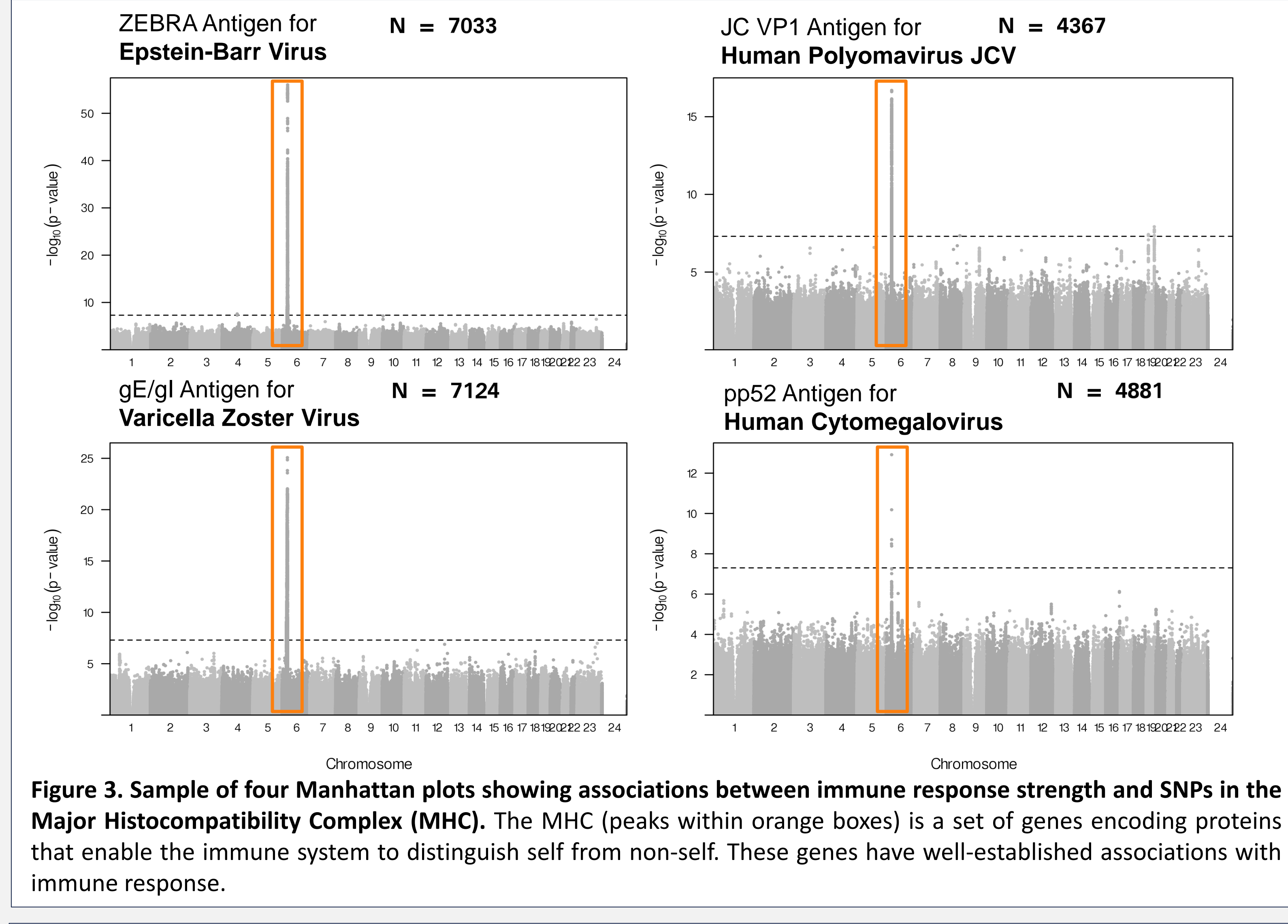
In a Genome-Wide Association Study (GWAS), we fit linear regression models to identify the single-nucleotide polymorphisms (SNPs) most strongly associated with immune response strength (Figure 1).

A SNP is a single base pair, like the blue rectangles here: At this SNP, an individual can have 0, 1, or 2 copies of the dark blue allele (■).

Our linear regression models use this information (G, for genotype) to predict y, the strength of immune response, in an equation such as this one:

$$y = \beta_0 + \beta_1 \times (G \in \{0, 1, 2\}) + \beta_{Age} \times (Age) + \dots + \epsilon$$

We include covariates such as age to account for variation in y due to non-genetic factors.



## Results

- Found associated SNPs for **17 antigens** against **10 pathogens**
- 99** independent ( $r^2 < 0.05$ ), significant ( $P < 5 \times 10^{-8}$ ) SNPs; **47** in genes
- Many of these genes associated with autoimmunity and vaccine response<sup>1,2</sup>
- Across all 22 antigens there were **45** independent, significant SNPs in the MHC (Figure 3)
- Identified a SNP in *FUT2* which suggests that secreted histo-blood group antigens could play a role in polyomavirus immune response (Figures 4, 5)

**Figure 5. The soluble A&B antigen synthesis pathway, which is dependent on the *FUT2* gene product  $\alpha 1,2$ fucosyltransferase.** *FUT2* has two Mendelian alleles: a dominant, functional enzyme (+), and a recessive, nonfunctional enzyme (-). *FUT2*(-/-) individuals (who have two nonfunctional gene copies) represent 20% of Europeans and are called non-secretors. This is because, without a functional enzyme, they are unable to secrete A and B blood group antigens into bodily fluids such as saliva and serum. Recent work has shown that non-secretors are highly resistant to norovirus infection<sup>3</sup>.

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**References:**  
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## Conclusions & Future Directions

- Different genes are associated with different antibodies.
- Some of these genes could elucidate the biological mechanisms underlying immune system interaction with specific pathogens.
- Future work could explore the genetic basis of pathogen-induced cancers & immune response, the biological function of immune-response-associated genes, and personalized prevention (vaccines) & intervention (drug targets) strategies.