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Genetic Variants Associated with Poor Responsiveness to Sulfonylureas in Filipinos with Type 2 Diabetes Mellitus

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Abstract

Introduction. Sulfonylureas (SUs) are commonly used drugs for type 2 diabetes mellitus (T2DM) in the Philippines. This study aimed to associate genetic variants with poor response to gliclazide and glimepiride among Filipinos.

Methodology. Two independent, dichotomous longitudinal substudies enrolled 139 and 113 participants in the gliclazide and glimepiride substudies, respectively. DNA from blood samples underwent customized genotyping for candidate genes using microarray. Allelic and genotypic features and clinical associations were determined using exact statistical methods.

Results. Three months after sulfonylurea monotherapy, 18 (13%) were found to be poorly responsive to gliclazide, while 7 (6%) had poor response to glimepiride. Seven genetic variants were nominally associated ($p<0.05$) with poor gliclazide response, while three variants were nominally associated with poor glimepiride response. For gliclazide response, 3 carboxypeptidase-associated variants (rs319952 and rs393994 of *AGBL4* and rs2229437 of *PRCP*) had the highest genotypic association; other variants include rs9806699, rs7119, rs6465084 and rs1234315. For glimepiride response, 2 variants were nominally associated: *CLCN6-NPPA-MTHFR* gene cluster – rs5063 and rs17367504 – and rs2299267 from the *PON2* loci.

Conclusion. Genetic variants were found to have a nominal association with sulfonylurea response among Filipinos. These findings can guide for future study directions on pharmacotherapeutic applications for sulfonylurea treatment in this population.

Key words: genetic variants, sulfonylureas, resistance, Filipino, gliclazide, glimepiride

INTRODUCTION

Despite the availability of new drugs, sulfonylureas (SU) remain one of the most prescribed drugs in the treatment of type 2 diabetes mellitus (T2DM).[1] Because of its relatively low price and availability, it is popular in low-resource countries like the Philippines, where local health centers and diabetes clubs distribute SUs through the Department of Health's Philippine Package of Essential NCD Intervention (Phil PEN) program.

However, despite patient compliance, SUs may fail to regulate high sugar levels among T2DM patients. In one study, there was a 21.3% monotherapy failure in Korean patients taking SUs.[2] Meanwhile among Filipino patients, a study showed that only 15% of those taking oral hypoglycemic agents (OHAs) achieved the American Diabetes Association (ADA) HbA1c target of <7.0%,[3] suggesting that Filipinos may have some degree of resistance towards OHAs. While this survey did not exclusively focus on SUs, given the mentioned availability

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of these drugs to Filipinos, it can be inferred that some variability may also be due to SU. Moreover, in a study that followed progressive up-titration using gliclazide modified release (gliclazide MR), 35% of the participants did not reach the desired HbA1c level.[4] On the other hand, glimepiride is usually found to be less effective than other OHAs or administered in combination with other drugs to reach the ADA standard of glucose level.[5-7]

Genetics can influence an individual's responsiveness to sulfonylureas. Variants of genes such as *TCF7L2* (transcription factor 7 like 2 gene), *ABCC8* (ATP binding cassette subfamily C member 8 gene), encoding the sulfonylurea receptor 1, *KCNJ11* (potassium inwardly rectifying channel subfamily J member 11 gene), *CYP2C9* (cytochrome P450 family 2 subfamily C member 9 gene), and *CYP2C19* (cytochrome P450 family 2 subfamily C member 19 gene) have been previously linked with gliclazide and glimepiride response.[8-11]

Nonetheless, interethnic differences may infer genetic variation in the trait of interest. For instance, *TCF7L2*, a well-known gene associated with therapeutic response to SUs exhibited varying risk alleles among German, Chinese, and Indian populations.[12,13] In another case, Japanese patients with a mutant-type allele of the *CYP2C9* gene showed a better response to glimepiride compared with the wild-type allele.[14] On the other hand, in Chinese T2DM patients, *CYP2C19* genetic polymorphisms are the more likely determinants of gliclazide response instead of *CYP2C9*.[15]

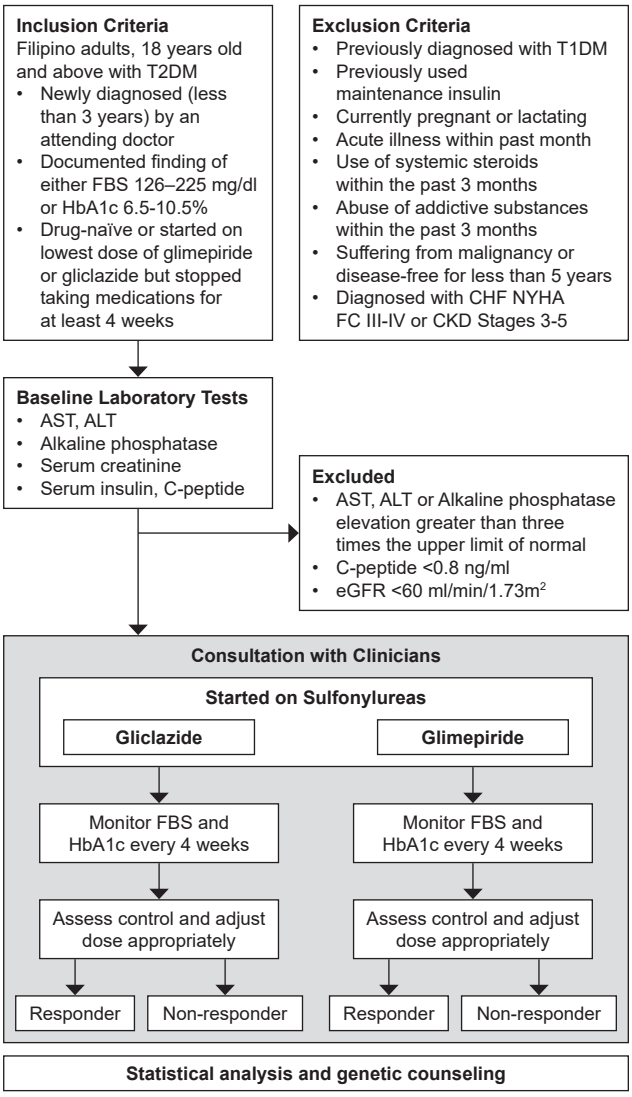

Figure 1. Flowchart of participant enrollment and follow-up.

However, there are no known studies that looked at genetic variants and their association with SU resistance among Filipinos. Although there were other variants that were associated with SU use, interethnic variability makes it pertinent to perform a separate study for Filipinos, who are underrepresented in the previous studies. Most studies were done on non-Filipino populations, mainly Caucasians, Blacks, Han Chinese, and even South Asians. We also reviewed the status of Malays, with little success. No documentation on specific targeting of Malay individuals was known to the authors. Thus, the current study investigated the association of genetic variants with treatment response to gliclazide and glimepiride. Among the SUs, the present study selected gliclazide and glimepiride because of their improved insulin release and diminished side effects such as hypoglycemic episodes and weight gain compared with older generation SUs.

The study results may aid in the creation of health policies for prescribing SUs to patients with T2DM. The findings may also serve as a first step in the development of test kits for personalized medicine to attain therapeutic targets.

METHODOLOGY

Study design and enrollment of participants

The study was implemented in compliance with the University of the Philippines Manila – Research Ethics Board (Study Protocol Code: UPMREB-2012-0187-NIH). Volunteer participants were enrolled from March 2014 to January 2019 from different institutions in the Philippines, such as Philippine General Hospital in Manila, Corazon Locsin Montelibano Memorial Regional Hospital in Bacolod City, Southern Philippines Medical Center in Davao City, and other government hospitals, health centers, and private clinics in Metro Manila and nearby provinces.

Screening of participants in this case-control study was performed following the inclusion and exclusion criteria (Figure 1). The study population is composed of adults (>18 years old) Filipinos with at least 3 generations of Filipino ascendancy. Screening involved baseline laboratory tests for fasting blood sugar (FBS), glycated hemoglobin (HbA1c), fasting serum insulin, C-peptide, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and serum creatinine.

Included participants were started on either gliclazide or glimepiride following the study's treatment algorithm

and administered by the attending physician. Medication adherence was assessed on the day of follow-up and computed as follows: (number of packets consumed/ number of packets prescribed) multiplied by 100%. Responders were defined as those whose HbA1c levels changed by more than or equal to 0.5% (absolute value difference) from baseline after 3 months of treatment, while poor responders were those whose HbA1c changed less than 0.5% from baseline after 3 months of treatment.[16,17]

The initial estimates for the minimum sample sizes were done by assuming a recessive model (as this model typically requires the largest sample sizes), an odds ratio of >2.5 (risk) or <0.4 (protective, an alpha of 0.05, and power of 80%), with a 1:2 case-control ratio. We recognize the limitation of alpha errors in the setting of multiple testing. To overcome this limitation, the conservative Bonferroni adjusted *p*-value <0.05 correction was initially considered. However, the study did not reach the estimated sample sizes due to the few prospective participants passing the screening criteria. The study screened more than 17,000 participants to come up with the present numbers. In particular, there were challenges in recruiting drug naive T2DM cases and those who were not on medication for the past 3 months.

Thus, in this study, the practical *q* value for all allelic and genotypic results for all variants is 1, and thus we are not able to reject the likelihood that the results are false positives. Nonetheless, we expect results using both nominal statistical inference and sensible biological insights, although with caution and reservation. Note that the assumptions are considered liberal as we considered the largest minimum based on the recessive model. Thus, when we analyzed the results, many of the variants found had a much lower alpha that became nominally significant at smaller sample sizes. This is true for additive models and the dominant models which require fewer sample sizes than the recessive model.

Besides the statistical inference, the significance of these findings can be enhanced in other ways, particularly, biological relevance/plausibility, multiplicity in results, and literature replicability. However, we will cite select findings with caution, especially if the findings are not supported by such information; nonetheless, these minor findings should still be considered as preliminary findings that need verification.

The actual sizes per subgroup were set at 62 cases and 124 controls to assume a power of 80% at alpha error <0.05 using the recessive genetic model. However, because of the lower-than-expected number of cases, further importance to the enrichment of variants per gene and observed biological theme/s was given.

DNA extraction and quantification

DNA extraction from whole blood samples was performed using QIAamp DNA Blood Mini Kit (QIAGEN, Victoria, Australia) following manufacturer instructions. Eluted DNA was quantified using the NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, MA, USA) at 260 nm. DNA samples with an $A_{260/280}$ of between 1.7 to 2.0, and a minimum concentration of 50 ng/ul were stored at -20°C until microarray genotyping.

Genotyping

The customized bead chips included 2,842 variants that were associated with various conditions, treatment responses, and adverse effects of various drugs, including those related to T2DM and SUs. These variants were researched extensively from different sources, such as Pharmacogenetics Knowledgebase (PharmGKB) (Thorn et al., 2013),[18] National Human Genome Research Institute Genome-wide Association Study (NHGRI GWAS Catalog),[19] PubMed, and selected patent databases such as Patentscope and Espacenet Variants with odds ratios (ORs) greater than 2.5 or less than 0.40 were preferentially included because of their perceived clinical relevance; variants with less established ORs were also included to assess their frequency in the local population. The selected SNPs were submitted to Illumina, Inc. for scoring to estimate their specificity and determine if the variants will be able to discriminate between responders and poor responders.

The variants were interrogated using Illumina iSelect Infinium Beadchip customized genotyping microarray (Illumina, CA, USA) using the manufacturer's prescribed procedures. Beadchips were scanned using an Illumina HiScan microarray scanner.

GenomeStudio v2.0 and gPlink v2.05.10 were used to evaluate the quality of sample data and for quality control. Variants with call frequencies of more than or equal to 95% were included in the study. Participants with an individual missingness rate (MIND) of more than 5% were excluded from further analysis. Other tests performed to exclude SNPs include frequency tests (minor allele frequency (MAF) <1%), genotype missingness rate (GENO) >5%, and Hardy-Weinberg equilibrium test (significant among controls >0.001).

Statistical analyses

For the clinical data, comparison of categorical variables used chi-square tests or Fisher exact test, as appropriate. For comparison between 2 quantitative variables, an independent t-test was performed.

Description of variants and associated genes were taken from *http://genome.ucsc.edu* (accessed April 20, 2022).[20]

Allelic and genotypic characteristics were assessed using gPlink v2.05.10. To test for allelic and genotypic association in a small sample set, the non-parametric Fisher-Irwin exact test was used. Correcting for multiple testing was done via the computation of *q* values.

To address the concern regarding the stability of the findings, p-values were used as the main determinants of association. The CI would be secondary, as it serves as a rough guide as to the directionality of the effect. In place of the *q* values, we focused on other parameters, such as biological relevance/plausibility, multiplicity in results, and literature replicability to increase confidence in the results, while interpreting the associations with adequate caution. As the sample sizes were small, the genetic association used Fisher-Irwin exact test for categorical variables.

For the genotypic association tests, the mode of inheritance or the effect of the genotypes was inferred based on the distribution of the genotypes among the case and control participants identified using gPlink v2.05.10. Crude ORs were used to infer the impact of an allele or a genotype on the phenotypic outcome. As with classical epidemiology, an OR greater than 1.0 denotes susceptibility or risk, and an OR less than 1.0 denotes protection. The ORs were computed using exact logistic regression; in this case, those with $p<0.05$ are considered to have a nominal association.

Because of the small sample sizes, we deferred doing multiple regression analyses and limited the interpretations to univariate analyses.

RESULTS

Gliclazide

Originally, 139 patients were enrolled in the gliclazide substudy (Figure 2A). Three participants (2 cases and 1 control) were removed due to a low genotyping rate (MIND >0.05). After screening, 136 participants remained after data quality control of which 18 were non-responders and 118 were responders.

Table 1 summarizes the clinical characteristics between cases and controls in the gliclazide substudy. Age was comparable between both groups. Although not significant, there is a noticeable trend of more males and smokers among the non-responders. Notably, both HbA1c and FBS were lower at baseline among non-responders compared with the responders. Mean HbA1c significantly decreased from baseline to the third month among gliclazide responders by 22% (8.55% to 6.63%, $p < 0.05$).

Among the 2,842 candidate variants investigated, 1,262 variants were excluded based on significant Hardy-Weinberg disequilibrium, genotypic missingness, and minor allele threshold test results (Figure 2). Seven variants were nominally associated with poor gliclazide response: rs2229437, rs319952, rs393994, rs9806699, rs1234315, rs7119, and rs6465084. However, there was no significant genotypic and allelic association observed after adjustment for multiple testing (Bonferroni-adjusted $\alpha = 3.2 \times 10^{-5}$).

Table 2 presents allelic features of nominally significant associated genes, while Table 3 presents the genotypic features of nominally significant associated genes.

Two variants, rs319952 and rs393994, were particularly interesting as they are both intronic polymorphisms of the AGBL carboxypeptidase 4 (*AGBL4)* gene. Both are intronic variants exhibiting similar recessive mode of inheritance. Both variants confer almost similar genotypic ORs of 6-7 increasing the confidence of common effects. Both have A as their risk alleles.

The variant rs2229437 had the lowest p-value. Remarkably, this variant is a missense SNP in another carboxypeptidase gene, the prolylcarboxypeptidase *(PRCP)* gene. Sorting Intolerant from Tolerant algorithm predicted a deleterious

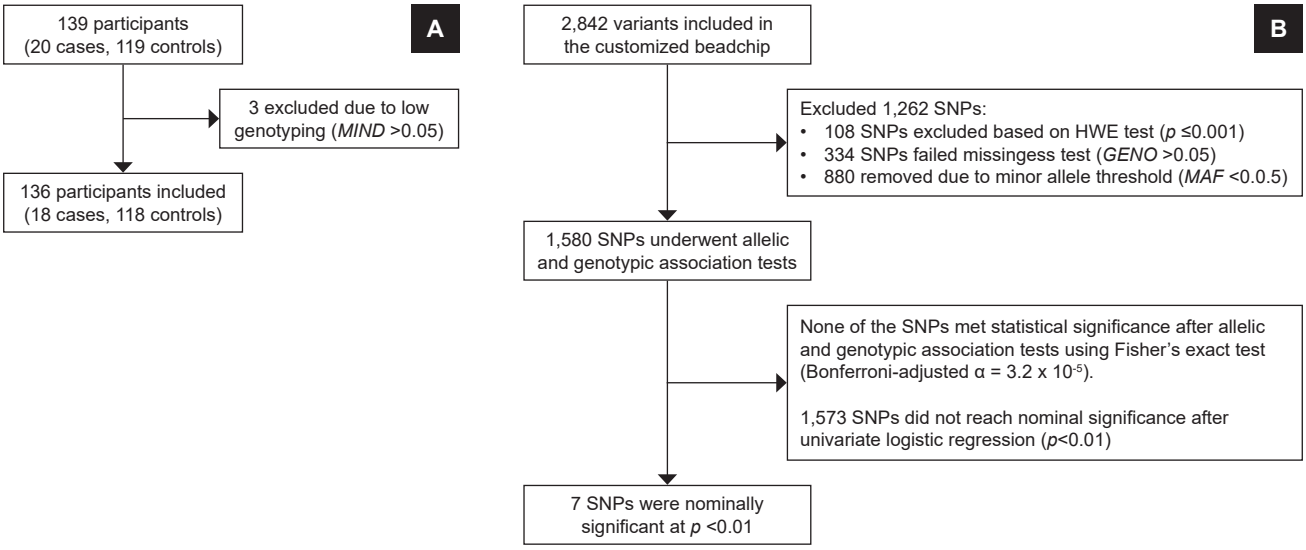

Figure 2. Schematic diagram of data processing and analysis for the gliclazide group. A total of 139 participants **(A)** and 2,842 SNPs **(B)** were analyzed to determine the association of genetic variants with poor gliclazide response.

Abbreviations: mind – individual missingness; SNP – single nucleotide polymorphism; HWE – Hardy-Weinberg equilibrium; geno – genotypic missingness; MAF – minor allele frequency.

Table 1. Clinical characteristics of participants in gliclazide substudy

Characteristics	Gliclazide poor responders (n = 18)	Gliclazide responders (n = 118)	*p*-value*
Age, years, mean (SD)	55.56 (12.77)	53.09 (10.12)	0.354
Male, %	44.44	26.27	0.056
Hypertension, %	55.56	47.46	0.261
Ever smoked, %	27.78	14.41	0.076
Alcohol use, %	16.67	32.20	0.090
BMI, kg/m^2, mean (SD)	26.64 (3.71)	26.02 (3.80)	0.519
Waist circumference, cm, mean (SD)	93.25 (9.37)	91.17 (10.16)	0.416
Baseline			
FBS, mg/dL, mean (SD)	143.94 (19.05)	167.07 (32.67)	0.004
HbA1c, %, mean (SD)	7.22 (0.66)	8.55 (1.15)	<0.001
Creatinine, mg/dL, mean (SD)	0.80 (0.29)	0.73 (0.23)	0.248
3rd month**			
FBS, mg/dL, mean (SD)	128.00 (35.33)	116.29 (22.91)**	0.065
HbA1c, %, mean (SD)	7.26 (0.79)	6.63 (0.85)**	0.003

Abbrev: BMI, body mass index; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation
*Significant at $p<0.05$ using Student's t-test or Fisher's exact test
**3rd-month values are significantly different compared with baseline values at $p< 0.05$ using paired t-test

Table 2. Allelic characterization of variants associated with poor gliclazide response

SNP	Implicated gene	Risk allele	Frequency		p-value*	q-value*	Predicted effect	Predicted Impact	
			Cases	Controls				SIFT	PolyPhen
rs2229437	*PRCP*	G	0.4444	0.2076	0.003247	1	Missense (E/D)	0.02 (deleterious)	0.009 (benign)
rs319952	*AGBL4*	A	0.8824	0.6504	0.005649	1	Intron variant	n/a	
rs393994	*AGBL4*	A	0.8611	0.6525	0.012310	1	Intron variant	n/a	
rs9806699	*ENSG00000259354// C15ORF48*	G	0.6389	0.4025	0.010840	1	5-upstream variant	n/a	
rs7119	*HMG20A*	A	0.5	0.2585	0.005146	1	3' untranslated region	n/a	
rs6465084	*GRM3*	A	1	0.8475	0.006797	1	Intron variant	n/a	

Abbrev: *PRCP*, prolylcarboxypeptidase; *AGBL4*, ATP/GTP binding protein like 4; *TNFSF4*, TNF superfamily member 4; *HMG20A*, high mobility group 20A; *GRM3*, glutamate metabotropic receptor 3; E/D, glutamic acid (E) to aspartic acid (D) mutation; SIFT, Sorting Intolerant Form Tolerant; Polyphen, Polymorphism Phenotyping.
*Variants are nominally significant at $p<0.05$.

Table 3. Genotypic characterization of variants associated with poor gliclazide response

SNP	Chrom No.	Model	Genotypes	Frequency		Crude OR	*p*-value*
				Cases	Controls		
rs2229437	11	DOM	GG and TG vs TT	77.78	36.44	6.02 (1.75, 26.73)	0.002
rs319952	1	REC	AA vs AG and GG	82.35	39.82	6.95 (1.80, 39.85)	0.002
rs393994	1	REC	AA vs AG and GG	77.78	38.98	5.41 (1.57, 23.98)	0.004
rs9806699	15	REC	GG vs AG and AA	44.44	12.71	5.39 (1.59, 18.14)	0.006
rs1234315	1	GENO	TC vs CC	5.56	45.76	0.08 (0.001, 0.60)	0.006
rs7119	15	ALLELIC	TT vs CC	38.89	18.64	1.33 (0.37, 4.52)	0.803
			AG vs GG	55.56	44.92	2.85 (0.77, 13.21)	0.138
rs6465084	7	REC	AA vs GG	22.22	3.39	14.13 (1.92, 114.88)	0.007

Abbrev: ADD, additive; DOM, dominant; DOMDEV, dominant deviant; REC, recessive.
*Variants are nominally significant at $p<0.05$

effect on its protein (SIFT = 0.02), although Polymorphism Phenotyping v2 (Polyphen v2) algorithm indicates that the resulting amino acid change from glutamic to aspartic acid has an otherwise benign impact (PolyPhen = 0.009). Upon univariate logistic regression analysis, the presence of the G allele resulted in an OR of 6.02 than the TT genotype (dominant model: 95% CI 1.75, 26.73; $p = 0.002$).

Other variants that were nominally associated with poor gliclazide response were: rs71119 (*HMG20A*), rs9806699 (*C15ORF48*), rs1234315 (*TNFSF4,* TNF superfamily member 4 geneTNF), and rs6465084 (*GRM3*, glutamate metabotropic receptor 3 gene).

Glimepiride

Among the 113 participants in the glimepiride substudy, five (1 case and 4 controls) were excluded due to a low genotyping rate (MIND >0.05), the control majority being expected due to the high control: case ratio. Thus, 7 non-responders and 101 responders were retained (Figure 3A). The clinical characteristics of the participants for this arm of the study are found in Table 4.

Table 5 presents the allelic features of nominally significant associated genes, while Table 6 presents the genotypic features of nominally significant associated genes.

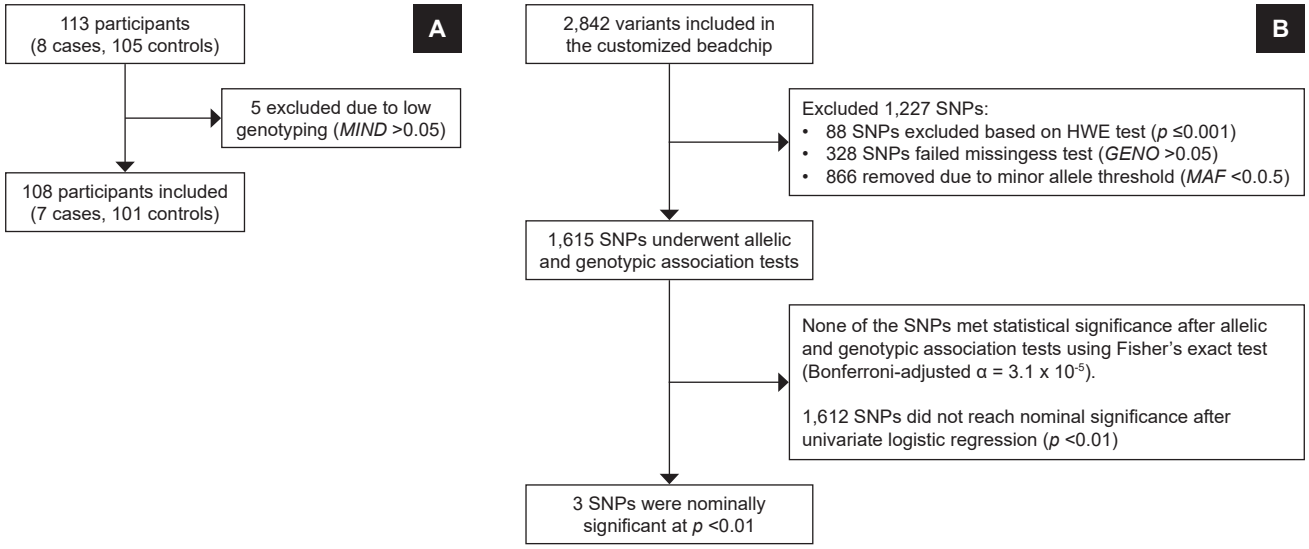

Figure 3. Schematic diagram of data processing and analysis for glimepiride group. A total of 139 participants **(A)** and 2,842 SNPs **(B)** were analyzed to determine the association of genetic variants with poor glimepiride response.

Abbreviations: mind – individual missingness; SNP – single nucleotide polymorphism; HWE – Hardy-Weinberg equilibrium; geno – genotypic missingness; MAF – minor allele frequency.

Table 4. Clinical characteristics of participants in glimepiride substudy

Characteristics	Glimepiride poor responders (n = 7)	Glimepiride responders (n = 101)	*p*-value*
Age, years, mean (SD)	46.14 (7.73)	52.16 (9.86)	0.117
Male, %	14.29	32.67	0.118
Hypertension, %	71.43	49.50	0.131
Ever smoked, %	28.57	24.75	0.411
Alcohol use, %	14.29	38.61	0.099
BMI, kg/m^2, mean (SD)	27.42 (3.69)	24.94 (3.25)	0.056
Waist circumference, cm, mean (SD)	92.64 (9.94)	88.01 (7.36)	0.119
Baseline			
FBS, mg/dL, mean (SD)	183.77 (40.62)	174.58 (31.03)	0.459
HbA1c, %, mean (SD)	8.54 (1.15)	8.86 (1.07)	0.448
Creatinine, mg/dL, mean (SD)	0.56 (0.13)	0.75 (0.23)	0.033
3rd month**			
FBS, mg/dL, mean (SD)	157.03 (57.46)	122.07 (25.95)**	0.002
HbA1c, %, mean (SD)	8.60 (1.33)	6.86 (0.85)**	0.001

Abbrev: BMI, body mass index; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation
*Significant at $p< 0.05$
**3rd-month values are significantly different compared with baseline values at $p<0.05$ using paired t-test

Table 5. Allelic characterization of variants associated with poor glimepiride response

SNP	Implicated gene	Risk allele	Frequency		*p*-value*	*q*-value*	Predicted effect	Predicted Impact	
			Cases	Controls				SIFT	PolyPhen
rs5063	*NPPA / near CLCN6*	T	0.5	0.2475	0.05627	1	Missense (V/M)	0.27 (tolerated)	0.58 (benign)
rs2299267	*PON2*	G	0.4286	0.1436	0.01347	1	Intron variant	n/a	
rs17367504	*MTHFR/ near CLCN6*	G	0.5	0.2673	0.07160	1	Intron variant	n/a	

Abbrev: *CLCN6,* chloride voltage-gated channel 6; *NPPA,* natriuretic peptide A; *PON2,* paraoxonase 2; *MTHFR,* methylenetetrahydrofolate reductase; V/M, valine (V) to methionine (M) mutation; SIFT, Sorting Intolerant From Tolerant; Polyphen, Polymorphism Phenotyping.
*Variants are nominally significant at p<0.05.

Table 6. Genotypic characterization of variants associated with poor glimepiride response

SNP	Chrom No.	Model	Genotypes	Frequency		Crude OR	*p*-value*
				Cases	Controls		
rs5063	1	DOM	TT and TC vs CC	100	41.58	13.04 (1.88, inf)	0.006
rs2299267	7	DOM	GG and AG vs AA	85.71	27.72	15.22 (1.73, 729.02)	0.008
rs17367504	1	DOM	GG and AG vs AA	100	43.56	12.04 (1.74, inf)	0.008

Abbrev: DOM, dominant. Variants are nominally significant at $p< 0.05$; exact logistic regression was done to compute the crude odds ratio.
*Variants are nominally significant at $p<0.05$

The age distribution is comparable between groups. As opposed to the gliclazide substudy, there are more males and alcohol users among responders of the glimepiride group. Mean HbA1c significantly decreased from baseline to the third month among glimepiride responders by 23% (8.86% to 6.86%, p <0.05).

Among the 2,842 variants selected for the study, 88 SNPs failed the HWE test (p ≤0.001), 328 variants failed the missingness test (GENO >0.05), while 866 were further removed due to low minor allele frequency (MAF <0.01).

It is interesting that although rs5063 is mainly considered as a missense variant in the *natriuretic peptide A (NPPA*) gene, resulting in a valine to methionine substitution, SIFT and PolyPhen v2 predicted tolerated and benign effects, and GTEx Portal indicated the variant as an Expression Quantitative Trait Loci (eQTL) for the nearby *CLCN6* and methyltetrahydrofolate reductase (*MTHFR*) genes.

Thus, 2 of the 3 nominally associated variants belong to a set that appears to influence both *CLCN6* and *MTHFR* genes (Table 5). The variants seem to have a similar dominant model with a high-risk effect. The presence of the rs5063 T allele conferred an OR of 13.04 towards poor glimepiride response than the CC genotype (95% CI: 1.88, inf; p = 0.006) (Table 6). Meanwhile, the presence of the G allele conferred an OR of 12.04 compared with the AA genotype (model: 95%, CI:1.74, inf; p = 0.008) in the variant, rs17367504 found in the same gene.

Another variant of interest would be rs2299267, an intronic variant of the paraoxonase 2 (*PON2*) gene. Seemingly acting in a dominant model, the G allele in the *PON2* gene variant conferred an OR of 15.22 times poor glimepiride response (Table 6) than the AA genotype (dominant model: 95% CI: 1.73, 729.02; p = 0.008).

DISCUSSION

Type 2 diabetes mellitus is commonly treated with SUs in the Philippines. However, some patients fail to meet treatment targets despite compliance. Several studies pointed out that genetics contribute to the variable response, and these genetic associations differ across various ethnicities. This study investigated such association among Filipinos using a candidate gene approach. Seven variants had been nominally associated with poor response to gliclazide and three variants with poor response to glimepiride.

Gliclazide

The three variants with the lowest p-values – rs2229437, rs319952, and rs393994 – are all found near genes that code for carboxypeptidases that are related to metabolic processes.

Two of the variants of the *ABGL4* gene, rs319952, and rs393994, have higher odds of poor gliclazide response. *ABGL4* codes for cytosolic carboxypeptidase 6, a metallocarboxypeptidase that mediates deglutamylation of target proteins to form tubulins like microtubules.[16,17] Microtubules negatively regulate insulin secretion in pancreatic beta cells, and their depolymerization is necessary for glucose-stimulated insulin secretion. High glucose levels destabilize microtubules and are balanced by new microtubule formation, which likely prevents glucose over-secretion. As a result, microtubule density is greater in dysfunctional beta cells of diabetic mice. Few studies have explored the connection between *ABGL4* and diabetes, more so sulfonylureas. Of these, one study identified *AGBL4* as one of the down-regulated genes using differential gene expression between T2DM patients and healthy controls.[21] Such downregulation may be explained by the destabilization of microtubules in patients with high glucose levels. Further studies are required to understand the contribution of these *AGBL4* variants to gliclazide nonresponse.

Curiously, another carboxypeptidase gene variant, rs2229437 in *PRCP*, a gene coding for prolylcarboxypeptidase was found to be highly, albeit nominally, associated with gliclazide response. It was previously found to play a role in appetite suppression and weight gain.[22] Pharmacological inhibition studies on *PRCP*-knockout mice showed that lower levels of *PRCP* activity decreased appetite and were resistant to diet-induced obesity.[23,24] Plasma *PRCP* concentrations were also found to be higher among diabetic fatty rats fed with a high-fat diet compared to their lean controls.[25] In the current study, participants with GG and TG genotypes were more likely to be poorly responsive to gliclazide compared with those with the TT genotype in a dominant model. The GG genotype is associated with a higher expression of the *PRCP* gene in subcutaneous adipose tissue,[26] which may result in higher levels of circulating *PRCP* and an increased likelihood of diabetes. Interestingly, the administration of metformin among rats and humans with high *PRCP* levels reversed this elevation.[25] In case the hypothesis is found to be correct in subsequent functional studies, it may be advisable to avoid giving patients gliclazide and prescribe metformin instead.

Of relative relevance would be rs1234315, which is within 1000 bp upstream of *SLC30A4-ASI*. This variant was previously reported to affect several drugs like statins.[27,28] The possible mechanism of the variant on how exactly it affects SUs is yet to be elucidated. Its function as a catalyst of pancreatic carboxypeptidases and zinc transporters may play a role in such a mechanism.

In retrospect, the exact role of the carboxypeptidases in the dynamics of the SUs was scarcely investigated. This paper thus suggests that such thematic association may provide clues to the mechanistic importance of carboxypeptidases in SU response.

Another interesting theme to entertain is glutamate metabolism. In addition to the polyglutamate-acting carboxy-

peptidases, another variant, rs6465084, implicated the involvement of *GRM3* (*glutamate metabotropic receptor 3*). The G-protein receptor is linked with cyclic adenosine monophosphate (AMP) signaling and has been implicated to influence insulin secretion in beta-cells through an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid or AMPA-regulated mechanism in the pancreas.[29] Thus, the possibility of glutamate processing affecting the secretagogue function of SUs becomes plausible.

Other nominally associated variants include rs7119, an intron variant of *HMG20A*, which is responsible for regulating the metabolism-insulin secretion coupling genes and functional maturity of β-cells. Single-tissue eQTLs show that individuals with the T allele have higher expression levels of *HMG20A*.[30] Knockdown of the gene resulted in reduced glucose-induced insulin secretion.[31] While there is no literature linking the variant to gliclazide response, gliclazide's mechanism of action involves the stimulation of insulin secretion through binding to the β-cell SU receptor (SUR1).[32] The altered expression of the *HMG20A* gene may affect the functional maturity of β-cells, which may consequently contribute to poor response to gliclazide. As genotypic associations are compared pairwise, the association of the variants to the trait is set as a group. The significance of the *HMG20A* variant, rs7119, mainly relies on the AG vs GG comparison. Thus, even if the other comparisons lack significance, the variant itself is associated with the trait.

Other associated variants are rs9806699 and rs1234315 upstream of *C15ORF48* and *TNFSF4*, respectively. These were scarcely studied and no previous data defines their function. Moreover, these variants were not previously linked to diabetes or response to oral hypoglycemic agents.

Glimepiride

Three variants were nominally associated with poor glimepiride response (p<0.01), two are found near the *CLCN6-NPPA-MTHFR* gene cluster and one from the *PON2 loci.* All three variants were not previously linked to poor sulfonylurea response.

Two associated variants were noted to be near the gene cluster *CLCN6-NPPA-MTHFR,* rs5063 and rs17367504, each resulting in more than ten times higher odds of poor glimepiride response. Although the SNPs are 50kb apart from each other, with different hypothetical effects - 5063 is an intronic variant of the *NPPA* gene, while rs17367504 is an intronic variant of *MTHFR*, both variants seem to influence the expression of *MTHFR*, *CLCN6,* and *NPPA* and *NPPA* in various tissues, including the *NPPA* antisense RNA.[33] The variants in the *MTHFR-CLCN6-NPPA-NPPA* gene cluster were investigated by a previous study providing novel insights into the mechanisms of cardiac dysfunction.[34,35] Moreover, the *MTHFR* gene is implicated in T2DM susceptibility.[36] These findings are interesting considering that the *MTHFR* gene is widely implicated in drug metabolism, such as with methotrexate, by acting through 1-carbon transfer.[37] However, such speculation and questions on the role of other implicated genes remain to be investigated.

Another variant that conferred a high OR is rs2299267, an intronic region of the *PON2* gene and upstream from the *PON1* and *PON3* genes. In a study differentiating the effect of SUs, specifically glimepiride and glibenclamide, it has been found that the SUs increased *PON1* hepatic activity.[38] As this finding may imply an influence on hepatic metabolism, studies that aim to understand the contribution of *PON* variants to glimepiride response are worth exploring in the future.

Nonetheless, the authors recognize the obvious limitation of the study's sample size. The lack of association in multiple testing resulting in false positives is possible.

Studies of similar candidate approaches with small sample sizes have been published. For instance, one study that shows the correlation of *KCNQ1* polymorphism with glycemic parameters only had 91 subjects (44 cases and 47 controls).[39] In addition, a longitudinal study on various metformin/sulfonylurea combinations of up to 6 months involved 88 individuals comprising of 17 cases and 71 controls.[40] Both demonstrated associations of genotypes with glycemic parameters. The main difference in approach is they utilized continuous glycemic variables. In contrast, our study used categorical glycemic parameters as these are real-life clinical parameters and to determine pharmacogenetic markers likely foreseen. Negative results were seen in several studies. For instance, a lack of association was found in assessing the use of GLP-1 analogue exenatide to control blood sugar that enrolled only 36 patients,[41] or in associating *CYP2C9 rs1067910* to glycemic responses to pooled sulfonylureas that had only 30 samples.[42] Both failed to demonstrate treatment effects.

We underscore that validation research using the markers of interest may be conducted in a larger-scale study of patients with T2DM. Alternatively, as some findings suggest thematic enrichment, functional studies can be conducted. The preliminary results of this study may provide impetus to evaluate the clinical relevance of the identified SNPs on SU treatment.

CONCLUSION

Interethnic variations compel the conduct of pharmacogenetic studies in scarcely studied populations, such as Filipinos. In this context, as sulfonylureas such as gliclazide and glimepiride are used on a national scale to treat T2DM, we observed several variants to be nominally associated with sulfonylurea response among Filipinos. With this data, new possibilities on the pharmacodynamics and pharmacokinetics of sulfonylureas are suggested, and the results of the current study may guide future directions in SU research.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Authors Contribution Statement
EPP and JBN conceived the study; developed the methodology; provided study materials; validated data; acquired financial support for the study.

EMC conceived the study; developed the methodology; provided study materials; validated data; acquired financial support for the study; reviewed and edited the manuscript; supervised and managed the research activity planning.

GJJ conceived the study; developed the methodology; provided study materials; validated data; reviewed and edited the manuscript; supervised the research.

EPP, JBN and AYCA synthesized the data; conducted the research; curated the data; prepared the original draft; reviewed and edited the manuscript; supervised and managed the research activity planning.

ELAR and MGF applied the statistical techniques; collected and curated the data; helped in the preparation of the original draft; reviewed and edited the manuscript; supervised and coordinated the research activity planning.

MVG and MUN validated data; collected and curated the data; reviewed and edited the manuscript; supervised and coordinated the research activity planning.

CAC, MDM, CVJ, PND, APM developed the methodology; collected data; reviewed and edited the manuscript.

AUC, JMQ, AML, DCB, NMM collected and curated the data; reviewed and edited the manuscript; supervised and coordinated the research activity planning.

VDR, KJAC and JPF supervised and coordinated the research activity planning.

NMM, VSR, KJAC, JPF, JB, JM, CDD and CEP synthesized the data; conducted the investigation process; curated the data; prepared the original draft; reviewed and edited the manuscript.

Author Disclosure
EPP is the Editor-in-Chief of the JAFES. EPP, JBN, EMCDP, AYCA have patent application at UP Manila. GJJ served as CME/ Speaker's Bureau of the following companies: MSD, J& J, Astra Zeneca, Boehringer-Ingelheim, Sanofi Aventis, Novo Nordisk, Abbott Nutrition, LRI-Therapharma, UMed, Woerwag. CAC represented the Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM) as the primary investigator and was given a research grant by Servier Laboratories through the PCEDM; received compensation as lecturer for the following companies: AstraZeneca,Getz Pharma, LRI-Therapharma, MSD, Natrapharm, Novo Nordisk, Sanofi, Servier and Zuellig-Lilly; received compensation for module development/presentations for Natrapharm and received support for registration to scientific meetings/ conventions from MSD, Natrapharm, Sanofi and Servier; received medical equipment and PPEs from BioFemme, LRI-Therapharma, Natrapharm and UAP; serves as the head of the Reproductive Endocrinology and Transgender Health Council of the PCEDM. PND received honoraria for lectures.

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