

# Genetic reduction of muscle glycogen is well tolerated in UK Biobank participants

Julian R Homburger, Beryl B Cummings, Julie C Ullman, Vyas Ramanan, Eric M Green, Robert R Graham  
Maze Therapeutics, South San Francisco, CA

## Introduction

Pompe disease is a glycogen storage disease caused by mutations in the enzyme acid alpha-glucosidase resulting in pathological accumulation of glycogen. Glycogen can accumulate in virtually all tissues, but the primary pathology affects skeletal and cardiac muscle. Inhibiting the synthesis of muscle glycogen could reduce the pathologic build-up of glycogen by acting as a substrate reduction therapy. Here, we aim to better understand the consequences of reduced muscle glycogen in a human population. Previous work (Savage, 2008) identified a predicted protein truncating variant (PTV) in the *PPP1R3A* gene (a regulator of glycogen metabolism) in ~1.1% of Europeans, which results in ~65% reduction in muscle glycogen. *PPP1R3A* functions as a key activator of muscle glycogen synthase 1 (GYS1) by dephosphorylating the enzyme and increasing activity. Figure 1 below demonstrates the pathway in which *PPP1R3A* LoF leads to reduction in muscle glycogen.

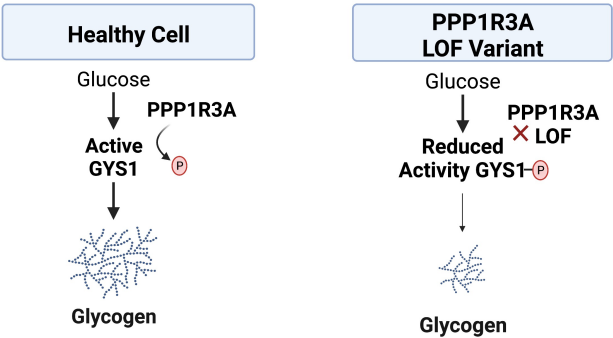


Figure 1: Loss of *PPP1R3A* results in a reduction in muscle glycogen

## Methods and approach

Large biobanks enable investigation of the consequences of genetic variation on many health-related phenotypes. The UK Biobank is a large study with longitudinal health data connected to genetic data on over 500,000 individuals. To assess the consequences of a predicted 65% loss of muscle glycogen, we performed an association study in the UK Biobank comparing phenotypes between *PPP1R3A* PTV carriers and non-carriers. Genetic association studies were performed using REGENIE (Mbatchou et. al. 2021), adjusted for age, sex, and the first 10 principal components of ancestry. Quantitative traits were normalized using an inverse rank normal transformation.

## No association between *PPP1R3A* PTV and quantitative phenotypes in UK Biobank

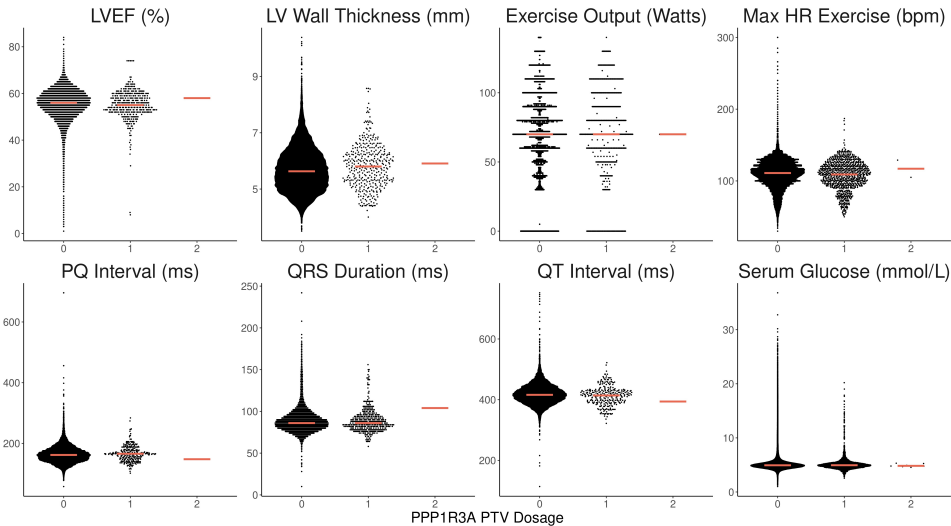


Figure 2: Phenotype values plotted by *PPP1R3A* dosage for UK Biobank participants. LVEF = Left Ventricular Ejection Fraction, LV – Left ventricle.

Table 1: No phenotype changes were associated with *PPP1R3A* dosage.

| Phenotype         | P-value | N       |
|-------------------|---------|---------|
| LVEF              | 0.871   | 27,716  |
| LV Wall Thickness | 0.168   | 27,579  |
| Exercise Output   | 0.100   | 49,616  |
| Max HR Exercise   | 0.444   | 49,603  |
| QRS Duration      | 0.527   | 29,507  |
| PQ Interval       | 0.366   | 16,694  |
| QT Interval       | 0.222   | 17,574  |
| Serum Glucose     | 0.477   | 294,042 |

## Results

We identified no associations between *PPP1R3A* PTV and cardiac parameters, including left ventricular ejection fraction (p=0.871) and wall thickness (p=0.168). There was no evidence of changes in EKG cardiac conduction intervals nor in any exercise performance measurements (n=49,616), including maximum heart rate (p=0.444) and maximum workload during an exercise test (p=0.100). We also observed no changes in serum glucose (p=0.71) or any other members of a panel of ~170 serum metabolites.

## No association between *PPP1R3A* PTV and key health outcomes

| Disease         | Effect (SE)    | P-value | N Cases |
|-----------------|----------------|---------|---------|
| Type 2 Diabetes | -0.094 (0.073) | 0.200   | 18,868  |
| Liver Cirrhosis | -0.041 (0.273) | 0.880   | 1,325   |
| Heart Failure   | -0.061 (0.127) | 0.630   | 6,117   |

In addition to the phenotypes above, we observed no phenome-wide significant associations between *PPP1R3A* PTV and rates of any ICD10 code with over 100 occurrences in UK Biobank.

## Conclusions

After performing an extensive phenome-wide association study in the UK Biobank, we find no significant associations between any key outcomes or phenotypes and loss of function of *PPP1R3A*. Our results demonstrate that loss of function variants in the *PPP1R3A* gene are not associated with adverse health outcomes in a large biobank population. This suggests that partial reduction in muscle glycogen (~65%) from birth is well tolerated and supports the potential safety of pharmacologic reduction of muscle glycogen. This study illustrates the power of large biobanks to provide insight into the consequences of perturbing protein function.

## References

Savage et. al., 2008. A Prevalent Variant in *PPP1R3A* Impairs Glycogen Synthesis and Reduces Muscle Glycogen Content in Humans and Mice. *PLoS Medicine*. 10.1371/journal.pmed.0050027  
Mbatchou, J., Barnard, L., Backman, J. et al., 2021. Computationally efficient whole-genome regression for quantitative and binary traits. *Nat Genet* 53, 1097–1103. <https://doi.org/10.1038/s41588-021-00870-7>  
UK Biobank - This research has been conducted using data from UK Biobank, a major biomedical database.