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Genetic variants on chromosome 19 (rs439401 and rs4420638) are associated with obesity and high blood pressure in the Algerian population

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Metabolic syndrome (MetS) represents a combination of at least three primary metabolic abnormalities from among obesity, hyperglycemia, dyslipidemia, and high blood pressure, once combined, they increase significantly the cardiovascular risk. The *APOE* gene is considered as a genetic risk factor for cardiovascular diseases, it has been linked to MetS or its traits in several populations. Our study aimed to analyze the association of three *APOE* gene polymorphisms with MetS risk and its components in a general population sample, and to highlight the potential influence of these polymorphisms on individual susceptibility to MetS. We performed this work using a population-based, cross-sectional study of a representative sample of 787 individuals (378 men and 409 women, aged between 30 and 64 years) recruited in the city of Oran, Algeria (the ISOR Study); the subjects were genotyped for four polymorphisms, rs7412, rs429358, rs4420638 and rs439401, located in the *APOE* gene, using the KASPar technology. rs439401 showed a significant association with hypertension (HBP). The T allele confers a high risk of hypertension with an odds ratio (OR) of 1.46 (95 % CI [1.12–1.9], $p = 0.006$). rs4420638 was significantly associated with obesity in the general population. The G allele provides protection against obesity, the resulting OR is 0.48 (95 % CI [0.29–0.81], $p = 0.004$). Although *APOE* variants were not associated with the risk of MetS, the *APOE* polymorphism alleles were associated with some of the metabolic parameters in Algerian subjects. The relation of *APOE* rs439401 alleles with a HBP is likely to be indicative of a state of stress of the population.
Key words: genetics; high blood pressure; diabetes; metabolic syndrome; obesity; Algerian population.

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Связь генетических вариантов rs439401 и rs4420638 в хромосоме 19 с ожирением и артериальной гипертензией у жителей Алжира

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Метаболический синдром (MetS) представляет собой комбинацию по меньшей мере трех основных показателей, ассоциированных с нарушением обмена веществ: ожирения, гипергликемии, дислипидемии и высокого артериального давления. Любое их сочетание значительно увеличивает риск развития сердечно-сосудистых заболеваний. Ген *APOE* считается генетическим фактором риска развития сердечно-сосудистых заболеваний, в некоторых популяциях он связан с метаболическим синдромом или его признаками. Настоящее исследование направлено на анализ ассоциации трех полиморфизмов гена *APOE* с риском развития метаболического синдрома и его компонентов в общей популяции, а также на выявление возможного влияния этих полиморфизмов на индивидуальную

восприимчивость к метаболическому синдрому. В рамках проекта ISOR было проведено популяционное перекрестное исследование репрезентативной выборки из 787 добровольцев (378 мужчин и 409 женщин в возрасте от 30 до 64 лет), проживающих в городе Оране (Алжир). Обследуемые были генотипированы по четырем полиморфизмам (rs7412, rs429358, rs4420638 и rs439401), расположенным в гене *APOE*, с использованием технологии KASPar. Полиморфизм rs439401 показал достоверную связь с повышенным артериальным давлением. Аллель T обусловливает высокий риск развития гипертензии с отношением шансов (OR) равным 1.46 (95 % CI [1.12–1.9], $p = 0.006$). Полиморфизм rs4420638 достоверно коррелировал с ожирением в общей популяции. Наличие аллеля G препятствует развитию ожирения (OR = 0.48; 95 % CI [0.29–0,81], $p = 0.004$). Хотя связи между вариантами гена *APOE* и риском развития метаболического синдрома не выявлено, однако найдена корреляция между полиморфными аллелями этого гена и рядом показателей обмена веществ у обследованных алжирцев. Связь полиморфизма rs439401 в аллелях гена *APOE* с гипертензией может указывать на состояние стресса у населения.
Ключевые слова: генетика; высокое артериальное давление; диабет; метаболический синдром; ожирение; алжирская популяция.

Introduction

The concept of the Metabolic Syndrome (MetS) emerged following the increase of the risk factors associated to cardiovascular diseases and diabetes (Reaven, 1988; Grundy et al., 2004). MetS represents a combination of at least three primary metabolic abnormalities among obesity, hyperglycemia, dyslipidemia, and high blood pressure, once combined, they increases significantly the cardiovascular risk (Kahn et al., 2005; Wilson et al., 2005; Hillier et al., 2006; Gami et al., 2007; Meigs et al., 2007).

In Algeria, the health network improvement led to a progressive aging of the population which allows for the emergence of abnormalities associated with aging and MetS. The TAHINA study (Epidemiological Transition And Health Impact in North Africa) conducted in 2005 showed a high prevalence of hypertension (24.9 %) and diabetes (12.2 %) in the Algerian population. Overweight has become a real public health problem, especially among women, 66.5 % are overweight and 30.1 % are obese. Cardiovascular disease and diabetes accounted for 26.1 and 4.4 % of deaths, respectively, in 2002 (Ministère de la Santé, 2007).

There have been at least six different published definitions for MetS, the most used is that of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (Balkau et al., 2007). The prevalence of MetS differs according to several parameters: definition, country, sex, age, and even according to the region in the same country. In Algeria, a recent study shows that the prevalence of metabolic syndrome was 20 % in the Oran population, it was higher in women than men (25.9 vs 13.7 %) (Houti et al., 2016).

Metabolic syndrome is a multifactorial disease that implicates both environmental and genetic factors (Chuang, 2008). Given the importance of APOE in the metabolism of lipoproteins; indeed, *APOE* gene was identified as genetic determinants of plasma lipid and lipoprotein concentrations in Caucasian and North African populations (Wilson et al., 1994; Boulenouar et al., 2013). We aimed to analyze the association of the *APOE* gene polymorphisms with MetS risk and its components in a general population sample from the city of Oran in Algeria, and to highlight the potential influence of these polymorphisms on individual susceptibility to MetS.

Abbreviations
ANDRS – Agence Nationale De Recherche en Santé
APOE – Apolipoprotein E
ATRSS – Agence Thématique de Recherche en Science de la Santé
BMI – Body mass index
DBP – Diastolic blood pressure
DNA – Deoxyribonucleic acid
d.f. – Degree of freedom
HDL – High-density lipoprotein
ISOR – InSulino-résistance à ORan
LDL – Low-density lipoprotein
MetS – Metabolic Syndrome
SBP – Systolic blood pressure
SNP – Single nucleotide polymorphism
T2D – Type 2 Diabetes

Material and methods

Ethical considerations. This study was granted ethics approval by the Algerian National Agency for the Development of Health Research (ATRSS exANDRS). All participants provided informed consent prior to enrolment.

Study population. Participants were recruited during the ISOR (InSulino-résistance à ORan) study, a population-based, cross-sectional study of a representative sample of 787 individuals (378 men and 409 women, aged between 30 and 64 years) recruited in the city of Oran, Algeria, from 2007 to 2009 (Boulenouar et al., 2013).

Data collection. Data were collected using a preconceived questionnaire on socioeconomic information, physical activity (the level of physical activity was defined in quartiles as "none", "low", "medium" and "high" after summing exercise scores for sporting activities, walking, housework and physical activity at work), tobacco use and alcohol intake, past medical history and family history, current medications, as well as anthropomorphic characteristics including height, weight, waist circumference, hip circumference, and blood pressure. Height and weight were measured while the subject was barefoot and lightly dressed. The BMI was calculated according to the Quetelet equation. Systolic and diastolic blood pressure values (SBP and DBP, respectively) were measured on the right arm with the subject in the sitting position, using a standard mercury sphygmomanometer. Measurements were made before and after completion of the questionnaire, with an interval of at least 10 minutes. The mean value of the blood pressure readings was considered for analysis. Regarding tobacco use, participants were categorized as either smokers (i.e. individuals reporting at least one cigarette per day) or non-smoker. After a 12h overnight fast, blood was collected

aseptically via venipuncture in an EDTA tube for DNA extraction and subsequent molecular analysis, and in a heparin tube for biochemistry tests.

Metabolic syndrome diagnosis criteria. In this study, we have adopted the definition of metabolic syndrome according to the criteria of the NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) (Alberti et al., 2005), the metabolic syndrome is diagnosed when a subject has three or more of the following risk factors:

- Abdominal obesity: waist circumference > 102/88 cm (Men/Women);
- Triglyceride level ≥ 1.50 g/l (1.69 mmol/l);
- HDL-cholestérol < 0.40/0.50 g/l (1.04/1.29 mmol/l) (Men/Women);
- Blood pressure ≥ 130/85 mmHg;
- Fasting glucose ≥ 1.10 g/l (6.1 mmol/l).

Type 2 diabetes diagnosis criteria. The definition adopted in this study is that of the American Diabetes Association (ADA) (Gavin, 1998):

1. Fasting plasma glucose ≥ 1.26 g/l (7 mmol/l) twice after 8 hours of fasting.
2. Occasional blood glucose ≥ 2 g/l (11.1 mmol/l) in the presence of symptoms of hyperglycemia (polyuria, polydipsia, unexplained weight loss).
3. Diabetics declared under treatment including oral antidiabetic and/or insulin.

High blood pressure diagnosis criteria. Hypertension (HBP) has been defined according to WHO criteria (Chalmers et al., 1999): mean systolic blood pressure greater than 140 mmHg and/or mean diastolic blood pressure greater than 90 mmHg and/or self-reported current treatment for hypertension with antihypertensive drugs.

Obesity diagnosis criteria. The body mass index (BMI) is calculated according to the Quetelet equation. A subject is considered obese if he has a BMI greater than or equal to 30 kg/m^2.

Biochemistry and molecular testing. A multichannel analyzer and dedicated kits (Humastar®, HUMAN Diagnostics, Wiesbaden, Germany) were used for the colorimetric, enzymatic measurement of cholesterol (kit: monotest cholesterol with cholesterol esterase, cholesterol oxidase and peroxidase), triglycerides (kit: peridochrom triglyceride with glycerol phosphate oxidase and peroxidase) and glucose (kit: glucose, glucose oxidase and peroxidase). Plasma LDL-cholesterol levels were calculated according to the Friedewald equation. High-density lipoprotein cholesterol levels were measured after sodium phosphotungstate/magnesium chloride precipitation of chylomicrons and VLDL and LDL-cholesterol and then centrifugation. Plasma insulin levels were measured using a microparticle enzyme immune assay running on an AxSYM analyzer (Abbott Laboratories, Abbott Park, Illinois, USA).

Genomic DNA was extracted from white blood cells by using the Stratagene® kit (Agilent Technologies, Les Ulis, France), according to the manufacturer's protocol. Three genetic polymorphisms were characterized in this study, the Epsilon polymorphism defined by defined by the rs7412 and rs429358 single nucleotide polymorphisms (SNPs), the rs439401 and the rs4420638, genotyping was performed by using KASPar technology (KBioscience, Hoddesdon, UK). The genotyping success rates ranged from 93 to 96 %.

Statistical analyses were performed with SAS 9.1 software (SAS Institute Inc., Cary, NC, USA). The Hardy–Weinberg equilibrium was tested using a χ^2 test with one degree of freedom (d. f.). Some of the biochemical traits (Fasting Glucose levels, Triglycerides and Insulin levels) were not normally distributed, we therefore log-transformed these parameters to obtain normal data distributions. Intergroup comparisons of means were performed with a general linear model, multivariate logistic regression analyses were used to calculate the odds ratios for MetS, Type 2 Diabetes (T2D), High Blood pressure (HBP) and obesity (Obes).The confounding variables were age, gender, smoking status and physical activity. After Bonferroni correction, only associations with an uncorrected p value below 0.017 were considered to be statistically significant.

Results

Characteristics of study subjects. The main anthropometric, biochemical and clinical characteristics have been measured, the baseline characteristics of the ISOR population study were described elsewhere (Houti et al., 2016).

Genotype and allele distributions. The allele and genotype distributions of the APOE polymorphisms were described in Table 1. There was no evidence of significant deviation from Hardy–Weinberg equilibrium in any distributions.

Prevalence of the metabolic syndrome and the main cardiometabolic risk factors. These data concerning the Oran population are presented in Table 2.

Diabetes mellitus (T2D) was diagnosed in 80 participants (10.6 %). The distribution of prevalence by sex shows no significant difference ($p = 0.39$), it was 11.6 % for men and 9.7 % for women.

The prevalence of obesity in the general population is 21.2 %. It affects more women (32.5 %) than men (9 %), with a significant difference in the prevalence distribution between men and women ($p < 0.0001$).

The prevalence of the metabolic syndrome in the Oran population is 20 %, the distribution of this pathology is also significantly different between the two sexes ($p < 0.0001$). Indeed, it affects more women (25.9 %) than men (13.7 %).

Hypertension affects 20.3 % of the study population. HBP is present in 21.2 % of men and 19.6 % of women, the prevalence distribution in men and women shows no significant difference ($p = 0.58$).

APOE epsilon polymorphism and cardiometabolic risk. No significant association was reported between genotypes of APOE epsilon polymorphism and the studied cardiovascular risk factors (T2D, Obesity, HBP and MetS status), the p values ranged from 0.04 to 0.92 (Table 3).

Polymorphism rs439401 and cardio-metabolic risk. In the ISOR study, rs439401 showed a significant association with hypertension (HBP). The T allele confers a high risk of hypertension with an odds ratio (OR) of 1.46 (95 % CI [1.12–1.9], $p = 0.006$). No associations with T2D, obesity and MetS were detected in the ISOR study (see Table 3).

Polymorphism rs4420638 and cardio-metabolic risk. Logistic regression analysis showed that the rs4420638 polymorphism was significantly associated with obesity in the general population. The G allele provides protection against obesity, the resulting OR is 0.48 (95 % CI [0.29–0.79], $p = 0.004$)

Table 1. Genotype and allele frequencies of epsilon polymorphism, rs439401 and rs4420638 in case and control groups

Parameter	MetS	Non MetS
Epsilon	Genotype frequency, N(%)	
ε2/ε2	1(0.7)	5(0.9)
ε2/ε3	14(9.7)	43(7.4)
ε2/ε4	0	3(0.5)
ε3/ε3	109(75.7)	457(78.8)
ε3/ε4	16(11.1)	66(11.4)
ε4/ε4	4(2.8)	6(1)
TOTAL	144(100)	580(100)
$pE_{H\text{-}W}$	0.77	0.68
	Allele frequency, %	
ε2	5.5	4.8
ε3	86.1	88.2
ε4	8.4	7
rs439401	Genotype frequency, N(%)	
CC	56(38.6)	228(39.1)
CT	65(44.8)	265(45.2)
TT	24(16.6)	90(15.4)
TOTAL	145(100)	583(100)
$pE_{H\text{-}W}$	0.48	0.79
	Allele frequency, %	
C	61	62
T	39	38
rs4420638	Genotype frequency, N(%)	
AA	117(79.6)	473(79.1)
AG	27(18.4)	118(19.7)
GG	3(2)	7(1.2)
TOTAL	147(100)	598(100)
$pE_{H\text{-}W}$	0.90	0.14
	Allele frequency, %	
A	88.8	89
G	11.2	11

Note: H-W, Hardy–Weinberg equilibrium.

(see Table 3). No effects of rs4420638 polymorphism on T2D, MetS, and HBP were detected in the ISOR study.

The associations described for rs439401 and rs4420638 remained significant even after adjusting for the APOE epsilon polymorphism.

Discussion

To our knowledge, this is the first study that evaluates the association of *APOE* gene polymorphisms (epsilon, rs439401 and rs4420638), with the risk of MetS and the main cardiometabolic risk factors, within the Algerian population.

We found no association between the three polymorphisms of the *APOE* gene and the metabolic syndrome in the Algerian population. However, some components of the metabolic syndrome considered as a cardiometabolic risk factors were significantly associated with *APOE* gene polymorphisms.

The logistic regression results showed that the ε2 allele increases the risk of obesity by 88 % in the ISOR study. Similar results were observed in a study among the population of Croatia's Roma minority (Zeljko et al., 2011).

It is possible that gene-nutrition interactions are responsible for the observed association between the ε2 allele and obesity. Indeed, changes in eating habits during the last decade would be responsible for increasing the prevalence of obesity, interacting with the ε2 allele (Boer et al., 1997; Talmud, 2007).

The polymorphisms rs439401 and rs4420638 have been associated in some of GWAS-type studies with changes in plasma lipid concentrations (Kathiresan et al., 2008; Aulchenko et al., 2009; Teslovich et al., 2010), but few studies have investigated the impact of these polymorphisms on metabolic and cardiovascular traits.

Our results on the Oran population, report for the first time, that the T allele of the rs439401 polymorphism increases the risk of arterial hypertension (OR 1.46, 95 % CI [1.12–1.90], $p = 0.006$). No similar results were reported. In the literature, the T allele of rs439401 is significantly associated with changes in BMI, insulin concentration, waist circumference, and triglyceride concentration. The TT genotype is positively associated with an increase in the values of these parameters only in psychologically stressed individuals (Kring et al., 2010). Our results are perhaps indicative of a state of stress of the population, resulting from the changes made in the Algerian population during the last two decades, particularly with

Table 2. Prevalence of the metabolic syndrome and its components in the ISOR population

Parameter	All ($n = 787$)		Men ($n = 378$)		Women ($n = 409$)		p
	n	%	n	%	n	%	
Abdominal adiposity	233	30.1	45	12.1	188	46.8	<.0001
High triglycerides	103	13.3	62	16.7	41	10.2	0.63
Low HDL-Cholesterol	342	44.2	99	26.6	243	60.4	<.0001
High fasting glucose	161	20.8	88	23.7	73	18.2	0.47
T2D	80	10.6	42	11.6	38	9.7	0.39
Obesity	167	21.2	34	9.0	133	32.5	<.0001
MetS	155	20.0	51	13.7	104	25.9	<.0001
HBP	160	20.3	80	21.2	80	19.6	0.58

Note: T2D, Type 2 Diabetes; MetS, Metabolic Syndrome; HBP, High Blood Pressure.

Table 3. Association between the studied genetic variants and the main cardiometabolic disorders in ISOR population

Parameter	Epsilon polymorphism			rs439401				rs4420638			
	Alleles (N)		OR [95 % CI]	Genotypes (N)		OR [95 % CI]	OR* [95 % CI]	Genotypes (N)		OR [95 % CI]	OR* [95 % CI]
T2D	Control	Case	ε2 vs ε3:	Control	Case	CT vs CC:		Control	Case	AG vs AA:	
	ε2 (52)	ε2 (6)	0.87 [0.34–2.22]	CC (254)	CC (22)	1.57 [0.88–2.79]	1.47 [1.03–2.09]	AA (515)	AA (63)	1.20 [0.65–2.22]	0.99 [0.56–1.75]
	ε3 (455)	ε3 (58)	$p = 0.77$	CT (285)	CT (38)	$p = 0.13$	$p = 0.03$	AG (124)	AG (16)	$p = 0.56$	$p = 0.98$
	ε4 (116)	ε4 (12)	ε4 vs ε3:	TT (95)	TT (16)	TT vs CC:		GG (9)	GG (0)		
			0.84 [0.42–1.68]			2.12 [1.02–4.39]					
	$p = 0.81$		$p = 0.63$	$p = 0.13$		$p = 0.04$		$p = 0.56$			
Obesity	ε2 (47)	ε2 (20)	ε2 vs ε3:	CC (233)	CC (57)	CA vs CC:	1.16 [0.89–1.51]	AA (463)	AA (136)	AG vs AA:	
	ε3 (414)	ε3 (111)	1.88 [1.01–3.51]	CT (262)	CT (74)	1.27 [0.84–1.92]	$p = 0.27$	AG (128)	AG (21)	0.51 [0.30–0.85]	0.48 [0.29–0.79]
	ε4 (115)	ε4 (22)	$p = 0.04$	TT (89)	TT (26)	$p = 0.26$		GG (10)	GG (0)	$p = 0.01$	$p = 0.004$
			ε4 vs ε3:			AA vs CC:					
			0.80 [0.48–1.37]			1.34 [0.76–2.35]					
	$p = 0.07$		$p = 0.41$	$p = 0.71$		$p = 0.31$		$p = 0.02$			
MetS	ε2 (48)	ε2 (18)	ε2 vs ε3:	CC (228)	CC (56)	AT vs AA:	1.06 [0.80–1.40]	AA (473)	AA (117)	AG vs AA:	
	ε3 (424)	ε3 (96)	1.74 [0.92–3.32]	CT (265)	CT (65)	1.04 [0.68–1.59]	$p = 0.69$	AG (118)	AG (27)	0.93 [0.57–1.53]	1.10 [0.71–1.70]
	ε4 (108)	ε4 (28)	$p = 0.09$	TT (90)	TT (24)	$p = 0.87$		GG (7)	GG (3)	$p = 0.78$	$p = 0.66$
			ε4 vs ε3:			TT vs AA:				GG vs AA:	
			1.29 [0.78–2.14]			1.13 [0.64–2.02]				3.19 [0.73–13.89]	
	$p = 0.22$		$p = 0.33$	$p = 0.95$		$p = 0.67$		$p = 0.68$		$p = 0.12$	
HBP	ε2 (54)	ε2 (13)	ε2 vs ε3:	CC (241)	CC (49)	CT vs CC:	1.46 [1.12–1.90]	AA (469)	AA (20)	AG vs AA:	
	ε3 (413)	ε3 (112)	1.18 [0.63–2.20]	CT (262)	CT (74)	1.46 [0.95–2.26]	$p = 0.006$	AG (128)	AG (127)	0.56 [0.33–0.96]	0.73 [0.47–1.14]
	ε4 (110)	ε4 (27)	$p = 0.60$	TT (86)	TT (29)	$p = 0.09$		GG (7)	GG (3)	$p = 0.03$	$p = 0.17$
			ε4 vs ε3:			TT vs CC:				GG vs AA:	
			0.97 [0.60–1.59]			1.90 [1.07–3.36]				2.24 [0.51–9.84]	
	$p = 0.87$		$p = 0.92$	$p = 0.11$		$p = 0.03$		$p = 0.09$		$p = 0.29$	

Note: T2D, Type 2 Diabetes; MetS, Metabolic Syndrome; HBP, High Blood Pressure; OR adjusted on age, sexe, physical activity, smoking status; OR* obtained for additive modele.

the security crisis in the country. These hypotheses require investigations on a larger sample and in which, the stress level must be measured accurately.

The G allele of rs4420638 seems to confer a protective effect against obesity (OR 0.48, 95 % CI [0.29–0.79], $p = 0.004$), no study was interested in measuring association between rs4420638 polymorphism and obesity previously. No association was reported for the rs4420638 with MetS, T2D and HBP similar results were observed in Tunisian population (Elouej et al., 2016).

The fact that rs4420638 has low linkage disequilibrium with the epsilon polymorphism in our population gives it an advantage over European populations, where these two polymorphisms are in strong linkage disequilibrium (Boulenouar et al., 2013). Thus, the study of the impact of rs4420638 would be independent of the effect of epsilon polymorphism, which makes our population very interesting from a genetic point of view for association analyzes involving rs4420638 polymorphism.

Conclusion

Although APOE variants were not associated with the risk of MetS, the *APOE* polymorphism alleles were associated with some of the metabolic parameters in Algerian subjects. The relation of *APOE* rs439401 alleles with a HBP seems been perhaps indicative of a state of stress of the population. These hypotheses require in the future investigations on a larger sample and in which, the stress level must be measured accurately.

The interaction gene-nutrition must be investigated, in the future; indeed, Algerian population known many changes in eating habits during the last decade, which would be responsible for increasing prevalence of obesity in our population and which can influence the effect of *APOE* polymorphism on the studied parameters.

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Authors' contributions. SMB and LH, designed research; SMB, LH and IHM conducted research; HOD, SLH, IHM, SMB and LH participated in the recruitment of subjects; HB built the database; HB performed the DNA extraction and genotyping; HB and SMB performed the statistical analyses; HB and SMB interpreted the results. IHM assayed biochemical parameters; HB wrote the paper under the supervision of SMB; HB and SMB had primary responsibility for final content. All authors read and approved the final manuscript.

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