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Genetic regulation of immunoglobulin G *N*-glycosylation

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Motivation and Aim: Glycans are complex carbohydrates attached to the surface of the protein. With glycosylation being amongst the most abundant post-translational modification, glycans are expected to have an important role in many physiological processes and most diseases. Although the main enzymes of the glycosylation pathway are known, little is understood about how this template-independent process is regulated to result in a faithful synthesis of a specific glycoform or how it is related with genetic regulation of complex traits and disease. To address these questions, we performed genome-wide association analyses (GWAS) of IgG *N*-glycosylation, followed by extensive *in-silico* functional follow-up.

Methods and Algorithms: We performed GWAS of 77 IgG *N*-glycosylation traits in eight European populations (discovery $N = 8090$, replication $N = 2368$) using HapMap2 imputed genotypes. We prioritised candidate genes according to pleiotropy with gene expression, coding region variants and enrichment in relevant gene-sets. We assessed pleiotropy with complex traits and diseases by comparing regional associations using Mendelian Randomisation based analysis.

Results: We found 27 loci significantly associated ($p \leq 2.4 \times 10^{-9}$) with IgG N-glycosylation. Twelve of these loci replicate findings from Lauc et al. [1] and Shen et al. [2], while 15 are novel. For 9 genes we found evidence of a non-synonymous amino acid change, 4 were pleiotropic with expression in B-cells and 11 with expression in peripheral blood. The remaining genes were prioritised based on the enrichment in antibody synthesis related pathways and cells. Based on the similarity of glycome-wide association estimates we proposed how these genes are connected in the functional network regulating main glycosylation enzymes. In six IgG N-glycosylation loci we found evidence of pleiotropy with autoimmune and inflammatory diseases. In one locus we also showed that IgG N-glycosylation is pleiotropic with both expression of ORMDL3, GSDMB and IKZF3 genes in B-cells and peripheral blood and risk for inflammatory bowel disease, rheumatoid arthritis, cirrhosis, asthma and allergy.

Conclusions: With this study we expanded the network of genes involved in glycosylation of immunoglobulin G providing us with further insights how these molecules could be involved in complex human diseases.

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References

1. Lauc G., Huffman J.E., Pučić M., Zgaga L., Adamczyk B., Mužinić A., … Rudan I. (2013) PLoS Genetics. 9(1). DOI 10.1371/journal.pgen.1003225.
2. Shen X., Klarić L., Sharapov S.Z., Mangino M., Ning Z., Wu D., … Aulchenko Y.S. (2017) Nat. Commun. 1-10.