

# Elevated N-glycosylation of immunoglobulin G variable regions in myasthenia gravis highlights a commonality across autoantibody-associated diseases

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[illegible]

Title

# Elevated N-glycosylation of immunoglobulin G variable regions in myasthenia gravis highlights a commonality across autoantibody-associated diseases

S1 [001]

## Abstract

S1 [002]

Elevated N-linked glycosylation of immunoglobulin G variable regions (IgG-VN-Glyc) is an emerging molecular phenotype associated with autoimmune disorders.

Elevated N-linked glycosylation ...  
... of immunoglobulin G variable regions ...  
... (IgG-VN-Glyc) ...  
... is an emerging molecular phenotype associated ...  
... with autoimmune disorders.

S1 [003]

To test the broader specificity of elevated IgG-VN-Glyc, we studied patients with distinct subtypes of myasthenia gravis (MG), a B cell-mediated autoimmune disease.

To test the broader specificity ...  
... of elevated IgG-VN-Glyc, ...  
... we studied patients ...  
... with distinct subtypes ...  
... of myasthenia gravis ...  
... (MG), ...  
... a B cell-mediated autoimmune disease.

S1 [004]

Our experimental design included adaptive immune receptor repertoire sequencing to quantify and characterize N-glycosylation sites in the global B cell receptor repertoire, proteomics to examine glycosylation patterns of the circulating IgG, and production of human-derived recombinant autoantibodies, which were studied with mass spectrometry and antigen binding assays to confirm occupation of glycosylation sites and determine whether they alter binding.

Our experimental design included adaptive immune receptor repertoire sequencing ...  
... to quantify ...  
... and characterize N-glycosylation sites ...  
... in the global B cell receptor repertoire, ...  
... proteomics ...  
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... of the circulating IgG, ...  
... and production ...  
... of human-derived recombinant autoantibodies, ...  
... which were studied ...  
... with mass spectrometry ...  
... and antigen binding assays ...  
... to confirm occupation ...  
... of glycosylation sites ...  
... and determine ...  
... whether they alter binding.

**S1 [005]** We found that the frequency of IgG-VN-Glyc motifs was increased in the B cell repertoire of MG patients when compared to healthy donors.

We found ...  
... that the frequency ...  
... of IgG-VN-Glyc motifs was increased ...  
... in the B cell repertoire ...  
... of MG patients ...  
... when compared ...  
... to healthy donors.

**S1 [006]** Motifs were introduced by both biased V gene segment usage and somatic hypermutation.

Motifs were introduced ...  
... by both biased V gene segment usage ...  
... and somatic hypermutation.

**S1 [007]** IgG-VN-Glyc could be observed in the circulating IgG in a subset of MG patients.

IgG-VN-Glyc could be observed ...  
... in the circulating IgG ...  
... in a subset ...  
... of MG patients.

**S1 [008]** Autoantigen binding, by patient-derived MG autoantigen-specific monoclonal antibodies with experimentally confirmed presence of IgG-VN-Glyc, was not altered by the glycosylation.

Autoantigen binding, ...  
... by patient-derived MG autoantigen-specific monoclonal antibodies ...  
... with experimentally confirmed presence ...  
... of IgG-VN-Glyc, ...  
... was not altered ...  
... by the glycosylation.

**S1 [009]** Our findings extend prior work on patterns of variable region N-linked glycosylation in autoimmunity to MG subtypes.

Our findings extend ...  
... prior work ...  
... on patterns ...  
... of variable region N-linked glycosylation ...  
... in autoimmunity ...  
... to MG subtypes.

**S1 [010]** Although occupied IgG-VN-Glyc motifs are found on MG autoantigen-specific monoclonal antibodies, they are not required for binding to the autoantigen in this disease.

Although occupied IgG-VN-Glyc motifs are found ...  
... on MG autoantigen-specific monoclonal antibodies, ...  
... they are not required ...  
... for binding ...  
... to the autoantigen ...

... in this disease.

## **S2 [011] Introduction**

**S2 [012]** The vast diversity of immunoglobulin G variable regions (IgG-V) is critical for host immunity.

The vast diversity ...  
... of immunoglobulin G variable regions ...  
... (IgG-V) ...  
... is critical ...  
... for host immunity.

**S2 [013]** This diversity arises through VDJ recombination and somatic hypermutation (SHM).

This diversity arises ...  
... through VDJ recombination ...  
... and somatic hypermutation ...  
... (SHM).

**S2 [014]** Historically, IgG-V diversity has been represented by amino acid sequence alone with little focus on post-translational modifications.

Historically, ...  
... IgG-V diversity has been represented ...  
... by amino acid sequence alone ...  
... with little focus ...  
... on post-translational modifications.

**S2 [015]** Recently, the presence of N-linked glycosylation in IgG-V (IgG-VN-Glyc) has been shown to contribute to diversity (1, 2).

Recently, ...  
... the presence ...  
... of N-linked glycosylation ...  
... in IgG-V ...  
... (IgG-VN-Glyc) ...  
... has been shown ...  
... to contribute ...  
... to diversity ...  
... (1, 2)...

**S2 [016]** IgG-VN-Glyc is contingent upon the presence of the predictive N-Glyc amino acid motif N-X-S/T, where X can be any amino acid except for proline.

IgG-VN-Glyc is contingent ...  
... upon the presence ...  
... of the predictive N-Glyc amino acid motif N-X-S/T, ...  
... where X can be any amino acid except ...  
... for proline.

**S2 [017]** This motif is most often introduced as a consequence of SHM (3).

This motif is most often introduced ...  
... as a consequence ...  
... of SHM ...  
... (3).

**S2 [018]** Less often it can be provided by the few germline gene segments (IGHV1-8, IGHV4-34, IGHV5-10-1, IGLV3-12, and IGLV5-37) in which it is encoded (4).

Less often it can be provided ...  
... by the few germline gene segments ...  
... (IGHV1-8, ...  
... IGHV4-34, ...  
... IGHV5-10-1, ...  
... IGLV3-12, ...  
... and IGLV5-37) ...  
... in which it is encoded ...  
... (4).

**S2 [019]** The percentage of IgG in healthy individuals that includes V-region glycosylation is approximately 15-25%; the range reflects different approaches of measurement (1).

The percentage ...  
... of IgG ...  
... in healthy individuals ...  
... that includes V-region glycosylation is approximately 15-25%; ...  
... the range reflects different approaches ...  
... of measurement ...  
... (1).

**S2 [020]** The occurrence of IgG-VN-Glyc also varies among the IgG subclasses, with skewing toward higher frequencies in antibodies of the IgG4 subclass (5).

The occurrence ...  
... of IgG-VN-Glyc also varies ...  
... among the IgG subclasses, ...  
... with skewing toward higher frequencies ...  
... in antibodies ...  
... of the IgG4 subclass ...  
... (5).

**S2 [021]** Higher frequencies of IgG-VN-Glyc than that which is found in healthy individuals have been observed in B cell malignancies (6–10) and in autoimmune diseases (11).

Higher frequencies ...  
... of IgG-VN-Glyc ...  
... than that ...  
... which is found ...  
... in healthy individuals have been observed ...  
... in B cell malignancies ...  
... (6–10) ...  
... and in autoimmune diseases ...

## **End of Sample Audit**

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