Systematic Review: Immunoglobulin G *N*-Glycans as Next-Generation Diagnostic Biomarkers for Common Chronic Diseases

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Abstract

Glycomics is a new subspecialty in omics systems sciences that offers significant promise for next-generation biomarkers on disease susceptibility, drug target discovery, and precision medicine. In this context, alternative immunoglobulin G (IgG) *N*-glycosylation has been reportedly implicated in several common chronic diseases, although systematic assessment is currently lacking in the literature. We conducted a systematic review of observational studies on IgG *N*-glycan variability and susceptibility to common chronic diseases. Observational studies reporting an association between diseases (such as colorectal cancer, dyslipidemia, ischemic stroke, rheumatoid arthritis, and systemic lupus erythematosus) and IgG *N*-glycans quantified by ultraperformance liquid chromatography were included. The glycans were categorized into 24 initial IgG glycan peaks (GPs). Notably, aging positively correlated with GP1, GP2, GP4–7, GP10, GP11, GP19, and GP24, while negatively correlated with GP8, GP12–15, GP17, GP18, GP20, GP21, and GP23 ($p < 0.05$). The absolute value of significant correlation coefficients of age and IgG glycans ranged from 0.043 to 0.645. We found that the high levels of GP1–4, GP6, GP7, and GP24 and low levels of GP9, GP13–15, GP18, and GP23 could potentially increase the risk of disease. In conclusion, the present systematic review suggests that the field of glycomics, and GP1–4, GP6, GP7, GP9, GP13–15, GP18, GP23, and GP24 in particular, holds promise for further candidate biomarker research on susceptibility to common chronic diseases.

Keywords: glycomics, next-generation biomarkers, immunoglobulin G *N*-glycans, diagnostic innovation, systematic review, chronic disease biomarkers

Introduction

MANY BIOLOGIC PROCESSES REQUIRE GLYCOSYLATION, a posttranscriptional modification that occurs in abundant, diverse, and complex forms. Glycosylation impacts cell biology structurally and functionally (Helenius, 2001; Ohtsubo and Marth, 2006). The addition of glycans modifies a great many extracellular and secreted proteins. In addition, glycan structures are determined by complex dynamic interactions among genetic and environmental factors as glycosylation does not have a direct genetic template (Benedetti et al., 2017; Kolarich et al., 2012). Therefore, the changes in glycans and glycosylation reflect the combined effects of genetics and environment. Glycosylation, which is closer to biological function, may offer significant promise for next-

generation biomarkers to diagnose and predict diseases more accurately (An et al., 2009; Kolarich et al., 2012).

Protein glycans can be *O*-linked and *N*-linked glycans, the latter being well understood and the most studied (An et al., 2009). It is known that proteins possess well-defined *N*-glycosylation sites, and *N*-glycans are stable within the individual but extremely sensitive to pathophysiological processes (Gornik et al., 2009). The improvement of *N*-glycosylation detection technology has gradually overcome the shortcomings of low flux, unstable results, and poor sensitivity and specificity. The methods for high-throughput *N*-glycan analysis are gradually being applied (Everest-Dass et al., 2018; Huffman et al., 2014).

Immunoglobulin G (IgG) is an excellent *N*-glycoprotein model as its glycosylation is well defined. IgG is the main

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component of antibody in serum and plays an important role in antibody-based immunity in humans. The structure of IgG is simple and has two functional domains, an antigen-binding fragment (Fab) and a crystallizable fragment (Fc). The Fc domain contains a highly conserved glycosylation site at asparagine 297, to which a variety of glycan structures can be attached (Shade and Anthony, 2013). Alternative Fc *N*-glycosylation markedly affects IgG structure and function and by extension, immune responses, thus acting as a switch between pro- and anti-inflammatory IgG functionality by regulating antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (Biermann et al., 2016; Dube and Bertozzi, 2005; Shade and Anthony, 2013).

The body of evidence shows that the decrease in galactosylation is generally associated with reducing anti-inflammatory function of circulating IgG (Gudelj et al., 2018a; Liu et al., 2018b; Nikolac et al., 2014; Ren et al., 2016). In parallel, the reduction of sialic acid to the terminus of the Fc glycan can be inducing IgG antibody-driven inflammation (Anthony and Ravetch, 2010; Shade and Anthony, 2013). IgG, deficient in the single fucose residue from the Fc glycan, can gain a 50-fold potency in terms of initiating ADCC (Shade and Anthony, 2013; Shigeru et al., 2009). The studies show that the change of fucose and bisecting GlcNAc in diseases is opposite (Gudelj et al., 2018a; Pucic et al., 2011).

Differential IgG *N*-glycosylation modulates the IgG effector functions, which makes IgG *N*-glycan analysis improve existing disease biomarkers (Gudelj et al., 2018a; Russell et al., 2018). However, translating biomarkers to clinical applications is a multistep process requiring analytical and clinical validity and clinical utility, among other considerations (Adua et al., 2017; Ge et al., 2018; Ioannidis and Bossuyt, 2017; Turnbull and Sasisekharan, 2010). The changes of IgG *N*-glycans in several chronic diseases are not uniformly consistent, and hence, the overall assessment of IgG *N*-glycans for the risk of diseases remains unclear.

We report a systematic review of observational studies to evaluate the changes in IgG *N*-glycans in common chronic diseases and with aging. In addition, this systematic review summarizes the lessons learned in the field of glycomics and discusses the various ways in which IgG *N*-glycans offer promise for future diagnostic and clinical applications.

Literature Search and Selection of Reports

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Knobloch et al., 2011; Shamseer et al., 2015).

We searched the PubMed and Cochrane Library Databases from January 2011 to November 2018, as well as the references of the identified articles. The beginning date was selected as 2011 because of the IgG glycome detection and analysis method of hydrophilic interaction chromatography (HILIC)-ultraperformance liquid chromatography (UPLC), first reported in 2011.

A literature search was performed using the following search strategy: (Immunoglobulin G OR IgG) AND (*N*-glycosylation OR *N*-glycan OR glycosylation OR glycan OR glycosylated). The literature search was limited to human studies. In addition, the reference lists of all identified studies were manually searched to identify any additional studies.

The articles not excluded based on title/abstract screening were retrieved for full-text review. We included all observational studies conducted in patients and where IgG *N*-glycans were characterized using the HILIC-UPLC. For inclusion, studies had to report the assessment of association between diseases and IgG *N*-glycans. We did not include studies published in languages other than English.

Comparative performance with other methods for high-throughput IgG *N*-glycans analysis, UPLC performs the following advantages (Huffman et al., 2014). First, UPLC provides a good reproducibility and relative quantitative analysis method. Second, the costs of equipment and required expertise are relatively low. IgG *N*-glycans were analyzed into 24 initial IgG glycan peaks (GPs), which were previously reported (Pucic et al., 2011). Total area normalization was applied to increase the comparability between samples, where the amount of glycans in each peak was expressed as a percentage of the total integrated area (Pucic et al., 2011). In addition, the structures of initial IgG GPs are clear (Pucic et al., 2011). For inclusion, studies had to report the assessment of association between diseases and IgG *N*-glycans. We did not include studies published in languages other than English.

Studies were excluded from the systematic review for the following reasons: (1) reviews, letters, expert opinions, case reports, or nonclinical studies; (2) studies had overlapping data or incomplete data; and (3) studies based on tissue, blood, or animals rather than whole-organism clinical research.

Data extraction and statistical analysis

Data extraction was conducted in duplicate by three authors based on title, author, year of publication, country of origin, sample size, and correlation coefficient (CC) for continuous variables or odds ratio (OR) with a 95% confidence interval (CI) for categorical variables. Two investigators will be responsible for extracting the data, which will be checked by a third investigator. Any disagreements in data extraction were discussed and resolved by a consensus meeting among the investigators.

For continuous scales of measurement outcomes, such as age and body mass index (BMI), results were to be expressed as CC with 95% CI and were analyzed using the R package “metacor.” Since most of the glycan traits deviated from the normal distribution, CC matrices of IgG *N*-glycan structures, age, and BMI were assessed independently by the Spearman rank correlation method. For dichotomous outcomes to be used to assess the effects of IgG *N*-glycans, the OR with 95% CI was to be used by the R package “meta.” Given that the evaluation indicators are not uniformly reported in many disease outcomes and the initial data are incomplete, in addition to the very large heterogeneity that may be encountered in different disease outcomes, we finally performed a systematic review of observational studies.

Results

Study characteristics

A flowchart for the process of searching and including studies is presented in Figure 1. A total of 1072 independent citations were identified after the duplicate exclusion, of which 17 full publications were retrieved for further reviews (Fig. 1 and Table 1). Of note, we divided the results into two parts depending on the data type.

FIG. 1. Flowchart for the process of searching and including studies.

The continuous variables included age (Kristic et al., 2014; Yu et al., 2016) and BMI (Nikolac et al., 2014; Russell et al., 2019), and the categorical variables included hypertension (HT) (Wang et al., 2016), type 2 diabetes (T2D) (Lemmers et al., 2017), dyslipidemia (DL) (Liu et al., 2018a), cardiovascular disease risk score (CDRS) (Menni et al., 2018), ischemic stroke (IS) (Liu et al., 2018b), Parkinson's disease (PD) (Russell et al., 2017), nonalcoholic fatty liver disease (NAFLD) (Zhao et al., 2018), ulcerative colitis (UC) (Trbojevic et al., 2015), Crohn's disease (CD) (Trbojevic et al., 2015), systemic lupus erythematosus (SLE) (Vuckovic et al., 2015), rheumatoid arthritis (RA) (Gudelj et al., 2018b; Sebastian et al., 2016), chronic kidney disease (CKD) (Barrios et al., 2016), and colorectal cancer (CRC) (Vuckovic et al., 2016).

A total of 13 full publications reported the association between IgG N-glycans and common chronic diseases, of which the disease outcomes of DL, IS, SLE, RA, and CRC fully satisfied the inclusion and exclusion criteria. HT, T2D, and PD were excluded due to not reporting the related evaluation indicators of OR. CDRS, NAFLD, UC, CD, and CKD were excluded because these studies only provided signifi-

cant evaluation indicators of OR. Finally, a total of nine studies were included in the qualitative synthesis. Based on the limited studies and very large heterogeneity that may be encountered in different disease outcomes, we performed a systematic review of observational studies.

Association of IgG N-glycans with common chronic diseases

For the association of IgG N-glycans with aging, we combined the data of 5 populations including 5818 participants. As shown in Table 2, the absolute value of significant CCs ranged from 0.043 to 0.645. Aging positively correlated with GP1, GP2, GP4–7, GP10, GP11, GP19, and GP24, while it negatively correlated with GP8, GP12–15, GP17, GP18, GP20, GP21, and GP23 ($p < 0.05$). The result of the association between IgG N-glycans and BMI was performed by combining the data of 4 populations including 4152 participants. The absolute value of significant CCs ranged from 0.028 to 0.107. BMI positively correlated with GP6 and GP9, while GP10 and GP16 negatively correlated with GP1, GP7, GP12–15, GP17, GP18, GP20, GP22, and GP24 ($p < 0.05$).

TABLE 1. CHARACTERISTICS OF INCLUDED STUDIES

Author	Year	Populations	Phenotype	Number of all case/control	Complete data	Evaluation indicators
Kristic et al.	2014	European	Age	5117	Yes	CC
Yu et al.	2016	Chinese	Age	701	Yes	CC
Nikolac et al.	2014	European	BMI	3515	Yes	CC
Russell et al.	2018	Australian	BMI	637	Yes	CC
Wang et al.	2016	Chinese and European	HT	4757	No	MD
Lemmer et al.	2017	European	T2D	1977/4007	No	MD, AUC
Liu et al.	2018a	Chinese	DL	150/488	Yes	OR, AUC
Mennie et al.	2018	European	CDRS	3937	No	OR
Liu et al.	2018b	Chinese	IS	230	Yes	OR, AUC
Russell et al.	2017	Australian	PD	94/102	No	MD, SEN, SPE
Zhao et al.	2018	Chinese	NAFLD	143/357	No	OR, AUC
Trbojevic et al.	2015	European	UC	507/320	No	OR, AUC
Trbojevic et al.	2015	European	CD	287/320	No	OR, AUC
Vuckovic et al.	2015	Chinese and European	SLE	261/247	Yes	OR, AUC
Sebastian et al.	2016	Chinese	RA	128/195	Yes	OR, AUC
Gudelj et al.	2018b	European	RA	179/358	Yes	OR, AUC
Barrios	2016	European	CKD	3274	No	OR, AUC
Vuckovic et al.	2016	European	CRC	760/538	Yes	OR, AUC

AUC, area under the curve; BMI, body mass index; CC, correlation coefficient; CD, Crohn's disease; CDRS, cardiovascular disease risk score; CKD, chronic kidney disease; CRC, colorectal cancer; DL, dyslipidemia; GP, glycan peak; HT, hypertension; IS, ischemic stroke; MD, mean difference; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PD, Parkinson's disease; RA, rheumatoid arthritis; SEN, sensitivity; SLE, systemic lupus erythematosus; SPE, specificity; T2D, type 2 diabetes; UC, ulcerative colitis.

TABLE 2. IMMUNOGLOBULIN G N-GLYCANS ASSOCIATED WITH AGE AND BODY MASS INDEX

GP	Age		BMI	
	r (95% CI) ^a	p	r (95% CI) ^b	p
GP1	0.241 (0.217–0.265)	<0.001	–0.036 (–0.007 to –0.065)	0.008
GP2	0.414 (0.393–0.435)	<0.001	–0.017 (–0.046 to 0.012)	0.124
GP3	/	/	/	/
GP4	0.588 (0.571–0.604)	<0.001	0.091 (0.062–0.120)	<0.001
GP5	0.245 (0.221–0.269)	<0.001	–0.002 (–0.032 to 0.023)	0.439
GP6	0.627 (0.611–0.642)	<0.001	0.048 (0.019–0.078)	0.0006
GP7	0.111 (0.085–0.136)	<0.001	–0.056 (–0.026 to –0.085)	0.0001
GP8	–0.121 (–0.095 to –0.147)	<0.001	0.003 (–0.027 to 0.032)	0.430
GP9	0.015 (–0.010 to 0.041)	0.122	0.051 (0.022–0.080)	0.0003
GP10	0.224 (0.199–0.248)	<0.001	0.028 (–0.001 to 0.057)	0.029
GP11	0.356 (0.333–0.378)	<0.001	0.062 (0.032–0.091)	0.0002
GP12	–0.250 (–0.226 to –0.274)	<0.001	–0.080 (–0.051 to –0.109)	<0.001
GP13	–0.262 (–0.238 to –0.286)	<0.001	–0.076 (–0.047 to –0.105)	<0.001
GP14	–0.645 (–0.629 to –0.660)	<0.001	–0.107 (–0.078 to –0.136)	<0.001
GP15	–0.351 (–0.323 to –0.374)	<0.001	–0.086 (–0.057 to –0.115)	<0.001
GP16	–0.007 (–0.033 to 0.018)	0.290	0.030 (–0.0003 to 0.059)	0.024
GP17	–0.043 (–0.017 to –0.068)	0.005	–0.070 (–0.040 to –0.099)	<0.001
GP18	–0.610 (–0.594 to –0.626)	<0.001	–0.083 (–0.054 to –0.112)	<0.001
GP19	0.057 (0.031–0.082)	<0.001	–0.022 (–0.051 to 0.008)	0.073
GP20	–0.121 (–0.094 to –0.149)	<0.001	–0.050 (–0.020 to –0.079)	0.0004
GP21	–0.064 (–0.039 to –0.090)	<0.001	0.010 (–0.019 to 0.039)	0.250
GP22	0.005 (–0.021 to 0.031)	0.353	–0.050 (–0.021 to –0.080)	0.0003
GP23	–0.304 (–0.281 to –0.328)	<0.001	–0.021 (–0.050 to 0.009)	0.084
GP24	0.069 (0.044–0.095)	<0.001	–0.028 (–0.058 to 0.0009)	0.029

^aThe results were performed by combining the data of 5 populations including 5818 individuals.

^bThe results were performed by combining the data of 4 populations including 4152 individuals.

/, The association of IgG N-glycans with age or BMI remained unclear.

CI, confidence interval; GP, glycan peak; IgG, immunoglobulin G.

TABLE 3. THE CHANGES OF IMMUNOGLOBULIN G N-GLYCANS IN COMMON CHRONIC DISEASES

GP	HT	T2D	DL	CDRS	IS	PD	NAFLD	UC	CD	SLE	RA	CKD	CRC
GP1	/	/	/	/	+	/	/	/	/	+	+	/	+
GP2	/	/	+	+	/	/	/	/	/	+	+	+	+
GP3	/	+	/	/	/	/	/	/	/	/	+	/	+
GP4	+	+	+	/	/	/	/	+	+	+	+	/	+
GP5	/	/	+	+	–	–	/	/	/	+	/	/	+
GP6	+	+	+	+	/	/	/	+	+	+	+	+	+
GP7	/	/	/	+	/	/	/	/	/	+	/	/	/
GP8	/	–	/	–	+	+	/	/	/	–	–	/	–
GP9	/	–	/	–	/	/	/	–	–	–	–	/	–
GP10	/	+	/	+	/	/	/	/	/	+	/	/	–
GP11	/	+	+	+	/	/	/	/	/	/	/	/	–
GP12	–	/	/	/	/	/	/	/	/	+	–	/	–
GP13	–	/	/	/	–	/	/	/	/	/	–	/	–
GP14	–	–	–	–	–	+	–	–	–	–	–	–	–
GP15	–	/	/	/	–	/	/	/	/	/	/	/	–
GP16	/	/	/	–	/	/	/	/	/	–	/	/	+
GP17	/	/	/	/	–	–	/	/	/	+	/	/	/
GP18	–	/	–	–	–	/	/	–	–	–	–	–	–
GP19	/	–	/	/	/	/	/	/	–	+	/	/	–
GP20	/	/	+	/	/	/	/	/	/	/	/	/	/
GP21	/	/	+	/	–	/	/	/	/	/	/	/	/
GP22	/	/	/	+	/	/	/	/	/	+	–	/	–
GP23	/	–	/	–	–	/	/	/	/	–	–	/	/
GP24	/	/	/	/	/	/	/	/	/	+	+	/	/

+, The high level of glycans could potentially increase the risk of diseases; –, the low level of glycans could potentially increase the risk of diseases; /, the associations of glycans with diseases remained unclear.

The high level of GP1–4, GP6, GP7, and GP24, and low level of GP9, GP13, GP15, GP18, and GP23 could increase the risk of common chronic diseases (Table 3). In combination with the result of aging, the high level of GP1–4, GP6, GP7, and GP24 and low level of GP9, GP13–15, GP18, and GP23 could increase the risk of common chronic disease. In addition, the changes of IgG N-glycans (GP5, GP8, GP10–12, GP14, GP16, GP17, GP19, GP21, and GP22) in several common chronic diseases were not consistent.

For example, low levels of GP5 and GP8 could increase the risk of IS and PD, which was contrary to the association with colorectal cancer, SLE, and DL. The high level of GP14 could increase the risk of PD, while the low level of GP14 could increase the risk of aging and several common chronic diseases; in addition, the CC of GP14 in aging was -0.645 . It was indicated that some GPs might be specific biomarkers for some diseases, which is interesting and needed to be verified with a larger sample size.

Discussion and Outlook

In the present systematic review, aging strongly associated with the changes of IgG N-glycans (the CCs of GP4, GP6, GP14, and GP18 were as high as 0.600). The previous study showed that the combination of only three IgG N-glycans could explain up to 58% of variance in age (Kristic et al., 2014), more than other biomarkers of age such as telomere lengths (Nakamura et al., 2002).

Aging is a complex process of accumulation of molecular, cellular, and organ damage, inducing loss of function and increased vulnerability to disease (North and Sinclair, 2012; Kroemer, 2009). In addition to the result with aging, we found that the high level of GP1–4, GP6, GP7, and GP24 and

low level of GP9, GP13–15, GP18, and GP23 could increase the risk of common chronic disease. The qualitative biomarkers to determine what conditions can increase the risk of common chronic disease were the first choice as diagnostic and predictive biomarkers for the common chronic disease. Therefore, GP1–4, GP6, GP7, GP9, GP13–15, GP18, GP23, and GP24 may be developed as clinically candidate biomarkers for common chronic diseases in the future.

In addition to candidate biomarkers for common chronic diseases, we look forward to looking for disease-specific biomarkers. Based on the limited available studies, we have not yet been able to provide a disease-specific IgG N-glycan profile. We are deeply aware that there is no uniform specification for reporting IgG N-glycans in diseases and there is not yet a glycan-based database. Therefore, we summarize the experience and lessons from the current studies to integrate information on analytical methods and promote transparent reporting of IgG N-glycans as diagnostic and predicted biomarkers for diseases before a significant amount of time and other resources are invested in large-scale studies.

The increasing evidences are gradually realizing that IgG N-glycans improve existing disease biomarkers (Gudelj et al., 2018a; Russell et al., 2018). However, there are still critical and common challenges to screening the biomarkers for the diagnosis, prediction, and prognosis of diseases. Most of the present study only provides a correlation between IgG N-glycans and diseases, and few studies report the sensitivity and specificity or other diagnostic performance metrics of biomarkers for diseases. In addition, the existing studies reported that the biomarkers are limited to use for diagnosis, and they need to be validated in prognosis and/or treatment management.

The present results of IgG N-glycan studies are part of the identification phase and are an important step before the

validation and standardization process. Therefore, we provide the following proposal to establish a complete glycan-based database and share resources for later in-depth and transformation applications.

First, there is a need to establish a standardized process of data analysis. Both univariate and multivariate analyses should be performed for screening the significant IgG *N*-glycans. Because most of the glycans were not normally distributed, the normalized transformations for IgG *N*-glycans were applied to add to the consistent comparability among IgG *N*-glycans. Usually, the *z*-score of normalized transformations for IgG *N*-glycans was performed. The false discovery rate (FDR) method, which was primarily applied to correct the multiple comparisons, controls the expected proportion of false rejections among all rejected theories. We should realize that CIs communicate both the strength of the relationship and the precision of the measure and are, therefore, more informative than point estimates accompanied by *p*-values.

There were internal associations among glycans, which could induce multicollinearity in the statistical models; therefore, the classical method of regression, including ridge or lasso or stepwise regression, should be used to select glycans to make dimension reduction according to the FDR and diagnostic and predicted effectiveness.

Second, the panel with multiple IgG *N*-glycans may be of high performance in diagnostic models. The result of multiple cancer-type study indicated that the distribution of IgG galactosylation could be a promising biomarker for cancer screening, of which area under the curve of the Gal-ratio was 0.871 (95% CI: 0.879–0.903) (Ren et al., 2016). The distribution of IgG galactosylation (referred to as Gal-ratio) was measured by calculating the relative intensities of agalactosylated (G0) versus monogalactosylated (G1) and digalactosylated (G2) *N*-glycans according to the formula of $G0/(G1 + G2 \times 2)$. Therefore, we combined IgG *N*-glycans into the panel biomarkers, which were calculated following a principle to see the change of only one glycosylation.

In total, 36 panel glycosylation biomarkers were performed (Supplementary Table S1). Considering that the high level of GP1–4, GP6, GP7, and GP24 and the low level of GP9, GP13–15, GP18, and GP23 might increase the risk of disease, we inferred that the high level of the panel biomarkers, including GP24 (high)/GP23 (low), and the low level of the panel biomarkers, including GP14 (low)/GP4 (high), GP15 (low)/GP6 (high), (GP8 + GP9) (low)/GP4 (high), and (GP8 + GP9) (low)/GP7 (high), might increase the risk of disease. Consistent with previous studies, the lower galactosylation [GP14/GP4, GP15/GP6, (GP8 + GP9)/GP4], and the opposite change of fucose [low level of (GP8 + GP9)/GP7] and bisecting GlcNAc (high level of GP24/GP23) are involved in an imbalance of the inflammatory response that increases the risk of diseases.

Limitations of the study are also noteworthy. First, all the publications included in this analysis were reported in case/control studies, indicating that the selection bias could possibly lead to overestimations of diagnostic accuracy compared with the cross-sectional study and cohort study. Second, there were few studies included, limiting the ability to generalize the results. As the studies of IgG *N*-glycans are reported normatively and comprehensive glycan-based databases are being established, future meta-analyses are warranted and called for when a larger body of literature is available.

Conclusions

Glycomics, a new subspecialty in omics systems sciences, offers significant promise for next-generation biomarkers on disease susceptibility, and can be expanded to inquiries on drug target discovery and precision medicine in the near future. Our findings collectively suggest that GP1–4, GP6, GP7, GP9, GP13–15, GP18, GP23, and GP24 offer promise for further candidate translational biomarker research in relation to common chronic disease susceptibility.

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Author Disclosure Statement

The authors declare that no conflicting financial interests exist.

Supplementary Material

Supplementary Table S1

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Abbreviations Used

ADCC = antibody-dependent cellular cytotoxicity
AUC = area under the curve
BMI = body mass index
CC = correlation coefficient
CD = Crohn's disease
CDRS = cardiovascular disease risk score
CI = confidence interval
CKD = chronic kidney disease
CRC = colorectal cancer
DL = dyslipidemia
Fc = fragment crystallizable
FDR = false discovery rate
GP = glycan peak
HDL = high-density lipoprotein cholesterol

HILIC = hydrophilic interaction chromatography
HT = hypertension
IgG = immunoglobulin G
IS = ischemic stroke
NAFLD = nonalcoholic fatty liver disease
OR = odds ratio
PD = Parkinson's disease
RA = rheumatoid arthritis
SEN = sensitivity
SLE = systemic lupus erythematosus
SPE = specificity
T2D = type 2 diabetes
UC = ulcerative colitis
UPLC = ultraperformance liquid chromatography