Association of cluster of differentiation 36 gene variant rs1761667 (*G>A*) with metabolic syndrome in Egyptian adults

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ABSTRACT

الأهداف: دراسة العلاقة بين جين CD36 rs1761667 *G>A* ومتلازمة الأيض عند المرضى المصريين.

الطريقة: أجريت هذه الدراسة على حالات مرضى متلازمة الأيض الذين يتابعون في مستشفى جامعة قناة السويس، مصر خلال الفترة من نوفمبر 2010م إلى أكتوبر 2011م. وقد تم استخلاص الحمض النووي من عينات الدم التي جُمعت من 100 مريض (مجموعة الدراسة) و100 شخص من الأصحاء (مجموعة الشاهد). ولقد تمت دراسة التغيرات الجينية لنيوكلوتيد المنفرد المتعدد الأشكال للجين CD36 rs1761667 *G>A* باستخدام تفاعل البلمرة المتسلسل بالوقت الفعلي.

النتائج: أظهرت نتائج هذا البحث أن توزيع الطرازات الثلاثة لجين CD36 لدى المرضى كانت *AA* 25، *AG* 70 و*GG* 5، بينما كانت في مجموعة الشاهد *AA* 51، *AG* 48 و*GG* 1. كما أوضحت الدراسة أن كل من الطرازان *AG, GG* كانتا أعلى لدى مرضى متلازمة الأيض مقارنةً مع مجموعة الشاهد بمعدل إحصائي ($p<0.001$). كما أن نسبة الأرجحية للإصابة بمتلازمة الأيض وصلت إلى الضعف مع حمل الأليل 95% CI 1.30-3.07 $p<0.001$. كذلك وُجد أن المرضى الذين يحملون الطرازالجيني (*GG*) أو (*AG*) يعانون بدرجة أعلى من ارتفاع ضغط الدم الانقباضي، و لهم محيط خصر أكبر، و لديهم اضطراب أكثر في الدهون بالدم مقارنةً بالمرضى الذين يحملون الطراز الجيني (*AA*) بمعدل إحصائي ($p<0.001$).

خاتمة: تشير نتائج البحث إلى وجود علاقة بين التغير الجيني لدى النيوكلوتيد المنفرد المتعدد الأشكال للجين CD36 rs1761667 *G>A*، والإصابة بمتلازمة الأيض، ومكوناته. ويعد النمط الجيني *AG* هو الأكثر بين المرضى مما قد يجعلهم أكثر عرضة للإصابة بأمراض القلب والأوعية الدموية.

Objectives: To investigate the relationship between cluster of differentiation (CD)36 gene variant rs1761667 (*G>A)* and metabolic syndrome (MetS) and its components in Egyptian patients.

Methods: This case-control study was conducted on MetS patients attending Suez Canal University Hospital, Egypt from November 2010 to October 2011. Peripheral blood was collected from 100 patients and 100 healthy controls for DNA extraction. The single nucleotide polymorphism (SNP) CD36 gene rs1761667 *G>A* was genotyped using real-time polymerase chain reaction, and the allele discrimination technique.

Results: Distribution of CD36 genotypes in the patient group was *AA* (n=25), *AG* (n=70), and *GG* (n=5), while in the control group it was *AA* (n=51), *AG* (n=48), and *GG* (n=1). Both *AG* and *GG* genotypes were significantly more prevalent among MetS patients ($p<0.001$). The odds ratio (OR) for the high risk allele (G) is 2 with 95% confidence interval from 1.30-3.07 ($p<0.001$). Patients with genotypes *AG* and *GG* had significantly higher systolic blood pressure, wider waist circumstance, and higher degree of dyslipidemia ($p<0.001$) than patients with genotype *AA*.

Conclusion: Our findings show that CD36 rs1761667 SNP is positively associated with increased risk of MetS and its components with genotype *AG* heterozygotes showing highest frequency among MetS patients.

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Metabolic syndrome (MetS) is a worldwide epidemic with huge socioeconomic costs.[1] The concept emerged over 8 decades ago, and was first described by Reaven[2] as "syndrome X". Nowadays, it is recognized by multiple criteria, mainly abdominal obesity, insulin resistance, hypertension, and dyslipidemia. This group of atherosclerotic risk factors is accompanied by prothrombotic and proinflammatory states that leads to type 2 diabetes mellitus (T2DM) and vascular diseases, including coronary heart disease and stroke.[3,4] In addition, MetS is a strong and independent predictor of cardiovascular mortality and sudden death.[5] The worldwide prevalence of MetS recently reviewed ranged from less than 10% to a staggering 84%, and is on the rise in developed and developing countries.[6-8] This wide range could be partly explained by the multiple definitions available. A few studies from the Middle East reported a prevalence of approximately 44% in Saudis, 46% in obese Yemenis, 35% in others, and 12% in adolescents.[9-11] It seems modest as the prevalence of obesity and diabetes mellitus (DM) in the Middle East is among the highest in the world.[12]

The risk of MetS is influenced by both genetic and environmental factors. Predisposing factors include age, gender, ethnicity, and lifestyle.[13] Low-grade inflammation detected underlying obesity and insulin-resistant states have been linked to abnormal fat metabolism. Altered expression of class B scavenger receptor cluster of differentiation (CD)36 was implicated in the pathogenesis of atherosclerosis, hyperglycemia, and metabolic disease.[14-16] Also, transgenic deletion of this receptor in rodents suggested a pivotal role for CD36 in mediating components of MetS through transport of fatty acids and uptake of oxidized lipids.[17] The CD36 is a broadly expressed 88 kDa membrane transporter glycoprotein that acts as a facilitator of fatty acid (FA) uptake, signaling molecule, and a receptor for a wide range of ligands.[18,19] In addition to FAs, CD36 binds to native lipoproteins and functions in the uptake of cholesteryl esters, facilitates the uptake of oxidized low/high-density lipoproteins (L/HDL) and cholesterol.[20] Due to its many ligands and functions, CD36 has been implicated in the pathophysiological pathway of several conditions linked with MetS, including diabetes, insulin resistance, inflammation, and atherosclerosis.[21,22] In humans, the CD36 gene extends over 32 kb on the long arm of chromosome 7q11.2. It consists of 15 alternatively spliced exons that are differentially regulated by several upstream promoters.[23] Genome-wide linkage scans have identified close by regions associated with features of MetS.[24-26] Furthermore, several single nucleotide polymorphisms (SNP) at the CD36 gene were shown to influence susceptibility to MetS, and associate with risk of heart disease and T2DM.[27] The CD36 rs1761667 (*G>A*) has not been tested in MetS patients, and the role of CD36 locus has not been investigated with Arab MetS patients. Therefore, this study was carried out to determine the allele frequency of CD36 rs1761667 (*G>A*) variant in a sample of healthy Egyptians, and Egyptians with MetS and compare with other population, and to examine whether this SNP is associated with the risk of MetS and its components in Arabs.

Methods. This case-control study was approved by the Ethics Committee of the Suez Canal University and carried out in accordance with the principles of Helsinki Declaration. The study group constituted of outpatients with MetS attending Suez Canal University Hospital from November 2010 to October 2011. The controls were recruited from apparently healthy university staff volunteers. All patients had MetS - defined as having at least 3 of the following 5 criteria: waist circumference ≥102 cm for men, or ≥88 cm for women; elevated triglycerides ≥150 mg/dl, or drug treatment for elevated triglycerides; low HDL-cholesterol (<40 mg/dl for men, and <50 mg/dl for women), or drug treatment for low HDL-cholesterol; high blood pressure (systolic ≥140 mm Hg or diastolic ≥90 mm Hg) or drug treatment for hypertension; and elevated fasting glucose ≥110 mg/dl or drug treatment for elevated glucose. Patients were excluded from the study if they are having any other major medical conditions (such as, coronary artery disease or other metabolic disorders). All study subjects were of Egyptian origin without any known other ethnic origin. An informed consent was obtained from patients and healthy controls. All subjects underwent complete physical examination and routine biochemical blood testing, including fasting blood glucose and lipid profile. Height, weight, and waist circumference were measured to calculate body mass index (BMI). Laboratory investigations were carried out using fully-automated spectrophotometer Hitachi-912 (Roche Diagnostics, Boehringer, Mannheim, Germany). Genomic DNA was extracted using the commercially available Spin-column technique kit for DNA extraction from human whole blood (QIAamp®DNA Blood Mini Kit, QIAGEN, 28159 Avenue Stanford, Valencia, CA 91355, USA). The extracted DNA samples were stored at -20°C for future use. Determination of CD36 gene polymorphism was carried out by real-time PCR (gene discrimination) using primers (Metabion GmbH, Martinsried, Germany) with the following sequence:

The sense primer. 5'- CGC AGA TCA CTA AAG TAT ATC TTT AAT TCT G -3'.

The anti-sense primer. 5'- AAT GAA CCA GTC AAT TTT GGA CAA C -3'

For the determination and detection of the polymerase chain reaction (PCR) products, 2 primers were used. The first one was VIC-primer for the detection of the wild type allele (A), and the other one was FAM for the polymorphic allele (G). The sequences of both probes (Metabion GmbH, Martinsried, Germany) were as follows: VIC-probe: ACCATTGTAACAATAGTGTGCCAAA. FAM-probe: AATAGCACAAATAAAGCACTTGTGCC. The PCR-mixture is composed of distilled water (7.72 µl), VIC probe (0.44 µl), FAM probe (0.44 µl), sense and anti-sense probes (0.20 µl each), Universal Master Mix (Fermentas, Leon-Rot, Germany) (11.0 µl), and template DNA (2.0 µl) to reach a total volume of 22 µl. After an initial step of 2 min at 50°C and 10 min at 95°C to activate the AmpliTaq Gold, the products were amplified using 40 cycles of 15 seconds at 95°C and one minute at 62°C.[28] Then, allele detection and genotyping calling were performed using Rotor-GeneTM 6000 (Corbett Research, Mortlake, New South Wales, Australia) with the available installed software.

Statistical analysis. Collected data were analyzed using the Statistical Package for Social Sciences version 13 (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as means and standard deviations (SD). Allele frequencies, genotype distributions, and odds ratio (OR) were compared using 2x2 contingency table analysis. A $p<0.05$ (2-sided) was considered significant.

Results. The study population included 100 MetS patients and 100 controls. Males constituted 67% of the study group and 62% of the controls. Clinical characteristic and biochemical values for patients and controls are shown in **Table 1**. There was no significant difference between patients and controls with respect to age, systolic and diastolic blood pressure, and fasting blood glucose. However, waist circumstance ($p=0.0102$) and BMI ($p=0.000$) were significantly higher in the study group. In addition, all measured lipid profile variables showed significant elevation in patients ($p=0.000$). The distribution of CD36 rs1761667 (*G>A*) genotypes and allele frequencies are presented in **Table 2**. The genotypic frequencies in patients were *AA* (25%), *AG* (70%), and *GG* (5%), while in the controls it was *AA* (51%), *AG* (48%) and *GG* (1%). Genotypes *AG* and *GG* were significantly more frequent in patients than controls ($p=0.000$). Also, *G* allele was significantly more represented in patients in comparison to controls ($p=0.000$). Genotype distributions for MetS patients and controls were in Hardy-Weinberg equilibrium. Patients were divided into groups according to their genotype **Table 3**. Comparing cardiovascular risk factors in the 3 groups showed that patients with genotypes *GG* and *AG* had significantly wider waist circumstance, higher systolic blood pressure, and higher degree of dyslipidemia than patients with genotype *AA* ($p=0.000$). The high risk allele *G* was more frequent than the *A*

Table 1 - Physical and biochemical characteristics of patient and control groups enrolled in a study conducted in Suez Canal University Hospital, Ismailia, Egypt.

Parameter	Study group	Control	*P*-value
Gender			
Male	67	62	
Female	33	38	
Age, years	47 ± 7	41 ± 6	0.061
Waist circumference, cm	112 ± 8	101 ± 6	0.0102*
Body mass index, kg/m^2	33.4 ± 3.2	28.7 ± 4.2	0.000*
Systolic blood pressure, mm Hg	145 ± 20	130 ± 25	0.38
Diastolic blood pressure, mm Hg	85 ± 15	85 ± 10	1.00
Fasting blood glucose, mg/dl	147 ± 21	101 ± 22	0.21
Total cholesterol, mg/dl	278 ± 35	155 ± 32	0.000*
Triglycerides, mg/dl	310 ± 25	145 ± 29	0.000*
HDL-cholesterol, mg dl	39 ± 8	51 ± 9	0.000*
LDL-cholesterol, mg/dl	181 ± 11	102 ± 10	0.000*

Values are presented as mean ± standard deviation. HDL - high-density lipoprotein; LDL - low-density lipoprotein, *p*-values were obtained using Student's t-test, *significant values.

Table 2 - Distribution of CD36 genotypes and allele frequencies in patient and control groups in a study conducted in Suez Canal University Hospital, Ismailia, Egypt.

Genetic parameter	Patients	Control	Odds ratio	Risk ratio	*P*-value
	(%)		(95% confidence interval)		
Genotype					
AA	(25)	(51)	1.00 (Reference)	1.00 (Reference)	
AG	(70)	(48)	2.97 (1.62 - 5.43)	1.52 (1.58 - 2.68)	0.000
GG	(5)	(1)	10.20 (1.13 - 92.03)	8.67 (1.18 - 63.09)	0.000
AG + GG	(75)	(49)	3.12 (1.71 - 5.68)	1.53 (1.80 - 2.98)	0.000
Allele					
A	(120)	(150)	1.00 (Reference)	1.00 (Reference)	
G	(80)	(50)	2.00 (1.30 - 3.07)	1.60 (1.41 - 2.65)	0.000

Two sided Chi-square test was used for *AG* heterozygote and *GG* homozygote with *AA* homozygote as control, CD - cluster of differentation, $p<0.05$ is significant

Table 3 - Patient characteristics and distribution of CD36 genotypes in patients included in a study conducted at Suez Canal University Hospital, Ismailia, Egypt.

Parameter	Genotypes		
	GG (n=5)	*AG* (n=70)	*AA* (n=25)
	mean ± standard deviation		
Age, years	45 ± 5	44 ± 5	47 ± 5
Waist circumference, cm	119 ± 7*	115 ± 8*	109 ± 6
Systolic blood pressure, mm Hg	180 ± 8*	160 ± 7*	145 ± 4
Diastolic blood pressure, mmHg	85 ± 15	85 ± 10	80 ± 15
Total cholesterol, mg/dl	235 ± 40*	225 ± 30*	190 ± 25*
Triglycerides, mg/dl	280 ± 50*	230 ± 35*	190 ± 35
HDL-cholesterol, mg dl	37 ± 5*	40 ± 4*	46 ± 7
LDL-cholesterol, mg/dl	170 ± 30*	145 ± 37*	100 ± 28

CD - cluster of differentation, HDL - high-density lipoprotein, LDL - low-density lipoprotein, *p<0.001 obtained using one way analysis of variance, and post hoc test showed a significant difference between genotypes *GG*, *AG*, and *AA* (reference group)

allele in patients in relation to controls (OR: 2; 95% confidence interval (CI): 1.30-3.07). Hence, indicating a significant positive association between the high risk CD36 gene variant rs1761667 and the risk of MetS. The risk is double than that of controls (p=0.000).

Discussion. The results of this study revealed that CD36 gene variant rs1761667 (*G*>*A*) is significantly associated with the risk of MetS. The MetS is a major and complex health problem, and is on the rise globally. However, its etiology remains unclear. Genetic factors are thought to be highly incriminated. Alkharfy et al[29] started to draw the genetic picture of this syndrome in Arabs by studying its association with endothelial nitric oxide synthase (eNOS) locus in a Saudi population. Changes in the expression and function of a major fat transporter, such as CD36, influence fatty acid and glucose metabolism, and hence could impact the risk of MetS.[17] The pathophysiologic involvement of CD36 in obesity, hyperglycemia, and MetS have been illustrated. Studies showed that small nucleotide deletions in CD36 gene exerted significant alterations in CD36 gene activity.[30] Also, CD36 genotypes were identified as a fundamental determinant of myocardial long chain fatty-acid uptake.[31] Several variants in the CD36 gene has now been shown to influence the susceptibility for the MetS, and associate with risk of cardiovascular disease and T2DM.[32,33]

In this study on variant rs1761667 (*G*>*A*) CD36 gene in Arabs showed that it is a common polymorphism and, interestingly, allele-*G* is the minor allele (25%), similar to, but less frequent than Caucasians (48%), Hispanics (46%), and the reverse to African Americans (61%) and Northern Indians (64%) where allele-*A* is the minor allele.[27,34-36] The fact that CD36 is also a receptor for *Plasmodium falciparum* infected erythrocytes and therefore linked to malaria susceptibility may influence the difference in frequency between ethnic groups. The genotype distribution in this study showed that *AG* and *GG* are significantly (p=0.000) more frequent among MetS patients than controls. The *AA* genotype, with its 2 protective wild-type allele, is more frequent among controls. Similar results were obtained from a study on North Indian population, which reported that the heterozygous genotype *AG* was significantly more frequent among T2DM patients.[27] Several CD36 SNPs including (rs1761667) were also found to contribute to the pathogenesis of MetS in African-Americans.[34] A study on Puerto Rican adults living in Boston revealed a significant association with MetS.[35] Another study found the same significant relationship among Caucasians between this promoter CD36 gene variant and insulin resistance and T2DM predisposing these patients to the risk of MetS.[36] Recently, a study on 2 other SNPs in Iranians found a significant association with MetS components (HDL and BMI) but not with the syndrome.[37] The regulatory region of the gene was shown to account for varied expression of the CD36 gene in normal and diseased conditions, since the variant is located in the upstream promoter region it determined the binding site for transcription factors.[38] Another common polymorphism (478 C/T) associated with CD36 deficiency was reported in Japanese patients with heart disease.[30]

The data of this study showed that the high risk allele *G* is significantly (p=0.000) more frequent with MetS patients. While allele *A* is more frequent among controls, carriers of allele *G* had a 2-fold higher risk of MetS (OR: 2; 95% CI: 1.30-3.07, p<0.001) than non-carriers of the allele. Furthermore, genotypes *GG* and *AG* are significantly associated with a wider waist circumference, higher systolic blood pressure, and higher levels of cholesterol, triglycerides and LDL, and lower HDL level (p=0.000). Many studies found that CD36 SNPs are associated with levels of adiponectin,[33] serum free FA,[39] triglyceride,[36] HDL and LDL,[38] and increasing the risk of cardiovascular disease and MetS. Evidence has shown that CD36 expression in monocytes is up-regulated by oxidized LDL, and its level increases in T2DM, hyperglycemia, and related atherosclerosis probably through its contribution to disturbed FA metabolism, suggesting a possible connection between atherosclerosis and insulin resistant states through CD36.[40] In addition, the increased hepatic CD36

protein expression in response to diets rich in FAs, and/or to obesity was found to contribute to aberrant liver FA uptake and subsequent dyslipidemia.[41]

We found a significant (p=0.000) association between the high risk allele G and systolic blood pressure. This is in agreement with other studies that found that CD36 polymorphisms were associated with hypertension.[42] However, our results did not indicate a significant association of this CD36 SNP with the level of fasting blood glucose. Yamashita[22] found a significant association of this CD36 gene variant with both high blood pressure and high blood glucose level. Also, in animal models, CD36 gene variants were significantly associated with high blood pressure and high blood glucose level.[43] This could be explained by the haplotype effects, ethnic differences, and multiple cut-off levels set. Other limitations of this study include the relatively small number of subjects, control group of volunteers, SNP selection is based on information from other studies conducted in non-Arabs. The gene-gene interaction and the prevalence of environmental factors would influence the results. However, the study design is helped with the age and gender-matched controls.

This study reports on the association of CD36 rs1761667 (*G>A*) SNP and MetS in Arabs. Genotype distribution differed significantly between patients and controls suggesting that the polymorphism may influence the risk of MetS. Further studies on the influence of this SNP and other CD36 mutations on intermediate phenotypes, and the risk of MetS and its complications will help disentangle the pathophysiology of this common syndrome.

In conclusion, MetS with all its definitions, remains a heterogeneous condition. The clinical and subclinical cardiovascular consequences of this syndrome are numerous, and the impact on cardiovascular morbidity and mortality is well established. Considering that CD36 plays a crucial role in MetS, we showed that the promoter SNP rs1761667 is significantly associated with MetS in Egyptian patients. Our results suggest that individuals having *GG* or *GA* genotypes are more susceptible to MetS, and are at higher risk of developing related complications. Moreover, it has provided a lead for future studies to examine the role of other CD36 variants in the development of MetS in Arabs.

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