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Association of CDH13 Gene Polymorphism and Metabolic Syndrome in Gambian Population

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ABSTRACT

Background: Polymorphism in *CDH13* gene, which encodes for the adiponectin receptor, T-cadherin, is a genetic risk factor associated with metabolic syndrome. *CDH13* rs3865188, which is found in the promoter region of the *CDH13* gene, has been found to be associated with metabolic syndrome and its traits in Asian and European Caucasian populations. However, to the best of our knowledge, it was yet to be assessed in a Black African population. **Objective:** The aim of this study was to investigate the association of *CHD13* rs3865188 and metabolic syndrome in a Gambian population. **Methods:** It was a genetic association study in a cross-sectional design in 136 Gambian participants. *CDH13* rs3865188 was genotyped using PCR master mix and sequencing. Blood sugar, triglyceride and high-density lipoprotein levels were determined by standard clinical laboratory methods. **Results:** *CDH13* rs3865188 was found to be significantly associated metabolic syndrome (p=0.034). Genotype AT appeared to be risk factor for metabolic syndrome (OR=2.41, 95% CI, 1.20–4.84, p=0.014). We found genotypes CC and CA in *CHD13* rs3865188 for the first time. **Conclusion:** Our study demonstrated significant association between *CDH13* rs385618 and metabolic syndrome in a Gambian population (Black African population for the first time). Individuals with genotype AT are at higher risk of developing metabolic syndrome.

Keywords: Metabolic syndrome, *CDH13* gene, genetic polymorphism.

1. BACKGROUND

Metabolic syndrome (MetS) is a complex syndrome with clustering of multiple cardiovascular risk factors. It is characterized by the simultaneous occurrence of abdominal obesity, insulin resistance, impaired glucose tolerance, hypertension and dyslipidemia; which are a combination of risk factors for the development of type 2 diabetes and/or cardiovascular disease (1-4).

It affects approximately 20-25% of the adult population worldwide largely due to factors such as ageing of the population, increased life expectancy and obesity, sedentarism and inadequate nutrition. Individuals with MetS are three times more likely to have a stroke or heart attack and two times more likely to die from these compared with individuals without the condition. Furthermore, it confers a fivefold greater risk of developing Diabetes mellitus compared to adults without the syndrome (4-7).

In Africa, the prevalence has been increasing, and it tends to increase with age. This increase in the prevalence in the continent is thought to be due to departure from traditional African to western lifestyles. The syndrome was found not to be limited to adults but is also becoming common among the young ones. In Lagos in Nigeria, the prevalence was found to be as high as over 80% among diabetic patients (8). It was found to be 60.6% in Cape Town, South Africa (9); 35.7% in Morocco (10); and 32.45% in western Cameroun (11). In The Gambia, the prevalence was found to be 42% and 33% as per the International Diabetes Federation (IDF) and Adult Treatment Panel (ATP) definitions respectively in the population studied (12).

Central obesity has been suggested to be the cardinal feature of the MetS; with its pathogenesis being associated with dysregulated adipose tissues and inflammatory cytokine overexpression (1). Excess accumulation of adipose tissue, particularly visceral fat, contributes to the development of insulin resistance, resulting in symptoms characteristic of MetS, which include: type 2 diabetes, dyslipidemia and hypertension (13, 14). Low levels of adiponectin - the main adipose tissue secreted protein - has been found to be a common denominator in the components of the MetS (15).

However, *CDH13* gene region, which encodes for the adiponectin receptor, T-cadherin, has been revealed to be the most crucial locus associated with adiponectin levels (16-18). Overall, there is a complex relationship between the *CDH13* gene locus variants and MetS; suggesting that the *CDH13* gene variants play a crucial role in the genetic determinants of MetS and related metabolic phenotypes (17).

The *CDH13* gene is localized at chromosome 16q23.3, spans 1.2 Mb, and contains 14 exons (16). Major alleles of the promoter single nucleotide polymorphism (SNP) of *CHD13* gene have been found to increase *CHD13* gene expression and increase in adiponectin levels; while polymorphisms in minor alleles lead to decreased levels of adiponectin (17, 19), a common denominator in the components of the syndrome (15). However, rs3865188, rs4783244, and rs12051272 in *CHD13* gene have been found to be associated deterioration in MetS traits despite increased adiponectin levels (18). This shows the crucial effect of polymorphisms in the gene in the development of MetS even when adiponectin levels are normal or high.

CDH13 genes rs3865188 has been found to be associated with plasma adiponectin levels in genome-wide association study (GWAS); and MetS and its traits in studies done in Asians and European Caucasians (16, 18-24). However, to the best of our knowledge, its association with MetS was yet to be assessed in an African population.

2. OBJECTIVE

The aim of this study was to investigate the association of *CHD13* rs3865188 and MetS as defined by International Diabetes Federation (IDF) (6) and MetS traits in a Gambian population.

3. MATERIAL AND METHODS

Ethics

This study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by The Gambia Government/Medical Research Council, The Gambia (GG/MRCG) Joints Ethics Committee (R019011v1.1).

Participants

It was a genetic association study in cross-sectional design conducted at Kanifing General Hospital (KGH) in The Gambia. KGH is located in Kanifing Municipality and serves the most populous municipality in The Gambia. Two hundred and thirty Gambian residents of African descent (at least of three generation), who visited the medical outpatient department (MOPD) and were of at least 18 years were recruited purposively as participants, and classified into two groups: MetS - if they fulfilled the MetS diagnosis criteria per IDF definition (6); and Nonmetabolic syndrome if they didn't fulfill the IDF definition. Participants diagnosed with HIV, hepatocellular carcinoma and chronic renal disease were excluded as these could affect their weights. Participants who did not give blood sample were also excluded. And those with Lebanese or Mauritanian (Middle Eastern (Arab)) descent were excluded too.

Interviews and Anthropometric Measurements

All participants were interviewed by two trained nurses using questionnaires in relation to their medical history and lifestyle characteristics. Each participant had their blood pressure, height, weight and waist circumference measured. Systolic and diastolic blood pressures were measured in a sitting position after at least 15 minutes rest using Omron blood pressure monitor (Omron-HEM-7124). Three blood pressure readings were done with a five-minute interval between readings. The average of the last two readings were recorded as blood pressure for a participant. Body weight of each participant was measured using Seca 9797 scale. Height of each participant was measured using Seca 213 Portable Stadiometer. Waist circumference for each participant was measured using non-elastic tape measure at a level midway between the lower rib margin and iliac crest with the tape all around the body in horizontal position as recommended by IDF (6). Body mass index was calculated as the ratio of weight in kilograms (kg) to the square of height in meters (m^2). Obesity was defined as a body mass index >30 kg/m^2.

Sample Collection and Assays

Five milliliter (5 mL) of peripheral venous blood was collected from each participant in an ethylene diamine-tetra acetic acid (EDTA) tube after 12 hours fasting. One milliliter of whole blood was put on Whatman 3MM Chr Chromatography Paper (Cytiva Europe GmbH) and allowed to dry at room temperature and preserved in plastic bags prior to DNA extraction. The remaining was used for biochemical analyses related to metabolic syndrome: blood glucose and triglyceride (TG) and high-density lipoprotein (HDL) levels. Blood sugar, TG and HDL were measured using Reflotron Plus (Roche Diagnostics GmbH) chemistry analyzer.

DNA extraction and Genotyping

Genomic DNA was extracted from Whatman 3MM Chr Chromatography Paper (Cytiva Europe GmbH) using Invitrogen PureLink Genomic DNA Kits (Thermo Fisher Scientific, Massachusetts, USA) according to manufacturer's instruction for dried blood spots. *CDH13* gene polymorphism was amplified using GoTaq Green Master Mix Promega polymerase chain reaction (PCR) (Promega corporation, Wisconsin, USA) using the following primer pair: Forward 5'- TCTCTGTGGTTGGTACTTGACC -3' and Reverse 5'- CCAGTCTCCCCAAACTCCTCA -3' at the Central Biomedical Laboratory of Brawijaya University, Malang, Indonesia. The PCR amplified 296-bp products were analyzed for genotyping using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA). DNA sequences were aligned using BLAST-NCBI program against reference sequence NM_001220488.2 to detect CDH13 rs3865188.

Statistical Analyses

Group differences between metabolic syndrome and nonmetabolic syndrome were assessed using Chi-square/Fisher's Exact test for categorical variables and

Independent samples T test for continuous variables. The relationship between metabolic traits and genotypes was assessed using chi square/Fisher's Exact test and ANOVA. The association between genotype and MetS was evaluated using odds ratios (ORs) and 95% confidence intervals (CIs) from Chi-square/Fisher's Exact tests and logistic regression analyses. Results are presented as mean ± SD. Statistical significance was defined as p-value < 0.05. All analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp., Armonk, NY, USA).

4. RESULTS

Anthropometric and Clinical Characteristics of the Participants

The 136 participants finally recruited were of average age 46.78±14.77 years, and 87.5% (n=119) were females. Majority of the participants, 54.4%(n=74), were found to have MetS and older than those without it (p < 0.001). There were significant differences in values for systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference (WC), body mass index (BMI), triglyceride (TG) and high-density lipoprotein (HDL) between those with and without MetS respectively, all at p < 0.001 (Table 1).

Variables	Total number (n=136)	Metabolic Syndrome (n=74)	Nonmetabolic Syndrome (n=62)	p value*
Age (years)	46.78±14.77	50.89 ± 12.54	41.87 ± 15.81	< 0.001
Sex (n (%))				0.027
Male	17(12.5)	5 (6.8)	12 (19.4)	
Female	119(87.5)	69 (93.2)	50 (80.6)	
SBP (mmHg)	134.84±28.35	145.47 ± 26.25	122.15 ± 25.55	< 0.001
DBP (mmHg)	88.16±14.10	92.47 ± 11.84	83.02 ± 14.91	< 0.001
DM (n (%))				< 0.001
Yes	56(41.2)	42 (56.8)	14 (22.6)	
No	80(58.8)	32 (43.2)	48 (77.4)	
HTN (n (%))				< 0.001
Yes	67(49.3)	49(66.2)	18 (29.0)	
No	69(50.7)	25 (33.8)	44 (71.0)	
WC (cm)	89.69 ±13.61	97.99 ± 9.92	79.79 ± 10.46	< 0.001
BMI (kg/m^2)	26.52±6.39	29.68 ± 6. 46	22.80 ± 3.78	< 0.001
BMI (kg/m^2) (n (%))				< 0.001
Underweight	10(7.4)	0 (0.0)	10 (16.1)	
Normal weight	48(35.3)	17 (23.0)	31 (50.0)	
Pre-obesity	45(31.3)	25 (35.1)	19 (30.6)	
Obese	33(24.3)	31(41.9)	2 (3.2)	
FBS (mmol/L)	8.12±4.01	9.37 ± 3.82	6.62 ± 3.73	< 0.001
TG (mmol/L)	1.58±0.37	1.80 ± 0.17	1.312 ± 0.37	< 0.001
HDL (mmol/L)	1.20±0.26	1.07 ± 0.18	1.36 ± 0.26	< 0.001

Table 1. Anthropometric and Clinical Characteristics of Participants. SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; WC, waist circumference; BMI, body mass index; FBS, fasting blood sugar; TG, triglyceride; HDL, high density lipoprotein. Participant groups were compared by Independent Samples T Test and Chi-square/Fisher's Exact test; *p<0.05 is considered to be significant.

Genotype and Allele Frequencies of CDH13 rs3865188 Among the Participants

The most common genotype found was AT (46.3%), followed by AA (43.4%), TT (8.8%), CC (0.7) and CA (0.7). Genotype AT is the most frequent (55.4%) in participants with MetS, while genotype AA is most frequent (51.6%) in those without the syndrome (Table 2).

Observed allele frequencies in the participants were 0.669, 0.320 and 0.011 for A, T and C respectively. Allele frequencies observed in MetS patients were (A: 0.649; T: 0.331; C: 0.020) and that of nonmetabolic syndrome (A: 0.694; T: 0.306; C: 0.0) (Table 2).

Variable	Total (n=136)	Metabolic syndrome (n=74)	Nonmetabolic syndrome (n=62)	p value
Genotype (n (%))				0.034
AA	59(43.4)	27 (36.4)	32 (51.6)	
AT	63(46.3)	41 (55.4)	22 (33.5)	
TT	12(8.8)	4 (5.4)	8 (12.9)	
CC	1(0.7)	1 (1.4)	0 (0.0)	
CA	1(0.7)	1 (1.4)	0 (0.0)	
Allele (n (%))				0.602
A	182(66.9)	96(64.9)	86(69.4)	
T	87(32.0)	49(33.1)	38(30.6)	
C	3 (1.1)	3(2.0)	0(0.0)	

Table 2. Genotype and Allele Frequencies of CDH13 rs3865188 Distribution among the Participants. *Participant groups were compared by chi-square/Fisher's Exact test, genotype CC; CA and allele C were not statistically analyzed due to sample size.

***CDH13* rs3865188 Polymorphism and Metabolic Syndrome Traits**

None of the MetS traits showed any significant association with *CDH13* rs3865188. It is only HDL that trends towards significance at p=0.053. Genotypically, values in SBP, DBP, FBS and TG were higher in those with genotype AT, but are not statistically significant. Genotype AA has higher levels in WC(p=0.291) and BMI (p=0.505); while HDL level was found to be lowest in genotype TT (p=0.053) (Table 3).

Association of *CDH13* rs3856188 and Metabolic syndrome

There is significant association between *CDH13* rs3865188 and MetS (χ2=6.80, df=2, p=0.034). Female sex was found to be significantly associated with MetS (p=0.02) (Table 4). From multiple regression analysis, *CDH13* rs3865188 polymorphism was found to be a positive predictor for MetS (p=0.037). Heterozygous genotype AT was found to be associated with MetS when compared to AA+TT [χ2=6.16, OR=2.41, CI (1.92–4.84), p=0.013] (Table 4). It has higher a risk of association with MetS as positive predictor when compared with AA (OR=2.21, 95% CI, 1.066–4.509, p=0.033), and TT (OR=3.73, 95% CI, 1.00–13.78, p=0.049); and with AA+TT (OR=2.41, 95% CI, 1.20–4.84, p=0.014) (Table 5)

(Table 6). Female sex was found to be at higher risk of metabolic syndrome [$\chi 2$=6.03, OR=4.08, CI (1.24–13.4), p=0.020] (Table 6).

5. DISCUSSION

In this study, majority of the participants (54.4%) were found to have MetS and were older. This is higher than the prevalence reported by Nkum et al (12). 58.0% of female participants has MetS which is an increase compared to 55.1% prevalence among the females reported by Nkum et al (12). This findings is in concordance with the assertion of the syndrome being on increase in the continent (8).

In our sample population, the most common genotype was AT (46.3%), followed by AA (43.4%), TT (8.8%) and then CC and CA at (0.7%) each. This is different from the findings reported in 1000 Genome project phase 3 from sample population area in The Gambia. First, they did not report genotype CC or CA (25). We have not also come across genotypes CC and CA being reported anywhere in relation to *CDH13* rs386155. Second, genotype AA (51.3%) was the most common in their population, followed by AT (37.2%) and then TT (11.5) ((25). All the participants in their study were those who reported to be of Mandinka ethnicity, while in ours, only 41.8% of participants reported to be of the same ethnicity. In our study, the genotype frequencies in Mandinka ethnicity are AA (50.9%), AT (35.1%), TT (12.3%), CC (0.0%), CA (1.8%). These genotype frequencies for AA, AT and TT are similar to what was reported in 1000 Genomes (AA (51.3%), AT (37.2%), TT (11.5%)) ((25). For other ethnicities in our study, most of them have at least 50.0% genotype AT (Fula (55.6%), Wollof (55.9%), others (50.00%)).

However, the overall genotypic frequencies in our participants, with genotype AT being the most frequent, are similar to the overall (for all) genotype frequency reported in 1000 Genomes Project; and genotype frequencies in African Caribbean in Barbados, Luhya in Webuye in Kenya and Yoruba in Ibadan, Nigeria. And for overall genotype frequencies in East Asia, South Asia and Europe (25).

The allelic distribution of A, T and C in our participants (A: 0.669, T: 0.320; C: 0.011). Frequencies for A and T are similar those reported in 1000 genomes phase 3 for overall African allelic distribution and those of subpopulations reported for Africa; while C allele was not reported in their findings (25).

Variable (MetS traits)	Total (n=134)	Genotype			
		AA (n=59)	AT (n=63)	TT (n=12)	p value*
SBP (mmHg)	134.70±28.28	133.71± 30.23	136.73 ± 26.89	128.92 ± 26.68	0.642
DBP (mmHg)	88.16±14.20	87.44 ± 14.32	89.11 ± 14.09	86.75 ± 15.05	0.761
DM (n (%))					0.997
Yes	55(41.0)	24(40.7)	26(41.3)	5(41.1)	
No	79(59.0)	35(59.3)	37(58.7)	7(58.3)	
HTN (n (%))					0.708
Yes	66(49.3)	27(45.8)	32(50.8)	7(58.3)	
No	68(50.7)	32(59.0)	31(62.0)	5(12.0)	
WC (cm)	89.49±13.61	90.97 ± 14.08	89.08 ± 13.34	84.33 ± 12.23	0.291
BMI (kg/m2)	26.52±6.43	27.20 ± 7.35	26.12 ± 5.74	25.25 ± 4.93	0.505
FBS (mmol/L)	8.08±4.00	7.67 ± 4.09	8.53 ± 3.95	7.74 ± 3.95	0.475
TG (mmol/L)	1.58±0.37	1.53 ± 0.34	1.62 ± 0.40	1.58 ± 0.36	0.381
HDL (mmol/L)	1.20±0.26	1.27 ± 0.27	1.16 ± 0.26	1.13 ± 0.19	0.053

Table 3. CDH13 rs3865188 and Metabolic syndrome Traits. MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; WC, waist circumference; BMI, body mass index; FBS, fasting blood sugar; TG, triglyceride; HDL, high density lipoprotein.Genotypic and allelic groups were compared by One-way ANOVA chi-square/Fisher's Exact test; *p<0.05 is considered to be significant.

Variable	$\chi 2$	df	OR	95% Confidence Intervals Upper-Lower	p value*
CDH13 rs3865188	6.08	2			0.034
AT	6.16	1	2.41	1.20–4.84	0.013
Female	6.03	1	4.08	1.24–13.4	0.020

Table 4. Association of Metabolic Syndrome with CDH13 rs3865188, Genotype AT and Female Sex using Chi square/ Fisher's Exact Test. *p<0.05 is considered to be significant.

None of metabolic syndrome traits was found to be significantly associated with *CHD13* rs3865188 in itself

Participants	Genotype n (%)			Odds ratio at 95% Confidence Intervals for genotypes:
	AA	AT	TT	
Metabolic Syndrome (n=72)	27 (37.5)	41 (56.9)	4 (5.6)	AT vs AA = 2.21(1.07-4.58) p= 0.033 TT Vs AA = 0.59 (0.16-2.19) p= 0.432 AT Vs TT = 3.72 (1.01-13.78) p= 0.049
Nonmetabolic syndrome (n=62)	32 (51.6)	22 (35.5)	8 (12.9)	AA Vs AT+TT = 0.56(0.28-1.12) p=0.102 AT Vs AA+TT = 2.41(1.20-4.84) p=0.014
	Allele Frequency			
Participant	A	T		
Metabolic Syndrome (n=72)	95 (65.5)	50 (34.5)		T Vs A = 0.84(0.50-1.40) p=0.504
Nonmetabolic syndrome (n=62)	86 (69.4)	38 (30.6)		

Table 5. Association of CDH13 rs3865188 and Metabolic Syndrome. Genotypic and allelic groups were by compared logistic regression; *p<0.05 is considered to be significant.

in our participants, with only HDL trending towards

Variable	OR	95% Confidence Intervals Upper-Lower	p value*
AT vs AA	2.21	1.07–4.51	0.033
AT Vs TT	3.73	1.00–13.78	0.049
AT Vs AA+AT	2.41	1.20–4.84	0.013
Female	4.08	1.24–13.4	0.020

Table 6. Increased Risk of Metabolic Syndrome with Genotype AT and Female Sex using Logistic Regression Analysis. *p<0.05 is considered to be significant.

statistical significance. This is in contrast to the findings in a study in Korea where *CDH13* rs3865188 was found to be strongly associated with MetS traits including blood pressure, fasting blood sugar and triglyceride level (22). A study in Japan found genotype AA to be significantly associated with higher fasting insulin and triglycerides, and lower HDL-cholesterol levels (18). In a French study, those with A allele of rs3865188 were found to be significantly associated with lower BMI (24). Findings in our study are similar those of Fava et al (20), though for a different SNP for *CDH13* gene where none of the components of MetS trait was found to be significantly associated the SNP they studied. The none significant association of any of the metabolic traits with *CDH13* rs3865188 in our study would suggest that, its contribution to the syndrome itself is much more important than to its individual components.

CDH13 rs3865188 polymorphism, which is found in the promoter region of the *CDH13* gene, has been found to be associated with MetS and its traits in Asian population (16, 19, 22); and European Caucasian population (24). To the best of our knowledge, the present study is the first to determine the association between *CDH13* gene polymorphism and MetS in a (Black) African population.

We have found a significant association between *CDH13* rs3865188 and MetS ($\chi 2=6.80$, df=2, p=0.034) in an (Black) African population for the first time. Similar findings were made in Asian population where the SNP has been reported to be associated with the syndrome or its traits or risk factors (16, 18, 22); and in a European Caucasian population (24).

The most common genotype in our study was AT (47.0%), followed by AA (44.0%), and then AT (9.0%). Majority, (59.6%), of participants with MetS has genotype AT; while those without it has genotype AA (51.6%) ($\chi 2=6.80$, df=2, p=0.034). Through multiple regression analysis, *CDH13* rs3865188 polymorphism was found to be a positive predictor for MetS (p=0.037). Those with AT genotype were found to be more at risk in our population. Although in previous studies, those individuals having T allele (mutant form) of rs3865188 were found to be worst off of components of MetS than those with A (wild-type) (22); in our study, when we compared those with mutant allele (AT+TT) to those without it (AA), the risk for MetS was not statistically significant (p=0.102). However, when we compared the heterozygous AT to AA, TT or AA+TT, it was found to have higher risk of the syndrome (p=0.033) (p=0.049) (p=0.014).

The role of *CDH13* gene in the development of MetS is that it encodes for T-cadherin which is the receptor for HMW and MMW adiponectin (26). Several genomic studies have revealed strong links between T-cadherin expression and adiponectin levels with the MetS (27). Hypoadiponectinemia is a common denominator of the constellation of risk facts that constitute MetS (15), the development of which, it is involved mainly through its insulin-sensitizing effect (20, 28).

Furthermore, T-cadherin has been found in pancreatic β-cells in insulin granules and required for insulin release; thereby contributing to the regulation of insulin secretion, which in turn affects metabolic functions independent of direct interactions with adiponectin (29). Expression levels of adiponectin and T-cadherin have been found to be interrelated; that both circulating and tissue-bound adiponectin levels depend on T-cadherin, and adiponectin levels, in turn, regulate tissue T-cadherin levels through a positive feedback loop that suppresses phospholipase-mediated T-cadherin cleavage from cell surface - suggesting interdependent regulation of the two proteins (30, 31). However, regressive changes in the *CDH13* gene promoter or coding sequence could reduce T-cadherin protein levels and ultimately the direction of adiponectin to specific tissues and affects its protective signaling functions (27); thereby offsetting the above suggested interdependent regulation. Kitamoto et al (18) found rs3865188 and two other SNPs of *CDH13* gene to be associated with exacerbation in MetS traits despite increased adiponectin levels. This was attributed to low expression of T-cadherin receptor despite high adiponectin level in these individuals with adiponectin-inducing alleles of *CDH13.* They described this condition as an adiponectin resistant state (18).

Denzel et al (26) demonstrated the significant role of T-cadherin for the uptake and functions of adiponectin in an experiment in which *CDH13*-deficient mice showed a phenotype similar to that of adiponectin-deficient mice, without response to adiponectin supplementation.

One of the mechanisms through which *CDH13* SNPs can affect the expression of the *CDH13* gene was reported to be by some of the SNPs around the CpG island within the regulatory region of the gene affecting the methylation levels of the gene region (32). Several specific CpG-island-associated gene methylation events were frequently observed in *CDH13* and hypermethylation of the promoter region as a major molecular mechanism for loss of *CDH13* expression (33, 34). Even though we were not able to assess the adiponectin levels in our study, the above mechanism could be one possible explanation by which *CDH13* rs3865188 can affect *CDH13* gene expression resulting in MetS even with normal or high levels of adiponectin.

6. CONCLUSION

The present study demonstrated significant association between *CDH13* rs385618 and metabolic syndrome

in an (Black) African population for the first time. However, no significant association was found between the polymorphism and individual metabolic syndrome traits. Individuals with genotype AT were found to be at higher risk of developing the disease.

- **Patient Consent Form**: Written informed consent was obtained from all study participants.
- **Author's contribution**: K.S.B., D.L., and D.W. substantially contributed to the conception and design of the work. K.S.B. gave substantial contribution to data acquisition. K.S.B., D.L., H.S. and D.W. gave a substantial contribution to the analyses and interpretation of data of the work. K.S.B., D.L., D.W., H.S. had a part in article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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REFERENCES

1. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006 Dec 14; 444(7121): 881-887. doi: 10.1038/nature05488.
2. Bosy-Westphal A, Onur S, Geisler C, Wolf A, Korth O, Pfeuffer M, et al. Common familial influences on clustering of metabolic syndrome traits with central obesity and insulin resistance: the Kiel obesity prevention study. Int J Obes (Lond). 2007 May; 31(5): 784-790. doi: 10.1038/sj.ijo.0803481.
3. Henneman P, Aulchenko YS, Frants RR, van Dijk KW, Oostra BA, van Duijn CM. Prevalence and heritability of the metabolic syndrome and its individual components in a Dutch isolate: the Erasmus Rucphen Family study. J Med Genet. 2008 Sep; 45(9): 572-577. doi: 10.1136/jmg.2008.058388.
4. Srivastava AK. Challenges in the treatment of cardiometabolic syndrome. Indian J Pharmacol. 2012 Mar; 44(2): 155-156. doi: 10.4103/0253-7613.93579.
5. Stern MP, Williams K, González-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care. 2004 Nov; 27(11): 2676-2681. doi: 10.2337/diacare.27.11.2676.
6. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006 May; 23(5): 469-480. doi: 10.1111/j.1464-5491.2006.01858.x.
7. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009 Oct 20; 120(16): 1640-1645. doi: 10.1161/CIRCULATIONAHA.109.192644.
8. Okafor CI. The metabolic syndrome in Africa: Current trends. Indian J Endocrinol Metab. 2012 Jan; 16(1): 56-66. doi: 10.4103/2230-8210.91191.
9. Erasmus RT, Soita DJ, Hassan MS, Blanco-Blanco E, Vergotine Z, Kegne AP, et al. High prevalence of diabetes mellitus and metabolic syndrome in a South African coloured population: Baseline data of a study in Bellville, Cape Town. S Afr Med J. 2012 Oct 8; 102(11 Pt 1): 841-844. doi: 10.7196/samj.5670
10. El Brini O, Akhouayri O, Gamal A, Mesfioui A, Benazzouz B. Prevalence of metabolic syndrome and its components based on a harmonious definition among adults in Morocco. Diabetes Metab Syndr Obes. 2014 Jul 31; 7: 341-346. doi: 10.2147/DMSO.S61245.
11. Marbou WJT, Kuete V. Prevalence of Metabolic Syndrome and Its Components in Bamboutos Division's Adults, West Region of Cameroon. Biomed Res Int. 2019 Apr 30; 2019: 9676984. doi: 10.1155/2019/9676984.
12. Nkum BC, Micah FB, Ankrah TC, Nyan O. Metabolic Syndrome in The Gambia: Comparison of the International Diabetes Federation and Adult Treatment Panel III Definitions. Open Science Journal of Clinical Medicine. 2015; 3: 27-32.
13. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature. 2003 Jun 12; 423(6941): 762-769. doi: 10.1038/nature01705.
14. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol. 2004 Jan; 24(1): 29-33. doi: 10.1161/01.ATV.0000099786.99623.EF.
15. Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: a review of current evidence. Endocr Rev. 2012 Aug; 33(4): 547-594. doi: 10.1210/er.2011-1015.
16. Wu Y, Gao H, Li H, Tabara Y, Nakatochi M, Chiu YF, et al. A meta-analysis of genome-wide association studies for adiponectin levels in East Asians identifies a novel locus near WDR11-FGFR2. Hum Mol Genet. 2014 Feb 15; 23(4): 1108-1119. doi: 10.1093/hmg/ddt488.
17. Teng MS, Hsu LA, Wu S, Sun YC, Juan SH, Ko YL. Association of CDH13 genotypes/haplotypes with circulating adiponectin levels, metabolic syndrome, and related metabolic

phenotypes: the role of the suppression effect. PLoS One. 2015 Apr 13; 10(4): e0122664. doi: 10.1371/journal.pone.0122664.
18. Kitamoto A, Kitamoto T, Nakamura T, Matsuo T, Nakata Y, Hyogo H, et al. CDH13 Polymorphisms are Associated with Adiponectin Levels and Metabolic Syndrome Traits Independently of Visceral Fat Mass. J Atheroscler Thromb. 2016; 23(3): 309-319. doi: 10.5551/jat.31567.
19. Jee SH, Sull JW, Lee JE, Shin C, Park J, Kimm H, et al. Adiponectin concentrations: a genome-wide association study. Am J Hum Genet. 2010 Oct 8; 87(4): 545-552. doi: 10.1016/j.ajhg.2010.09.004.
20. Fava C, Danese E, Montagnana M, Sjögren M, Almgren P, Guidi GC, et al. A variant upstream of the CDH13 adiponectin receptor gene and metabolic syndrome in Swedes. Am J Cardiol. 2011 Nov 15; 108(10): 1432-1437. doi: 10.1016/j.amjcard.2011.06.068.
21. Chung CM, Lin TH, Chen JW, Leu HB, Yang HC, Ho HY, et al. A genome-wide association study reveals a quantitative trait locus of adiponectin on CDH13 that predicts cardiometabolic outcomes. Diabetes. 2011 Sep; 60(9): 2417-2423. doi: 10.2337/db10-1321.
22. Choi JR, Jang Y, Kim Yoon S, Park JK, Sorn SR, Park MY, et al. The Impact of CDH13 Polymorphism and Statin Administration on TG/HDL Ratio in Cardiovascular Patients. Yonsei Med J. 2015 Nov; 56(6): 1604-1612. doi: 10.3349/ymj.2015.56.6.1604.
23. Park J, Kim I, Jung KJ, Kim S, Jee SH, Yoon SK. Gene-gene interaction analysis identifies a new genetic risk factor for colorectal cancer. J Biomed Sci. 2015 Sep 11; 22(1): 73. doi: 10.1186/s12929-015-0180-9.
24. Nicolas A, Aubert R, Bellili-Muñoz N, Balkau B, Bonnet F, Tichet J, et al. T-cadherin gene variants are associated with type 2 diabetes and the Fatty Liver Index in the French population. Diabetes Metab. 2017 Feb; 43(1): 33-39. doi: 10.1016/j.diabet.2016.05.005.
25. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, et al. A global reference for human genetic variation. Nature. 2015 Oct 1; 526(7571): 68-74. doi: 10.1038/nature15393.
26. Denzel MS, Scimia MC, Zumstein PM, Walsh K, Ruiz-Lozano P, Ranscht B. T-cadherin is critical for adiponectin-mediated cardioprotection in mice. J Clin Invest. 2010 Dec; 120(12): 4342-4352. doi: 10.1172/JCI43464.
27. Sternberg J, Wankell M, Subramaniam VN, Hebbard LW. The functional roles of T-cadherin in mammalian biology. AIMS Molecular Science; 2017; 4(1): 62-81. doi: 10.3934/molsci.2017.1.62
28. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006 Jul; 116(7): 1784-1792. doi: 10.1172/JCI29126.
29. Tyrberg B, Miles P, Azizian KT, Denzel MS, Nieves ML, Monosov EZ, et al. T-cadherin (Cdh13) in association with pancreatic β-cell granules contributes to second phase insulin secretion. Islets. 2011 Nov-Dec; 3(6): 327-337. doi: 10.4161/isl.3.6.17705.
30. Matsuda K, Fujishima Y, Maeda N, Mori T, Hirata A, Sekimoto R, et al. Positive feedback regulation between adiponectin and T-cadherin impacts adiponectin levels in tissue and plasma of male mice. Endocrinology. 2015 Mar; 156(3): 934-946. doi: 10.1210/en.2014-1618.
31. Fujishima Y, Maeda N, Matsuda K, Masuda S, Mori T, Fukuda S, et al. Adiponectin association with T-cadherin protects against neointima proliferation and atherosclerosis. FASEB J. 2017 Apr; 31(4): 1571-1583. doi: 10.1096/fj.201601064R.
32. Putku M, Kals M, Inno R, Kasela S, Org E, Kožich V, et al. CDH13 promoter SNPs with pleiotropic effect on cardiometabolic parameters represent methylation QTLs. Hum Genet. 2015 Mar; 134(3): 291-303. doi: 10.1007/s00439-014-1521-1526.
33. Kalari S, Pfeifer GP. Identification of driver and passenger DNA methylation in cancer by epigenomic analysis. Adv Genet. 2010; 70: 277-308. doi: 10.1016/B978-0-12-380866-0.60010-1.
34. Takeuchi T. CDH13 (cadherin 13, H-cadherin (heart)). Atlas Genet Cytogenet Oncol Haematol. 2011; 15: 808-810.