Mexican Carriers of the *HNF1A* p.E508K Variant Do Not Experience an Enhanced Response to Sulfonylureas

Diabetes Care 2018;41:1726–1731 | https://doi.org/10.2337/dc18-0384

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OBJECTIVE

To assess whether an ethnic-specific variant (p.E508K) in the maturity-onset diabetes of the young (MODY) gene hepatocyte nuclear factor-1α (*HNF1A*) found in Mexicans is associated with higher sensitivity to sulfonylureas, as documented in patients with MODY3.

RESEARCH DESIGN AND METHODS

We recruited 96 participants (46 variant carriers and 50 age- and sex-matched noncarriers). Response to glipizide (one 2.5–5.0-mg dose), metformin (four 500-mg doses), and an oral glucose challenge was evaluated using a previously validated protocol. Glucose and insulin levels and their areas under the curve (AUCs) were compared between groups.

RESULTS

Carriers of the p.E508K variant had a lower maximum insulin peak during the glipizide challenge as compared with noncarriers with diabetes ($P < 0.05$). Also, carriers had a lower insulin response after the oral glucose challenge. Following an oral glucose tolerance test in the presence of metformin, carriers of the p.E508K variant with diabetes had a lower maximum insulin peak and total and incremental insulin AUC value as compared with noncarriers with diabetes ($P < 0.05$). A similar but nonsignificant trend was seen in participants without type 2 diabetes.

CONCLUSIONS

Carriers of variant p.E508K in *HNF1A* have a reduced insulin response rather than the increased sensitivity to sulfonylureas seen in patients with MODY3.

Type 2 diabetes is the leading cause of death and a major burden for public health of Mexican and Latino populations (1). Ethnic-specific genetic variants have been described in populations with a Native American heritage (such as Mexicans). The Slim Initiative in Genomic Medicine for the Americas (SIGMA) Type 2 Diabetes Consortium has reported associations with a common haplotype in *SLC16A11* (2) through a genome-wide association study in ~9,000 participants and a rare missense variant (c.1522G > A [p.E508K]) in the gene encoding the hepatocyte nuclear factor-1α (*HNF1A*) through whole-exome sequencing in ~4,000 participants (3), both of which are rare or absent in non–Native American populations. The Mexican population results from a recent admixture of European and Native American populations with similar proportions and a relatively low African ancestry (<5%). This admixture is

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Received 21 February 2018 and accepted 1 May 2018.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-0384/-/DC1.

**A complete list of the members of the Slim Initiative in Genomic Medicine for the Americas Type 2 Diabetes Consortium can be found in the Supplementary Data online.*

known as the mestizo population. Therefore, exome-sequencing in Mexican mestizos has resulted in the identification of genetic variants mainly derived from our Native American heritage. In particular, the *HNF1A* variant, located in exon 8, causes a partial defect in the function of the transcription factor (3), which is expressed in liver and pancreas. Though the p.E508K variant is associated with a fivefold increased risk for developing type 2 diabetes, patients with the variant were clinically undistinguishable in terms of age of onset, adiposity, and glycemia from type 2 diabetes case subjects (3). The variant is present in 0.2% of the Mexican participants with type 2 diabetes in the SIGMA exome-sequencing analyses (3). Loss-of-function mutations in *HNF1A* cause maturity-onset diabetes of the young type 3 (MODY3) (4,5). MODY3 is characterized by an early onset of the disease, normal body weight, glycosuria, and high risk for microvascular complications (6–8). In addition, patients with MODY3 have high sensitivity to sulfonylureas; this feature underlies the current indication for sulfonylurea therapy in these patients, over metformin or insulin (8,9), and represents one successful example of precision medicine in diabetes.

Because p.E508K causes partial loss of function in *HNF1A*, we hypothesized that carriers of this variant might also exhibit heightened sensitivity to sulfonylureas. The aim of our study was to advance precision medicine by evaluating the insulin and glycemic responses to glipizide and metformin in p.E508K carriers and age- and sex-matched noncarriers. We followed the approach used in the Study to Understand the Genetics of the Acute Response to Metformin and Glipizide in Humans (SUGAR-MGH), a standardized pharmacogenetic protocol (10,11).

RESEARCH DESIGN AND METHODS

The study was supported by the SIGMA Type 2 Diabetes Consortium and performed in accordance with the SUGAR-MGH protocol (10). The study protocol was approved by the Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

Subjects and Setting

Mexican mestizos (defined as Mexican individuals whose father, mother, and grandfathers were born in Mexico and who do not belong to any other ethnic group [i.e., Jewish, Japanese, etc.]) aged ≥18 years, males or nonpregnant females, healthy control subjects (n = 33), and patients with type 2 diabetes (n = 16) were recruited at the diabetes outpatient clinic of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán in Mexico City, a center attending individuals from the general population. An additional recruitment of carriers and noncarriers of the p.E508K *HNF1A* variant was done among users of the diabetes outpatient clinic of the Instituto Nacional de Ciencias Médicas y Nutrición or among the first-degree relatives of the E508K variant carriers. Genotyping of the p.E508K variant (rs483353044) was performed using a TaqMan probe. For the assay, we included control subjects previously sequenced and selected carrying the three possible genotypes for this single nucleotide polymorphism. Case subjects with type 2 diabetes were eligible if they were being treated with no more than two oral antidiabetic agents and had an HbA_{1c} ≤7.5% (58 mmol/mol). Noncarriers were matched by age (±5 years), sex, BMI (±2 kg/m^2), and status of diabetes.

Volunteers were excluded from participation if they were pregnant, nursing, or women at risk of becoming pregnant; if they had age of onset of diabetes before 25 years of age, known history of liver or kidney disease, allergy to sulfonamides, history of porphyria, impaired renal function (estimated glomerular filtration rate <60 mL/min/1.73 m^2), established coronary artery disease, or history of bariatric surgery, seizures, or stroke; if they were taking medications that could affect glycemic parameters; or if they were planning radiologic or angiographic studies requiring contrast within 1 week of completion of the study. All participants read and signed an informed consent document.

Interventions

The study consisted of two visits (Fig. 1) (10). Prior to visit 1, participants with type 2 diabetes taking an oral antidiabetic agent underwent a 7-day washout period. Blood samples were obtained between 8:00 A.M. and 9:00 A.M. in the morning after an 8–12-h overnight fast. A complete medical and family history as well as anthropometric measurements were obtained. Participants were weighed on calibrated scales, and height was determined with a floor scale stadiometer; BMI was calculated as weight in kilograms divided by the square of height in meters. Participants with a fasting glucose ≤80 mg/dL were not eligible to receive the sulfonylurea challenge for safety reasons; those with fasting glucose 80–99 mg/dL received 2.5 mg of glipizide, and those with a fasting glucose ≥100 mg/dL received 5 mg. After glipizide administration, blood samples were collected at 30, 60, 90, 120, 180, and 240 min for glucose and insulin measurements. After the 240-min period, breakfast was given, and patients were

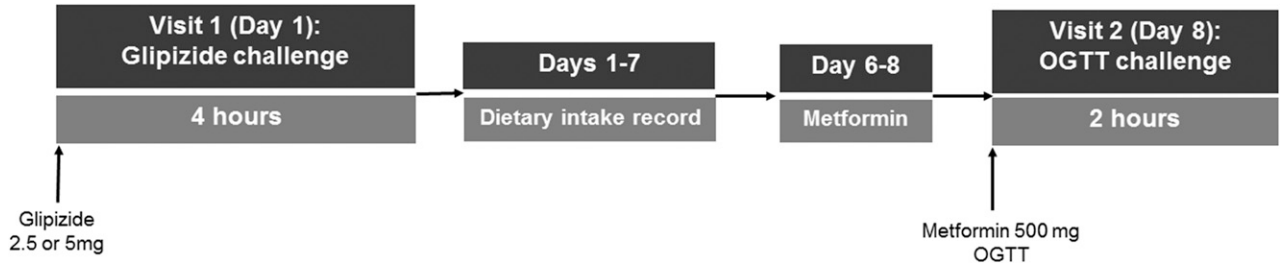

Figure 1—Outline of the study period and intervention. Subjects were divided according to their carrier and noncarrier status and then according to their type 2 diabete status into four groups. Subjects with type 2 diabetes had a medication washout period of 7 days before the procedure. Visit 1 consisted of biochemical evaluation and a glipizide challenge that lasted 4 h and included measurements at times 0, 30, 60, 90, 120, 180, and 240 min. From days 1 to 7, all participants were instructed to fill in a dietary intake record; at day 6, they had to take 500 mg of metformin at night and again before a 2-h OGTT, with blood measurements at times 0, 30, 60, and 120 min.

discharged once their glucose levels were ≥80 mg/dL.

At day 6 after the initial visit and provided they had normal renal function on safety laboratory testing, participants were instructed to take metformin (500 mg) at night. On day 7, they received metformin (500 mg) in the morning and in the evening. On day 8, they returned for their second visit, when they received one last dose of 500 mg metformin 60 min before a 75-g oral glucose tolerance test (OGTT). Blood samples were collected at 5, 10, 15, 30, 60, and 120 min for glucose and insulin measurements. Once visit 2 was completed, participants with treated type 2 diabetes were allowed to restart their routine antidiabetic therapy.

Glucose and insulin levels and their areas over the curve (AOCs) and areas under the curve (AUCs), respectively, after the glipizide dose were used to assess the sulfonylurea response. AUCs for insulin and glucose were also used to evaluate the response to the oral glucose challenge. Metformin response was evaluated by comparing fasting glucose after the metformin challenge and HOMA of insulin resistance (HOMA-IR) scores between visits 1 and 2.

Serum insulin concentration was measured using a chemiluminescent immunoassay (Access 2; Beckman Coulter). HbA_{1c} levels were estimated using high-performance liquid chromatography (Variant II Turbo; Bio-Rad). Plasma glucose and lipid concentrations (cholesterol, triglycerides, and HDL cholesterol), uric acid, creatinine, and hepatic enzymes were measured using commercially available assays (UniCel DxC 600 Synchron Clinical System; Beckman Coulter). LDL cholesterol was calculated with the Friedewald equation when triglycerides were <250 mg/dL. Plasma apolipoproteins B and AI were measured using immunonephelometry (Beckman Coulter).

Statistical Analyses

To evaluate differences between groups in clinical, sociodemographic, and biochemical measures, we performed a Student *t* test and Mann-Whitney *U* test for parametric and nonparametric quantitative variables, respectively. Frequency distribution of the categorical variables in the four groups was compared using χ^2 tests. Logarithmic transformations were applied to approximate normality in those variables showing a nonparametric distribution using the Kolmogorov-Smirnov test.

The primary outcome measure was insulin peak concentration during the glipizide challenge and during the OGTT after metformin exposure. As complementary analyses to evaluate differences in insulin secretion, action, and response in carriers and noncarriers, we calculated AUCs of insulin concentrations across time after the glipizide challenge and insulin and glucose concentration after the metformin challenge using the trapezoidal method adjusted for baseline concentrations; the AOC, to evaluate changes in glucose concentrations during the glipizide challenge, was calculated using the formula AOC = $FG_0 \times 4 \times$ AUC, in which FG_0 was fasting glucose before glipizide administration and the estimated AUC for glucose during the challenge calculated using the trapezoidal method. The Δ values were also calculated to assess changes in glucose and insulin over time, comparing maximum and minimum concentration peaks and fasting and baseline levels of both parameters. Data are presented as mean ± SD or median and interquartile range, where appropriate. Categorical variables are reported as frequencies and percentages.

RESULTS

Study Participants

We screened 2,981 individuals; of them, 79 were p.E508K carriers. Forty-six carriers fulfilled the inclusion criteria and accepted to participate. Fifty healthy noncarriers free of diabetes were included to match the characteristics of the carriers (by age, sex, BMI, and status of type 2 diabetes) (Supplementary Fig. 1). Among carriers, 14 had type 2 diabetes, and 32 were normoglycemic. In the noncarrier group, 16 participants with type 2 diabetes and 33 without diabetes were included (Table 1). The matching process was successful; no differences in age, sex, BMI, HbA_{1c}, glipizide dosage, and time of exposure to type 2 diabetes were found between groups. All participants filled in a dietary intake record to verify dietary adherence and metformin intake as indicated.

Insulin and Glucose Response During the Glipizide Challenge

The primary outcome measure was to evaluate if carriers of the *HNF1A* p.E508K variant have an enhanced response to sulfonylureas by comparing the peak insulin concentration between groups. After the glipizide challenge, the insulin peak was lower in p.E508K carriers with type 2 diabetes compared with their noncarrier peers ($P = 0.03$) (Fig. 2*A*). The difference remained significant when the baseline insulin concentration was considered (Supplementary Table 1). The same trend was observed for the normoglycemic group, but the differences did not attain statistical significance (Fig. 2*B*). No significant difference was seen in the total AUC and the incremental AUC insulin concentrations between carrier and noncarrier subjects, regardless of their type 2 diabetes status, following the glipizide challenge (Supplementary Fig. 1).

Most measures of glucose response during the glipizide challenge did not differ between the p.E508K genotype groups (Fig. 2*C* and *D*). However, the AOC for glucose response was significantly lower in carrier individuals with type 2 diabetes compared with noncarriers ($P = 0.046$) (Supplementary Table 1). The frequency of plasma glucose levels <50 mg/dL trend was lower in carriers of the p.E508K variant compared with noncarriers, but the difference did not reach statistical significance (22.9% vs. 10.9%; $P = 0.12$). Only three participants with type 2 diabetes had hypoglycemia during the glipizide challenge: two from the noncarrier group and one from the carrier group.

Insulin and Glucose Response During the OGTT Challenge

During the OGTT challenge (under metformin), the peak insulin level was lower for the p.E508K carriers with type 2 diabetes as compared with noncarriers with type 2 diabetes (Fig. 3). Fasting glucose concentrations after the OGTT challenge under metformin, our primary outcome of interest, were significantly lower for carrier individuals without type 2 diabetes compared with noncarriers ($P = 0.01$) (Supplementary Table 2). Among participants with type 2 diabetes, significantly lower insulin peak concentration and total AUC insulin level were observed for carriers compared with the noncarriers. These comparisons did not achieve statistical significance in the normoglycemic group, but a similar trend was observed (Supplementary Table 3). There were no significant differences in glucose concentrations during the 2-h OGTT for the p.E508K carriers compared with noncarriers (Fig. 3). Insulin action was not different between genotype groups (Supplementary Table 3).

As expected, HOMA-IR scores were higher in participants with type 2 diabetes,

Table 1—Biochemical and demographic characteristics of the studied population

	Without type 2 diabetes			With type 2 diabetes		
	p.E508K(+) (*n* = 32)	p.E508(−) (*n* = 33)	*P* value	p.E508K(+) (*n* = 14)	p.E508(−) (*n* = 16)	*P* value
Age (years)	38.41 ± 15.71	41.55 ± 13.10	0.38	55.64 ± 13.90	53.44 ± 8.47	0.60
BMI (kg/m^2)	28.51 ± 5.28	27.96 ± 5.66	0.63	27.14 ± 4.45	29.94 ± 5.82	0.15
Age at diagnosis of type 2 diabetes (years)	—	—	—	52.93 ± 13.94	49.94 ± 8.79	0.48
Duration of type 2 diabetes	—	—	—	2.0 (1.0–6.5)	1.0 (1.0–5.0)	0.75
Glucose (mg/dL)	95.75 ± 10.65	99.19 ± 10.65	0.23	127.36 ± 30.61	135.60 ± 38.88	0.55
Insulin (mU/mL)	7.4 (4.5–12.4)	4.9 (3.0–12.1)	0.69	6.8 (3.5–8.7)	10.35 (5.27–17.2)	0.21
HOMA-IR	1.82 (1.3–3.0)	1.68 (0.96–2.3)	0.40	—	—	—
HbA_{1c}, % (mmol/mol)	5.39 ± 0.47 (37.62 ± 4.92)	5.59 ± 0.46 (35.40 ± 5.25)	0.09	6.37 ± 0.86 (45.75 ± 7.65)	6.34 ± 0.70 (46.14 ± 9.35)	0.91
Total cholesterol (mg/dL)	180.41 ± 25.09	186.19 ± 41.44	0.50	184.94 ± 34.56	177.36 ± 35.16	0.56
Triglycerides (mg/dL)	140.0 (118.0–179.0)	124.0 (97.0–192.0)	0.59	110.0 (95.0–164.0)	147.5 (118.2–204.0)	0.27
HDL cholesterol (mg/dL)	41.12 ± 7.04	42.50 ± 10.54	0.54	45.28 ± 12.92	44.44 ± 9.15	0.84
LDL cholesterol (mg/dL)	108 (87.5–121.9)	103 (83.0–135.8)	0.35	106.0 (92.2–126.6)	103.7 (93.7–126.8)	0.47
Apolipoprotein B (mg/dL)	95.65 ± 18.68	100.88 ± 23.89	0.34	97.81 ± 20.47	103.62 ± 23.73	0.87
ALT (IU/L)	19.0 (16.0–31.0)	26.0 (15.0–32.0)	0.63	24.0 (20.0–29.0)	33.0 (18.7–64.2)	0.33
AST (IU/L)	22.0 (19.0–26.5)	26.0 (21.0–32.0)	0.10	25.0 (23.0–31.0)	28.0 (21.7–37.2)	0.47
GGT (IU/L)	15.0 (12.0–22.5)	21.0 (15.0–32.0)	0.15	17.0 (13.0–33.0)	25.0 (16.2–37.5)	0.38

Comparison of individuals with and without type 2 diabetes and with and without the p.E508K variant in the *HNF1A* gene. Data are mean ± SD or median (interquartile range) unless otherwise noted. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase.

regardless of their genotype status. A trend for lower HOMA-IR scores was observed after metformin therapy in carriers without type 2 diabetes. No statistical difference was found in the ΔHOMA-IR score between genotype groups (Supplementary Table 3), suggesting that the p.E508K variant did not modify the metformin response.

CONCLUSIONS

HNF1A mutations cause decreased insulin secretion and a set of clinical features that characterize the MODY3 phenotype. Among them, an enhanced response to sulfonylureas enables the transition from insulin to oral drugs for a large percentage of MODY3 patients (12). In Mexicans, 2% of those with type 2 diabetes who

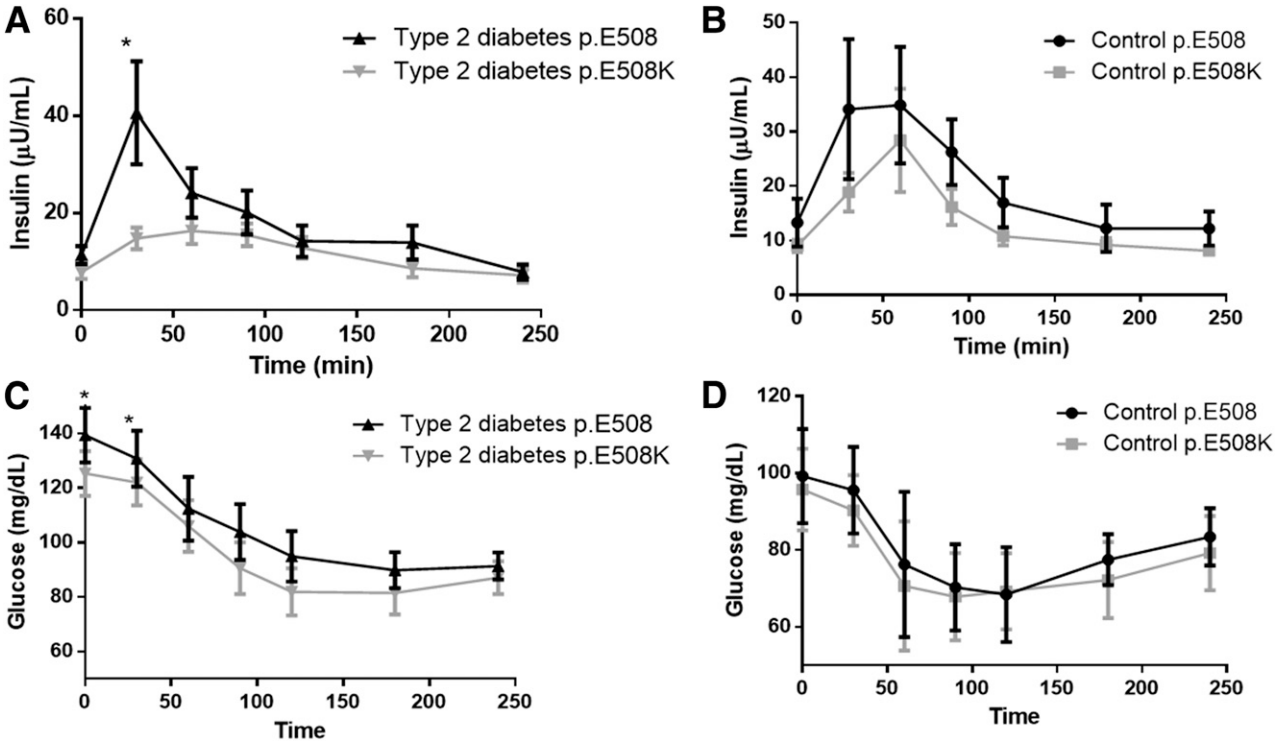

Figure 2—Comparison of insulin (*A* and *B*) and glucose (*C* and *D*) response curves after the administration of 2.5 or 5 mg of oral glipizide in carriers and noncarriers of the *HNF1A* p.E508K variant with (*A* and *C*) and without (*B* and *D*) type 2 diabetes. *$P < 0.05$.

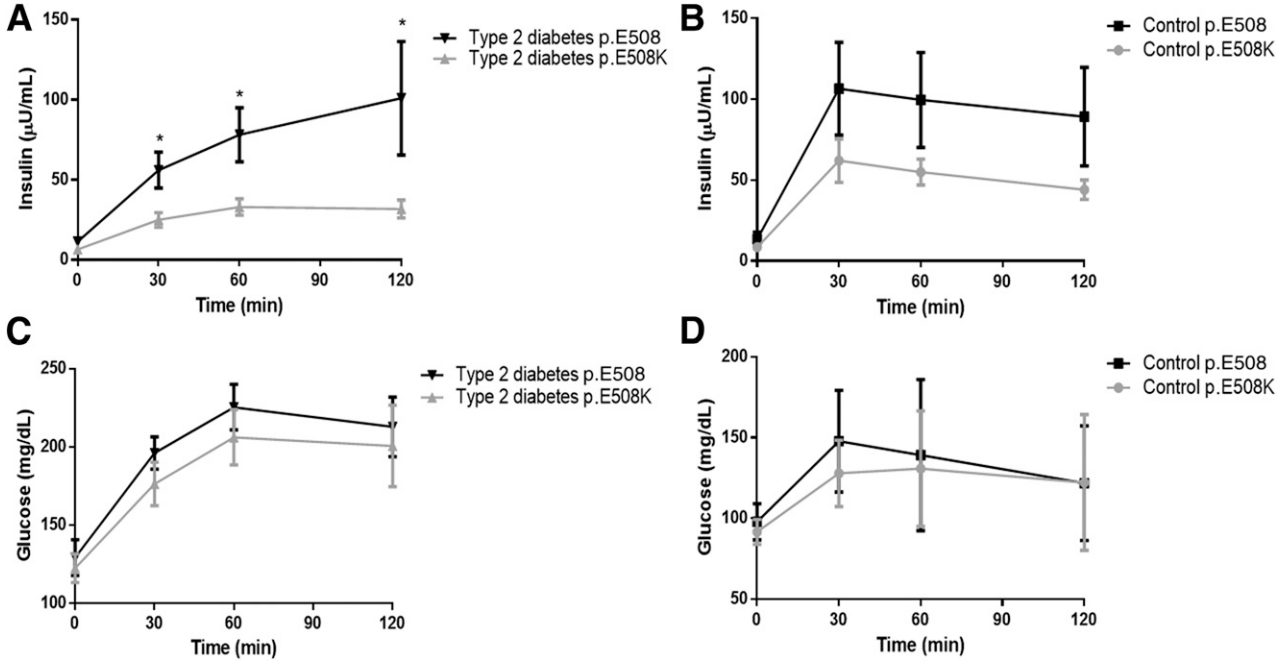

Figure 3—Comparison of insulin (*A* and *B*) and glucose (*C* and *D*) response curves in an OGTT after the administration of 500 mg metformin in carriers and noncarriers of the *HNF1A* p.E508K variant with (*A* and *C*) and without (*B* and *D*) type 2 diabetes. $*P < 0.05$.

participated in the exome-sequencing component of the SIGMA Type 2 Diabetes study carried an ethnic-specific *HNF1A* variant (p.E508K). This variant is associated with a lower transcriptional activity (40%) on the *HNF1A* responsive promoters, a lower nuclear localization (15%), and lower protein expression (50%). However, the decreased transactivation was not as severe as that seen in three MODY-causing *HNF1A* mutations. Also, some clinical features of the p.E508K carriers were not in accordance with the MODY3 profile (i.e., age of onset). Based on the partial loss of transcriptional activity conferred by the Mexican-specific *HNF1A* p.E508K variant, we hypothesized that carriers of this variant might also exhibit heightened sensitivity to sulfonylureas. If confirmed, this finding would have had substantial pharmacogenetic implications in regards to the diagnosis and treatment of this form of diabetes in Mexico. In this study, we do show that carriers of the risk variant (particularly those with type 2 diabetes) have a remarkably lower insulin response during an OGTT. However, in contrast to our expectations, carriers with type 2 diabetes had a less vigorous insulin response when challenged with the sulfonylurea glipizide compared with noncarriers. Following an OGTT in the presence of metformin, carriers with type 2 diabetes also demonstrated a reduced insulin response as compared with noncarriers with type 2 diabetes. In participants free of diabetes, there was no evidence that carriers respond better to sulfonylureas than noncarriers. In addition, they were no more likely to develop hypoglycemia during sulfonylurea administration. Thus, it appears that identification of this variant will not affect treatment selection.

The unexpected reduced insulin response to glipizide or glucose in carriers with diabetes compared with noncarriers may be due to a more aggressive form of the disease that accelerates β-cell failure when compared with common type 2 diabetes, rendering sulfonylureas less effective in variant carriers. Though no significant differences in age of onset were noted between carriers and noncarriers in the original SIGMA study (3), it is possible that once diabetes sets in, β-cell failure proceeds more rapidly. This is not consistent with what is seen in MODY3 and may be specific to the Mexican context or to this variant. Longitudinal studies are needed to establish whether variant carriers with diabetes progress to insulin therapy faster than noncarriers.

Pearson et al. (9) proposed that neither the type of *HNF1A* mutation nor the mutation site influences the sulfonylurea response in patients with MODY3. Interestingly, carriers of some variants did not exhibit the enhanced sulfonylurea response, such as those with the p.W206X stop mutation, whose severe phenotype is due to the loss of the DNA-binding domain (13). The *HNF1A* p.E508K variant is located in the middle of the transactivation domain. Additional studies with a large enough sample of cases with different types of variants (including frameshift, missense, nonsense, or splice site mutations) and over a longer term are needed to understand why some, but not all, of *HNF1A* variants are associated with the enhanced sulfonylurea response (14–16).

HNF1A variants modify the response to other glucose-lowering agents, besides sulfonylureas. Recently, an enhanced glycosuric response to a sodium–glucose cotransporter 2 inhibitor in a small group of MODY3 cases has been reported (17). This finding was unexpected because sodium–glucose cotransporter 2 expression is downregulated in MODY3 cases. Thus, the large number of genes regulated by *HNF1A* opens the possibility of additional pharmacogenetic effects to be identified in patients with MODY3 and carriers of other *HNF1A* variants.

The clinical spectrum of the *HNF1A* variants has been expanded with the evidence provided by the exome-sequencing

collaborative studies. Two ethnic-specific variants (G319S for Oji-Cree [18] and p.E508K for Mexicans) have moderate functional consequences, and clinical expression is similar to type 2 diabetes. Recently, Najmi et al. (19) reported the *HNF1A* variants found in the Framingham Heart Study Offspring cohort, the Jackson Heart Study cohort, and the extreme type 2 diabetes cohort. They found 27 nonsynonymous variants in 4,115 participants (prevalence 0.6%); 9 of them were novel. Some, but not all, were associated with type 2 diabetes, with the p.E508K variant having the highest odds ratio. Because current bioinformatic programs do not establish pathogenicity conclusively, the authors used functional assays to classify variants as likely or unlikely pathogenic. They proposed that those variants with a transcriptional activity of $<$60% are likely to be pathogenic (odds ratio 5.04 [95% CI 1.99–12.8]; P = 0.0007).

Our study has its own strengths and limitations. This study was performed using a previously validated pharmacogenetic study protocol applicable both in healthy subjects and case subjects with type 2 diabetes. Pharmacogenomic evaluations are relevant for the development of precision medicine, as well as for understanding the physiological responses in carriers of genetic variants of interest. We recognize that we do not have a large number of study subjects. However, it is enough to test the hypothesis. In the sample of individuals with type 2 diabetes, considering an α of 0.05 and log-transformed maximum insulin peak concentrations, we have a power to detect differences between carriers and noncarriers of 87.75% (β = 0.12). Overall, for the maximum insulin peak concentrations, considering an α of 0.05, the sample size has 80.73% power to detect differences in log-transformed insulin concentrations between carriers and noncarriers (β = 0.19).

In conclusion, this report extends the clinical characterization of the *HNF1A* p.E508K variant. It is associated with lower insulin response to glucose and the lack of an enhanced response to glipizide. Further research must be performed in order to understand the penetrance of this variant and the spectrum of its contribution to different clinical manifestations of diabetes.

Acknowledgments. The authors thank Saúl Cano Colín (Unidad de Biología Molecular y Medicina Genómica, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad de México, Mexico) for technical assistance and Dr. Gladys Faba (Instituto Nacional de Salud Pública, Cuernavaca, Morelos, Mexico) for advice in the editing of this manuscript. A.J.M. thanks Grupo de Investigación con Enfoque Estratégico en Bioingeniería y Medicina Regenerativa for support.

Funding. Research reported in this study was supported by a research-initiated grant by PATIA. Some resources were provided by the SIGMA Type 2 Diabetes Consortium. Partial funding was provided by Consejo Nacional de Ciencia y Tecnología Projects 262077 and Infraestructura 2015-255096.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.J.M. collected clinical information and wrote the manuscript. O.Y.B.-C. analyzed the data and participated in the preparation of the manuscript. O.A.-C., P.A.-V., G.A.W., I.C.-B., D.V.G.-V., R.M., L.M.-H., M.S.-G., T.L.V.-R., M.L.O.-S., R.R.-G., J.C.F., M.T.T.-L., and C.A.A.-S. researched, revised, and edited the manuscript. C.A.A.-S. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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