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The association between subclass-specific IgG Fc *N*-glycosylation profiles and hypertension in the Uygur, Kazak, Kirgiz and Tajik populations

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ABSTRACT

Hypertension results from the interaction of genetic and acquired factors. IgG occurs in the form of different subclasses, of which the effector functions show significant variation. The detailed differences between the glycosylation profiles of the individual IgG subclasses may be lost in a profiling method for total IgG *N*-glycosylation. In this study, subclass-specific IgG Fc glycosylation profile was investigated in the four northwestern Chinese minority populations, namely, Uygur (UIG), Kazak (KZK), Kirgiz (KGZ) and Tajik (TJK), composed of 274 hypertensive patients and 356 healthy controls. The results showed that 10 directly measured IgG *N*-glycan traits (i.e. IgG1G0F, IgG2G0F, IgG2G1FN, IgG2G1FS, IgG2G2S, IgG4G0F, IgG4G1FS, IgG4G1S, IgG4G2FS, and IgG4G2N) representing galactosylation and sialylation are significantly associated with hypertension, with IgG4 consistently showed weaker associations of its sialylation, across the four ethnic groups. We observed a modest improvement on the AUC of ROC-curve when the IgG Fc *N*-glycan traits are added into the glycan-based model (difference between AUCs, 0.044, 95% CI: 0.016-0.072, P= 0.002). The AUC of the diagnostic model indicated that the subclass-specific IgG Fc *N*-glycan profiles provide more information reinforcing current models utilizing age, gender, BMI and ethnicity, and demonstrate the potential of subclass-specific IgG Fc *N*-glycosylation profiles to serve as a biomarker for hypertension. Further

research is however required to determine the additive value of subclass-specific IgG Fc *N*-glycosylation on top of biomarkers which are currently used.

Summary Table

What is known about topic?

- The prevalence of hypertension in the Chinese minority populations residing in the northwestern China ranked at the forefront of China.
- Previous studies showed an association between hypertension and IgG *N*-glycome composition in European (i.e. Croatian Korčula, Croatian Vis, and Scottish Orkney), Asian (i.e. Chinese Han and Chinese Kazak) populations.
- The relationship between IgG glycosylation and hypertension in other populations remains unknown.
- Previous studies on total IgG *N*-glycans do not allow to distinguish between Fc and Fab associated *N*-glycans, as such the contribution of changes in Fab *N*-glycosylation cannot be excluded.

What this study adds?

- This study provides evidence that the decreased IgG galactosylation and sialylation were correlated with hypertension in the four ethnic groups (i.e. Uygur, Kazak, Kirgiz and Tajik) residing in the northwestern China.
- We describe the differences between the plasma Fc glycosylation profiles particularly of IgG1, IgG2 and IgG4 in detail, which may be lost in a profiling method for total IgG *N*-glycosylation.
- The AUC of the glycan-based model indicated that the IgG glycan profiles provide more information reinforcing current models utilizing gender, age, BMI and ethnicity, and demonstrate the potential of subclass-specific IgG Fc *N*-glycosylation profiles to serve as a biomarker for hypertension.

INTRODUCTION

Hypertension is a chronic, asymptomatic condition that increases individuals' risk of developing several diseases, including coronary artery disease, stroke, and renal failure.[1] Hypertension was the leading risk factor for global disease in 2010,[2] and over 20% of adults (⩾18 years) worldwide were hypertensive, accounting for nearly 10 million deaths in 2014.[3] The prevalence of hypertension continues to increase in China from 18% in 2002 to 23.2% in 2015,[4] in which participants were recruited by the use of a stratified multistage cluster sampling design.

Glycosylation is one of the most widespread post-translational modifications capable of increasing significant structural diversity to proteins, which is known to reflect the physiological state of an organism and changes thereof.[5] For immunoglobulin G (IgG), which occupies a central role in the immune system, it is known that the conserved *N*-glycan located at asparagine 297 on the fragment crystallisable (Fc) part of IgG can modulate inflammatory responses: a lack of core fucose, galactose and *N*-acetylneuraminic (sialic) acid increases the ability of IgG to induce antibody-dependent cell-mediated cytotoxicity (ADCC).[6] In spite of the pivotal role of IgG glycosylation in many physiological and pathological processes, the monitoring of IgG glycosylation is often neglected in clinical and immunological research.[7]

IgGs consist of four subclasses (i.e. IgG1–4), which bind their antigen targets via the fragment antigen binding (Fab) domain and exert their effector functions via the fragment crystallizable (Fc) domain.[8] Fc glycans are essential structural components of the IgG molecule and minor changes in glycan composition can significantly alter the conformation of the Fc region changing the interaction with receptor proteins and thus modulating the effector functions of IgG. The assignment of glycans to the specific Fc glycosylation sites of IgG subclasses is pivotal for deducing the functional implications of the observed glycosylation features.[9] Additionally, each of the IgG subclasses has a unique binding profile to each Fc gamma receptors (FcγRs), and their expression profiles are highly variable between different immune cells of myeloid and NK cell origin.[10] Most of the modulating effects of IgG Fc glycans have been reported for IgG1 and may not apply to IgG2, stressing the relevance of subclass and site specific IgG glycosylation profiling.[9] The differences between the Fc *N*-glycosylation profiles of the individual IgG subclasses may be lost in total IgG *N*-glycosylation (Fc and Fab associated *N*-glycans).

The prevalence of hypertension in the Chinese minority populations residing in the Xinjiang Uygur Autonomous Region located in the northwestern China is relatively higher than that in the Chinese Han in China.[11] The northwestern Chinese minority populations, including Uygur (UIG), Kazak (KZK), Kirgiz (KGZ) and Tajik

(TJK), etc., are overwhelmingly Muslim, and have their own language, religious beliefs and lifestyles differed largely from either Han Chinese or European populations.[12] They are classically well-defined isolated populations, and these ethnic groups differ substantially in terms of morphological and genetic characteristics.[13] These differences in genetics and environmental factors together with abnormal higher prevalence of hypertension might imply different pathogenesis of hypertension.

Our previous study has reported that individual variation of *N*-glycosylation of IgG might contribute to hypertension in European (i.e. Croatian Korčula, Croatian Vis, and Scottish Orkney) and Asian (i.e. Chinese Han and Chinese Kazak) populations.[14,15] Investigating other populations would be an expedient way to evaluate the generalizability of the current findings. In this study, we further validated these findings by investigating Fc *N*-glycosylation profiles of human IgG subclasses, investigated to what extent the Fc *N*-glycome of IgG subclasses correlates with the occurrence of hypertension, and demonstrated the potential of subclass-specific IgG Fc *N*-glycosylation profiles to serve as a biomarker for hypertension in the four northwestern Chinese minority populations.

MATERIALS AND METHODS

Study population

This population-based, case-control survey was conducted in the Xinjiang Uygur

Autonomous Region, China, from August 2014 to August 2016. A total of 630 participants were recruited from 170 UIG, 150 KZK, 168 KGZ and 142 TJK. The demographic characteristics of the participants, including ethnicity, gender, age, and history of medications, were collected by a questionnaire.

Participants were included if they aged more than 18 years, self-reported the respective UIG, KZK, KGZ and TJK ethnicity without intermarriage history with other ethnic groups within at least the past three generations. Individuals with a diagnosis of specific severe diseases concerning the cardiovascular system, respiratory system, genitourinary system, digestive system, and hematic system, were excluded. All participants gave written informed consent. This study was approved by the local community leaders and the ethics committee of the Capital Medical University, Beijing, China.

Anthropometric measurements, including weight, height, etc., were obtained using standardized techniques.[14] The body mass index (BMI) was calculated by the formula weight (in kilograms)/height (in square meters). Peripheral bloods of the participants were collected in EDTA-anti-coagulated tubes after an overnight fast. Fasting blood glucose (FBG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG) and serum total cholesterol (TC) were assayed under the standard procedures in the local hospital.

Dyslipidemia defined based on the 2016 Guidelines for Prevention and Treatment of Dyslipidemia in Adults in China: TC⩾6.2 mmol/L, TG⩾2.3 mmol/L, LDL⩾4.1 mmol/L or HDL<1.0 mmol/L.[16] Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times in a day with a mercury sphygmomanometer. Hypertension was defined as an average SBP⩾140 mmHg or an average DBP⩾90 mmHg, or self-reported current hypertension.[17]

IgG Fc *N*-glycopeptide analysis

IgG was isolated from the plasma samples of all the participants after overnight fasting, and each IgG subclass was analyzed by nano-reverse phase UPLC-MS using a sheath-flow ESI sprayer interface as described previously.[18,19] Glycopeptide data were extracted by in-house python script. In short, m/z was recalibrated internally, and intensities of top four isotopologues per charge per glycopeptide were extracted from LC elution bins. Glycopeptide area was produced by summing intensities across all relevant isotopologues and charge states. The *N*-glycopeptide signals were normalized by dividing each by the total signal intensity of all *N*-glycopeptides belonging to that subclass, yielding percentage data amounting to 100% per subclass. Along with the 20 glycopeptide structures per subclass of IgG, an additional 7 derived traits (agalactosylation, galactosylation, monogalactosylation, digalactosylation, sialylation, bisecting *N*-acetylglucosamine [GlcNAc] and fucosylation) representing

composite traits were defined by taking into account these glycopeptide structures amounts per each subclass:[8,14]

Agalactosylation (A) = G0 + G0F + G0FN + G0N

Galactosylation (G) = G1 + G1F + G1FN + G1N + G2 + G2F + G2FN + G2N

Monogalactosylation (M) = G1 + G1F + G1FN + G1N

Digalactosylation (D) = G2 + G2F + G2FN + G2N

Sialylation (S) = G1FS + G1FNS + G1S + G1NS + G2FS + G2FNS + G2NS + G2S

Bisecting GlcNAc (B) = G0FN + G0N + G1FN + G1FNS + G1N + G1NS + G2FN + G2FNS + G2NS + G2N

Fucosylation (F) = G0F + G0FN + G1F + G1FN + G1FNS + G1FS + G2F + G2FN + G2FNS + G2FS

Statistical analysis

To remove experimental variation from measurements, normalization and batch correction were performed on the LC-MS glycopeptide data.[8] Normality distributions were checked by the Kolmogorov-Smirnov tests. Continuous variables underlying normality distribution were described by mean together with standard deviation (SD), otherwise median together with interquartile range were used. Considering that nearly all the glycan traits cannot be assumed normal distributed, Mann-Whitney U test was

used to compare the differences of IgG subclass-specific Fc glycopeptides between the hypertension patients and the healthy controls. Associations between glycans and disease status were performed using a logistic regression with age, gender, ethnicity, BMI, FBG and dyslipidemia included as covariates. Pooling analysis was carried out by introducing dummy variables representing the different ethnic groups.

Dimension reduction based on LASSO (least absolute shrinkage and selection operator) method was performed to select *N*-glycopeptide traits used in the discriminant analysis.[14] To classify the hypertension patients with the healthy controls, a logistic regression model was applied. Two different predicted models were considered: a baseline model included gender, age, BMI and ethnicity as the covariates, and a glycan-based model included the significantly differed IgG Fc glycopeptides together with the aforementioned covariates. Receiver operating characteristic (ROC) curve analyses were used to evaluate the diagnostic ability in classifying the hypertension patients from the healthy controls. The area under the receiver operating characteristic curve (AUC) of the 2 classification models were compared using MedCalc (Version 17.9.7).

All the analyses were performed using the SPSS (Version 21.0, IBM) software and R packages (Version 2.7.2). For the multiple corrections, the false discovery rate (FDR) was used based on the Benjamini-Hochberg procedure.[20] All the tests were 2-

sided, and $P < 0.05$ was considered statistically significant.

RESULTS

By performing LC-ESI-MS analysis on IgG glycopeptides, Fc glycosylation profiles of IgG1, IgG2 and IgG4 were determined for 630 participants (i.e. 170 UIG, 150 KZK, 168 KGZ, and 142 TJK) in the study. Fc glycopeptides of IgG2 and IgG3 share the same peptide sequence,[21] and so the commonly used protein G enrichment of IgG gives a joint profile for both IgG2 and IgG3. It has been shown to capture IgG1, 2 and 4, but has a much lower binding affinity for IgG3 under the enrichment conditions we use,[7] thus allowing for near-separate glycoprofiling of IgG2.

All 630 participants provided complete biometrics and glycan level data, and were therefore used in the further analyses. Descriptive information on the hypertension patients and the healthy controls for each of the four ethnic groups are shown separately (Table S1) and pooled together in Table 1. The age, gender, BMI, SBP, DBP, TC, HDL, LDL and FBG significantly differed in hypertension patients compared to healthy controls.

The comparisons of directly measured subclass-specific IgG Fc glycomic composition between hypertension patients and healthy controls of each ethnicity and of the pooled participants from all four ethnic groups are shown in Table S2, while derived traits are shown in Table S3 and Figure 1. Subclass-specific IgG Fc *N*-

glycopeptides were significantly associated with hypertension in the pooled participants from all four ethnic groups after controlling for gender, age, BMI, dyslipidemia, FBG and ethnicity as summarized in Table S2 and Table S3. Ten directly measured IgG subclass-specific Fc glycopeptide structures and 14 derived glycan traits are significantly associated with hypertension in the pooling of the four ethnic groups, primarily reflecting the decrease of galactosylation and sialylation in hypertension patients. Subclass-specific IgG Fc glycopeptides that statistically differred between the hypertensive patients and healthy controls in the pooling of four ethnic groups were not consistently significant among the comparisons between each ethnicity, although these differences were in similar trends (Table S2 and Table S3).

Two different models were built using Logistic regression (Table 4, Figure 2). The AUC of 0.688 (95% CI: 0.650-0.724) in the baseline model utilized gender, age, BMI and ethnicity as the covariates, and 0.732 (95% CI: 0.696-0.766) in the glycan-based model utilized five significantly differed subclass-specific IgG Fc glycopeptide *N*-glycans (IgG1G0F, IgG2G0F, IgG4G0F, IgG4G2FS and IgG4G2N) together with the aforementioned covariates, respectively. The AUCs showed modest improvement in the glycan-based diagnostic model compared to the baseline model, with an increment of 0.044 (95% CI: 0.016-0.072, $P = 0.002$).

DISCUSSION

Using LC-ESI-MS, this study represents the first comprehensive analysis of Fc *N*-glycosylation profiling of human IgG subclasses showing similar associations with hypertension in the four ethnic minorities in northwestern China. In this study, ten directly measured subclass-specific IgG Fc *N*-glycan traits indicative of galactosylation and sialylation presented a significant association with hypertension. The IgG subclasses displayed subtle differences in directly measured glycopeptide structures, with significant differences in sialylation resulting primarily between the IgG1 and IgG2 subclasses, the potential reason for any underlying difference in biological role. When the five selected glycan traits (IgG1G0F, IgG2G0F, IgG4G0F, IgG4G2FS and IgG4G2N) were added into the glycan-based model, the AUC showed modest improvement (difference between AUCs, 0.044, 95% CI: 0.016-0.072, P = 0.002).

We previously demonstrated that plasma *N*-glycome is associated with blood pressure, with increased triantennary glycans and decreased core-fucoseglycans in the subjects with elevated blood pressure, in both Chinese (Han and Kazak) and Croatian (Korčula and Vis).[22] Previously we showed that galactosylation and sialylation of total IgG decreased, and fucosylated structures and bisecting GlcNAc of total IgG increased in patients of hypertension.[15] In addition, 14 IgG subclass-specific Fc glycopeptide structures, along with one derived glycosylation trait in subclasses IgG2

and IgG4, are correlated with SBP and/or DBP in the Kazakh population.[14] Here, we advanced the understanding of the association between the subclass-specific IgG Fc glycopeptides, which may be lost in total IgG *N*-glycosylation, and hypertension in the four northwestern Chinese minority populations. Our findings of decreasing galactosylation and sialylation in hypertensive patients are consistent with those in Chinese Han, Kazak and European populations. However, the non-significant changes of core-fucosylation and bisecting GlcNAc in hypertension patients and healthy controls are inconsistent with our previous findings in Chinese Han, Kazak and European populations.

Glycans do not have a direct genetic template, thus glycan structures attached to proteins are determined by complex dynamic interactions between genetic and environmental factors.[23] The *HNF1A* gene, known for its common variants associated with type 2 diabetes (T2DM),[24] is a genetic locus significant associated with total plasma *N*-glycome as a regulator of fucosylation identified in the individuals of European ancestry.[26] Moreover, *HNF1A* regulates expression of *FUT8*,[26] and is associated with the susceptibility of T2DM in the individuals of European ancestry.[27] However, some variants in *HNF1A* and *FUT8* were not statistically associated with the susceptibility of T2DM patients of Uyghur.[25] The Chinese ethnic groups (e.g., Tajik, Uyghur, Kazakh, Kirgiz and Hui) are admixed populations with both eastern

and western Eurasian ancestries, thus resulting in complex genetic diversity.[13] The widespread differences in genetic structure and environmental conditions among these ethnic groups may partly explain the inconsistent association between IgG Fc *N*-glycans and hypertension among the different ethnic groups.[14]

The marked decrease in galactosylation and increase in agalactosylation of the three subclasses (IgG 1, 2 and 4) observed in this study have been demonstrated in many other diseases and traits, such as the Parkinson's disease and the effects of age on allergic disease.[8,26] Additionally, in many autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus, juvenile onset chronic arthritis, and Crohn's disease, marked increase in agalactosylation has been demonstrated.[27-29] It can be assumed that the increase in agalactosylation and the resulting pro-inflammatory effect may be associated with many other diseases. Lack of galactosylation is associated with a pro-inflammatory state of IgG through activation of the complement cascade.[30] The previous study also demonstrated that high galactosylation promotes cooperative signaling of the FcγRIIB with dectin-1 resulting in an inhibitory signaling pathway that blocks pro-inflammatory effector functions.[31] A possible explanation for this decreased galactosylation is post-translational modifications of the enzyme β4-galactosyltransferase-1.[32] Thus the decrease in galactosylation may be the common pathogeny of multiple diseases

associated with decreased immunosuppressive potential of circulating IgG.

We find that sialylation of IgG1 and IgG2 decreased in individuals with the state of hypertension. With regards to IgG4, the observed differences could have been attributed to a decrease in analytical precision resulting from the low concentrations of IgG4 in comparison to other IgG subclasses. More work is required, in particular on antigen specific IgG subclasses, to improve our understanding of the role of IgG glycosylation.

Sialylation plays an important role in the inflammatory potential of IgG. Addition of sialic acid to IgG converts its function from pro- to anti-inflammatory by decreased binding to Fcγ receptors.[33] IgG acquires anti-inflammatory properties upon Fc sialylation, which is reduced upon the induction of an antigen-specific immune response. This differential sialylation may provide a switch from innate anti-inflammatory activity in the steady state to generating adaptive pro-inflammatory effects upon antigenic challenge.[32] Therefore decreased sialylation might play pathogenic roles in hypertension, but the pathogenic mechanism of sialylation was unclear.

Alterations of the immune response have been implicated in the pathogenesis of hypertension for more than 5 decades.[15] Chae et al observed significantly graded relationships between blood pressure and levels of sICAM-1 as well as IL-6, which

suggested the increased blood pressure should be a stimulus for inflammation.[34] Marvar et al further found that hypertension has been involved in both central and peripheral mechanisms of Tlymphocyte activation and vascular inflammation produced by angiotensin II-induced hypertension.[35] Additionally, several inflammatory markers including C-reactive protein (CRP) are strongly associated with the risk of hypertension.[36] Therefore, the association between inflammation and hypertension suggest that IgG glycosylation might contribute to the pathogenesis of hypertension via the alternation of the inflammation, and as such could be a valuable prognostic model for hypertension.

As glycan profiles are associated with genetic, metabolic and environmental influences, this adds to their predictive potential. We observed a modest improvement when adding the IgG Fc *N*-glycopeptide profiles to clinical risk factors. The AUC of the glycan-based model indicated that the IgG glycan profiles provide more information reinforcing current models utilizing gender, age, BMI and ethnicity.

The case-control nature of this study makes it impossible to infer the causal-effect relationship between IgG Fc *N*-glycans and hypertension. One of the shortcomings in this study is the lack of prospective follow-up for the hypertension outcome. While the study design adopted in this project shows a significant association between hypertension and IgG subclass-specific Fc *N*-glycopeptide

glycosylation, it is not conclusive as to whether the expressed IgG subclass Fc *N*-glycopeptide glycosylation proceeds the symptoms of hypertension in the study cohorts. As such, no causal claims can be made as the AUCs can only be interpreted in a case-control setting where patients have already been diagnosed for and are being treated for this health event. Notwithstanding this, the current study not only presents the potential for the IgG subclass-specific glycan information to be indicative of hypertension, but additionally reinforces current diagnostic models of hypertension. Another potential limitation of this study was that some cases were on their antihypertensive medication when their blood samples were collected. Thus, it was not possible to distinguish between antihypertensive medication effects on the IgG glycome and effects associated with the pathophysiology of the disease itself. It should be noted that other risk factors related to hypertension, such as family history of hypertension and smoking, were not obtainable during this study and were not included. The absence of controlling for potential risk factors may confound the association, but at certain extend the consistent results among populations investigated with different ethnic background might help this study to profile objectively the association observed between IgG glycosylation and hypertension. Future studies in prospective cohorts should be conducted to investigate how this biomarker potential could be used for personalized approaches in prevention and

treatment of the disease as well as its role in hypertension complications.

To conclude, we found that the robust associations of subclass-specific IgG Fc *N*- glycosylation profiles may serve as an informative biomarker indicative of the pro-inflammatory and biological state shared by hypertension. Future studies should be directed at in-depth pathophysiological insights that can be derived from IgG Fc *N*-glycan associations with hypertension. It is expected that prospective follow-up studies with additional information about inflammatory biomarkers and genetic studies might further shed light on the causality, the potential as a biomarker for complex inflammatory processes, and the true predictive capacity of IgG subclass specific Fc *N*-glycans in hypertension.

CONFLICT OF INTEREST

G. Lauc is the founder and owner of Genos Ltd, a private research organization that specializes in high-throughput glycomic analysis and has several patents in this field. J. Štambuk, I. Trbojević-Akmačić, A. Momčilović and G. Razdorov are employees of Genos Ltd.

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Figure Legends:

Figure 1 Comparisons of derived subclass-specific IgG Fc *N*-glycomic composition between hypertension patients and healthy controls.

Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes represent the 2.5th and 97.5th percentiles.

Figure 2 ROC curve illustrated the performance of the models in diagnosing hypertension of the four ethnic groups.

When glycan traits are added into the glycan-based model, the AUCs indicated that the IgG glycan profiles provide more information reinforcing the baseline models utilizing gender, age, BMI and ethnicity. (difference between AUCs, 0.044, 95% CI: 0.016 - 0.072, P= 0.002).

ROC = receiver operating characteristic; AUC = area under the curve

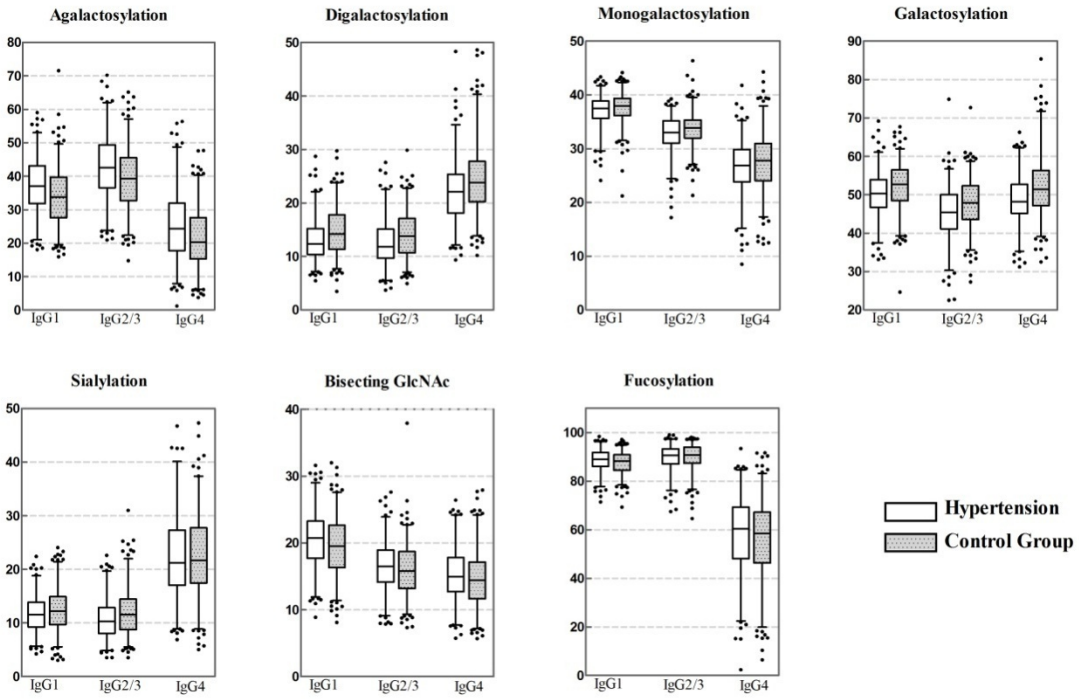
Agalactosylation
Digalactosylation
Monogalactosylation
Galactosylation
Sialylation
Bisecting GlcNAc
Fucosylation
IgG1
IgG2/3
IgG4
Hypertension
Control Group

Figure 1

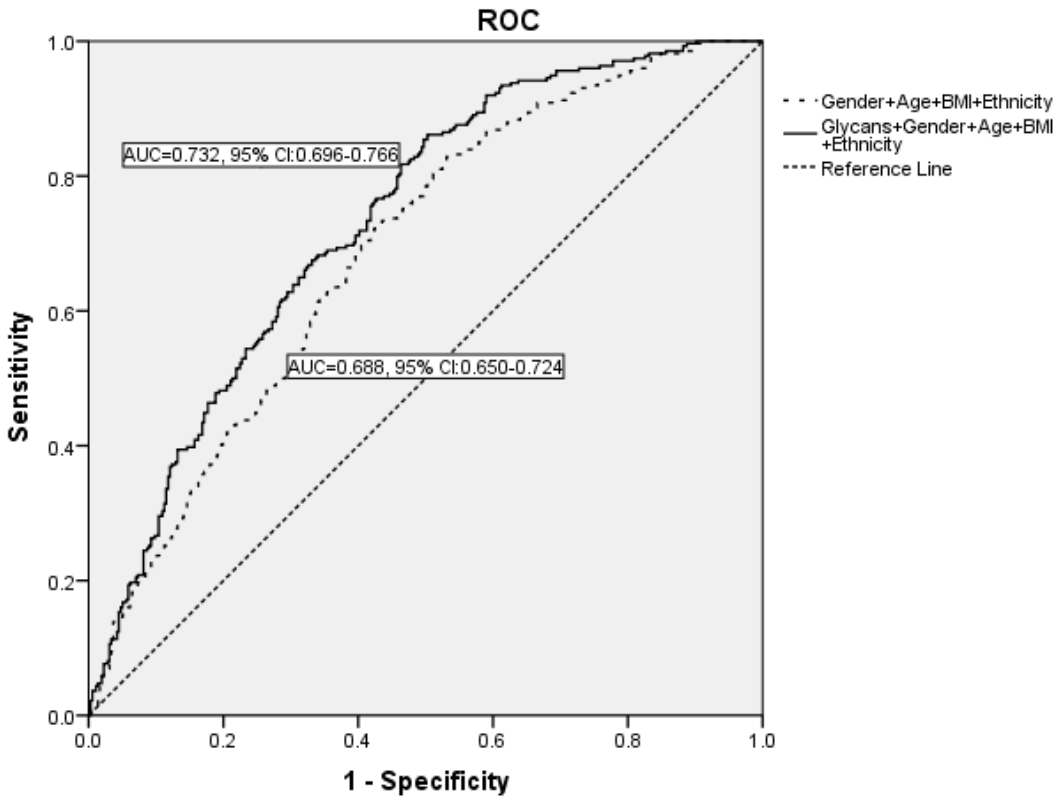
ROC
Sensitivity
1 - Specificity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
AUC=0.732, 95% CI:0.696-0.766
AUC=0.688, 95% CI:0.650-0.724
Gender+Age+BMI+Ethnicity
Glycans+Gender+Age+BMI +Ethnicity
Reference Line

Figure 2

Table 1. Characteristics of the study subjects in pooling of the four ethnic groups

Variables	Hypertension (n=274)	Control group (n=356)	*P* values
Age (years)	57.07±12.42	49.83±14.88	<0.001*
Gender (male)	126 (50.80%)	122 (40.90 %)	<0.001*
BMI (kg/m^2)	26.76±4.59	24.92±4.71	<0.001*
SBP (mmHg)	151.20±18.44	112.67±11.83	<0.001*
DBP (mmHg)	94.58±12.49	71.72±9.18	<0.001*
TC (mmol/L)	4.72±1.11	4.41±1.20	0.004*
TG (mmol/L)	2.82±0.99	2.84±1.37	0.989
HDL (mmol/L)	1.83±0.75	1.61±0.70	<0.001*
LDL (mmol/L)	2.72±1.62	2.29±1.10	<0.001*
FBG (mmol/L)	5.90±1.40	5.40±1.31	<0.001*
Dyslipidemia	206 (75.18%)	289 (81.12%)	0.069

Data are shown as mean ± standard deviation.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: Total cholesterol; TG: Triglycerides; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; FBG: fasting blood glucose.

Mann-Whitney U test: Age, BMI, SBP, DBP, TC, TG, HDL, LDL, FBG, Dyslipidemia; χ^2 test: Gender.

* $P<0.05$ was considered statistically significant.

Table 2. Directly measured subclass-specific IgG Fc *N*-glycomic composition in the hypertension patients and the healthy controls for the pooling of the four ethnic groups.

Glycans	Median (IQR)		AOR (95% CI)	*P-adjusted*	FDR
	Hypertension	Control group			
IgG1G0F	25.79 (21.39,30.29)	23.20 (19.69,27.92)	1.05 (1.02,1.08)	5.00E-04	7.50E-03*
IgG2G0F	32.96 (27.35,39.22)	30.62 (25.11,35.99)	1.05 (1.02,1.07)	2.00E-04	1.20E-02*
IgG2G1FN	4.67 (3.71,5.47)	4.83 (3.92,5.66)	0.80 (0.69,0.92)	2.50E-03	2.14E-02*
IgG2G1FS	3.64 (3.07,4.28)	3.99 (3.22,4.52)	0.74 (0.61,0.90)	2.40E-03	2.40E-02*
IgG2G2S	0.42 (0.25,0.62)	0.45 (0.23,0.78)	0.44 (0.25-0.79)	6.00E-03	4.00E-02*
IgG4G0F	17.53 (12.12,24.14)	14.66 (10.81,20.97)	1.05 (1.02,1.07)	3.00E-04	6.00E-03*
IgG4G1FS	2.36 (1.77,2.92)	2.42 (1.67,3.07)	0.73 (0.59,0.91)	5.20E-03	3.90E-02*
IgG4G1S	0.33 (0.25,0.40)	0.35 (0.24,0.44)	0.10 (0.02,0.42)	1.70E-03	2.04E-02*
IgG4G2FS	5.40 (3.89,7.64)	6.35 (4.45,8.55)	0.89 (0.83,0.95)	2.00E-04	1.20E-02*
IgG4G2N	1.74 (1.09,2.29)	1.77 (1.23,2.46)	0.79 (0.66,0.94)	7.50E-03	4.50E-02*

False discovery rate (FDR) was controlled using Benjamini–Hochberg procedure.

Only the directly measured subclass-specific IgG Fc *N*-glycan traits which presented significant differences describing glycomic composition are shown. The other directly measured *N*-glycan traits are available in Supplementary Table S2.

Logistic regression controlled for gender, age, BMI, dyslipidemia, FBG and ethnicity

* $P<0.05$ was considered statistically significant.

Table 3. Derived subclass-specific IgG Fc *N*-glycomic composition in the hypertension patients and healthy controls for the pooling of the four ethnic groups.

	Median (IQR)				
Glycans	Hypertension	Control group	AOR (95% CI)	*P-adjusted*	FDR
A1	37.04 (31.81,43.13)	33.76 (27.55,39.74)	1.04 (1.02,1.06)	1.30E-03	6.07E-03*
M1	37.50 (35.63,38.86)	37.93 (36.17,39.37)	0.93 (0.87,0.99)	1.50E-02	3.50E-02*
D1	12.38 (10.37,15.20)	14.23 (11.35,17.79)	0.95 (0.90,0.99)	2.14E-02	4.28E-02*
G1	50.28 (46.67,53.90)	52.74 (48.48,56.46)	0.96 (0.93,0.99)	6.00E-03	1.87E-02*
S1	11.58 (9.23,13.86)	12.20 (9.69,14.92)	0.93 (0.89,0.98)	1.04E-02	2.91E-02*
A2	42.59 (36.51,49.42)	39.25 (32.65,45.60)	1.04 (1.02,1.06)	5.00E-04	4.67E-03*
M2	33.01 (31.01,35.18)	33.87 (31.95,35.35)	0.91 (0.86,0.96)	1.00E-03	5.60E-03*
D2	11.81 (9.68,15.11)	13.82 (10.72,17.12)	0.93 (0.89,0.97)	2.30E-03	9.20E-03*
G2	45.39 (41.10,50.02)	47.90 (43.56,52.31)	0.95 (0.92,0.98)	4.00E-04	5.60E-03*
S2	10.29 (8.05,12.83)	11.54 (8.74,14.43)	0.93 (0.89,0.98)	5.10E-03	1.79E-02*
A4	24.30 (17.77,31.96)	20.26 (15.26,27.63)	1.03 (1.01,1.05)	8.00E-04	5.60E-03*
M4	26.89 (23.81,29.82)	27.76 (24.02,30.96)	0.96 (0.93,0.99)	1.88E-02	4.05E-02*
D4	22.10 (18.15,25.35)	23.82 (20.28,27.80)	0.96 (0.93,0.99)	1.25E-02	3.18E-02*
G4	48.17 (45.17,52.74)	51.39 (47.15,56.26)	0.95 (0.92,0.97)	1.00E-04	2.80E-03*

False discovery rate (FDR) was controlled using Benjamini–Hochberg procedure.

A, agalactosylation; M, monogalactosylation; D, digalactosylation; G, galactosylation; S, sialylation; B, bisecting GlcNAc; F, fucosylation. Number represents specific IgG subclass.

Only the derived subclass-specific IgG Fc *N*-glycan traits which presented significant differences describing glycomic composition are shown. The other derived *N*-glycan traits are available in Supplementary Table S3

Logistic regression controlled for gender, age, BMI, dyslipidemia, FBG, and ethnicity

* $P<0.05$ was considered statistically significant.

Table 4. The glycan-based model included the significantly differed subclass-specific IgG Fc glycopeptide *N*-glycans together with gender, age, BMI and ethnicity

Variables	β	S.E.	Wald χ^2	AOR	*P* values	95% CI
Gender	-0.37	0.18	4.12	0.69	4.24E-02	(0.48,0.99)
Age	0.02	0.01	11.85	1.03	5.77E-04	(1.01,1.04)
BMI	0.09	0.02	22.59	1.10	2.00E-06	(1.06,1.14)
Ethnicity	-0.30	0.09	10.67	0.74	1.09E-03	(0.62,0.89)
IgG1G0F	0.01	0.02	0.44	1.01	5.07E-01	(0.98,1.05)
IgG2G0F	0.00	0.02	0.02	1.00	8.87E-01	(0.97,1.04)
IgG4G0F	0.02	0.02	2.29	1.02	1.30E-01	(0.99,1.06)
IgG4G2FS	-0.12	0.04	9.56	0.88	1.99E-03	(0.82,0.96)
IgG4G2N	-0.20	0.11	3.54	0.82	6.00E-02	(0.67,1.01)

AOR = adjusted odds ratio; 95%CI = 95% confidence interval.

Table S1. Characteristics of the study subjects in the four ethnic groups: Uygur, Kazak, Kirgiz and Tajik

Variables	UIG			KZK			
	Hypertension (n=90)	Control group (n=80)	*P* values	Hypertension (n=52)	Control group (n=98)	*P* values	Hypertension (n=90)
Age (years)	62.88±11.62	59.19±13.83	0.061	49.33±10.48	41.68±10.97	<0.001*	54.85±12.92
Gender (male)	25(27.8%)	40(50.0%)	0.338	25(48.1%)	20(20.4%)	<0.001*	38(42.2%)
BMI (kg/m^2)	25.41±4.95	24.71±4.76	0.349	25.83±4.08	22.68±4.38	<0.001*	28.97±3.90
SBP (mmHg)	151.09±18.44	115.75±8.83	<0.001*	149.46±15.08	105.92±12.67	<0.001*	156.37±22.93
DBP (mmHg)	96.39±12.75	73.44±6.14	<0.001*	95.58±9.18	68.27±9.97	<0.001*	92.37±15.99
TC (mmol/L)	4.88±1.29	4.77±0.95	0.54	4.42±0.76	3.35±0.96	0.004*	4.55±1.08
TG (mmol/L)	1.84±0.46	1.89±0.40	0.518	1.88±0.71	1.15±0.53	0.989	1.70±0.44
HDL (mmol/L)	3.61±2.21	3.09±0.77	0.049	2.75±0.78	2.19±0.93	<0.001*	2.72±0.81
LDL (mmol/L)	2.90±0.73	3.32±1.48	0.020*	1.85±0.50	1.59±0.79	<0.001*	2.72±0.83
FBG (mmol/L)	6.23±1.41	6.11±1.02	0.542	5.37±1.10	4.56±1.00	<0.001*	5.83±1.48

Data are shown as mean ± standard deviation.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: Total cholesterol; TG

Mann-Whitney U test: Age, BMI, SBP, DBP, TC, TG, HDL, LDL, FBG; $\chi 2$ test: Gender.

* P <0.05 was considered statistically significant.

KGZ		TJK		
Control group (n=78)	*P* values	Hypertension (n=65)	Control group (n=77)	*P* values
40.96±12.12	<0.001*	54.85±12.92	40.96±12.12	<0.001*
27（34.6%）	0.091	38(56.7%)	34(33.7%)	0.091
27.53±3.70	0.026	28.97±3.90	27.53±3.70	0.026
117.79±9.43	<0.001*	156.37±22.93	117.79±9.43	<0.001*
72.84±10.08	<0.001*	92.37±15.99	72.84±10.08	<0.001*
4.79±1.23	0.223	4.56±1.12	4.74±1.28	0.279
1.68±0.41	0.805	2.74±0.84	2.78±1.25	0.834
2.93±1.04	0.180	1.71±0.52	1.72±0.45	0.979
2.75±1.20	0.864	2.72±0.81	2.93±1.04	0.180
5.44±1.50	0.128	5.80±1.50	5.40±1.54	0.124

: Triglycerides; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol;

FBG: fasting blood glucose.

age	假设方差相等	.601	.440	-6.598	140	.000	40.96	12.119
BMI	假设方差相等	.000	.999	-2.253	140	.026	27.5303	3.70212
SBP	假设方差相等	39.486	.000	-13.482	140	.000	117.79	9.433
DBP	假设方差相等	4.220	.042	-8.838	140	.000	72.84	10.081
TC	假设方差相等	4.832	.030	-1.086	140	.279	4.7391	1.27868
HDL	假设方差相等	1.136	.288	.026	140	.979	1.7168	.44732
LDL	假设方差相等	5.689	.018	1.347	140	.180	2.9322	1.03752
TG	假设方差相等	1.916	.168	.210	140	.834	2.7762	1.24591
GLU	假设方差相等	.191	.663	-1.549	140	.124	5.4038	1.53688

4.5568							
1.12102							
nation	0	356	2.61	1.114	.059		
	1	274	2.30	1.118	.068		
HC	0	356	.81	.391	.021		
	1	274	.75	.433	.026		27.5303
						12.119	3.70212

40.96	12.12	40.96±12.12
27.53	3.70	27.53±3.7
117.79	9.43	117.79±9.43
72.84	10.08	72.84±10.08
4.74	1.28	4.74±1.28
1.72	0.45	1.72±0.45
2.93	1.04	2.93±1.04
2.78	1.25	2.78±1.25
5.40	1.54	5.4±1.54

117.79	72.84	4.7391	1.7168	2.9322	2.7762	5.4038
9.433	10.081	1.27868	.44732	1.03752	1.24591	1.53688

Variables	UIG		KZK		KGZ		T
	Hypertension (n=90)	Controls (n=80)	Hypertension (n=52)	Controls (n=98)	Hypertension (n=90)	Controls (n=78)	Hypertension (n=65)
Age (years)	62.88±11.62	59.19±13.83	49.33±10.48	41.68±10.97	54.85±12.92	40.96±12.12	54.85±12.92
Gender (male)	25(27.8%)	40(50.0%)	25(48.1%)	20(20.4%)	38(42.2%)	27（34.6%）	38(56.7%)

JK
Controls (n=77)
40.96±12.12
34(33.7%)

Table S2. Directly measured subclass-specific IgG Fc *N*-glycomic composition in hypertension p

Glycans	UIG			KZK		
	Mann-Whitney test		Logistic regression	Mann-Whitney test		Logistic regression
	Z	*P* values	*P-adjusted*	Z	*P* values	*P-adjusted*
IgG1G0	-0.71	4.80E-01	1.91E-01	-0.19	8.50E-01	1.45E-01
IgG1G0F	-2.28	**2.24E-02**	9.77E-02	-4.77	**1.84E-06**	2.90E-03
IgG1G0FN	-1.53	1.25E-01	1.53E-01	-0.99	3.22E-01	6.54E-01
IgG1G0N	-0.64	5.23E-01	2.28E-01	-3.02	**2.49E-03**	1.92E-02
IgG1G1	-1.88	6.01E-02	6.69E-02	-0.35	7.25E-01	3.01E-01
IgG1G1F	-0.42	6.73E-01	6.53E-01	-2.91	**3.56E-03**	1.94E-02
IgG1G1FN	-0.21	8.31E-01	9.07E-01	-3.94	**8.11E-05**	1.09E-02
IgG1G1FNS	-0.18	8.57E-01	4.08E-01	-5.34	**9.14E-08**	2.00E-04
IgG1G1FS	-1.40	1.60E-01	1.42E-01	-1.90	5.70E-02	7.16E-01
IgG1G1N	-0.22	8.29E-01	1.58E-01	-1.66	9.64E-02	7.16E-02
IgG1G1NS	-1.23	2.20E-01	4.74E-01	-2.00	**4.53E-02**	3.16E-02
IgG1G1S	-1.55	1.21E-01	5.81E-01	-1.71	8.73E-02	7.99E-02
IgG1G2	-1.44	1.51E-01	1.33E-01	-2.54	**1.10E-02**	5.79E-02
IgG1G2F	-0.87	3.83E-01	6.96E-01	-4.42	**9.74E-06**	3.00E-03
IgG1G2FN	-1.56	1.19E-01	5.16E-01	-2.19	**2.87E-02**	1.96E-01
IgG1G2FNS	-0.36	7.21E-01	5.38E-01	-2.74	**6.06E-03**	1.60E-03
IgG1G2FS	-0.96	3.39E-01	5.54E-01	-2.78	**5.43E-03**	1.21E-01
IgG1G2N	0.00	1.00E+00	2.16E-01	-1.26	2.09E-01	4.23E-01
IgG1G2NS	0.00	1.00E+00	7.02E-01	-1.54	1.23E-01	1.46E-02
IgG1G2S	-1.99	**4.61E-02**	1.25E-01	-1.50	1.33E-01	3.94E-01
IgG2G0	-1.23	2.20E-01	1.11E-01	-2.01	**4.40E-02**	6.91E-02
IgG2G0F	-0.09	9.28E-01	8.80E-01	-5.89	**3.91E-09**	<.0001
IgG2G0FN	-0.33	7.45E-01	6.34E-01	-1.82	6.93E-02	1.85E-01
IgG2G0N	-0.70	4.86E-01	1.51E-01	-3.96	**7.59E-05**	3.70E-03
IgG2G1	-1.54	1.25E-01	8.18E-01	-0.91	3.62E-01	4.51E-01
IgG2G1F	-0.54	5.88E-01	4.15E-01	-3.43	**6.00E-04**	2.30E-03
IgG2G1FN	-0.35	7.25E-01	6.65E-01	-6.52	**7.23E-11**	<.0001
IgG2G1FNS	-1.11	2.66E-01	1.52E-01	-4.95	**7.49E-07**	<.0001
IgG2G1FS	-0.27	7.84E-01	7.85E-01	-3.72	**2.02E-04**	1.00E-03
IgG2G1N	-0.29	7.70E-01	9.62E-01	-0.19	8.50E-01	2.59E-01
IgG2G1NS	0.00	1.00E+00	7.67E-01	-0.25	7.99E-01	6.72E-01
IgG2G1S	-1.35	1.76E-01	1.59E-01	-2.51	**1.20E-02**	3.48E-02
IgG2G2	-0.49	6.28E-01	3.74E-01	-4.48	**7.53E-06**	1.23E-02
IgG2G2F	-0.01	9.92E-01	7.76E-01	-4.70	**2.56E-06**	2.00E-04
IgG2G2FN	-0.10	9.21E-01	7.62E-01	-4.11	**3.94E-05**	7.00E-04
IgG2G2FNS	-0.14	8.88E-01	9.34E-01	-0.59	5.54E-01	2.74E-01
IgG2G2FS	-0.20	8.44E-01	8.18E-01	-3.05	**2.27E-03**	1.49E-02
IgG2G2N	-1.34	1.79E-01	7.50E-01	-4.94	**7.96E-07**	5.00E-04
IgG2G2NS	0.00	1.00E+00	8.84E-01	-1.33	1.82E-01	1.35E-02
IgG2G2S	-0.03	9.73E-01	1.22E-01	-1.63	1.03E-01	7.65E-01
IgG4G0	-0.67	5.05E-01	1.72E-01	-2.98	**2.87E-03**	5.09E-01
IgG4G0F	-0.17	8.65E-01	8.49E-01	-7.34	**2.18E-13**	<0.0001
IgG4G0FN	-0.29	7.72E-01	6.19E-01	-5.75	**8.73E-09**	<.0001
IgG4G0N	-0.81	4.15E-01	3.01E-01	-2.97	**3.02E-03**	1.09E-01

IgG4G1	-1.43	1.51E-01	3.02E-01	-4.60	**4.13E-06**	<.0001
IgG4G1F	-1.11	2.65E-01	3.03E-01	-0.83	4.05E-01	3.42E-01
IgG4G1FN	-0.52	6.05E-01	5.13E-01	-1.55	1.22E-01	2.54E-01
IgG4G1FNS	-0.17	8.63E-01	7.64E-01	-0.57	5.67E-01	3.59E-01
IgG4G1FS	-0.38	7.02E-01	1.42E-01	-0.40	6.87E-01	9.60E-01
IgG4G1N	-1.06	2.89E-01	3.19E-01	-4.94	**7.80E-07**	<.0001
IgG4G1NS	-0.95	3.40E-01	4.43E-01	-1.57	1.16E-01	2.90E-01
IgG4G1S	-0.93	3.54E-01	5.35E-02	-0.78	4.34E-01	8.20E-03
IgG4G2	-0.24	8.09E-01	6.68E-01	-4.00	**6.33E-05**	1.80E-03
IgG4G2F	-1.85	6.48E-02	2.00E-01	-2.72	**6.43E-03**	2.88E-02
IgG4G2FN	-1.94	5.28E-02	2.67E-01	-1.61	1.07E-01	4.29E-01
IgG4G2FNS	-2.50	**1.23E-02**	3.20E-01	-3.04	**2.33E-03**	1.39E-01
IgG4G2FS	-2.01	**4.46E-02**	5.72E-02	-4.02	**5.82E-05**	1.00E-03
IgG4G2N	-0.87	3.83E-01	4.52E-01	-7.17	**7.42E-13**	<0.0001
IgG4G2NS	-1.16	2.48E-01	6.47E-01	-2.32	**2.02E-02**	1.13E-01
IgG4G2S	-0.20	8.44E-01	2.58E-01	-1.15	2.49E-01	5.04E-01

False discovery rate (FDR) was controlled using Benjamini–Hochberg procedure.
Bold in *P*- adjusted represent $P < 0.05$.
Logistic regression controlled for gender, age, BMI, dyslipidemia, FBG and ethnicity

atients and healthy controls for each of the four ethnic groups and the pooling of the four eth

KGZ			TJK		
Mann-Whitney test		Logistic regression	Mann-Whitney test		Logistic regression
Z	*P* values	*P-adjusted*	Z	*P* values	*P-adjusted*
-1.08	2.79E-01	3.81E-01	-1.91	5.61E-02	4.73E-01
-0.88	3.80E-01	8.61E-01	-3.19	**1.40E-03**	7.78E-01
-0.74	4.57E-01	6.09E-01	-3.47	**5.28E-04**	8.90E-01
-1.16	2.45E-01	3.42E-01	-2.15	**3.19E-02**	3.02E-01
-0.07	9.43E-01	5.32E-01	-0.53	5.99E-01	3.95E-01
-0.13	8.96E-01	7.12E-01	-0.71	4.75E-01	5.89E-01
-0.31	7.60E-01	6.98E-01	-0.13	8.98E-01	2.99E-01
-0.37	7.08E-01	6.76E-01	-0.63	5.30E-01	7.11E-01
-0.45	6.51E-01	5.21E-01	-0.85	3.97E-01	7.67E-01
-0.39	6.96E-01	4.37E-01	-0.11	9.13E-01	2.51E-01
-1.36	1.72E-01	2.92E-01	0.00	1.00E+00	1.37E-01
-0.43	6.67E-01	5.37E-01	-2.40	**1.64E-02**	1.96E-01
-0.46	6.44E-01	7.53E-01	-1.97	**4.89E-02**	9.02E-01
-0.86	3.92E-01	8.06E-01	-3.38	**7.34E-04**	6.31E-01
-0.88	3.77E-01	9.71E-01	-2.12	**3.43E-02**	5.61E-01
-0.72	4.73E-01	7.59E-01	-1.94	5.29E-02	9.52E-01
-0.63	5.26E-01	3.27E-01	-3.65	**2.58E-04**	9.34E-01
-0.34	7.31E-01	8.12E-01	-0.92	3.58E-01	6.63E-01
-0.22	8.29E-01	8.33E-01	0.00	1.00E+00	5.03E-01
-0.48	6.28E-01	4.19E-01	-2.12	**3.40E-02**	9.20E-01
-0.08	9.33E-01	2.97E-01	-0.04	9.66E-01	4.58E-01
-1.04	2.99E-01	5.14E-01	-3.21	**1.35E-03**	8.59E-01
-1.40	1.63E-01	1.77E-01	-2.89	**3.80E-03**	8.09E-01
-0.10	9.20E-01	5.94E-01	-0.07	9.42E-01	5.43E-01
-0.26	7.98E-01	7.70E-01	-0.46	6.44E-01	2.25E-01
-0.51	6.11E-01	3.48E-01	-1.46	1.45E-01	4.24E-01
-0.67	5.02E-01	5.10E-01	-1.00	3.17E-01	9.57E-01
-0.66	5.08E-01	7.10E-01	-0.19	8.46E-01	9.17E-01
-1.60	1.11E-01	1.70E-02	-1.88	5.97E-02	9.82E-01
-0.67	5.02E-01	7.39E-01	-0.70	4.86E-01	2.71E-01
-0.99	3.24E-01	5.81E-01	0.00	1.00E+00	5.34E-01
-1.68	9.24E-02	7.86E-02	-0.68	4.97E-01	6.35E-01
-0.09	9.25E-01	7.49E-01	-1.48	1.38E-01	2.95E-01
-1.37	1.71E-01	2.78E-01	-2.94	**3.24E-03**	3.87E-01
-1.26	2.08E-01	2.28E-01	-1.80	7.21E-02	8.81E-01
-1.43	1.52E-01	2.71E-01	-0.81	4.16E-01	8.57E-01
-1.52	1.28E-01	9.91E-02	-3.26	**1.12E-03**	7.99E-01
-0.22	8.25E-01	7.08E-01	-0.66	5.08E-01	3.16E-01
-0.82	4.10E-01	5.18E-01	0.00	1.00E+00	1.77E-01
-1.39	1.64E-01	2.20E-01	-3.00	**2.74E-03**	6.84E-01
-1.21	2.26E-01	3.60E-01	-1.57	1.17E-01	6.56E-01
-0.57	5.72E-01	9.69E-01	-2.45	**1.44E-02**	7.34E-01
-0.04	9.65E-01	7.18E-01	-3.09	**2.01E-03**	8.91E-01
-0.99	3.24E-01	3.01E-01	-1.09	2.76E-01	2.93E-01

-0.32	7.53E-01	9.37E-01	-2.10	**3.57E-02**	6.72E-01
-0.45	6.51E-01	9.73E-01	-0.02	9.82E-01	4.80E-01
-0.24	8.10E-01	9.98E-01	-1.17	2.43E-01	8.69E-01
-1.30	1.94E-01	3.99E-01	-0.48	6.34E-01	8.04E-01
-0.83	4.06E-01	2.02E-01	-1.14	2.55E-01	2.33E-01
-0.43	6.64E-01	9.44E-01	-2.53	**1.14E-02**	5.84E-01
-1.13	2.58E-01	5.43E-01	-1.54	1.22E-01	6.62E-02
-0.78	4.35E-01	6.13E-01	-0.11	9.10E-01	9.78E-01
-0.19	8.49E-01	4.58E-01	-0.93	3.50E-01	4.83E-01
-0.07	9.40E-01	8.82E-01	-2.65	**8.08E-03**	6.42E-01
-0.84	3.99E-01	7.07E-01	-1.32	1.87E-01	9.21E-01
-1.16	2.47E-01	2.81E-01	-2.48	**1.30E-02**	9.83E-01
-0.45	6.51E-01	3.93E-01	-2.67	**7.51E-03**	5.42E-01
-0.73	4.63E-01	8.06E-01	-1.26	2.08E-01	8.39E-01
-1.90	5.69E-02	3.88E-01	0.00	1.00E+00	7.36E-01
-0.97	3.32E-01	5.75E-01	-1.79	7.42E-02	6.22E-01

nic groups.

Pooling of 4 ethnic groups			
Mann-Whitney test		Logistic regression	*FDR*
Z	*P* values	*P-adjusted*	
-0.19	8.50E-01	4.02E-01	4.72E-01
-4.77	**1.84E-06**	5.00E-04	**7.50E-03**
-0.99	3.22E-01	2.72E-01	3.63E-01
-3.02	**2.49E-03**	8.70E-01	8.70E-01
-0.35	7.25E-01	7.66E-01	8.21E-01
-2.91	**3.56E-03**	3.05E-01	3.90E-01
-3.94	**8.11E-05**	4.65E-02	1.21E-01
-5.34	**9.14E-08**	8.50E-01	8.65E-01
-1.90	5.70E-02	6.46E-02	1.55E-01
-1.66	9.64E-02	4.53E-01	5.13E-01
-2.00	**4.53E-02**	7.09E-02	1.58E-01
-1.71	8.73E-02	4.70E-02	1.18E-01
-2.54	**1.10E-02**	4.01E-02	1.20E-01
-4.42	**9.74E-06**	3.73E-02	1.18E-01
-2.19	**2.87E-02**	6.17E-02	1.54E-01
-2.74	**6.06E-03**	8.39E-01	8.83E-01
-2.78	**5.43E-03**	6.94E-02	1.60E-01
-1.26	2.09E-01	8.92E-02	1.85E-01
-1.54	1.23E-01	4.26E-01	4.91E-01
-1.50	1.33E-01	3.41E-02	1.14E-01
-2.01	**4.40E-02**	3.33E-01	4.00E-01
-5.89	**3.91E-09**	2.00E-04	**1.20E-02**
-1.82	6.93E-02	2.73E-01	3.55E-01
-3.96	**7.59E-05**	8.44E-01	8.73E-01
-0.91	3.62E-01	1.42E-01	2.44E-01
-3.43	**6.00E-04**	3.18E-01	3.97E-01
-6.52	**7.23E-11**	2.50E-03	**2.14E-02**
-4.95	**7.49E-07**	9.36E-02	1.81E-01
-3.72	**2.02E-04**	2.40E-03	**2.40E-02**
-0.19	8.50E-01	2.31E-01	3.15E-01
-0.25	7.99E-01	4.61E-01	5.13E-01
-2.51	**1.20E-02**	1.24E-02	6.76E-02
-4.48	**7.53E-06**	2.26E-02	1.04E-01
-4.70	**2.56E-06**	2.98E-02	1.12E-01
-4.11	**3.94E-05**	2.75E-02	1.18E-01
-0.59	5.54E-01	1.70E-01	2.69E-01
-3.05	**2.27E-03**	2.15E-02	9.92E-02
-4.94	**7.96E-07**	1.41E-01	2.49E-01
-1.33	1.82E-01	4.30E-02	1.23E-01
-1.63	1.03E-01	6.00E-03	**4.00E-02**
-2.98	**2.87E-03**	1.86E-01	2.87E-01
-7.34	**2.18E-13**	3.00E-04	**6.00E-03**
-5.75	**8.73E-09**	1.59E-01	2.57E-01
-2.97	**3.02E-03**	2.03E-01	2.98E-01

-4.60	**4.13E-06**	9.41E-02	1.76E-01
-0.83	4.05E-01	6.98E-01	7.61E-01
-1.55	1.22E-01	8.77E-02	1.88E-01
-0.57	5.67E-01	2.26E-01	3.16E-01
-0.40	6.87E-01	5.20E-03	**3.47E-02**
-4.94	**7.80E-07**	2.15E-01	3.07E-01
-1.57	1.16E-01	1.43E-01	2.39E-01
-0.78	4.34E-01	1.70E-03	**2.04E-02**
-4.00	**6.33E-05**	3.22E-01	3.94E-01
-2.72	**6.43E-03**	2.80E-02	1.05E-01
-1.61	1.07E-01	1.10E-01	1.99E-01
-3.04	**2.33E-03**	3.01E-02	1.00E-01
-4.02	**5.82E-05**	2.00E-04	**1.20E-02**
-7.17	**7.42E-13**	7.50E-03	**4.50E-02**
-2.32	**2.02E-02**	1.98E-01	2.96E-01
-1.15	2.49E-01	9.29E-02	1.86E-01

Table S3. Derived subclass-specific IgG Fc *N*-glycomic composition in hypertension patients and h

Glycans	UIG			KZK		
	Mann-Whitney test		Logistic regression	Mann-Whitney test		Logistic regression
	Z	*P* values	*P-adjusted*	Z	*P* values	*P-adjusted*
A1	-1.83	6.74E-02	1.53E-01	-4.41	**1.03E-05**	4.20E-03
M1	-0.73	4.64E-01	5.90E-01	-3.76	**1.73E-04**	6.41E-02
D1	-1.25	2.10E-01	4.97E-01	-4.32	**1.53E-05**	3.50E-03
G1	-1.25	2.11E-01	4.62E-01	-4.33	**1.48E-05**	2.50E-03
S1	-1.82	6.83E-02	1.54E-01	-2.64	**8.34E-03**	1.81E-01
B1	-0.46	6.49E-01	6.89E-01	-0.56	5.75E-01	7.74E-01
F1	-2.28	**2.25E-02**	2.88E-02	-1.16	2.44E-01	9.98E-01
A2	-0.01	9.94E-01	8.93E-01	-5.45	**4.94E-08**	<.0001
M2	-0.50	6.17E-01	4.74E-01	-5.32	**1.02E-07**	<.0001
D2	-0.46	6.49E-01	8.51E-01	-5.17	**2.30E-07**	<.0001
G2	-0.18	8.55E-01	8.09E-01	-5.47	**4.42E-08**	<.0001
S2	-0.34	7.37E-01	7.74E-01	-3.23	**1.22E-03**	5.80E-03
B2	-0.14	8.90E-01	8.57E-01	-2.03	**4.20E-02**	1.91E-02
F2	-1.28	2.01E-01	5.14E-01	-0.46	6.47E-01	4.22E-01
A4	-0.28	7.82E-01	7.50E-01	-7.23	**4.95E-13**	<0.0001
M4	-0.26	7.91E-01	8.61E-01	-4.82	**1.45E-06**	2.00E-04
D4	-0.05	9.62E-01	9.67E-01	-6.31	**2.71E-10**	<.0001
G4	-0.17	8.65E-01	8.59E-01	-8.00	**1.24E-15**	<0.0001
S4	-0.66	5.12E-01	8.18E-01	-1.70	8.95E-02	2.04E-01
B4	-0.05	9.64E-01	8.58E-01	-0.09	9.31E-01	5.68E-01
F4	-0.98	3.29E-01	2.43E-01	-3.72	**1.96E-04**	2.90E-03

False discovery rate (FDR) was controlled using Benjamini–Hochberg procedure.
Bold in *P*- adjusted represent $P < 0.05$.
Logistic regression controlled for gender, age, BMI, dyslipidemia, FBG and ethnicity
A - agalactosylation, M - monogalactosylation, D- digalactosylation, G - galactosylation (total), S - s

ealthy controls for each of the four ethnic groups and the pooling of the four ethnic groups.

KGZ			TJK			
Mann-Whitney test		Logistic regression	Mann-Whitney test		Logistic regression	Mann-Wh
Z	*P* values	*P-adjusted*	Z	*P* values	*P-adjusted*	Z
-1.02	3.09E-01	6.21E-01	-3.64	**2.70E-04**	9.44E-01	-4.41
-0.38	7.03E-01	7.79E-01	-0.30	7.67E-01	4.22E-01	-3.76
-0.88	3.77E-01	7.99E-01	-3.34	**8.34E-04**	7.48E-01	-4.32
-0.72	4.71E-01	9.89E-01	-3.22	**1.27E-03**	8.97E-01	-4.33
-0.96	3.38E-01	2.42E-01	-3.72	**1.96E-04**	9.33E-01	-2.64
-0.55	5.83E-01	5.50E-01	-1.86	6.24E-02	4.24E-01	-0.56
0.00	1.00E+00	5.64E-01	-0.27	7.91E-01	4.05E-01	-1.16
-1.12	2.62E-01	3.25E-01	-3.59	**3.34E-04**	8.90E-01	-5.45
-0.27	7.91E-01	4.06E-01	-1.01	3.14E-01	7.36E-01	-5.32
-1.30	1.92E-01	3.59E-01	-3.44	**5.80E-04**	8.45E-01	-5.17
-1.35	1.75E-01	3.16E-01	-2.84	**4.48E-03**	9.67E-01	-5.47
-1.76	7.88E-02	4.28E-02	-3.00	**2.66E-03**	9.02E-01	-3.23
0.00	1.00E+00	6.24E-01	-1.23	2.18E-01	7.71E-01	-2.03
-0.76	4.44E-01	1.85E-01	-0.34	7.33E-01	1.49E-01	-0.46
-0.45	6.51E-01	9.73E-01	-2.61	**9.09E-03**	8.10E-01	-7.23
-0.02	9.80E-01	9.44E-01	-1.62	1.06E-01	6.99E-01	-4.82
-0.64	5.24E-01	4.30E-01	-2.25	**2.42E-02**	5.48E-01	-6.31
-0.20	8.42E-01	5.02E-01	-0.90	3.70E-01	8.07E-01	-8.00
-0.32	7.53E-01	8.97E-01	-3.13	**1.74E-03**	8.07E-01	-1.70
-0.68	4.98E-01	7.22E-01	-2.69	**7.14E-03**	7.92E-01	-0.09
-0.02	9.88E-01	7.90E-01	-0.44	6.58E-01	5.70E-01	-3.72

ialylation, B - bisecting GlcNAc, F - fucosylation. Number represents specific IgG subclass.

Pooling of 4 ethnic groups		
itney test	Logistic regression	*FDR*
P values	*P-adjusted*	
1.03E-05	1.30E-03	**6.07E-03**
1.73E-04	1.50E-02	**3.50E-02**
1.53E-05	2.14E-02	**4.28E-02**
1.48E-05	6.00E-03	**1.87E-02**
8.34E-03	1.04E-02	**2.91E-02**
5.75E-01	4.74E-01	6.98E-01
2.44E-01	3.44E-01	5.35E-01
4.94E-08	5.00E-04	**4.67E-03**
1.02E-07	1.00E-03	**5.60E-03**
2.30E-07	2.30E-03	**9.20E-03**
4.42E-08	4.00E-04	**5.60E-03**
1.22E-03	5.10E-03	**1.79E-02**
4.20E-02	1.25E-01	2.32E-01
6.47E-01	2.29E-01	3.76E-01
4.95E-13	8.00E-04	**5.60E-03**
1.45E-06	1.88E-02	**4.05E-02**
2.71E-10	1.25E-02	**3.18E-02**
1.24E-15	1.00E-04	**2.80E-03**
8.95E-02	8.42E-01	1.12E+00
9.31E-01	2.14E-01	3.74E-01
1.96E-04	6.83E-01	9.56E-01