

# Novel loci associated with plasma immunoglobulin G N-glycosylation identified by a multivariate analysis

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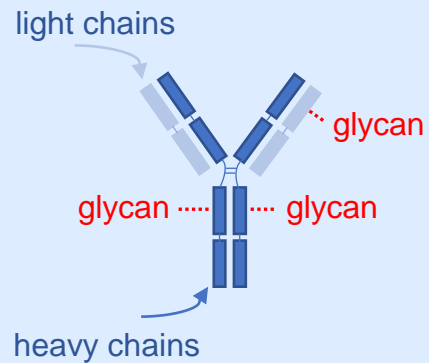
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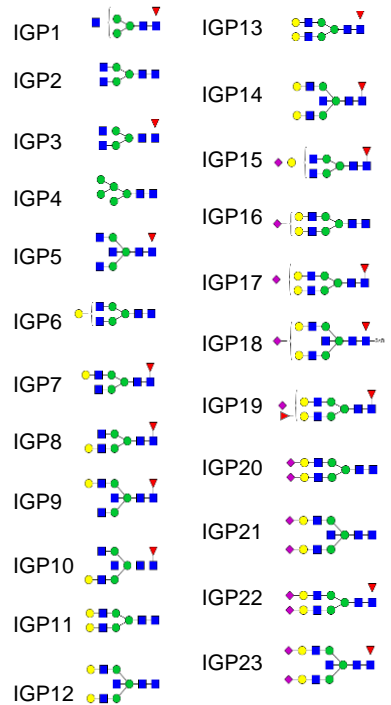
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# Introduction

## IgG structure

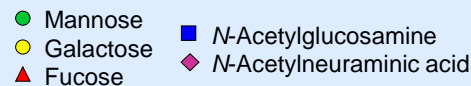
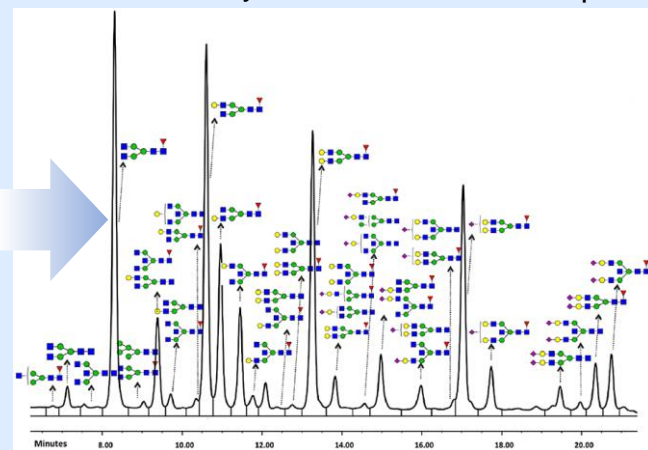


## Glycans attached to IgG



- All IgG molecules are **N-glycosylated**
- N-glycosylation of IgG influences its effector functions and plays a regulatory role in the immune system
- Changes in IgG N-glycosylation pattern are associated with different diseases
- Studying the genetic control of IgG glycosylation helps to uncover molecules and pathways regulating IgG N-glycome composition
- Previous genome-wide association studies (GWAS) identified and replicated **22** genetic loci associated with plasma IgG N-glycosylation

Glycans attached to IgG can be released and measured by UPLC. **IGP1-23** correspond to peaks



## Study aim

The aim of our study was to identify novel loci associated with plasma IgG N-glycosylation traits.

Our aim was achieved by applying a multivariate approach to the largest currently available dataset linking genotypes with IgG glycan measurements.

## Methods

- We used GWAS summary statistics for plasma IgG N-glycosylation traits obtained in the study by Klarić et al., 2020 (*Science Advances*, PMID:32128391) for European-ancestry cohorts with a total sample size of 8,090 individuals
- We grouped 23 glycan traits into **9** groups based on their general structural and chemical properties and performed a multivariate analysis

## Groups of N-glycosylation traits

- 1) **N-glycosylation:** IGP1, IGP2, IGP3, IGP4, IGP5, IGP6, IGP7, IGP8, IGP9, IGP10, IGP11, IGP12, IGP13, IGP14, IGP15, IGP16, IGP17, IGP18, IGP19, IGP20, IGP21, IGP22, IGP23
- 2) **Monogalactosylation:** IGP6, IGP7, IGP8, IGP9, IGP10, IGP15
- 3) **Digalactosylation:** IGP11, IGP12, IGP13, IGP14, IGP16, IGP17, IGP18, IGP20, IGP21, IGP22, IGP23
- 4) **Galactosylation:** IGP6, IGP7, IGP8, IGP9, IGP10, IGP11, IGP12, IGP13, IGP14, IGP15, IGP16, IGP17, IGP18, IGP20, IGP21, IGP22, IGP23
- 5) **Monosialylation:** IGP15, IGP16, IGP17, IGP18
- 6) **Disialylation:** IGP20, IGP21, IGP22, IGP23
- 7) **Sialylation:** IGP15, IGP16, IGP17, IGP18, IGP20, IGP21, IGP22, IGP23
- 8) **Fucosylation:** IGP1, IGP3, IGP5, IGP7, IGP8, IGP9, IGP10, IGP13, IGP14, IGP15, IGP17, IGP18, IGP22, IGP23
- 9) **BisectingGlcNAc:** IGP5, IGP9, IGP10, IGP12, IGP14, IGP18, IGP23

# Results

- We identified a total of 32 loci associated with at least one group of IgG *N*-glycosylation traits with *P*-value < 5.6e-09 (5e-08/9)
- Median number of trait groups associated with the identified loci was 6 (range 1-9)
- **6 loci have not been reported in previous IgG *N*-glycome genetic studies**



Six novel loci associated with IgG *N*-glycosylation trait groups identified by the multivariate analysis

Lead SNP	Chr: position (GRCh37.p13)	Effective/ reference allele	EAF*	Top trait group**	<i>P</i> -value	N#	Number of traits groups§	Nearest gene(s)
rs12049042	1:246288812	C/T	1.3%	Galactosylation	1.20e-09	4,417	1	<i>SMYD3</i>
rs11895615	2:26113120	C/T	70.3%	BisectingGlcNAc	5.69e-10	8,024	1	<i>ASXL2</i>
rs1372288	3:142901537	C/T	23.3%	<i>N</i> -glycosylation	8.73e-11	8,090	2	<i>CHST2, SLC9A9</i>
rs12635457	3:196203979	A/G	63.6%	<i>N</i> -glycosylation	1.61e-13	8,016	1	<i>RNF168</i>
rs479844	11:65551957	A/G	42.0%	<i>N</i> -glycosylation	1.97e-13	8,089	3	<i>OVOL1</i>
rs4561508	17:16848750	C/T	89.5%	<i>N</i> -glycosylation	1.38e-10	8,002	2	<i>TNFRSF13B</i>

\* Effective allele frequency

\*\* Trait group most significantly associated with the locus

# Number of subjects in a multivariate analysis

§ Total number of trait groups associated with the locus

## Conclusion

Our results significantly expand the number of identified IgG *N*-glycome-associated loci and demonstrate the efficacy of the multivariate analysis methods in investigating the genetic architecture of complex traits

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