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COMPREHENSIVE MOLECULAR DETERMINATION OF MIR-128A RS11888095 GENE VARIATION AND ITS ASSOCIATION WITH THE PREDISPOSITION TO METABOLIC SYNDROME

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ABSTRACT

Metabolic syndrome (MetS) is a cardiometabolic condition including the presence of central obesity, insulin resistance, dyslipidemia, and hypertension with a rising trend among the Middle Eastern populations. miRNAs play a significant role in controlling metabolic process and the genetic variation of these molecules can contribute to the development of diseases. This case-control study examined the relationship between miR-128a rs11888095 C>T polymorphosis and MetS risk among a Saudi cohort. 105 patients with MetS and 105 age- and sex-matched controls were incorporated. Genotyping was performed by ARMS-PCR and the associations were tested by logistic regression. T allele was more common in MetS patients as compared to the controls (0.39 vs. 0.25, p = 0.0001). The CT genotype was associated with increased risk (OR = 2.65, 95% CI: 1.48–4.73, p = 0.001), while the TT genotype showed a higher estimated risk (OR = 4.27, 95% CI: 1.03–17.76, p = 0.045). Carriers of T alleles were still at high risk (OR = 2.75, p = 0.0005) in the dominant model. Other important metabolic characteristics linked to genotype were glucose, lipids, waist circumference and blood pressure ($p < 0.05$). These results indicate that miR-128a rs11888095 can predispose to MetS and can be considered a possible biomarker to determine the risk factors.

KEYWORDS: Metabolic syndrome, miR-128a, rs11888095, polymorphism, microRNA, Saudi population, insulin resistance

INTRODUCTION

Metabolic syndrome (MetS) is a set of related metabolic disorders, such as central obesity, glucose intolerance, hypertension, and dyslipidemia, which combined predict the development of type 2 diabetes mellitus (T2DM) and cardiovascular disease [1]. MetS has become a significant burden in the global population with particularly high rates being reported in the Middle Eastern population, including Saudi Arabia, where almost a third of adults have been affected [2–4]. The cause of this increasing prevalence is usually attributed to the rapid changes in lifestyles, urbanization and dietary changes which interrelate with predisposing genetic factors. The genetic factors contribute greatly to the occurrence of MetS with heritability estimates of some of the components of this syndrome being more than 50% [5,6]. Conventional genetic research, however, has mostly concentrated on protein-coding genes and only explains some of the observed variation in metabolic characteristics [1]. It has prompted more interest in non-coding genome regulatory mechanisms, especially those engaged in post-transcriptional regulation of genes. MicroRNAs (miRNAs) have become one of these regulatory factors, playing a significant part in gene regulation. These tiny non coding RNAs control gene expression by facilitating a process of mRNA degradation or preventing the process of translation, affecting a broad spectrum of biological processes [7]. They have a high regulatory range, and a significant percentage of the mammalian mRNAs are expected to be regulated by miRNAs [8].Regarding the metabolic disease, miRNA has been found to play a key role in adipose tissue, insulin signaling, inflammation, and lipid metabolism, which points to its central role in ensuring metabolic homeostasis [9,10]. Among them, miR-128 is a miRNA that has gained growing interest as a metabolically relevant miRNA that plays a wide variety of regulatory roles. It has been previously demonstrated that miR-128 regulates lipid metabolism, cholesterol homeostasis, adipocyte differentiation, and energy balance [11,12]. Moreover, miR-128 has been associated with insulin signaling, and its mal-regulation might be associated with the inability to glucose metabolism and insulin resistance [13]. This evidence indicates that miR-128 has a general involvement in the regulation of metabolic pathways directly involved with MetS.

Notably, genetic variation in the codons or regulatory regions of miRNAs can affect their regulatory activity. SNPs in miRNA genes can change their expression, maturation, or affinity to their target, and can thereby regulate downstream gene regulation [14]. One of such variants of potential functional relevance is the miR-128a rs11888095 C>T polymorphism. It is postulated that this polymorphism influences the secondary structure of the precursor miRNA, which can have an impact on its processing and biological activity [15]. Even though there is limited research on miR-128a genetic variation, the current evidence has indicated that it may be involved in

metabolic disorders. It has been previously reported that miR-128-related variants are related to type 2 diabetes and its complications [16]. It is important to note that a study that was carried out in a Saudi population showed that miR-128 was associated with the risk of T2DM and that it is associated with metabolic parameter changes, which once again confirms its applicability in this region [17]. Moreover, circulating miRNAs, such as metabolic regulation miRNAs, are suggested to be potential biomarkers of MetS and related diseases [18]. Although these improvements have been made, the correlation of miR-128a polymorphisms with MetS itself is under-investigated, especially among the Middle Eastern populations.
Since miR-128 is a key player in metabolism and the MetS prevalence is on the rise in Saudi Arabia, exploring genetic diversity around such miRNA could be a valuable source of information regarding the predisposition to the disease. Thus, the aim of the current research was to determine the correlation between the miR-128a C>T polymorphism at the locus of the rs11888095 and the risk of metabolic syndrome and its connection with significant clinical and metabolic variables in a Saudi population.

METHODS AND MATERIALS

Design and Population of the studies

The aim of this case-control study was to examine the relationship between C>T polymorphism at miR-128a rs11888095 and the predisposition to metabolic syndrome (MetS) in Saudi cohort. A total of 210 participants were recruited (105 patients with MetS and 105 age and sex matched healthy controls). The participants were recruited in hospitals in Tabuk and Alwajh region, Saudi Arabia. The Ethics Committee of the University of Tabuk approved study protocol (HAP-07-001) and all procedures were carried out in accordance with institutional guidelines.

Inclusion and Exclusion Criteria

Cases

The criteria that were used to select the patients included that they must be aged 18 to 65 years, and must have a confirmed MetS diagnosis using the International Diabetes Federation (IDF) and ATP III criteria. MetS was identified by three or more of the following components: (i) ethnicity-specific waist circumference cut-off based central obesity;
(ii) fasting blood glucose ≥100 mg/dL or previously diagnosed type 2 diabetes mellitus (T2DM); (iii) triglycerides ≥150 mg/dL; (iv) HDL cholesterol <40 mg/dL in males or <50 mg/dL in females; (v) blood pressure 130 or higher/85 or higher mmHg or antihypertensive therapy.
The participants were not included in case they had type 1 diabetes, gestational diabetes, pancreatitis, or chronic diseases that were not related to MetS such as chronic liver disease, chronic kidney disease, autoimmune diseases, or cancer.

Controls

Non-cases were adults aged 18–65 years, and matched to cases by age and sex. They were not diagnosed with MetS and they had less than two metabolic abnormalities. Every control was fasting with normal blood glucose (less than 100 mg/dL), normal lipid profiles (triglycerides less than 150mg/dl; HDL cholesterol over 40mg/dl in males or over 50mg/dl in females), and normal blood pressure (less than 130/85mmHg).

Sample Size Calculation

A standard formula was used to estimate the sample size based on the prevalence study as outlined by Jones et al. (2003), given a confidence level of 95% (Z = 1.96), a predicted prevalence of 50% (P = 0.5) and a margin of error of 10% (e = 0.1). The minimum sample size was calculated to be 96 subjects in groups. To be more statistically reliable, sample size was expanded to 105 participants per group.

Clinical Examination and Diagnosis.

Metabolic syndrome is diagnosed by clinical assessment, which includes the history of medicine and family history, physical examination and laboratory analysis of blood pressure and biochemical parameters. The National Institutes of Health defines metabolic syndrome as a diagnosis that is made when a person exhibits three or more of the following conditions or is taking medication to treat the same:
(i) Increased waist circumference: ≥ 35 inches (89 cm) in women or ≥ 40 inches (102cm) in men.
(ii) Elevated triglycerides: ≥ 150 mg/dL (1.7 mmol/L).
(iii) Reduced HDL cholesterol: < 40 mg/dL (1.0 mmol/L) in men or < 50 mg/dL (1.3 mmol/L) in women.
(iv) Elevated blood pressure: ≥ 130/80 mmHg.
(v) High levels of serum glucose: 100 mg/dL or more (5.6 mmol/L or more) when fasting.

Collection and Extraction of DNA.

All participants had their peripheral blood samples (3 mL) taken in EDTA tubes during regular clinical practice. The DNeasy Blood Kit (Qiagen, Hilden, Germany) was used according to the protocol of the manufacturer to extract genomic DNA.
Electrophoresis of 0.8% agarose gel was used to determine the quality of extracted DNA and DNA concentration was determined using NanoDrop. The samples of DNA were kept in 4 o C until further use.

Genotyping of miR-128a rs11888095 C>T (ARMS-PCR)

Amplification refractory mutation system polymerase chain reaction (ARMS-PCR) was used to genotype miR-128a rs11888095 C>T polymorphism. Primer3 software was used to design primers (Table 1).

The total volume of the reaction was 25 µL, included 50 ng of genomic DNA, 0.25 µL of each primer (Fo, Ro, FI, and RI), 10 µL of GoTaq Green PCR Master Mix (Promega, Madison, WI, USA), and nuclease-free water. The thermal cycling conditions were as follows; first denaturation at 95 o C, 40 cycles of denaturation at 95 o C, 35 seconds, annealing at 55 o C, 40 seconds, extension at 72 o C, 45 seconds and finally, extension at 72 o C, 10 minutes. Agarose gel electrophoresis was used to separate PCR products. An internal control was a 441 bp band. The T allele produced a fragment of 202 bp and the C allele produced a fragment of 295 bp.

Table 1. Genotyping primers of the C rs11888095 T polymorphism of miR-128a.

Gene	Sequence	Allele	Band Size	Tm
miR128 Fo	5-AGTATGGAATTTTTACTGTGTTGTCTGT-3		441 bp	55 °C
miR128 Ro	5-GCCAATTATTGCAAAATATTAAATGTATATGG-3			
miR128 FI	5-ATGTATGCTTTGAATACTGTGAAGGAT-3	T-allele	202 bp	
miR128 RI	5-ATACTATACCACACTCCTTATATGCATTG-3	C-allele	295 bp	

Statistical Analysis

To compare group differences two-sample t-test or one-way analysis of variance (ANOVA) were used when continuous variables, and chi-square (X^2) was used when categorical variables. Chi-square (X^2) goodness-of-fit test was used to determine deviations of Hardy-Weinberg equilibrium (HWE). The chi-square test was used to compare the difference between the miR-128a rs11888095 C>T genotype frequencies between the cases and the controls. Odds ratios (ORs) and risk ratios (RRs) were used to estimate associations between alleles and genotypes and prevalence of metabolic syndrome. The computations of risk differences (RDs) were made with 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant. Graphpad Prism 6.0 or SPSS 16 were the statistical programs used.

RESULTS

Hardy-Weinberg Equilibrium and Accuracy of Genotyping: The Hardy-Weinberg equilibrium (HWE) of the miR-128a rs11888095 C>T polymorphism in the control group was not significant ($X^2 = 3.638$, $p = 0.056$), which indicated that there was no significant deviation. Concordance rate was further confirmed by randomly selecting 10% of control samples to repeat, and achieved over 99 concordances.

Demographic and Clinical Characteristics: The demographic and clinical characteristics of the study participants are summarized in Table 2. There was no significant difference between MetS patients and controls in the age ($p = 0.890$) or sex distribution ($p = 0.601$), which indicated the appropriate matching between the groups.

Nonetheless, the body mass index (BMI), triglycerides, fasting blood glucose, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), insulin levels, and HOMA-IR levels were considerably greater in MetS patients than controls (all $p < 0.05$). The level of HDL cholesterol was lower in MetS patients, but not statistically significant ($p = 0.054$). The two groups did not have any significant differences in the total cholesterol or LDL cholesterol.

Table 2. Key features of the MetS and the control groups.

Parameters	Metabolic syndrome MetS	Control	*p*-Value
Age (Year)	41.9 ± 11.2	44.12 ± 9.90	0.890
Gender (M/F)	105(75/30)	100 (60/45)	0.601
BMI (kg/m^2)	32.70 ± 4.89	24.98 ± 3.90	<0.001
Triglycerides (mg/dL)	134(78.10–176.20)	68.94(52.90–95.59)	<0.001
Fasting blood glucose (mg/dL)	94.70 ± 66.72	74.69 ± 14.79	0.018
Total cholesterol (mg/dL)	162.60 ± 39.19	144.87 ± 38.76	0.143
Waist circumference (cm)	109.15 ± 11.83	91.44 ± 12.80	<0.001
SBP (mmHg)	129.80 ± 12.20	116.18 ± 14.43	<0.001
DBP (mmHg)	90.68 ± 9.48	78.40 ± 9.50	<0.001
HDL-C (mg/dL)	34.35 ± 10.80	37.30 ± 16.30	0.054
LDL-C (mg/dL)	94.89 ± 41.60	96.75 ± 39.48	0.763
Insulin (pmol/L)	14.81 ± 11.24	9.89 ± 5.65	<0.001
HOMA-IR	5.80 ± 4.64	2.78 ± 6.64	<0.001

Note: MetS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance. Values are expressed as mean ± standard deviation

(SD) or median (interquartile range, IQR), as appropriate. Log transformation was applied where necessary, and comparisons were performed using Student's t-test.

Genotype and Allele Distributions

Table 3 shows the miR-128a rs11888095 C>T genotypes and frequencies. In MetS patients, the proportions of CC, CT and TT genotypes were 28.57, 64.76 and 6.66 respectively, compared to controls where the proportions of the same were 52.38, 44.76 and 2.85 respectively. There was a big difference between the genotype allocation in MetS patients and controls ($p = 0.0001$). In addition, the frequency of the T allele was also significantly more in the sample of patients than in the sample of controls (0.39 vs. 0.25), whereas the frequency of C allele was also lower (0.61 vs. 0.75).

Table 3. Genotype and allele distribution of miR-128a rs11888095 polymorphism C>T in patients with MetS and controls.

Subjects	n	CC n (%)	CT n (%)	TT n (%)	C allele	T allele	χ^2	df	*p*-Value
Cases	105	30 (28.57)	68 (64.76)	7 (6.66)	0.61	0.39	12.79	2	0.0001
Controls	105	55 (52.38)	47 (44.76)	3 (2.85)	0.75	0.25	—		

Correlation of Genotypes and MetS Risk

The association between miR-128a rs11888095 C>T genotypes and MetS risk was analyzed by logistic regression analysis using various genetic models (Table 4).

In the codominant model, the CT genotype was significantly associated with increased MetS risk (OR = 2.65, 95% CI: 1.49–4.74, $p = 0.001$), while the TT genotype also showed a significant association (OR = 4.27, 95% CI: 1.03–17.77, $p = 0.045$). In the dominant model (CT+TT vs. CC), carriers of the T allele had a significantly higher risk of MetS (OR = 2.75, 95% CI: 1.55–4.87, $p = 0.0005$). In the recessive model (TT vs. CC+CT), no significant association was observed (OR = 2.42, 95% CI: 0.61–9.66, $p = 0.207$). The T allele was found to play a significant role in adding MetS risk (OR = 1.89, 95% CI: 1.252.88, $p = 0.002$). In the overdominant model, MetS was strongly linked to CT genotype, as opposed to CC + TT genotypes (OR = 2.68, 95% CI: 1.303.95, $p = 0.003$).

Table 4. Association between miR-128a rs11888095 C>T polymorphism and risk of MetS under different genetic models

Genetic Model	Genotypes	Controls N=105	MS N=105	OR (95% CI)	RR (95% CI)	*P* Value
	CC	55	30	**1 (Ref.)**	**1 (Ref.)**	-
Codominant	CT	47	68	2.65(1.4855 to 4.7363)	1.58(1.2084 to 2.0743)	0.001
	TT	03	07	4.27(1.0301 to 17.7652)	2.15(0.8261 to 5.6314)	0.045
Dominant	CC	55	30	**1 (Ref.)**	**1 (Ref.)**	-
	CT+TT	50	75	2.75(1.5538 to 4.8672)	1.61(1.2398 to 2.1106)	0.0005
Recessive	CC+CT	102	98	**1 (Ref.)**	**1 (Ref.)**	-
	TT	03	07	2.42(0.6106 to 9.6596)	1.70(0.6532 to 4.4242)	0.207
Additive (Allelic)	C	157	128	**1 (Ref.)**	**1 (Ref.)**	-
	T	53	82	1.89(1.2507 to 2.8793)	1.40(1.1098 to 1.7741)	< 0.002
Over Dominant	CC+TT	58	37	**1 (Ref.)**	**1 (Ref.)**	-
	CT	47	68	2.68(1.3017 to 3.9516)	1.49(1.1378 to 1.9613)	0.003

Note: OR, odds ratio; RR, risk ratio; CI, confidence interval. The reference group (Ref.) was used for comparison in each genetic model. Associations were evaluated using logistic regression analysis.

Correlation with Clinical and Metabolic Measures

Table 5 shows the relationship between miR-128a rs11888095 C>T genotypes and clinicopathological characteristics of MetS patients. There were no significant relationships between the genotype distribution and age ($p = 0.382$) or sex ($p = 0.075$). Nevertheless, there was a strong correlation between the type of genotype andlevel of fasting blood glucose ($p = 0.031$). There was also a significant correlation between the genotype distribution and the waist circumference ($p = 0.0017$), triglyceride levels ($p = 0.004$), HDL cholesterol ($p = 0.001$), and blood pressure ($p = 0.0001$). Conversely, there was no regular relationship established between genotype and total cholesterol levels.

Table 5. Correlation between miR-128a C T genotypes at rs11888095 and clinicopathological outcomes in MetS patients.

Variable	Category	N=105	CC	CT	TT	X^2	df	*P* value
Age	≥ 50 years	80	22	54	4	1.92	2	0.382
	< 50 years	25	08	14	3			
Gender	Male	75	19	53	3	5.18	2	0.075

	Female	30	11	15	4			
Fast Blood Glucose (mg/dL)	≥ 100	75	16	54	05	6.94	2	0.031
	< 100	30	14	14	02			
Waist circumference (cm)	≥ 102 (men) / ≥ 89 (women)	80	18	59	3	12.81	2	0.0017
	< 102 (men) / < 89 (women)	25	12	9	4			
Cholesterol (mg/dL)	≥ 200	30	11	14	5	9.39	2	0.009
	< 200	75	19	54	2			
HDL-C (mg/dL)	< 40 (men) / < 50 (women)	45	21	22	2	12.67	2	0.001
	≥ 40 (men) / ≥ 50 (women)	60	09	46	5			
Triglycerides (mg/dL)	≥ 150	33	16	14	3	10.81	2	0.004
	< 150	72	14	54	4			
Blood pressure	≥ 130/80 mmHg	35	22	09	4	35.75	2	0.0001
	< 130/80 mmHg	70	8	59	3			

Note: Values are presented as counts. χ^2, chi-square test; df, degrees of freedom. Statistical significance was set at $p < 0.05$.

DISCUSSION

The current case-control study offers data that linked the miR-128a rs11888095 C>T polymorphism to the predisposition of metabolic syndrome (MetS) in a Saudi population. In this cohort, the miR-128a rs11888095 polymorphism differs significantly between patients and controls. Patients with MetS have significantly higher rates of the CT genotype and T allele (64.76% and 0.39) than controls (44.76% and 0.25). These findings indicate that the T allele considerably raises illness susceptibility, with p = 0.0001. This was found to be consistent across a variety of genetic models. Besides genetic associations, we found that there were significant correlations between genotype distribution and main metabolic and cardiometabolic characteristics. Together, our results contribute to the emerging research that miRNA-based genetic variation can contribute to metabolic dysregulation, especially in populations that undergo rapid changes in lifestyles and environments.

An interesting finding of this work is that the T allele is more common among the MetS patients (0.39 vs. 0.25; Table 3). Carriers with the CT genotype exhibited an apparent increase in risk (OR = 2.65) with a moderate magnitude of effect and carriers with the TT genotype exhibited a greater estimated risk (OR = 4.27). One should, however, be cautious in using the TT estimate since the confidence interval was quite broad. This is probably because there were only a few cases with this genotype in the sample of the study. Although this is limited, the overall trend indicates the presence of a dose-dependent relationship, with the presence of the T allele being a contributing factor to MetS susceptibility. The absence of a meaningful relationship based on the recessive model further proves the potentiality of the existence of a single copy of the variant allele that can make a difference in the risk of the disease (Table 4). The findings also show a strong correlation between the risk of Metabolic Syndrome and the miR-128a rs11888095 polymorphism. Patients are substantially more likely to have the T allele and CT genotype, and a dominant model demonstrates a strong risk connection (P = 0.0005). These results imply that the T allele functions as a genetic susceptibility factor.

MicroRNAs are already known as post-transcriptional regulators that can control the expression of genes by degrading the mRNA or by silencing the translation process, thus modulating a big variety of biological processes [7,8]. One of them, miR-128, has gained growing interest because of its role in metabolic control. Past researchers have established miR-128 to be involved in lipid metabolism, adipocyte differentiation and insulin signaling pathways [11,19]. On this finding, it is reasonable to suppose that genetic variation in miR-128 can modify its regulatory role and play a role in causing metabolic imbalance. The miRNA processing or expression could be affected by the polymorphism of the rs11888095 in this context, altering downstream metabolic pathways. Genotype distribution in our study was significantly correlated with a number of metabolic parameters such as fasting blood glucose, triglycerides, HDL cholesterol, waist circumference, and blood pressure (Table 5). All these characteristics are the features of MetS and the consequences of the underlying processes low-grade chronic inflammation and insulin resistance. The identified correlation with glycemic indices is in line with the existing literature that indicates miR-128 has been associated with insulin-signaling pathways, such as IRS1/PI3K/AKT signaling [20,21]. The disturbance of these pathways may negatively affect the glucose uptake and lead to the development of insulin resistance, which is one of the primary symptoms of MetS.

On the same note, the susceptibility to MetS is also markedly increased by the miR-128a rs11888095 polymorphism. Particularly affecting blood pressure, waist circumference, fasting glucose, and lipid profiles, the T allele and CT genotype are associated with increased risk and clinical severity. These results establish this variation as a crucial genetic marker for dysregulated metabolism. The correlation of miR-128a polymorphism with lipid related parameters such as triglycerides and HDL cholesterol as observed in our research (Table 5) is consistent with the role of miR-128 in lipid homeostasis. Previous research has demonstrated that miR-128 is capable of controlling the genes that are related to cholesterol transportation and triglyceride metabolism [12,11]. Changes in these regulatory processes can also help to explain the dyslipidemic profile of MetS patients. Moreover, we also observed an association with waist circumference (Table 5) which could indicate a possible

role in adipose tissue regulation perhaps via its effects on adipogenesis and lipid storage. Additionally, we also found that miR-128a genotypes were associated with blood pressure (Table 5) which could also suggest that this polymorphism can affect the vascular functioning. MicroRNAs have been involved in endothelial control, vascular remodeling and inflammatory signaling, which are some of the factors that cause hypertension to develop [22–24]. Though the mechanisms are not directly explored in our study, the associations observed are in line with a larger role of miR-128 in cardiometabolism regulation.

The methodologically, hardy-weinberger equilibrium was found to be in line with the genotype distribution within our control group, indicating the reliability of the genotyping method. Besides this, the reproducibility which we found to be high in repeated genotyping also gives further confidence to our data. The matching of age and sex and case control design also minimize possible confounding, and increases the validity of the observed associations. These results are especially applicable to the context that is the Middle East population where MetS prevalence has grown significantly in the past decades [25,26]. In spite of this increasing burden, little is known in genetic studies in this region. The discovery of miR-128a rs11888095 as a possible susceptibility factor sheds some light on the genetic structure of MetS in this group and emphasizes the necessity to explore population-specific risk factors.

Clinically, the finding of genetic variants that relate to MetS can be an addition to better risk stratification. Carriers of the risk allele might be prone to the development of metabolic abnormalities and may be more susceptible to intervention at a younger age. Moreover, miRNAs are also becoming a target of research in terms of therapy, as they are key in controlling the expression of genes. Despite the fact that additional research is required, especially that of functional validation, the current findings confirm the possibility of using miR-128a in the future in the context of precision medicine. Ultimately, integrating miRNA-related genetic markers into clinical practice can contribute to the early detection of high-risk individuals and inform preventive interventions.

CONCLUSION

Our findings suggest that miR-128a C>T polymorphism at rs11888095 is associated with a high level with a higher risk of metabolic syndrome in a Saudi population. The T allele is seen to increase the risk by virtue of its association with major metabolic characteristics to include glucose dysregulation, dyslipidemia, central obesity and hypertension. These results display the significance of miRNA-related genetic variation in the pathogenesis of MetS and the possible usefulness of miR-128 as a biomarker and a therapeutic target. The future research should support these findings with further studies and investigate the clinical uses of these findings in the framework of precision medicine.

Conflicts of Interest: The authors have no conflict of interest to declare.

Ethical approval: The study was approved by the Research Ethics Committees of University of Tabuk (HAP-07-001).

Informed Consent Statement: Written informed consent was obtained from all MetS patients to publish this paper.

Data Availability Statement: all data supporting the reported results can be found in the Prince Fahad Bin Sultan Chair for Biomedical Research, Faculty of Applied Medical Sciences, University of Tabuk, Tabuk, Saudi Arabia.

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