

Identification of genetic variants in pharmacogenetic genes associated with type 2 diabetes in a Mexican-Mestizo population

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Abstract. Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic pathologies in the world. In developing countries, such as Mexico, its prevalence represents an important public health and research issue. Determining factors triggering T2DM are environmental and genetic. While diet, exercise and proper weight control are the first measures recommended to improve the quality of life and life expectancy of patients, pharmacological treatment is usually the next step. Within every population there are variations in interindividual drug response, which may be due to genetic background. Some of the most frequent first line T2DM treatments in developing countries are sulfonylureas (SU), whose targets are ATP-sensitive potassium channels (K_{ATP}). Single nucleotide polymorphisms (SNPs) of the K_{ATP} coding genes, potassium voltage-gated channel subfamily J member 11 (*KCNJ11*) and ATP binding cassette subfamily C member 8 (*ABCC8*) have been associated with SU response variability. To date, there is little information regarding the mechanism by which these SNPs work within Mexican populations. The present study describes the distribution of three SNPs [*KCNJ11* rs5219 (E23K), *ABCC8* rs757110 (S1369A) and rs1799854 (-3C/T)] among Mestizo Mexican (MM) T2DM patients, and compares it with published data on various healthy subjects and T2DM populations. Through this comparison, no difference in

the *KCNJ11* rs5219 and *ABCC8* rs757110 allelic and genotypic frequencies in MM were observed compared with the majority of the reported populations of healthy and diabetic individuals among other ethnic groups; except for African and Colombian individuals. By contrast, *ABCC8* rs1799854 genomic and allelic frequencies among MM were observed to be significantly different from those reported by the 1000 Genomes Project, and from diabetic patients within other populations reported in the literature, such as the European, Asian and Latin-American individuals [T=0.704, G=0.296; CC=0.506, CT=0.397, TT=0.097; 95% confidence interval (CI); P≤0.05]; except for South Asian and Iberian populations, which may reflect the admixture origins of the present Mexican population. This genetic similarity has not been observed in the other Latin-American groups. To the best of our knowledge, this is the first study of *ABCC8* rs757110 and rs1799854 SNP frequencies in any Mexican population and, specifically with diabetic Mexicans. Knowledge of the genetic structure of different populations is key to understanding the interindividual responses to drugs, such as SU and whether genotypic differences affect clinical outcome.

Introduction

Diabetes is a type of metabolic disease characterized by hyperglycemia resulting from either defective insulin secretion, insulin action or the two (1). The most prevalent type of diabetes is type 2 diabetes mellitus (T2DM), which is one of the leading causes of morbidity globally, as well as the third-highest risk factor for premature mortality (2).

In Mexico, T2DM has led mortality rates since 2005 and today it represents the leading cause of death in the country (3,4) with a prevalence of 11.8% (5). Costs associated with medical treatment of T2DM are ~450 million dollars annually (6), while ~75% of diagnosed patients do not observe adequate glycemic control even with medical assistance. These factors make T2DM a critical concern for the Mexican State's public health and research systems.

While genetic factors causing T2DM have not yet been sufficiently defined, they are currently under extensive study. Numerous T2DM-associated genes present as single nucleotide polymorphisms (SNPs) whose frequencies vary among

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Abbreviations: MM, Mestizo Mexican; T2DM, type 2 diabetes mellitus; SNP, single nucleotide polymorphism; SU, sulfonylurea; K_{ATP} , ATP-sensitive potassium channel; ME, metformin

Key words: diabetes, pharmacogenetics, potassium voltage-gated channel subfamily J member 11, ATP binding cassette subfamily C member 8, Mestizo Mexican

different populations. Genetic variations associated with either pharmacological targets or drug metabolism are of particular interest, as different responses to pharmacological treatments may be explained by the presence of a genetic mutation or the combination of various genotypes (7).

The initial pharmacological treatments for T2DM are oral hypoglycemics (OH), with sulfonylureas (SU) and metformin (ME) being the two most commonly administered in developing countries. SU are a type of oral OHs, which inhibit ATP-sensitive potassium channels (K_{ATP}), thus inducing glucose-independent insulin release by the β -pancreatic cells (8). However, not all T2DM patients respond to the anti-diabetic action of SU (primary failure) and those who initially respond adequately may experience a decrease in its efficacy following the years (as variable as 1-2 to 10 or more years) of treatment (secondary failure) (9,10). SUs are frequently combined with ME, a drug which reduces hepatic glucose production and insulin resistance (11). It has been observed that the short-term reduction of glycated hemoglobin A1c (HbA1c) is similar in SU and ME monotherapies (12), and that this drug combination reduces HbA1c more efficiently than SU alone (13). When compared, observations on the adjuvant effects of SU/ME-based treatments are inconclusive; while certain authors have associated hypoglycemic events of different severity and weight increase to SUs, either alone or in combination with ME (14), others have reported no effect on body weight when combining SUs with ME (15). However, due to their low cost and accessibility, SUs (alone or combined with ME) remain the most frequent first-line T2DM treatment in the world, particularly in developing countries, such as Mexico (16,17). The UK Prospective Diabetes Study demonstrated that only 25% of patients achieved glycemic control of <7% in HbA1c over a nine-year follow-up period of monotherapy on either SU or ME (10).

Of the genetic polymorphisms that have already been reviewed extensively and whose clinical implications have already been analyzed (18,19), there are a number, which appear to be well suited for pharmacogenetic studies. Various SNPs have been reported among K_{ATP} -channel encoding genes [potassium voltage-gated channel subfamily J member 11 (*KCNJ11*) and ATP binding cassette subfamily C member 8 (*ABCC8*)] as the therapeutic target of SU (20). Many of these genes are associated with T2DM predisposition or progression, as well as with SU response variability. A specific SNP frequency may vary between different populations; therefore, it is important to evaluate and compare its distribution among different human populations, in order to better understand whether there is an association between drug response variability, patients' glycemic control and genetic architecture.

In the present study, the frequencies of three pharmacologically important SNPs are described in a Mestizo Mexican (MM) population and, in order to compare these with other reported populations, the distribution of *KCNJ11* rs5219 (E23K), *ABCC8* rs757110 (S1369A) and rs1799854 (-3C/T) is presented in MM T2DM patients. The aim of the present study is to increase the understanding of the genetic characteristics of specific populations. This may facilitate with elucidating the causes of therapeutic failure and the findings may also be extrapolated and/or compared to other populations in order to improve treatment options and patient management.

Materials and methods

Patient selection and study design. This study was observational and included 247 T2DM patients recruited from July 2014 to October 2016 from two health centers: 145 from Centro de Salud Portales and 102 T2DM patients from Centro de Salud Mixcoac, both located in Mexico City's Benito Juárez Health Jurisdiction (Mexico). Out of the total adult patient population, 165 were females while 82 were males. Patient eligibility criteria were as follows: Self-proclaimed MM ancestry of at least three generations; age between 18 and 90 years; individuals diagnosed with T2DM according to the American Association of Diabetes criteria (1); individuals taking OHs, the SU glibenclamide alone or combined with ME, for at least 3 months. All participants were enrolled in their health centers after providing written informed consent. Patient clinical history, anthropometrics and biochemical characteristics were obtained from their clinical records (a summary of this data is presented in Table I).

Genotyping. Genomic DNA was obtained by taking 6 ml peripheral blood through arm phlebotomy in glass EDTA-tubes (Vacutainer®; BD Biosciences, Franklin Lakes, NJ, USA) from each patient. Patients were fasted at the time of blood sampling. Genomic DNA was isolated from 200 μ l total blood, using the UltraClean® BloodSpin® DNA Isolation kit (Mo Bio Laboratories, Inc., Carlsbad, CA, USA), and the DNA-extraction protocol was performed according to the manufacturer's instructions. DNA quality was achieved by electrophoresis in Invitrogen 1% agarose gels (UltraPure™ Agarose; Thermo Fisher Scientific, Inc., Waltham, MA, USA), at 100 V over 50 min. DNA concentration was measured by spectrophotometry (Jenway 7305; Cole-Parmer Ltd., Staffordshire, UK). The *KCNJ11* rs5219 (E23K), *ABCC8* rs757110 (S1369A) and rs1799854 (-3C/T) polymorphisms were determined using 20 ng total genomic DNA per reaction, by allelic discrimination via quantitative polymerase chain reaction (qPCR) using a ViiA™ 7 Real-Time PCR system and TaqMan® SNP assays (Applied Biosystems; Thermo Fisher Scientific, Inc. Waltham, MA, USA) using the standard cycling conditions as follows: An initial denaturation stage 95°C for 10 min, 40 cycles of denaturation 95°C for 15 sec, and annealing at 60°C for 1 min, and post read stage or final extension at 60°C for 30 sec.

Statistical analysis. The SNP frequencies of *KCNJ11* rs5219, *ABCC8* rs757110 and rs1799854 were determined through direct counting, the remaining analyses were performed using SPSS 23.0 for Windows (IBM Corp., Armonk, NY, USA). The SNP frequencies of the patients from both health centers were compared by performing χ^2 test of independence. In addition, biochemical and anthropometric data were compared using two-way analysis of variance (ANOVA). The total frequencies for each SNP were compared with those of other populations using the χ^2 test of independence. $P < 0.05$ with 95% CI was considered to indicate a statistically significant difference.

Results

Mexican-Mestizo sample characteristics. No statistically significant differences were identified after comparing

Table I. Demographic baseline disease characteristics.

Parameter	Total (n=247)	Female (n=165)	Male (n=82)
Age (years)	60.43±0.75	60.05 ±0.91	61.24±1.34
Weight (kg)	70.87±1.06	69.25±1.23	74.40±1.98
Body mass index (kg/m ²)	29.51±0.37	30.26±0.45	27.89±0.62
Diabetes diagnosis (years)	10.27±0.61	9.57±0.64	11.92±1.34
Triglycerides (mg/dl)	199.06±8.02	199.59±9.44	197.90±15.24
Glycated hemoglobin A1c (%)	7.55±0.15	7.53±0.19	7.60±0.26
Fasting plasma glucose (mg/dl)	141.86±4.06	144.55±5.22	135.76±5.99
Cholesterol (mg/dl)	194.82±2.71	197.24±3.45	189.39±4.12

Values are presented as means ± standard error of the mean.

biochemical and anthropometric data from the individuals from the two health centers (data not shown). Within the whole sample, there were approximately twice as many females as there were males (162 females and 83 males); 61.5% of the patients were overweight (55.7% of females and 73.8% of males); ~25% of the subjects presented with grade I obesity (27.9% in females and 20.0% in males). The mean period since the first T2DM diagnosis was 10 years, with a mean of 7.55±0.15% for HbA1c and 141.86±4.06 mg/dl for fasting plasma glucose (FPG). A summary of anthropometrics and biochemical characteristics of our subjects is presented in Table I.

No significant differences were observed in genotypic and allelic frequency distribution between the two health centers (data not shown). The genotyping frequencies of the three SNPs in the whole sample were in Hardy-Weinberg equilibrium (Table II). The obtained allelic and genotypic frequencies were compared with those reported for other non-diabetic populations using data from the 1000 Genomes Project (21) and from literature on T2DM patients; the comparative of each SNP is presented in Tables III-V (22-38). For the present study, studies were included that involved populations of T2DM subjects that were comparable with the current sample.

SNP comparison with other populations. *KCNJ11* rs5219 (E23K) allelic and genotypic frequencies in MM individuals were not identified to be different between all of the T2DM populations that were compared [predominantly European (EUR) and Asian]. To the best of our knowledge, there were only two other studies from Mexican rs5219 allelic frequencies, which demonstrated no difference compared with the MM population: T2DM Mestizo from Yucatan and T2DM Mayans. In the 1000 Genomes Project populations, MM frequencies were only statistically different from African individuals (P=2.17E-12 and P=2.31E-19 for allelic and genotypic frequencies, respectively) and admixed American-Colombians

Table II. Genotypic frequencies of the analyzed polymorphisms.

SNP	Frequency	%	P-value
E23K			0.69
GG	93	37.7	
GA	112	45.3	
AA	42	17.0	
Total	247	100.0	
-3C/T			0.55
CC	125	50.6	
CT	98	39.7	
TT	24	9.7	
Total	247	100.0	
S1369A			1.63
AA	75	30.4	
AC	131	53.0	
CC	41	16.6	
Total	247	100.0	

P<3.84 using the χ^2 test for Hardy-Weinberg equilibrium.

from Medellin (P=0.002 and P=7.20E-05 for allelic and genotypic frequencies, respectively; Table III).

MM *ABCC8* rs757110 (S1369A) allelic and genotypic frequencies behave similarly to rs5219. The only statistical differences were observed when compared with African individuals (P=1.45E-13 and P=1.72E-23 for allelic and genotypic frequencies, respectively) and American-Colombians from Medellin (P=6.13E-04 and P=2.52E-06 for allelic and genotypic frequencies, respectively). Currently, to the best of our knowledge, there are no other studies regarding allelic or genotypic frequencies of this SNP in a Mexican population (Table IV).

ABCC8 rs1799854 (-3C/T) SNP allelic and genotypic frequencies from MM were significantly different from all of the compared T2DM populations (primarily European and Asian). In comparison to non-diabetic populations from the 1000 Genomes Project, MM allelic and genotypic frequencies were significantly different from African individuals, East Asians, the majority of EUR individuals, and other admixed Americans from Colombia, Peru, Puerto Rico and individuals of Mexican ancestry from Los Angeles. Only in Iberic EUR and South Asian individuals did the 1000 Genomes Project report non-significant differences in allelic and genotypic frequencies compared with MM (Table V). Currently, to the best of our knowledge, there are no other studies on the frequencies of these SNPs among Mexican populations of non-diabetic or diabetic individuals.

Discussion

In the present study, in the MM from Mexico City, rs5219 allelic and genotypic frequencies were not different from the majority of the reported populations of healthy and diabetic individuals among other ethnic groups, except for the African and Colombian subjects; the same observation applies to

Table III. Potassium voltage-gated channel subfamily J member 11 rs5219 (E23K) allelic and genotypic frequency comparison.

Author (year)	Population	T	n	G	N	p χ^2	TT	n	TG	n	GG	n	p χ^2	Refs.
1000 Genomes Project														
Auton <i>et al</i> (2015)	MM	0.603	298	0.397	196	-	0.377	93	0.453	112	0.17	42		(21)
	AFR	0.977	1291	0.023	31	2.17E-12 ^a	0.956	632	0.047	27	0.003	2	2.31E-19 ^a	
	EAS	0.662	667	0.338	341	0.387	0.429	216	0.466	235	0.105	53	0.386	
	SAS	0.604	591	0.396	387	0.988	0.38	186	0.448	219	0.172	84	0.997	
	EUR	0.647	651	0.353	355	0.52	0.4	201	0.495	249	0.105	53	0.406	
	EUR IBS	0.617	132	0.383	82	0.839	0.374	40	0.486	52	0.14	15	0.815	
	AMR	0.707	491	0.293	203	0.121	0.496	172	0.424	147	0.081	28	0.084	
	AMR CLM	0.803	151	0.197	37	0.002 ^a	0.638	60	0.33	31	0.032	3	7.20E-05 ^a	
	AMR MXL	0.594	76	0.406	52	0.897	0.328	21	0.531	34	0.141	9	0.54	
	AMR PEL	0.682	116	0.318	54	0.243	0.435	37	0.494	42	0.071	6	0.092	
	AMR PUR	0.712	148	0.288	60	0.104	0.519	54	0.385	40	0.096	10	0.086	
Type 2 diabetic														
Hernandez- Escalante <i>et al</i> (2014)	AMR YCN	0.633	164	0.367	95	0.662	-	-	-	-	-	-	-	(22)
Lara-Riegos <i>et al</i> (2015)	AMR MYN	0.654	75	0.346	40	0.449	-	-	-	-	-	-	-	(23)
He <i>et al</i> (2008)	EAS (China)	0.62	124	0.38	76	0.805	0.35	35	0.54	54	0.11	11	0.34	(24)
Yokoi <i>et al</i> (2006)	EAS (Japan)	0.614	1954	0.386	1226	0.873	0.384	610	0.462	734	0.155	246	0.959	(25)
Holstein <i>et al</i> (2009)	EUR (Germany)	0.604	116	0.396	76	0.988	0.385	37	0.437	42	0.177	17	0.975	(27)
Gloyn <i>et al</i> (2001)	EUR (UK)	0.593	427	0.407	293	0.885	0.369	133	0.447	161	0.183	66	0.97	(28)
Sesti <i>et al</i> (2009)	EUR (Italy)	0.642	674	0.358	376	0.569	0.385	202	0.514	270	0.101	53	0.338	(29)
Ragia <i>et al</i> (2012)	EUR (Grece)	0.668	235	0.332	117	0.339	0.455	80	0.426	75	0.119	21	0.423	(30)
Javorsky <i>et al</i> (2012)	EUR (Slovakia)	0.599	121	0.401	81	0.954	0.366	37	0.465	47	0.168	17	0.984	(31)
Klen <i>et al</i> (2014)	EUR (Slovenia)	0.622	194	0.378	118	0.783	0.378	59	0.487	76	0.135	21	0.76	(32)
Nicolac <i>et al</i> (2009)	EUR (Croatia)	0.607	277	0.393	179	0.954	0.382	87	0.452	103	0.167	38	0.997	(33)
Chistiakov <i>et al</i> (2009)	EUR (Russia)	0.496	128	0.504	130	0.128	0.217	28	0.558	72	0.225	29	0.045 ^a	(34)
Sokolova <i>et al</i> (2015)	WAS (East Russia)	0.649	1926	0.351	1042	0.501	0.428	635	0.442	656	0.13	193	0.647	(35)

^aP<0.05 (95% confidence interval); p χ^2 , χ^2 test of independence; MM, type 2 diabetic Mestizo Mexican (1000 Genomes Project third release); AFR, African individuals (1000 Genomes Project third release); EAS, East Asian individuals (1000 Genomes Project third release); SAS, East South Asian individuals (1000 Genomes Project third release); EUR, European individuals (1000 Genomes Project third release); IBS, Iberian population in Spain; AMR, Admixed American; CLM, Colombians from Medellin, Colombia; MXL, Mexican ancestry from Los Angeles, USA; PEL, Peruvians from Lima, Peru; PUR, Puerto Ricans from Puerto Rico (1000 Genomes Project third release); YCN, type 2 diabetic from Mestizo Yucatan; MYN, T2D Mayan.

rs757110 (Tables III and IV). It appears that the distribution of these polymorphisms prevails among the majority of populations, while the ancestral allele is most frequent among African individuals. The results from the Colombian population may reflect the ancestral admixture history of the country, where the African component is widely spread across the Pacific and Caribbean regions (39-41).

In Mexican populations, rs5219 is the only SNP reported for K_{ATP} -coding genes, exhibiting no differences between the

alleles of healthy and T2DM subjects, even when the geographical and ethnic profile of the three Mexican samples were markedly different: The healthy volunteers were Mestizo from the South East (22), the T2DM group had Mayan Amerindian ancestry (23) and our group (MM) was formed by Mestizo individuals, primarily from the central area of Mexico.

To the best of our knowledge, this is the first report of *ABCC8* rs757110 and rs1799854 SNPs in Mexican populations, and more specifically, in diabetic Mexican patients.

Table IV. ATP binding cassette subfamily C member 8 S1369A allelic and genotypic frequency comparison.

Author (year)	Population	T	n	G	n	p χ^2	TT	n	TG	n	GG	n	p χ^2	Refs.
1000 Genomes Project														
Auton <i>et al</i> (2015)	MM	0.569	281	0.431	213		0.304	75	0.53	131	0.166	41		(21)
	AFR	0.975	1289	0.025	33	1.45E-13 ^a	0.953	630	0.044	29	0.003	2	1.72E-23 ^a	
	EAS	0.639	644	0.361	364	0.195	0.395	199	0.488	246	0.117	59	0.331	
	SAS	0.585	572	0.415	406	0.819	0.354	173	0.462	226	0.184	90	0.652	
	EUR	0.648	652	0.352	354	0.252	0.404	203	0.489	246	0.107	54	0.238	
	IBS	0.617	132	0.383	82	0.49	0.374	40	0.486	52	0.14	15	0.567	
	AMR	0.693	481	0.307	213	0.069	0.47	163	0.447	155	0.084	29	0.030 ^a	
	CLM	0.793	149	0.207	39	6.13E-04 ^a	0.606	57	0.372	35	0.021	2	2.52E-06 ^a	
	MXL	0.586	75	0.414	53	0.808	0.328	21	0.516	33	0.156	10	0.932	
	PEL	0.682	116	0.318	54	0.098	0.435	37	0.494	42	0.071	6	0.041	
PUR	0.678	141	0.322	67	0.111	0.462	48	0.433	45	0.106	11	0.061		
Type 2 diabetics														
Zhang <i>et al</i> (2007)	EAS (China)	0.565	130	0.435	100	0.954	0.33	38	0.47	54	0.2	23	0.676	(38)
Yokoi <i>et al</i> (2006)	EAS (Japan)	0.592	1884	0.408	1296	0.742	0.358	570	0.468	744	0.174	276	0.655	(25)
Klen <i>et al</i> (2014)	EUR (Slovenia)	0.619	193	0.381	119	0.471	0.378	59	0.481	75	0.141	22	0.536	(32)
Nicolac <i>et al</i> (2009)	EUR (Croatia)	0.607	277	0.393	179	0.585	0.395	90	0.425	97	0.18	41	0.301	(33)
Sokolova <i>et al</i> (2015)	East Russia (West Asia)	0.623	1763	0.377	1065	0.436	0.393	556	0.46	651	0.146	207	0.414	(35)

^aP<0.05 (95% confidence interval); p χ^2 , χ^2 test of independence; CDMX, type 2 diabetics from Mestizo Mexico City (all of the following are 1000 Genomes Project third release): AFR, African; EAS, East Asian; SAS, South Asian; EUR, European; IBS, Iberian population in Spain; AMR, Admixed American; CLM, Colombians from Medellin, Colombia; MXL, Mexican ancestry from Los Angeles, USA; PER, Peruvians from Lima, Peru; PUR, Puerto Ricans from Puerto Rico.

rs757110 allelic and genotypic frequencies behaved similarly to rs5219 SNP, which was to be expected as it is well known that these SNPs form a haplotype. Yet, rs1799854 SNP frequencies seem extremely different to those reported by the 1000 Genomes Project and the literature on various diabetic populations (Table V). A comparison between allelic and genotypic frequencies in the investigated group and those populations reported by the 1000 Genomes Project, demonstrated differences between all but three samples: South Asian, European and Iberic. The Iberic population may have affected the comparison result of the EUR sample, as it was included in the EUR group in the 1000 Genome Project data. This was consistent with the fact that other EUR diabetic populations from different ethnic origins were statistically different when compared with the MM group (UK, Croatia and Poland). These results may reflect the Hispanic admixture dating from Mexico's colonial past; however, it is interesting and unexpected that this was not observed in the other Latin-American populations reported. It was demonstrated by the results of the previous Mexican health and nutrition national survey (ENSANUT 2012) that diabetes diagnosis and first level medical attention have improved considerably in Mexico (5), yet the percentage of treated patients actually maintaining adequate glycemic control remains poor. If this lack of control is genetic, at least partially, the differences observed in Mexican genetic SNP frequencies may significantly contribute to explaining treatment failure. This first screening may facilitate with understanding where focus and investigations

are required to establish whether genetic structure and pharmacological failure are associated.

It would be interesting to observe whether a healthy control group of MM individuals from central Mexico behaves the same as diabetic subjects, and to analyze groups of different ethnicity within the country to establish whether those results are consistent with or different from the present study.

The SNPs, rs5219 (E23K) and rs757110 (S1369A) form a haplotype, where K23/A1369 has been identified as a risk genotype (35,42,43). While electrophysiological studies have demonstrated that channels containing the K allele and K23/A1369 are less sensitive to ATP inhibition (44,45), the SU response of these polymorphic channels appears to be different depending on the drug. For example, it has been shown that K23/A1369 channels are more sensitive to SU gliclazide, yet these same channels are less sensitive to inhibition by SUs, such as tolbutamide and glimepiride, while glibenclamide demonstrated no significant inhibition difference in any haplotype (45,46). In another study, K allele carriers exhibited significantly higher secondary treatment failure than E allele homozygous (29) treated with SU and ME; however, Dawed *et al* (19) demonstrated that secondary failure on patients treated with a combination of SU and ME, carrying the K allele polymorphism of rs5219 may be more involved with diabetes progression than with SU response (19).

In Mexico, the most common first level treatment for T2DM combines ME with glibenclamide administration (5).

Table V. ATP binding cassette subfamily C member 8 -3C/T Allelic and genotypic frequency comparison.

Authors (year)	Population	C	n	T	n	p χ^2	CC	n	CT	n	TT	n	p χ^2	Refs.
1000 Genomes Project														
Auton <i>et al</i> (2015)	MM	0.704	348	0.296	146	-	0.506	125	0.397	98	0.097	24	-	(21)
	AFR	0.862	1139	0.138	183	0.006 ^a	0.741	490	0.241	159	0.018	12	7.96E-04 ^a	
	EAS	0.449	453	0.551	555	2.41E-04 ^a	0.198	100	0.502	253	0.3	151	2.20E-06 ^a	
	SAS	0.681	666	0.319	312	0.724	0.481	235	0.401	196	0.119	58	0.865	
	EUR	0.58	583	0.42	423	0.067	0.33	166	0.499	251	0.171	86	0.031 ^a	
	EUR IBS	0.612	131	0.388	83	0.17	0.393	42	0.439	47	0.168	18	0.169	
	AMR	0.464	322	0.536	372	5.35E-04 ^a	0.225	78	0.478	166	0.297	103	1.30E-05 ^a	
	AMR CLM	0.516	97	0.484	91	0.006 ^a	0.266	25	0.5	47	0.234	22	0.001 ^a	
	AMR MXL	0.422	54	0.578	74	5.10E-05 ^a	0.172	11	0.5	32	0.328	21	1.35E-07 ^a	
	AMR PEL	0.312	53	0.688	117	1.91E-08 ^a	0.071	6	0.482	41	0.447	38	3.15E-14 ^a	
AMR PUR	0.567	118	0.433	90	0.044 ^a	0.346	36	0.442	46	0.212	22	0.022 ^a		
Type 2 diabetics														
He <i>et al</i> (2008)	EAS (China)	0.41	82	0.59	118	2.50E-05 ^a	0.14	14	0.54	54	0.32	32	1.03E-08 ^a	(24)
Yokoi <i>et al</i> (2006)	EAS (Japan)	0.474	1507	0.526	1673	8.91E-04 ^a	0.233	371	0.481	765	0.286	454	2.90E-05 ^a	(25)
Matharoo <i>et al</i> (2013)	SAS (India)	0.568	227	0.433	173	0.044 ^a	0.405	81	0.325	65	0.27	54	0.006 ^a	(36)
Gloyn <i>et al</i> (2001)	EUR (UK)	0.464	412	0.536	476	5.35E-04 ^a	0.191	85	0.545	242	0.264	117	3.50E-06 ^a	(28)
Nicolac <i>et al</i> (2009)	EUR (Croatia)	0.489	223	0.511	233	0.002 ^a	0.197	45	0.583	133	0.219	50	1.30E-05 ^a	(33)
Dworacka <i>et al</i> (2007)	EUR (Poland)	0.45	36	0.55	44	2.54E-04 ^a	0.25	10	0.4	16	0.35	14	6.00E-06 ^a	(37)

^aP<0.05 (95% confidence interval); p χ^2 , χ^2 test of independence; CDMX, type 2 diabetics from Mestizo Mexico City (all of the following are 1000 Genomes Project third release): AFR, African; EAS, East Asian; SAS, South Asian; EUR, European; IBS, Iberian population in Spain; AMR, Admixed American; CLM, Colombians from Medellin, Colombia; MXL, Mexican ancestry from Los Angeles, USA; PER, Peruvians from Lima, Peru; PUR, Puerto Ricans from Puerto Rico.

In this first analysis, whose objective was mainly SNP frequency description, the authors included patients receiving glibenclamide or ME either as a mono- or combined therapy, as the SNP distribution is not affected by treatment. In future studies, the aim will be to investigate clinical implications of using ME-only treated patients as a control group to distinguish the ME effect.

The *ABCC8* rs1799854 polymorphism has been associated with a predisposition for diabetes (25,47,48). In terms of pharmacogenetics, certain studies have found that the TT genotype may be associated with an increase in HbA1c and triglyceride levels in SU-treated diabetics (33,49), and deemed partially determinant of hyperglycemia-cardiovascular risk factor in rs1799854 heterozygotes (37). However, other authors report no significant associations when analyzing FPG and BMI (28,50). Even when results in the case of this SNP are contradictory, the difference in the allelic and genotypic frequencies observed in our sample in comparison with the majority of reported cases, indicates a considerable requirement to evaluate their implications in diabetes progression and drug response in the MM population.

The SNP frequencies of rs5219 and rs757110 polymorphisms appear to be well conserved among the majority of populations, including Mexicans, there is not yet a clear association between them and the pharmacological effects.

The present results may contribute to future studies to clarify whether there is a real association.

The aim of the present study was to describe the genetic architecture of three pharmacogenetically important SNPs of *ABCC8* and *KCNJ11* within an MM population. To the best of our knowledge, this study is the first to report allelic and genotypic frequencies of *ABCC8* rs757110 and rs1799854 SNPs in an MM population. Diabetes is a major concern in Mexico, and current pharmacological treatment is considered insufficient, as shown by the latest national health survey. Therefore, understanding the characteristics of our population is a priority for elucidating a viable hypothesis to improve our knowledge of this complex pathology. It is known that interindividual responses to SU are affected by clinical factors, such as baseline glucose levels, disease duration, β -cell function and insulin resistance levels (51). However, multiple gene interaction may explain the marginal impact of each individual SNP, indicating, the necessity to construct an interaction model.

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