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Research Article

Lack of Association of the HMGA1 Gene Variants with Metabolic Syndrome Risk and Response to Oral Anti-Diabetic Drugs

Mirna K. Faiq [1*], Eman S. Saleh[2], Omar B. Fathalla [3]

[1] Department of Clinical Pharmacy, College of Pharmacy, University of Tikrit, Salah-din, Iraq
[2] Department of Clinical Laboratory Sciences, College of Pharmacy, University of Baghdad, Baghdad, Iraq
[3] Kirkuk Health Department, Ministry of Health and Environment, Kirkuk, Iraq

* Corresponding author email: mirna.k.faiq@tu.edu.iq

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ABSTRACT

Background: Metabolic syndrome is partially heritable. High mobility group A1, an architectural transcription factor, affects the homeostasis of glucose. The marked inter-individual differences between type 2 diabetes patients in response to oral anti-diabetic drugs have become an issue for effective prescribing and dosing. The objective of this study was designed to assess whether different single nucleotide polymorphisms of the high mobility group A1 gene are associated with metabolic syndrome, and clarify the effect of these variants on response to combination therapy of metformin, sitagliptin, and glimepiride used by metabolic syndrome with diabetes patients.

Subjects and Methods: From February until Augusts 2022, a total of 91 Iraqi participants (61 patients with metabolic syndrome and 30 controls). The diabetes patients were divided into two groups responders and non-responders, based on their HbA1c. Polymorphisms in HMGA1 and genotyping were identified by Sanger sequencing of genomic DNA.

Results: The high prevalence of CC and GG genotypes of rs1023028442 and rs112081775 respectively was seen in the Iraqi population. Minor allele frequency of rs1023028442 was higher among metabolic patients without diabetes with (Minor Allele Frequency =0.08) compared to the control group with (Minor Allele Frequency = 0%). While (Minor Allele Frequency =0.1) of rs112081775 was seen in metabolic patients without diabetes compared to (Minor Allele Frequency =0.02) in the control group. The non-significant difference in genotyping and allele carriage frequencies of the high mobility group A1 gene was seen between total metabolic syndrome patients and the control group. Based on their response to therapy non-significant difference was seen between those with wild and carrier genotypes.

Conclusions: This study suggests a lack of association of the rare high mobility group A1 gene variants with metabolic syndrome risk and response to oral anti-diabetic drugs.

Introduction

Metabolic syndrome (Mets) is a group of metabolic dysregulate including insulin resistance, hypertension, atherogenic dyslipidemia, and central obesity (1). The "National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria define metabolic syndrome as the presence of any three of the following five traits: abdominal obesity, defined as a waist circumference ≥102 cm in men and ≥88 cm in females, serum triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides, serum high-density lipoprotein (HDL) cholesterol <40 mg/dL in males and <50 mg/dL in females or drug treatment for low HDL cholesterol, systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥85 mmHg or drug treatment for elevated blood pressure" (2). Individuals with metabolic syndrome are at increased risk for severe complications, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (3). Estimates of metabolic syndrome heritability vary between 10% and 30% (4–6), indicating that metabolic syndrome is partially hereditary. Single-nucleotide polymorphisms (SNPs) are found extensively in human DNA sequences and some are considered to be disease-related. In the last few years, genome-wide association studies (GWAS) have identified many candidate SNPs which are associated with metabolic traits including obesity, diabetes, high blood pressure, and dyslipidemia. In humans, the high mobility group A1 (HMGA1) gene is present on chromosome 6p21 (NC_000006.12) that positively regulates the activity of the Insulin Receptor (INSR) promoter, which binds to the INSR transcription start site causing positive regulation of INSR expression and insulin signal transduction (7). The treatment of type 2 diabetes is largely empirical and predicting specific responses to therapeutics in any patient is difficult (8). Because HMGA1 decline or variant specifies a distinct defect that decreases insulin receptor concentrations and insulin resistance, type 2 DM pathogenesis may respond differently to various therapies, such as an insulin sensitizer (9). The impact of HMGA1 has been investigated in two large Italian and Turkish populations, both affected by metabolic syndrome. Findings indicated that the HMGA1 rs139876191 variant was significantly associated with metabolic syndrome in both populations. This study will conduct to: assess whether different SNPs of the HMGA1 gene are associated with metabolic syndrome risk and clarify the effect of their variant on response to combination therapy of metformin, sitagliptin, and glimepiride used by metabolic syndrome with diabetes patients.

Subjects and Methods

Study population

This case-control study was carried out at Kirkuk city/ Iraq, internal medicine clinic under the supervision of an internal medicine specialist from February until Augusts 2022. One hundred were selected to participate in this study. Only (91) subjects completed the courses of the study successfully. These subjects were recruited into the following groups: Group 1: 31 metabolic syndrome patients with type 2 diabetes (MetS + T2D). Group 2: pathological control group contains 30 metabolic syndrome patients without diabetes (MetS - T2D). Group 3: Control Group (Looks healthy, contains 30 people who have no components of metabolic syndrome criteria such as diabetes mellitus, hypertension, dyslipidemia, and obesity).

Inclusion criteria

Patients and control groups with ages over 30 years old of either sex are accepted to participate in the study. Metabolic syndrome was defined using the NCEP ATP III guidelines (2). Diabetes patients on triple medication including metformin, sitagliptin, and glimepiride who adhere to these medications and do not change them for at least 3 months.

Exclusion criteria

Type 1 diabetes, any type of malignancy, pregnant and lactating women, autoimmune diseases, and patients with Inborn Errors of metabolism were excluded from this study.

Demographical, Anthropometric, and Biochemical Evaluation

Data was collected using a researcher-made questionnaire which consisted of individual and personal factors. Including age, gender, and whether they are a smoker or not. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Blood pressure was measured with an MDF® desk mercury sphygmomanometer. Blood samples were collected following 12 h overnight fast. Fasting serum glucose was measured by the enzymatic colorimetric method using a glucose oxidize test. HbA1c determined by latex enhanced immunoassay method. Serum total cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-cholesterol), and low-density lipoprotein-cholesterol (LDL-cholesterol) were determined by enzymatic colorimetric methods using commercial kits provided by (GIESSES®DIAGNOSTICS, Italy). Very low-density lipoprotein-cholesterol (VLDL-cholesterol) is calculated as about one-fifth of triglyceride levels (10).

Sample Collection

Blood collected after at least 12 hours of fasting from patients and control, by vein puncture with plastic disposable syringes took up to 5mL of venous blood, and 2 ml was added to EDTA tube for detection of SNP for HMGA1.

DNA extraction

The Promega ReliaPrepTM Blood gDNA Miniprep System for Genomic DNA (Promega Corp., WI, USA) provides a practical approach for purifying DNA from blood samples. Polymerase chain reaction (PCR) was used for enzymatic amplification with the Master Taq polymerase enzyme and a hybrid thermal cycler.

Primers

The HMGA1 gene DNA sequences were taken from the NCBI GenBank database. Primer Premier 3 software was used to generate PCR primers (Table 1), with a melting temperature of (58 to 62°C), a primer length of (18 to 23) nucleotides, and a PCR amplicon length of (800 to 1000) base pairs.

Table 1: The sequences of the primers, annealing temperature, product size (bp)

Primer Name	Sequence 5`-3`	Annealing Temp. (°C)	Product size (bp)
HMGA-F	TGTAAAACGACGGCCAGTGTTTGTGGTTCTTGGTTCTTG	58	972
HMGA-R	CAGGAAACAGCTATGACGCTTCTTCACCTACCAGTTT		

summarized in **(Table 2)**.

Sequencing analysis

PCR products were sent for Sanger sequencing using ABI3730XL, an automated DNA sequencer, by Macrogen Corporation – Korea. The results were received by email and then analyzed using geneious software.

Ethical considerations

The study protocol was approved with the number (RECAUBCP4102021B) on the 4th of October 2021 by the local ethical committee of the college of pharmacy-Baghdad University, with verbal informed consent from patients.

Statistical analysis

The statistical analysis was done using IBM SPSS software for Windows version 26.0 (IBM Corp., Armonk, NY, U.S.). Continuous variables were expressed in mean ± standard deviation (SD) for normally distributed data and median (IQR) for skewed distributed data. Allele and genotypes were presented in number and frequency. The Shapiro-Wilk test and Kolmogorov-Wilk test were used to test the normality of the results. The unpaired t-test was used for normally distributed data and the Mann-Whitney U test was used for not normally distributed data to determine a significant difference in demographic characteristics and parameters between the groups. The chi-square test or Fisher exact test was used to test group differences in proportions. Odds Ratios (OR) with 95% confidence bounds were further calculated. Phi-coefficient analysis was used to investigate the correlation between each genotype and the tendency to be a responder to therapy. A p-value of <0.05 was considered statistically significant.

Table 2: Demographic data and the clinical characteristics parameters based on their response to anti-diabetic therapy

Iraqi population	Measurements	MetS + T2D N=31	MetS - T2D N=30	Control N=30
Gender				
-Male	N (%)	12(38.7%)	14(46.7%)	17(56.7%)
-Female		19(61.3%)	16(53.3%)	13(43.3%)
Age in years	Median(IQR)	54(45-64)	53(40-62)	48(35-56)
Smoker	N (%)	5(16.1%)	1(3.3%)	12(40%)
WC (cm)	mean ± SD	107.2 ± 11.5	107.6 ± 13.5	91.3 ± 11.2
BMI (kg/m^2)	mean ± SD	29.5 ± 4.6	31.5 ± 4.4	27.25 ± 3.9
TC (mg/dl)	mean ± SD	161 ± 41.7	203 ± 42.7	133.1 ± 60.4
TG (mg/dl)	Median(IQR)	150(111-184)	188(142.6-223)	98(98-141.7)
HDL (mg/dl)	mean ± SD	55.4 ± 12.03	56.9 ± 15.9	48.3 ± 8.4
LDL (mg/dl)	Median(IQR)	77(37-96)	102(97-136)	55(53-110.5)
VLDL (mg/dl)	Median(IQR)	30(22-36.8)	37.6(28.5-44.7)	19(19-28.4)
SBP (mmHg)	Median(IQR)	120(120-150)	130(120-142)	120(120-130)
DBP (mmHg)	Median(IQR)	85(80-100)	90(80-95)	80(80-80)
HbA1c (%)	Median(IQR)	7.3(6.5-8.9)	6(5-6.3)	5.8(5-6)
FBG (mg/dl)	Median(IQR)	124(112-160)	103(88.8-114.8)	102(89.5-112.3)

Normally distributed data expressed as mean ± SD. While not normally distributed data expressed as median (interquartile range). MetS, metabolic syndrome patients. Mets+T2D, metabolic syndrome patients with type 2 diabetes. Mets-T2D, metabolic syndrome patients without type 2 diabetes. WC, waist circumference. TC, total cholesterol.TG, triglyceride. HDL, high density lipoprotein. LDL, low density lipoprotein. VLDL, very low density lipoprotein. SBP, systolic blood pressure. DBP, diastolic blood pressure. HbA1c, Hemoglobin A1c. FBG, Fasting blood glucose.

Results

The demographic, anthropometric, clinical, and biochemical characteristics of all individuals enrolled in this study are summarized in (Table 2).

The Subjects enrolled in the present study were matched. The mean ages are (54.5 ± 10.3 and 54.7 ± 11.4) years for the responder, and non-responder groups respectively (P = 0.961). The study results revealed a significant difference in systolic/diastolic blood pressure between each group which is higher in the non-responder group. As seen in (Table 3).

The extracted DNA concentration in all samples was found to be in a range of 20- 35ng/µl detected by using Quantus fluorometer TM. Analysis of rs1023028442 SNP of HMGA1 gene using Sanger sequencing (Figure 1A). Single "C" peak indicative of a C homozygous allele. Single "T" peak indicative of a T homozygous allele. The presence of the "C" and "T" peaks is indicative of the C/T heterozygous allele. While Analysis of rs112081775 SNP of HMGA1 gene using Sanger sequencing (Figure 1B). Single "G" peak indicative of a G homozygous allele. Single "A" peak indicative of a homozygous allele. The presence of the "G" and "A" peaks is indicative of the G/A heterozygous allele.

Table 3: Demographic data and the clinical characteristics parameters based on their response to anti-diabetic therapy:

Parameters	Responder group (N=18) (HbA1c ≤7.5)	Non-responder group (N=13) (HbA1c >7.5)	P-value
Age(years)	54.5 ± 10.3	54.7 ± 11.4	0.961
Gender			
-Male	8(44.4%)	4(30.7%)	0.484
-Female	10(55.6%)	9(69.3%)	
DM disease duration (years)	9(1-19.3)	5(1-10.5)	0.233
Duration of using OADs (months)	3.5(3-12)	8(3-15)	0.388
Smoker	3(16.7%)	2(15.4%)	1
WC (cm)	109.05 ± 11.79	104.7 ± 11.11	0.306
BMI (kg/m^2)	29.7 ± 5.4	29.2 ± 3.25	0.785
TC (mg/dl)	158.4 ± 42.9	165.8 ± 41.2	0.636
TG (mg/dl)	143(111-2143.7)	150(111-182)	0.968
HDL (mg/dl)	56 ± 13.1	54.5 ± 10.8	0.740
LDL (mg/dl)	61.5(37-91.5)	78(43.5-103.7)	0.256
VLDL (mg/dl)	28.6(22-42.8)	29.2(22-39.1)	0.849
SBP (mmHg)	120(120-135)	130(122.5-155)	**0.032***
DBP (mmHg)	80(80-90)	90(82.5-100)	**0.033***

Normally distributed data expressed as mean ± SD. While not normally distributed data expressed as median (interquartile range). The 2-tailed standard t test was used for comparisons of means. The Mann-Whitney U Test was used for comparisons of median. Fisher exact test was used for categorical variables. OADs, oral anti-diabetic drugs. TC, total cholesterol.TG, triglyceride. HDL, high density lipoprotein. LDL, low density lipoprotein. VLDL, very low density lipoprotein. SBP, systolic blood pressure. DBP, diastolic blood pressure. HbA1c, Hemoglobin A1c. * Statistically significant.

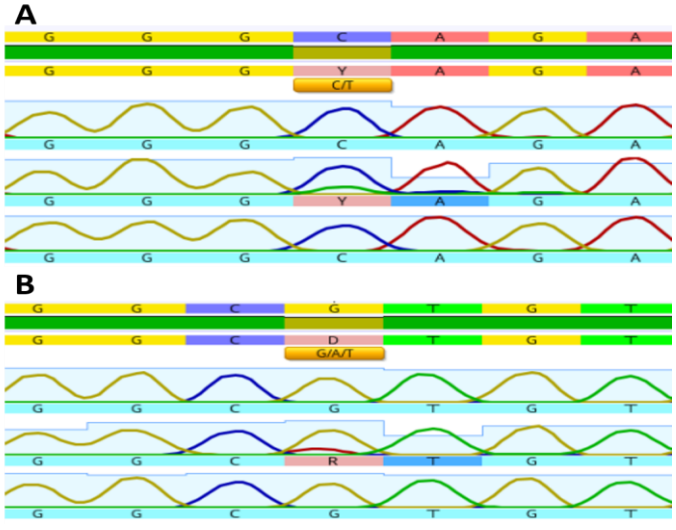

Figure 1: Analysis of A: rs1023028442 SNP of HMGA1 gene. B: rs112081775 SNP of HMGA1 gene

Table 4: Distribution of HMGA1 genetic polymorphism in Iraqi populations:

SNP	rs1023028442			rs112081775		
Genotype	CC N. (%)	C>T N. (%)	MAF	GG	G>A	MAF
MetS (Total)	54(88.5%)	7(11.5%)	0.057	53(86.9%)	8(13.1%)	0.065
*Mets+T2D	29(93.5%)	2(6.5%)	0.032	29(93.5%)	2(6.5%)	0.032
*Mets-T2D	25(83.3%)	5(16.7%)	0.08	24(80%)	6(20%)	0.1
Controls	30(100%)	0(0%)	0	29(96.7%)	1(3.3%)	0.02

SNP, single nucleotide polymorphism. rs: reference SNP. MAF, minor allele frequency. CC, and GG are the wild genotype. C>T, and G>A are the carrier (variant genotype). MetS, metabolic syndrome patients. *Mets+T2D, metabolic syndrome patients with type 2 diabetes. *Mets-T2D, metabolic syndrome patients without type 2 diabetes.

The high prevalence of CC and GG genotypes of rs1023028442 and rs112081775 respectively was seen in the Iraqi population enrolled in the current study. Minor allele frequency of rs1023028442 was higher among metabolic patients without diabetes with (MAF=0.08) compared to the control group with (MAF= 0%). While (MAF=0.1) of rs112081775 was seen in metabolic patients without diabetes compared to (MAF=0.02) in the control group. As illustrated in (Table 4).

Based on their nationality, there is no significant difference seen in the distribution of multiple genotypes and alleles frequency of the HMGA1 gene. As illustrated in (Table 5).

The non-significant difference in genotyping and allele carriage frequencies of the HMGA1 gene was seen between total metabolic syndrome patients and the control group. The odds ratio for developing metabolic syndrome was 8.4 times for C>T genotype carriers (CI=0.463- 152.08) compared to the CC genotype of rs1023028442 SNP. Followed by G>A genotype with an odd ratio of 4.4 (CI=0.52-36.74); compared to the GG genotype of rs112081775 SNP. As illustrated in (Table 6).

Table 5: HMGA1 multiple genotypes and alleles frequency distribution based on their nationality

SNP	Genotype	Arab N=32 N (%)	Kurd N=22 N (%)	Turkmen N=37 N (%)	P value
rs1023028442	CC	29(90.6%)	21(95.5%)	34(91.9%)	0.801
	C>T	3(9.4%)	1(4.5%)	3(8.1%)	0.890
Allele frequency	C	61(95.3%)	43(97.75%)	71(95.95%)	0.808
	T	3(4.7%)	1(2.25%)	3(4.05%)	0.894
rs112081775					
	GG	29(90.6%)	21(95.5%)	32(86.5%)	0.532
	G>A	3(9.4%)	1(4.5%)	5(13.5%)	0.550
Allele frequency	G	61(95.3%)	43(97.75%)	69(93.25%)	0.550
	A	3(4.7%)	1(2.25%)	5(6.75%)	0.567

A Chi-square test or Fisher exact test was used to identify the statistical difference between the groups. CC and GG: the wild genotype. rs: reference SNP.

Table 6: Comparison of the frequency of genotypes and alleles frequency between total metabolic syndrome patients and control group

SNP	Genotypes	Total Mets N=61	Control N=30	Fisher exact (P value)	OR (95% CI)	P value
rs1023028442	CC	54(88.5%)	30(100%)	-	1(Referent)	-
	C>T	7(11.5%)	0(0%)	0.09	8.4(0.463-152.08)	0.1
Allele frequency	C	115(94.25%)	60(100%)	-	1(Referent)	-
	T	7(5.75%)	0(0%)	0.09	7.8(0.44-139.9)	0.1
rs112081775						
	GG	53(86.9%)	29(96.7%)	-	1(Referent)	-
	G>A	8(13.1%)	1(3.3%)	0.2	4.4(0.52-36.74)	0.1
Allele frequency	G	114(93.4%)	59(98.3%)	-	1(Referent)	-
	A	8(6.6%)	1(1.7%)	0.2	4.1(0.50-33.89)	0.1

Fisher exact test. OR, odd ration. CI, confidence interval. SNP, single nucleotide polymorphism. Mets, metabolic syndrome patients. CC and GG: the wild genotype. rs: reference SNP.

The results of this study indicated that there wasn't a significant difference in response to therapy between those with wild and carrier genotypes. Also, regarding the difference in allele frequencies between the responder and non-responder groups, the results show no significant difference. As illustrated in (Table 7).

Phi-coefficient analysis was used to investigate the correlation between each genotype and the tendency to be a responder to therapy. All genotypes showed either a positive or negative relationship with a response but doesn't reach the statistically significant level as seen in (Table 8).

Table 7: Distribution of HMGA1 gene polymorphism SNPs with its allele's frequency in the diabetes patients' group

SNPs	Genotype	Responder group (N=18) (HbA1c ≤7.5) N (%)	Non-responder group (N=13) (HbA1c >7.5) N (%)	p-value
rs1023028442	CC	17(94.4%)	12(92.3%)	0.811
	C>T	1(5.6%)	1(7.7%)	1
Allele frequency	C	35(97.2%)	25(96.2%)	0.814
	T	1(2.8%)	1(3.8%)	1
rs112081775	GG	18(100%)	11(84.6%)	0.167
	G>A	0(0%)	2(15.4%)	0.167
Allele frequency	G	36(100%)	24(92.3%)	0.171
	A	0(0%)	2(7.7%)	0.171

Chi square test or Fisher exact test was used to identify the statistical difference between the groups. CC and GG letters: the wild genotype. rs: reference SNP.

Table 8: Correlation between each genotype and the likelihood of being a responder

SNP	Genotype	Phi-coefficient	p-value
rs1023028442			
	CC	0.043	0.811
	C>T	-0.043	0.811
rs112081775			
	GG	0.309	0.085
	G>A	-0.309	0.085

Phi-correlation coefficient was used to find the correlation between each genotype and the likelihood of being a responder. CC and GG: The wild type. rs: reference SNP.

Discussion

Metabolic syndrome has been associated with type 2 diabetes (11-13). Several studies suggest that metabolic syndrome patients are five times more likely to develop type 2 diabetes (14). Type 2 diabetes shows evidence of underlying heterogeneity and also is a complex disease, it is hard to identify all genetic risk factors from several Genome-wide association studies (GWAS), although GWASs are powerful tools in the study of complex diseases (15). There were no previous studies have evaluated whether the various causes of diabetes, alter the response to oral hypoglycemic treatment. Patients with diabetes caused by hepatocyte nuclear factor 1alpha (HNF-1alpha) gene mutations have occasionally been documented as being sensitive to the hypoglycemic effects of sulphonylurea (16). The treatment of type 2 diabetes consists mainly of oral anti-diabetic drugs (OADs) that stimulate insulin secretion, such as sulfonylurea, reduce liver glucose production like biguanides (17), and increase the biological activity of incretin hormones like sitagliptin (18). The marked inter-individual differences among patients with type 2 diabetes have become a problem for effective prescribing and dosing. In this study, two polymorphisms (rare variants) appeared in the HMGA1 gene (rs1023028442 and rs112081775) and these two SNPs were not previously mentioned in any study before this study.

Genome-wide association studies and other genetic analyzes have been done to detect genes involved in metabolic syndrome. Though the genetic mutations identified so far account for only a fraction of the heredity of metabolic syndrome, it is unclear how these variants affect susceptibility to the disorder (19). HMGA1 gene is playing (a critical role in glycemic balance as a structural transcription factor). HbA1c was measured at least 3 months after drug prescription and determined using the commercial kit provided by (GIESSE®DIAGNOSTIC, Italy). The strategy used to treat the patients was "treat to target," which is defined as failing to achieve HbA1c levels ≤ 7.5%. An A1C < 7% is recommended for most patients, a higher A1C target should be taken into account in adolescents and children as well as patients over the age of 65 and those with co-existing chronic conditions, impairments in daily living activities, cognitive impairment, or living in long-term care facilities (20).

There was no significant difference in response to treatment between those with the wild and carrier genotype. Also, regarding the difference in allele frequencies between the responder and non-responder groups, the results show no significant difference.

A key characteristic of Kirkuk is its diversity – Kurds, Arabs, Turkmen, Shia, Sunni, and Christians (Chaldeans and Assyrians) all coexist in Kirkuk, with even a small Armenian Christian population. This study involves the three most common nationalities Arabs, Kurds, and Turkmens and there is no significant difference seen in the distribution of multiple genotypes and allele frequency of HMGA1 gene rs1023028442 and rs112081775 SNP.

Limitation:

This study was limited by its small sample size and single-center focus, as well as, this study enrolled only metabolic syndrome patients in Kirkuk city; therefore, Caution is needed in generalizing the results of this study with other populations.

Conclusion

A non-significant difference in genotyping and allele carriage frequencies of the HMGA1 gene variants of rs1023028442 and rs112081775 SNPs was seen between total metabolic syndrome patients and the control group. Additionally, non-significant difference was seen in response to therapy between those with wild and carrier genotypes. So this study indicates a lack of association of the rare HMGA1 gene variants with metabolic syndrome risk and response to oral anti-diabetic drugs.

Conflict of interests

The authors declared no conflicts of interest concerning to the authorship and/or publication of this article.

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ORCID

Mirna K. Faiq 0000-0002-6558-9309
Eman S. Saleh 0000-0003-1764-0058
Omar B. Fathalla 0000-0002-8272-5229

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