Prevalence of ApoB100 rs693 gene polymorphism in metabolic syndrome among female students at King Abdulaziz University

Rana A. Alghamdi, Maryam H. Al-Zahrani, Maha J. Balgoon, Nuha A. Alkhattabi

Article Info
Article history:
Received 20 November 2020
Revised 12 February 2021
Accepted 17 February 2021
Available online 25 February 2021

Keywords:
Metabolic syndrome
Obesity
ApoB100 rs693 gene
Polymorphism
Coronary heart disease
Young female

Abstract
Apolipoprotein B100 (ApoB100) is a glycoprotein and a member of the adipokine family. It plays a central role in lipoprotein metabolism. Many research studies have revealed a strong relation between ApoB100 and metabolic syndrome (MetS) and insulin resistance.

In our research, we examined the relationship between ApoB100 rs693 gene polymorphism, body mass index (BMI) and the probability of MetS in young female students studying at King Abdulaziz University (KAU) in Saudi Arabia. The study group comprised 141 females whose ages ranged from 18 to 25 years. Anthropometric measurements and biochemical parameters were measured alongside a genetic analysis of ApoB100 rs693.

The BMI, glucose concentration and total cholesterol level were found to be significantly associated with the ApoB100 rs693 gene. The differences noted between control and MetS groups regarding glucose concentrations were statistically significant (P = 0.001).

A growing number of young females are being diagnosed with MetS in KAU because of unhealthy eating habits, in combination with the absence of physical exercise, causing increased body weight and the potential progression of chronic diseases. Our study showed that the allele associated with hypertensive individuals at ApoB100 rs693 and MetS may have a direct genetic influence. Further research on expanded sample sizes, however, is required in order to draw rigid conclusions.

1. Introduction
Metabolic syndrome (MetS) is a non-communicable (aggregation) disease (NCD) that causes early morbidity and mortality (Terzic and Waldman, 2011). MetS is a mixture of health conditions that causes an elevation in the risk of coronary heart disease (CHD) and diabetes mellitus type 2 (DMT2) (Hunt et al., 2004). Symptoms include elevated triglycerides (TG) and apolipoprotein B (ApoB100) which contains lipoproteins, being low in high-density lipoprotein (HDL), having high blood pressure and being obese (Harper and Jacobson, 2010).

MetS has been increasing in the past few years especially in overweight and obese people. About 25% of the world’s population was estimated to have MetS (O’Neill and O’Driscoll, 2015). This study will particularly determine the prevalence of MetS in female students at King Abdulaziz University.

ApoB100 is one of the apolipoproteins that plays an essential part in lipoprotein metabolism. It is present in the plasma in two forms: a short form called apolipoprotein B-48, and a longer form known as apolipoprotein B100. The previous are components of lipoproteins, which present as fat and fat-like particles such as cholesterol in the bloodstream (Las et al., 2009).

ApoB100-48 is formed in the intestine and it is the precursor of chylomicrons that carry fat and cholesterol from the intestine into the bloodstream after food is digested. Chylomicrons are also important for the absorption of fat-soluble vitamins (Welty et al., 1999). ApoB100 is produced in the liver and is the building block for very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), and low-density lipoproteins (LDLs). These linked molecules carry both fats and cholesterol in the bloodstream (Devaraj and Jialal, 2019; Segrest et al., 2001).
ApoB100 is a anchor for the receptor-mediated elimination of low density lipoprotein LDL (LDL is one of a lipoproteins group, which causes mainly heart diseases (Ference et al., 2017)) particles from the circulation (Kowal et al., 1989). A positive relation between CHD and LDL cholesterol with ApoB100 levels has been reported (Bruznell et al., 1984).

The gene coded for human ApoB100 has been located on the short arm of chromosome 2p23-24 with an approximate length of 43 kilobases and 29 exons (Chan, 1992; Deeb et al., 1986). Substantial gene diversity involves two ApoB100 signal peptide alleles, is a 43 kb in length with 81 bp coding for 27 and 24 amino acid peptides (Visvikis et al., 1990).

Several Single nucleotide polymorphisms (SNPs), have been found in the ApoB100 gene. Although the role of most of them is still under investigation, it has been reported that rs693 is the most common SNP which affects susceptibility to MetS. In the literature it has been associated with lipemic levels (Alves et al., 2020), it increased the risk of breast cancer in a study done by Liu in 2013 (Liu et al., 2013) and with lipid traits and cardiovascular disease risk factors (Park et al., 2011).

In the current study, we first tested the correlation between the ApoB100 polymorphism rs693 and MetS phenotypes. BMI, blood pressure, insulin resistance and waist circumference (WC) were used as indicator of obesity. To validate the functional consequence of ApoB100 polymorphisms, we measured ApoB100 expression levels in human adipocytes.

2. Methodology

Written consent was collected from all participants as the objectives and methodology of the study were clarified to them. The respondents were asked to fill out a survey containing questions about their lifestyle, body mass index (BMI) and general health issues. The study was approved by the Biomedical Ethics Unit, Faculty of Medicine, KAU [Approval Number 172–18].

A value of BMI < 18.5 kg/m² was considered as underweight, 18.5–24.9 kg/m² was considered as normal weight, 25.0–29.9 kg/m² was considered as pre-obese (overweight), and a BMI of 30 and more was considered as obese (Al-Nozha et al., 2005). Hypertension was defined as systolic blood pressure (SBP) of >140 mm Hg, diastolicblood pressure (DBP) of >90 mm Hg (Joint National Committee on Prevention Evaluation, and Treatment of High Blood Pressure, 1997). The data collected from 141 students at KAU was analyzed into tables as needed. Blood samples of around 5 ml from each volunteer were collected in plain and ethylenediaminetetraacetic acid (EDTA) tubes. Normal routine tests were performed on the blood samples, such as white blood cells (WBC) count, total cholesterol (TC), HDL, TG, LDL and uric acid concentrations in serum using commercial kits (Human Gesellschaft für Biochemica und Diagnostica GmbH, Germany). Serum levels of insulin resistance kit were purchased from Elsabience Biotechnology Co. Ltd, Hubei, China.

Genomic DNA was isolated from whole blood collected in EDTA anticoagulated tubes using a commercial kit (QIAamp DNA Blood Mini Kit; Hilden, Germany), according to the manufacturer’s instructions. All DNA sample concentrations were measured using the Thermo Scientific NanoDrop 2000 Spectrophotometer in order to determine the purity of the samples. The Spectrophotometer was adjusted by using nuclease-free water as a blank to which samples were added using the Micro-Volume Pedestal method. DNA samples were genotyped using the 2 × TaqMan Master Mix, (Applied Biosystem, cat no. 4304437). All PCR primers of the selected gene candidates and the fluorescent dual-labeled TaqMan Probes were manually designed using primer 3 software. The region of interest within the ApoB100 gene (rs693) [A/G] was amplified by using Polymerase Chain Reaction (PCR) technique. The forward primer (5'-ACATTCGCTCTCGTGATCTCTTAG-3') and the reverse primer (5'- GTCTCTGGAGATTTGCCGCCTCATG-3') sets were used.

2.1. Statistical analysis

Statistical analysis of the data was carried out using the Statistical Package for Social Science SPSS (version 23.0). Variables were expressed by mean ± standard deviation (SD). Variables were compared by the chi-square test, Odds ratios (OR) and a 95% confidence interval (CI) . The significant difference between normal individuals and those with obesity was illustrated using an unpaired student “t” test for parametric parameters.

The result was considered statistically significant when p < 0.05. Genotype distribution from the Hardy–Weinberg equilibrium was assessed using a chi squared test with one degree of freedom.

Genotype distributions are shown as a percentage value (%). The proportions of genotypes and alleles were compared by X² analysis, with a p-value according to chi-square tests, Odds ratios (OR) and a 95% confidence interval (CI). The differences in means were assessed using an unpaired student ''t” test for parametric parameters.

The data were expressed as mean ± standard error of mean, BMI: Body mass index, WC: Waist Circumferences, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBS: Fasting blood glucose, FB: Fasting blood glucose, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: triglycerides, WBC: White Blood Cells, IR: Insulin resistance. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the population studied

The clinical characteristics of the MetS and the control groups are shown in Table 1. The mean BMI (kg/m²) of these groups was 30.3 ± 8.2 and 22.1 ± 4.6, respectively. When comparing MetS subjects to controls, the findings showed a highly significant difference.
between these groups regarding measurements of BMI ($p < 0.001$), WC ($p < 0.001$), fasting blood sugar (FBS) ($p < 0.001$), Serum triglycerides TG ($p < 0.001$), and WBS ($p < 0.006$). No significant difference between MetS and the control group with respect to SBP and DBP.

According to the participants’ ($n = 141$ female students) BMI measurements as shown in Table 2, $47\%$ ($n = 66$ students) were of normal weight, the majority of whom made up $56\%$ of the control group ($n = 62$). While $21\%$ ($n = 29$ students) were overweight, and all of them were recorded within the control group constituting $26\%$ of the total participants ($n = 29$). On the other hand, $1\%$ ($n = 25$ students) were overweight, and $15\%$ ($n = 21$ students) were obese. Consequently, most of the students were within the standard range of the BMI. The majority of the MetS group was noted to be on the overweight scale or obesity scale with $47\%$ ($n = 14$ students) and $40.7\%$ ($n = 12$ students) respectively.

3.2. Genotype analysis

The genetic information obtained from study samples from, $n = 141$ (30 MetS and 111 control), female students was used in this analysis. All genotype distributions for the variables tested were in Hardy-Weinberg equilibrium (Edwards, 2008).

3.2.1. Comparison of the genotypic distribution (AA/AG) of ApoB100 rs693AG SNPs between MetS and control subjects

A chi-square test of independence was performed to examine the relation between MetS and control subjects. The relation between these variables was not significant, $X^2 (1, N = 109) = 1.54, p = 0.283$, demonstrating no significant difference between MetS and the control group with respect to the AA/AG genotype (Table 3).

3.2.2. Comparison of the genotypic distribution (AA/GG) of ApoB100 rs693AG SNPs between MetS and control subjects

A chi-square test of independence was performed to examine the relationship between MetS and control subjects. The relation between these variables was not significant, $X^2 (1, N = 111) = 1.359, p = 0.244$, demonstrating no significant difference between MetS and the control group in respect to the AA/GG genotype (Table 3).

3.2.3. Comparison of allele distribution (A/G) of ApoB100 rs693AG SNPs between MetS and control subjects

A chi-square test of independence was performed to examine the relation between MetS and control subjects. The relation between these variables was not significant, $X^2 (1, N = 109) = 1.54, p = 0.283$, although the normal allele A had 35 carriers compared to $65\%$ of the MetS cases. In a recent publication, Wang et al. (2018) found that the polymorphisms of rs693 for the plasma TC, TG, HDL-C and LDL-C levels have greater levels of T allele non-carriers. A report confirmed that ApoB100 is an indicator for atherogenic risk because it is found to be associated with low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (non–HDL-C) (Wilkins et al., 2016). ApoB100 is present within each lipoprotein particle, also in VLDL, chylomicron and intermediate density lipoprotein, with about $90\%$ of ApoB100 is found in LDL (Sniderman and Marcovina, 2006). A report confirmed a significant relationship between ApoB100 and MetS independent of the LDL-C level in patients with DMT2 (Lim et al., 2015).

A study conducted on a group of females in Saudi Arabia found that the prevalence of MetS increases with an elevated BMI (Balgoon et al., 2019). In comparing genotypic distribution (AA/AG) of ApoB100 rs693AG SNPs between MetS and control subjects the results showed no significant difference, $X^2 (1, N = 109) = 1.54, p = 0.283$, although the normal allele A had 35 carriers compared to the G allele with 65 carriers. In a recent publication, Wang et al. (2018) found that T allele (CT + TT) carriers associated with rs693 for the plasma TC, TG, HDL-C and LDL-C levels have greater levels of T allele when compared to T allele non-carriers (Wang et al., 2018). Another Chinese study found that the polymorphisms of rs693 and rs1042031 in the ApoB100 gene increases the risk of breast cancer independently of the BMI (Liu et al., 2013).

Regardless of genotypes, our findings suggest that the rs693 of ApoB100 is significantly associated with higher levels of TG, TC, BMI and glucose in the MetS population as compared with the control group. These findings agree with a study reporting the association of rs693 polymorphisms found to be significantly linked to higher levels of ApoB100, TG, TC and LDL-C, and lower levels of HDL-C (Niu et al., 2017). Phillips and his colleagues found that some ApoB100 polymorphisms other than ApoB100 rs693 may contribute to the risk of MetS (Phillips et al., 2011). Another research study showed a strong association between the rs1469513 variant and AA/GG genotype had (OR 0.563, 95% CI (0.213–1.490)). The relative risk for A/G were 1.093 and the OR and risk associated with MetS in A/G allele were: (OR 0.834, 95% CI (0.821–1.456)).

4. Discussion

Saudi Arabia is recognized as one of the world’s top nations with regards to high rates of diabetes and obesity which have a major impact on most of the population in all age groups (Alqarni, 2016). MetS is a clustering of risk factors for DMT2, CHD, fatty liver and several cancers. Among the population, the prevalence of metabolic syndrome seems to be growing, notably in women of childbearing age (Ramos and Olden, 2008). Metabolic syndrome, associated with environmental factors, is strongly assumed to be due to genetic predisposing factors (Joy et al., 2008). ApoB100, synthesized by the liver, and mainly located on the surface of LDL, is a marker protein for atherosclerosis and other diseases and plays a key role in cholesterol homeostasis (Walldius et al., 2001).

Many candidate gene polymorphisms, such as estrogen receptor alpha, are associated with metabolic syndrome (Gh attendi et al., 2013). They include tumor necrosis factor alpha (Gupta et al., 2012), angiotensin converting enzyme (Xi et al., 2012), increasing fat mass, obesity-associated protein and cholesteryl ester transfer protein (Povel et al., 2011). ApoB100 is an indicator for atherogenic risk because it is found to be associated with low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (non–HDL-C) (Wilkins et al., 2016). ApoB100 is present in each lipoprotein particle, also in VLDL, chylomicron and intermediate density lipoprotein, with about $90\%$ of ApoB100 is found in LDL (Sniderman and Marcovina, 2006). A report confirmed a significant relationship between ApoB100 and MetS independent of the LDL-C level in patients with DMT2 (Lim et al., 2015).

A study conducted on a group of females in Saudi Arabia found that the prevalence of MetS increases with an elevated BMI (Balgoon et al., 2019). In comparing genotypic distribution (AA/AG) of ApoB100 rs693AG SNPs between MetS and control subjects the results showed no significant difference, $X^2 (1, N = 109) = 1.54, p = 0.283$, although the normal allele A had 35 carriers compared to the G allele with 65 carriers. In a recent publication, Wang et al. (2018) found that T allele (CT + TT) carriers associated with rs693 for the plasma TC, TG, HDL-C and LDL-C levels have greater levels of TC when compared to T allele non-carriers (Wang et al., 2018). Another Chinese study found that the polymorphisms of rs693 and rs1042031 in the ApoB100 gene increases the risk of breast cancer independently of the BMI (Liu et al., 2013).

Regardless of genotypes, our findings suggest that the rs693 of ApoB100 is significantly associated with higher levels of TG, TC, BMI and glucose in the MetS population as compared with the control group. These findings agree with a study reporting the association of rs693 polymorphisms found to be significantly linked to higher levels of ApoB100, TG, TC and LDL-C, and lower levels of HDL-C (Niu et al., 2017). Phillips and his colleagues found that some ApoB100 polymorphisms other than ApoB100 rs693 may contribute to the risk of MetS (Phillips et al., 2011). Another research study showed a strong association between the rs1469513 variant and AA/GG genotype had (OR 0.563, 95% CI (0.213–1.490)). The relative risk for A/G were 1.093 and the OR and risk associated with MetS in A/G allele were: (OR 0.834, 95% CI (0.821–1.456)).

3.2.5. The association of ApoB100 rs693 AG SNPs with the clinical characteristics of the study population

Table 5 presents the association of ApoB100 rs693AG SNPs with the clinical characteristics of the study population. In control and MetS subjects, BMI, glucose concentration and TC concentration were significantly associated with the ApoB100 gene but none of the obesity related parameters (TC, TG and HDL) were associated with genotypes of ApoB100 (Table 5).

### Table 2

| Body Mass Index of female students of KAU participant in the study. | Control (n = 111) | MetS (n = 30) | Total (n = 141) |
|---------------------------------------------------------------|-----------------|--------------|----------------|
| Underweight                                                   | 29 (26%)        | 0            | 29 (21%)       |
| Normal                                                        | 62 (56%)        | 4 (13%)      | 66 (47%)       |
| Overweight                                                    | 11 (10%)        | 14 (47%)     | 25 (18%)       |
| Students with obesity                                        | 9 (8%)          | 12 (40.7%)   | 21 (15%)       |


of ApoB100, plasma lipid profiles, and phenotypes associated with obesity (Doo et al., 2015).

In conclusion, our findings revealed a significant association between polymorphisms of the ApoB100 gene (rs693) and the prevalence of metabolic syndrome and increased its risk with only its component traits i.e., higher levels of TG, TC, BMI and glucose in the study population. This finding supports the conclusion that in the investigated Saudi female population, ApoB100 gene (rs693) can still be a very informative marker as a Saudi-specific DNA fingerprinting as well as for evaluating the function of the ApoB100 gene in MetS components. However, a larger scale study is essential to confirm the viability of this marker in different ethnicities.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Acknowledgements

This project was funded by the Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, Saudi Arabia, under grant no. G: 206-665-1440. The authors, therefore, acknowledge DSR with thanks for technical and financial support.

| Table 3 | Comparison of the genotypic distribution of ApoB100 rs693AG SNPs between MetS and control subjects. |
|---------|--------------------------------------------------|
| Genotypes n (Freq%) | Control n = 111 | MetS = 30 | Total n = 141 | p |
| A/A | 8 (38.1%) | 13 (61.9%) | 21 (100%) | 0.3005 |
| A/G | 45 (51.1%) | 43 (48.9%) | 88 (100%) | 0.8375 |
| G/G | 47 (52.2%) | 43 (47.8%) | 90 (100%) | 0.678 |
| Allele n (Freq%) | Control | MetS | Total | p |
| A | 31 (47%) | 35 (53%) | 66 (34.8%) | 0.629 |
| G | 60 (51.5%) | 65 (47.8%) | 134 (75.2%) | 0.729 |

A p-value < 0.05 was considered statistically significant.

| Table 4 | The association between ApoB100 rs693AG SNPs and the risk of MetS. |
|---------|--------------------------------------------------|
| Genotypes | Relative risk for MetS | OR (95% CI) | 95% Confidence Interval |
| AA/AG | 1.267 | 0.588 | 0.0.222 | 1.559 |
| AA/GG | 1.296 | 0.563 | 0.213 | 1.490 |

OR: Odd Ratio, CI: Confidence Interval.

| Table 5 | The association between ApoB100 rs693AG SNPs and the clinical characteristics of the study population. |
|---------|--------------------------------------------------|
| Parameters | Gene | Control n = 111 | MetS = 30 | p value |
| BMI (kg/m^2) | AA | 24 ± 5 | 36 ± 13 | 0.28 |
| | AG | 22 ± 5 | 31 ± 10 | 0.0001* |
| | GG | 21 ± 4 | 30 ± 4 | 0.0001* |
| WC (cm) | AA | 170 ± 91 | 253 ± 74 | 0.23 |
| | AG | 200 ± 81 | 210 ± 105 | 0.84 |
| | GG | 237 ± 82 | 248 ± 75 | 0.57 |
| FBS (mg/dl) | AA | 95 ± 23 | 114 ± 42 | 0.032* |
| | AG | 97 ± 28 | 107 ± 20 | 0.63 |
| TC (mg/dl) | AA | 164 ± 79 | 267 ± 94 | 0.11 |
| | AG | 159 ± 117 | 229 ± 80 | 0.003* |
| HDL (mg/dl) | AA | 157 ± 66 | 181 ± 54 | 0.32 |
| | AG | 157 ± 66 | 181 ± 54 | 0.32 |
| | GG | 149 ± 90 | 174 ± 87 | 0.52 |
| LDL (mg/dl) | AA | 2 ± 2 | 2 ± 1 | 0.06 |
| | AG | 1 ± 2 | 1 ± 1 | 0.16 |
| | GG | 2 ± 2 | 1 ± 1 | 0.16 |
| TG (mg/dl) | AA | 44 ± 29 | 45 ± 37 | 0.81 |
| | AG | 62 ± 54 | 59 ± 71 | 0.53 |
| | GG | 73 ± 187 | 146 ± 130 | 0.015 |
| Insulin (µU/mL) | AA | 1 ± 0.2 | 2 ± 1 | 0.80 |
| | AG | 3 ± 11 | 1 ± 0.3 | 0.21 |
| | GG | 3 ± 8 | 1 ± 0.2 | 0.35 |
| IR (%) | AA | 5 ± 1 | 10 ± 9 | 0.57 |
| | AG | 12 ± 38 | 6 ± 2 | 0.68 |
| | GG | 16 ± 52 | 5 ± 1 | 0.33 |

BMI: Body mass index, WC: Waist Circumferences, FBS: Fasting blood glucose, FB: Fasting blood glucose, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: low-density lipoprotein, TG: triglycerides, IR: Insulin resistance. A p-value < 0.05 was considered statistically significant.

*Significant.
References

Al-Nozha, M.M., Al-Mazrou, Y.Y., Al-Maatouq, M.A., Afrafah, M.R., Khalil, M.Z., Khan, N.B., Al-Marzouki, K., Abdullah, M.A., Al-Khodri, A.H., Al-Harthi, S.S., et al., 2005. Obesity in Saudi Arabia. Saudi Med. J. 26, 824–829.

Alqarni, S.S. M., 2016. A review of prevalence of obesity in Saudi Arabia. J. Obes. Eat. Disord. 2, 25.

Alves, E., Henriques, A., Tonet-Furioso, A., Paula, R., Gomes, L., Moraes, C., Nóbrega, O., 2020. The APOB rs693 polymorphism impacts the lipid profile of Brazilian older adults. Braz. J. Med. Biol. Res. 53.

Balgoon, M.J., Al-Zahrani, M.H., Alkhattabi, N.A., Alzahrani, N.A., 2019. The correlation between obesity and metabolic syndrome in young female university students in the Kingdom of Saudi Arabia. Diab. Metab. Syndr. Clin. Res. Rev. 13, 2399–2402.

Brenzullo, J.D., Sniderman, A.D., Albers, J.J., Kitterovitch Jr, P.O., 1984. Apoproteins B and AI and coronary artery disease in humans. Arterioscler. Off. J. Am. Heart Assoc. Inc 4, 79–83.

Chan, L., 1992. Apolipoprotein B, the major protein component of triglyceride-rich and low density lipoproteins. J. Biol. Chem. 267, 25621–25624.

Das, B., Pawar, N., Saini, D., Seshadri, M., 2005. Genetic association study of selected candidate genes (ApoB, LPL, Leptin) and telomere length in obese and hypertensive individuals. BMC Med. Genet. 10, 99.

Deeb, S.S., Disteche, C., Motulsky, A.G., Lebo, R.V., Kan, Y.W., 1986. Homologous localization of the human apolipoprotein B gene and detection of homologous RNA in monkey intestine. Proc. Natl. Acad. Sci. 83, 419–422.

Devaraj, S., 2019. Biochemistry, Apolipoprotein B. StatPearls [Internet].

Deeb, S.S., Disteche, C., Motulsky, A.G., Lebo, R.V., Kan, Y.W., 1986. Homologous localization of the human apolipoprotein B gene and detection of homologous RNA in monkey intestine. Proc. Natl. Acad. Sci. 83, 419–422.

Doo, M., Won, S., Kim, Y., 2015. Association between the APOB rs1469513 polymorphism and obesity is modified by dietary fat intake in Koreans. Nutrition 31, 653–658.

Edwards, A.W.F., 2008. G. H. Hardy (1908) and Hardy-Weinberg Equilibrium. Genetics 179, 1143–1150.

Ference, B.A. et al., 2017. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur. Heart J. 38 (32), 2459–2472.

Ghattas, M.H., Mehanna, E.T., Alzahrani, N.A., 2013. Association of estrogen receptor alpha gene polymorphisms with metabolic syndrome in Egyptian women. Metabolism 62, 1437–1442.

Harper, C.R., Jacobson, T.A., 2010. Using apolipoprotein B to manage dyslipidemic patients: time for a change? In: Paper presented at: Mayo Clinic Proceedings. Mayo Foundation.

Hunt, K.J., Resende, R.G., Williams, K., Haffner, S.M., Stern, M.P., 2004. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. Circulation 110, 1251–1257.

Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 1997. The 6th Report of the Joint National Committee on Prevention, detection, evaluation, and treatment of high blood pressure. Arch. Intern. Med. 157, 2413–2446.

Joy, T., Lahiry, P., Pollex, R.L., Hegele, R.A., 2008. Genetics of metabolic syndrome. Curr. Diab. Rep. 8, 141.

Kowal, R.C., Herz, J., Goldstein, J.L., Esser, V., Brown, M.S., 1989. Low density lipoprotein receptor-related protein mediates uptake of cholesteryl esters derived from apoprotein E-enriched lipoproteins. Proc. Natl. Acad. Sci. 86, 5810–5814.

Lim, Y., Yoo, S., Lee, S.A., Chiu, S.O., Heo, D., Moon, J.C., Moon, S., Boo, K., Kim, S.T., Seo, H.M., et al., 2015. Apolipoprotein B is Related to Metabolic Syndrome Independently of Low Density Lipoprotein Cholesterol in Patients with Type 2 Diabetes. EndocrinoMetab (Seoul) 30, 208–215.

Liu, X., Wang, Y., Qu, H., Hou, M., Cao, W., Ma, Z., Wang, H., 2013. Associations of Polymorphisms of rs693 and rs1042031 in Apolipoprotein B Gene With Risk of Breast Cancer in Chinese. Jpn. J. Clin. Oncol. 43, 362–368.

Niu, C., Luo, Z., Yu, L., Yang, Y., Chen, Y., Luo, X., Lai, F., Song, Y., 2017. Associations of the APOB rs693 and rs17240441 polymorphisms with plasma APOB and lipid levels: a meta-analysis. Lipids Health Dis 16, 166–166.

O'Neill, S., O'Driscoll, L., 2015. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes. Rev. Off. J. Int. Assoc. Study Obes. 16, 1–12.

Park, M.-H., Kim, N., Lee, J.-Y., Park, H.-Y., 2011. Genetic loci associated with lipid concentrations and cardiovascular risk factors in the Korean population. J. Med. Genet. 48, 10–15.

Phillips, C.M., Gounidi, L., Bertrais, S., Field, M.R., McManus, R., Hercberg, S., Lainor, D., Planells, R., Roche, H.M., 2011. Gene-nutrient interactions and gender may modulate the association between ApoA1 and ApoB gene polymorphisms and metabolic syndrome risk. Atherosclerosis 214, 408–414.

Pavel, C., Boer, J., Reiling, E., Feskens, E., 2011. Genetic variants and the metabolic syndrome: a systematic review. Obes. Rev. 12, 952–967.

Ramos, R.C., Olden, K., 2008. The prevalence of metabolic syndrome among US women of childbearing age. Am. J. Public Health 98, 1122–1127.

Segrest, J.P., Jones, M.K., De Loof, H., Dashti, N., 2001. Structure of apolipoprotein B-100 in low density lipoproteins. J. Lipid Res. 42, 1346–1367.

Sniderman, A.D., Marcovina, S.M., 2006. Apolipoprotein AI and B. Clin. Lab. Med. 26, 733–750.

Terzic, A., Waldman, S., 2011. Chronic diseases: the emerging pandemic. Clin. Transl. Sci. 4, 225.

Visvikis, S., Chan, L., Siest, G., Drouin, P., Ernbling, E., 1990. An insertion deletion polymorphism in the signal peptide of the human apolipoprotein B gene. Human Genetics 84, 373–375.

Walddius, C., Jungner, I., Holme, I., Aastveit, A.H., Kolar, W., Steiner, E., 2001. High apolipoprotein B, low apolipoprotein AI, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. The Lancet 358, 2026–2033.

Wang, Y.-T., Li, Y., Ma, Y.-T., Yang, Y.-N., Ma, X., Li, X.-M., Liu, F., Chen, B.-D., 2018. Association between apolipoprotein B genetic polymorphism and the risk of calcific aortic stenosis in Chinese subjects, in Xinjiang, China. Lipids Health Dis 17. 40–40.

Welty, F.K., Lichtenstein, A.H., Barrett, P.H.R., Dolnikowski, G.G., Schaefer, E.J., 1999. Human apolipoprotein (Apo) B-48 and ApoB-100 kinases with stable isotopes. Arterioscler. Thromb. Vasc. Biol. 19, 2966–2974.

Wilkins, J.T., Li, R.C., Sniderman, A., Chan, C., Lloyd-Jones, D.M., 2016. Discordance between apolipoprotein B and LDL-cholesterol in young adults predicts coronary artery calcification: the CARDIA study. J. Am. Coll. Cardiol. 67, 193–201.

Xi, B., Rudler, R., Chen, J., Pan, H., Wang, Y., Mi, J., 2012. The ACE insertion/deletion polymorphism and its association with metabolic syndrome. Metabolism 61, 891–897.