



# Genetics and the Glycomatrix in C3G Glomerulopathy

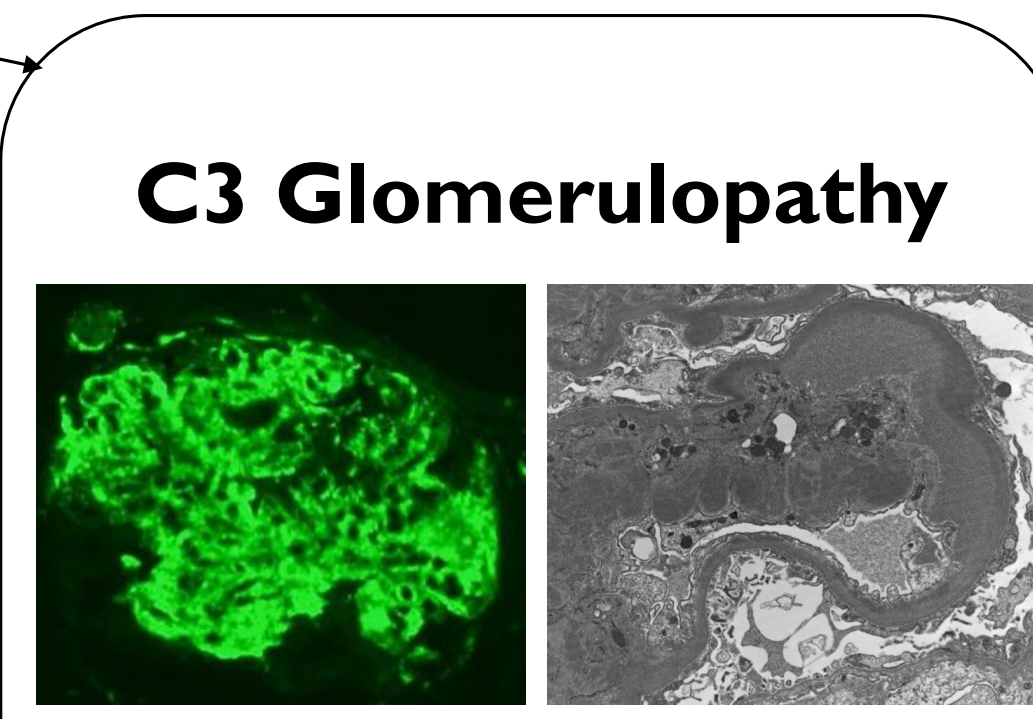
Jill J. Hauer, Fengxiao Bu, Xue Xiao, Kathy L. Frees, Nicolo Ghiringhelli Borsa, Amanda O. Taylor, Carla M. Nester, Richard J. Smith  
Molecular Otolaryngology and Renal Research Laboratories, University of Iowa



## C3G is a complex disease that develops in the renal glomerulus.

### Disease Drivers

- Autoantibodies to Complement Proteins
- Genetic Variation in Complement Proteins
- Environmental Triggers of Complement Activity
- Unknown Driver(s) of Disease and/or Complement Activity



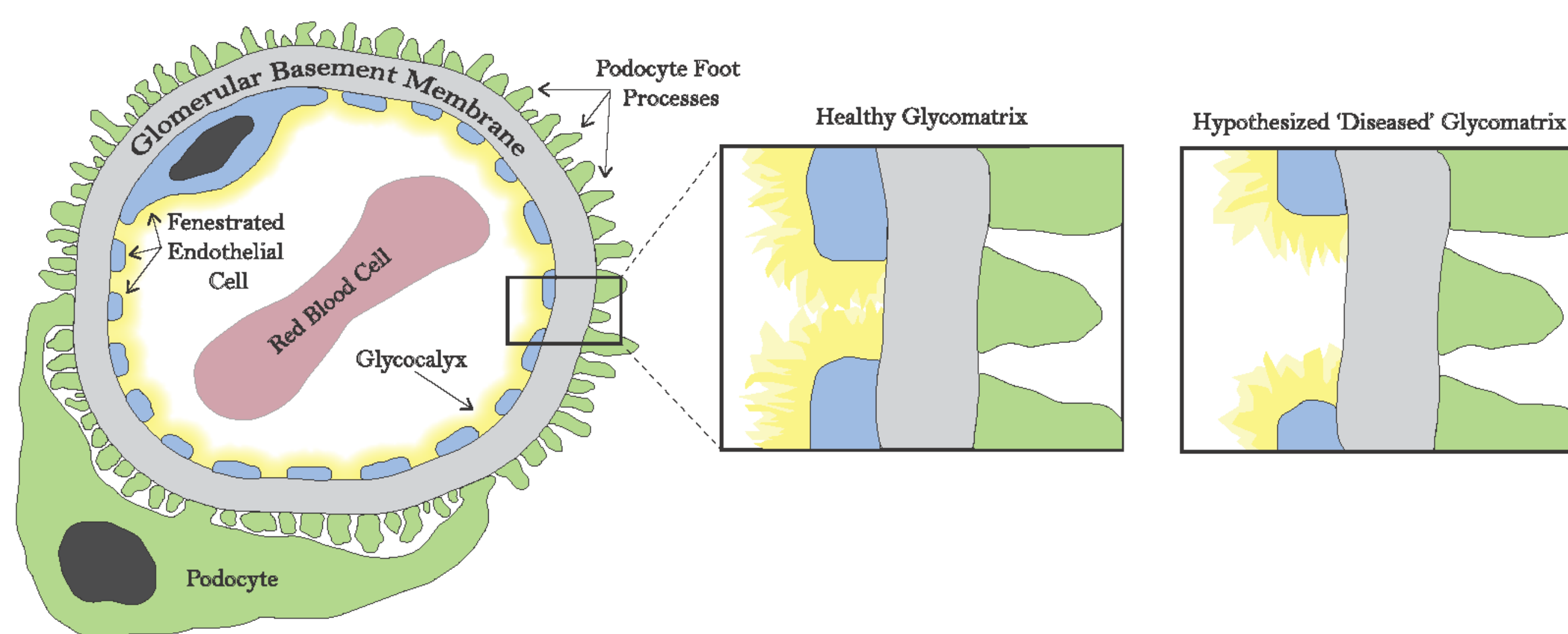
### Disease Outcomes

- Stable Disease Retains Native Kidney ~50%
- Progressive Disease Loss of Native Kidney ~50%

Every person with C3G has a different combination of antibodies, genetic variants, and course of disease. Our goal, is to use this information to understand C3G and develop effective treatment strategies. Some important questions we are currently asking in our research include:

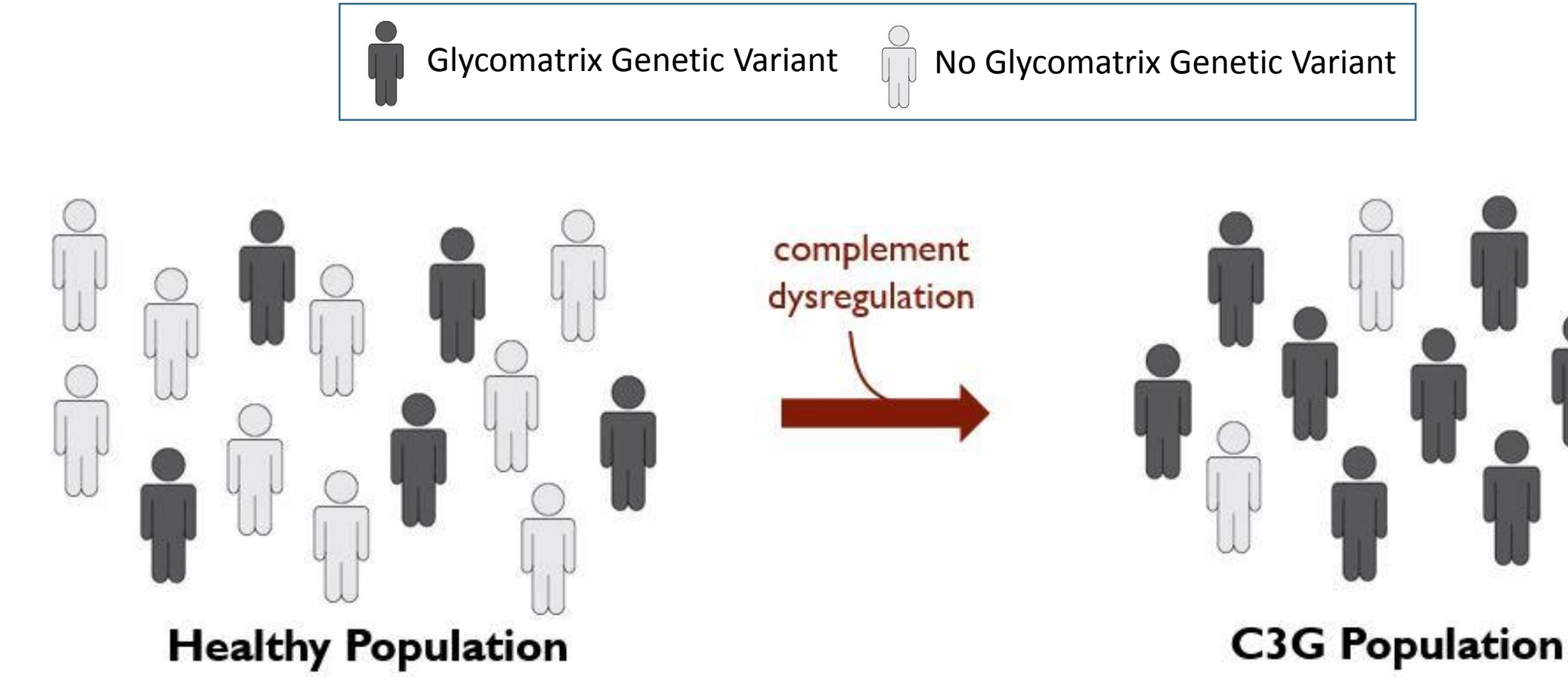
- Are there other disease drivers that we have not yet identified?
- Because C3G is a disease that affects the kidney, are there genetic variants in the genes associated with the glomerulus that affect disease development and/or progression?
- If many disease drivers exist, is it possible that some drivers are more common than others?

## The glomerular microenvironment is very complex and highly specialized.



The glomerular microenvironment is responsible for the selective filtration of our blood. This image represents the cross-section of a glomerular capillary. In the lumen of the capillary where blood flows, you can see the capillary walls coated with fenestrated endothelial cells. On top of the cells is blanket of glycoproteins and other components, which we call the glycocalyx. Together, we call the glycocalyx and the glomerular basement membrane the "glycomatrix". In C3G, the glycomatrix is the location where complement proteins are damaging the kidney.

## Does the glycomatrix play a role in C3G?



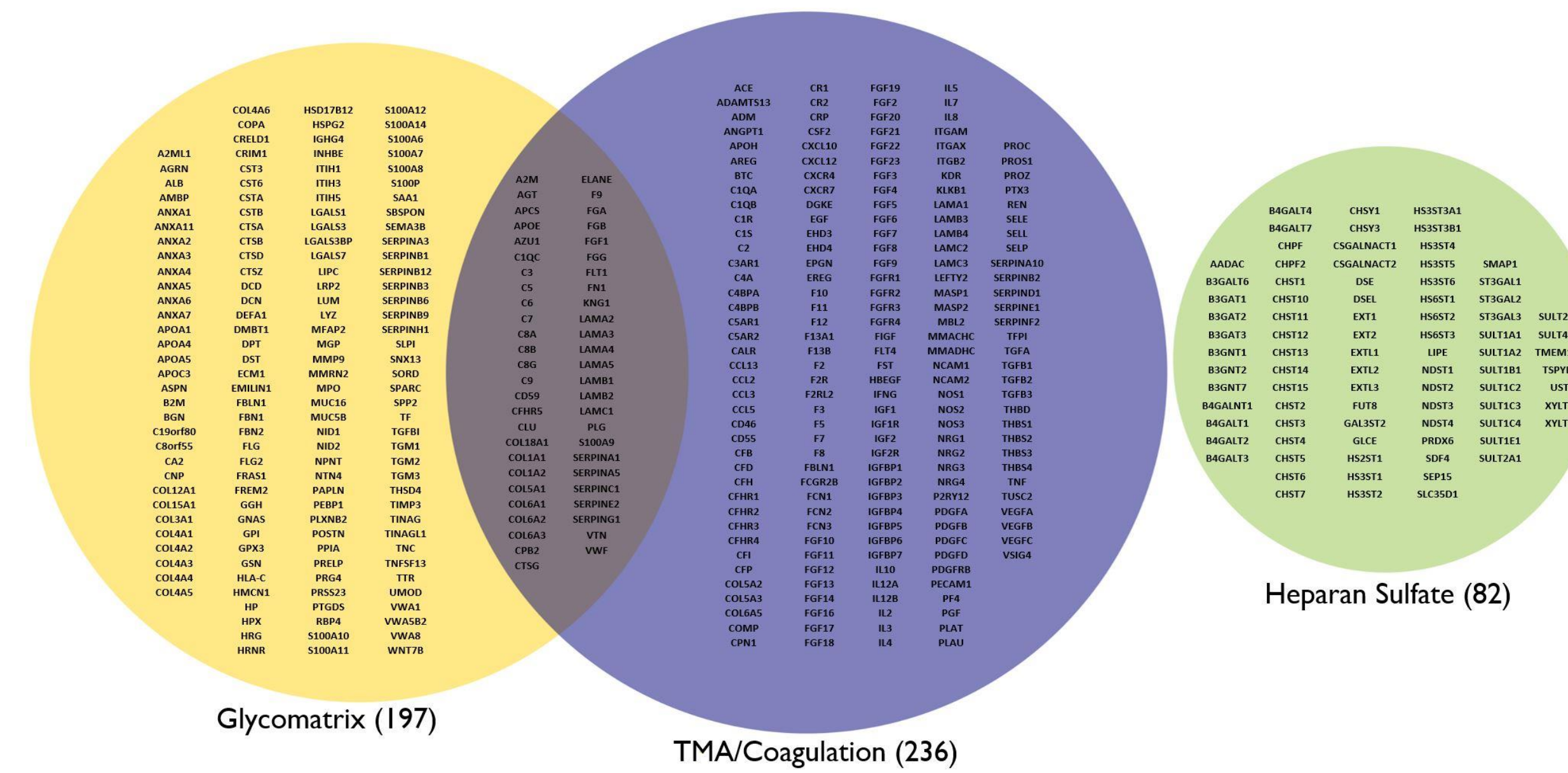
### Hypothesis

We hypothesized that genetic variations (either rare or common) in the glycomatrix may impact outcome in C3G by leaving the glomerulus more or less vulnerable to complement-mediated damage when complement dysregulation occurs.

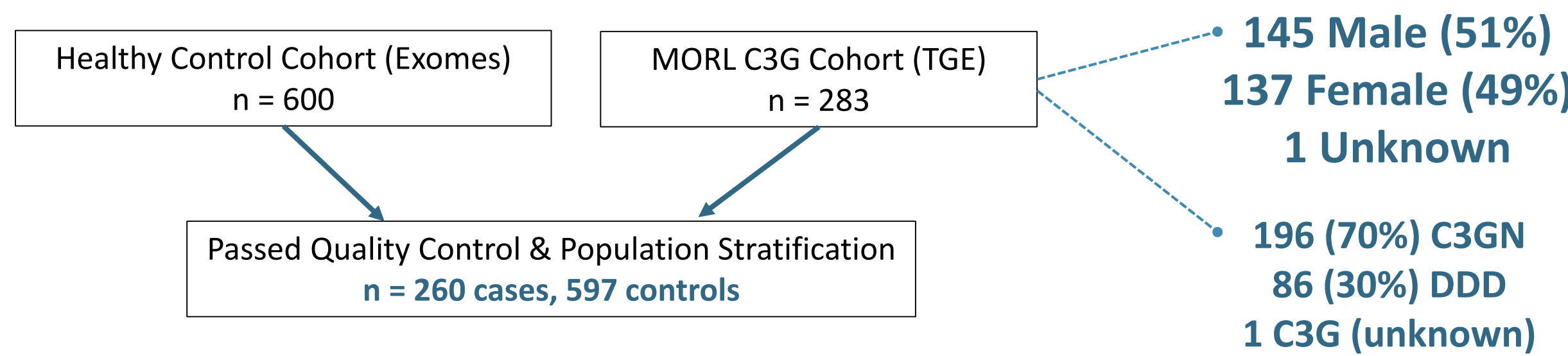
### Study Design

- Develop a panel to screen all glycomatrix (and other) genes
- Select a C3G patient cohort and a control cohort
- Complete quality control tests on these two cohorts
- Complete the sequencing
- Analyze and compare the datasets

## Our sequencing panel is composed of 3 main 'families' of genes.



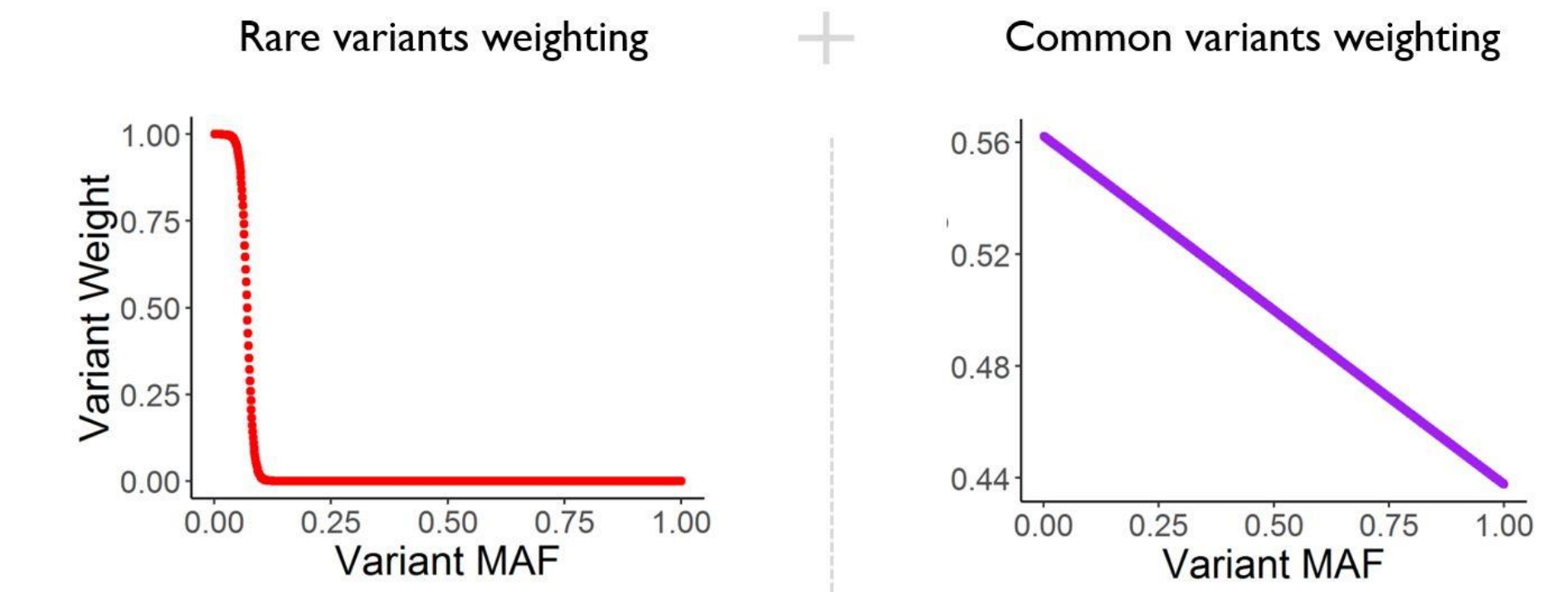
## We analyzed both C3G and unaffected cohorts.



## Rare & common variants were assessed using a combined SKAT test.

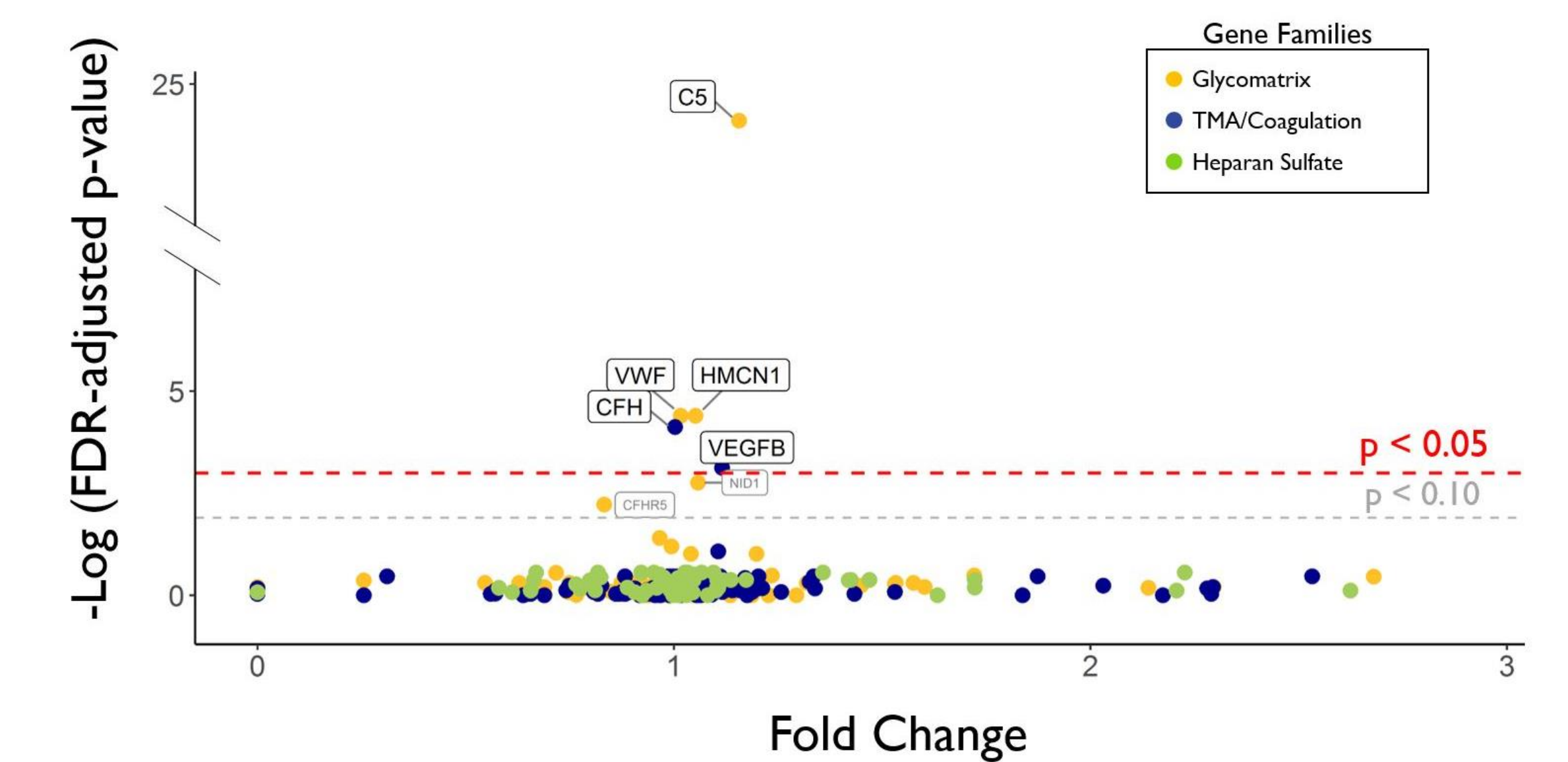
$$Q_s = \tilde{y}^T G G^T \tilde{y}$$

G = weighted genotypes  
ỹ = phenotypes adjusted by covariates of population

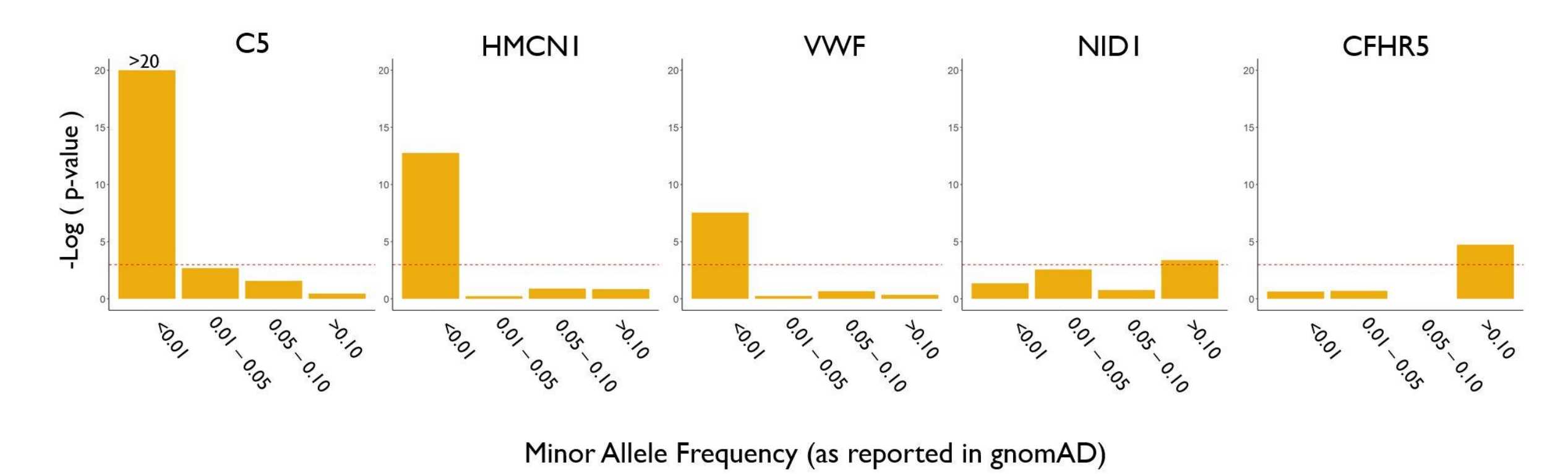


(Ionita-Laza et al., 2013)

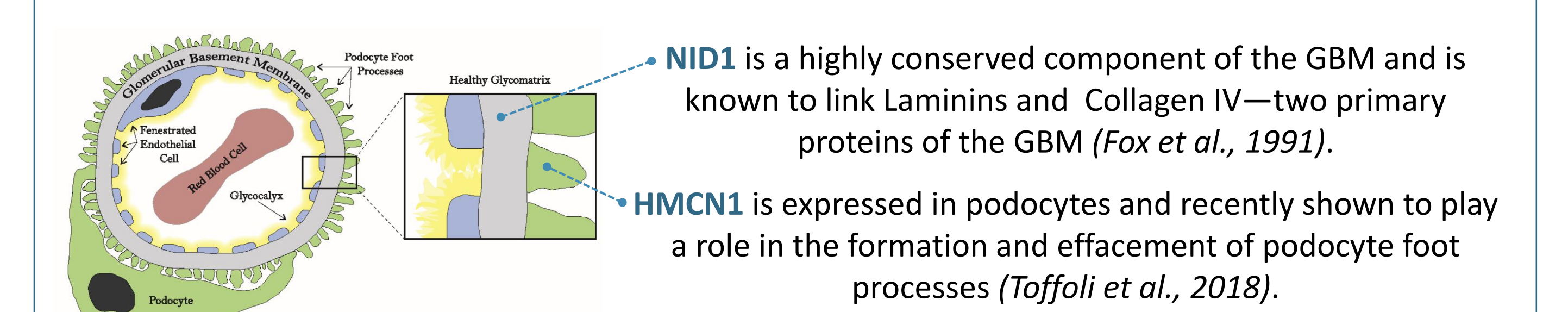
## Glycomatrix genes were enriched for genetic variation in C3G.



Genetic variant enrichment in the glycomatrix in C3G patients is seen with both rare and common genetic variants and occurs in the gene-specific manner (below).



## The genes found in this study play important roles in the glycomatrix.



## What have we learned about the glycomatrix in C3G?

- The C3G patient cohort is enriched for genetic variation in several genes that are associated with the glycomatrix structure and function.
- The enrichment we see comes from both rare and common genetic variants and is gene-dependent.
- The genes we have identified play important roles in the glycomatrix structure and function and support our hypothesis that the glycomatrix may be vulnerable to complement damage in C3G.

## What are the next steps in this research study?

- Develop experiments which will test the function of the genes with significant enrichment in C3G. This will help us understand if the genetic variants we found are disrupting the gene's normal function.
- Work with our collaborators to test other C3G cohorts to determine if we can replicate our findings in a separate population. If we can, these data will provide more evidence to support our hypothesis.
- Understand how we can use this information to better inform clinical decisions and patient care for C3G.