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The Association of Cholesterol Transport ABCG 1 Polymorphism Towards the Susceptibility of Metabolic Syndrome Risk Factorin Thai Adolescents

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Abstract

Asian countries now suffers from a double burden issue that involves metabolic syndrome (Met S) even in the adolescent age. Many factors have been considered to explain this situation including genetic variation contribution to the susceptibility of said metabolic syndrome. ATP-Binding Cassette G1 (ABCG1) is known in its role in cholesterol efflux that is strongly related in lipid accumulation and insulin performance. In addition to this gene modulation work in reverse cholesterol transport that is also connected with the occurrence of metabolic syndrome. However, the effect of polymorphism in rs 1044317 remains unclear. A total of 434 subjects in adolescent age were genotyped for ABCG1 rs1044317 by restricted fragmented length polymorphism polymerase chain reaction method. All the anthropometric and laboratory date was extracted by an approved protocol. The correlation of each variables was detected using SPSS ver.21. Frequencies of alleles and genotypes of the ABCG1 polymorphism were similar in both sexes. A significant correlation detected between adjusted males' group with an increased level of interleukin-6 in wide genotype and an increased fasting blood sugar level in adjusted females' group in variant genotype. The existence of rs1044317 ABCG1 SNP affected the susceptibility of specific criteria of Met S in Thai adolescence population. Additionally, there is a gender difference in the incidence of Met S, indicating a possible gene–gender interaction of the ABCG1 polymorphism in Met S among Thai adolescents.

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Background

Metabolic syndrome (Met S) is now spreading across the nation, including Asian countries and Thailand.[1,2] This problem not only affects adulthood but the sign of Met S has been shown since childhood. This condition may lead to many non-communicable diseases like cardiovascular disease, diabetes, and many others as they are getting older. The prevalence of diabetes in the adult population in Thailand is more than 8% in both male and female groups, and the prevalence of metabolic syndrome in children population, based on cross-sectional research done in 2014, was around 4%.3 Originally, Met S in children was defined as a direct consequence of childhood obesity. However, cardio-metabolic (CM) risk traits such as high blood pressure, hyperglycemia, dyslipidemia, and low grade inflammatory are now common in children even in the absence of obesity.[4] Furthermore, ethnic variations occur in the distribution of CM risk in children.[5] Therefore, the genetic component is also substantial evidence contributing to the susceptibility of Met S.[6]

ATP-Binding Cassette G1 (ABCG1), a member of the large family of ABC transporters, is known involves in lipid homeostasis and accumulation especially shown in some SNP (Single Nucleotides Polymorphism) of this gene.[7,8] Recently, there is a growing body of evidence suggesting that modulation of ABCG1 expression might be contributed to the development of obesity and lead to a high potency of diabetes based on conducted animal study.[9,10] Due to those findings, the author considers ABCG1 and its polymorphism might contribute to the susceptibility and development of Met S. Even though there were some studies about 3' UTR single nucleotide polymorphism (SNP) ABCG1 rs 1044317 yet the result remained unclear and incoherent.[11]

In this study, we examined if there is a correlation between the existences of ABCG1 polymorphism (rs1044317) with the MetS or cardio-metabolic risk factors in Thai adolescents. Blood biochemistries such as total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c), blood glucose and inflammatory marker was taken as the marker in the development of MetS since it supports the theory where excess adiposity participate in Met S and insulin resistance, which has been associated with a pro-inflammatory state.[12-14]

Materials and Methods

Study Subjects

This cross-sectional study consists of 434 subjects which were the participant of the "Association of early life exposures and long-term health and cognitive development outcomes in adolescents in northeast, Thailand" project, a community-based study that was performed in the adolescence of Khong Kaen province at age around 14 to 16 years old (2013). This study used the DNA samples and data which was stared from 2020. This study was approved from the research ethic committee of human research internal review board, Mahidol University (MU-CIRB) was received the approval this study protocol (MU-CRIB 2016/020.1708).

Anthropometry and Clinical Measurements

Weight, height, and waist circumference were the attained data for anthropometry measurement. Weight was measured with a standardized digital scale (Seca digital scale model 813, Sec a Corporation, Hamburg, Germany) and height was measured with measuring tape on the millimeter scale. The weight and height of each participant were calculated with the same method as adults. The waist circumference was measured with inelastic tape in millimeter. Each participant was asked to sit on the chair to measure blood pressure using an automatic blood pressure monitor.

Laboratory Analysis

Fasting blood sugar (FBS), serum triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL) levels were analyzed directly by enzymatic assay. Indirectly, the low-density lipoprotein cholesterol (LDL) levels were calculated using the Friedewald formula.[15] Hemoglobin A1 C (HbA1C) level was measured by the high-performance liquid chromatography (HPLC) technique. The inflammatory markers, interleukin-6 (IL-6), and Tumor Necrotic Factor alpha (TNF-α) were analyzed using Enzyme-Linked Immunosorbent Assay (ELISA) method based on the suggested method from another study.[16] For high sensitivity c-reactive protein (hs-CRP), it was analyzed using the immunoturbidity method according to laboratory procedures.

Metabolic Syndrome (Met S) Criteria In Adolescents

In the present study, the criteria were adapted from IDF (2015) that released 5 criteria of Met S for adolescence. An adolescent (10-16 years old) can be categorized in Met S when they have following cardio-metabolic risk factors; waist circumference (WC) ≥90th percentile and followed by 2 of 4 other criterias (triglycerides (TG level≥150 mg/dL, high-density lipoprotein cholesterol (HDL) <40mg/dL, blood pressure (BP) systolic ≥130/ diastolic ≥85 mmHg and fasting blood sugar (FBS) ≥ 100 mg/dL.[17,18]

Genotyping

Genomic DNA samples were extracted from thawed peripheral leukocytes in EDTA-treated blood using the Flexi Gene DNA kit (Qiagen, Hilden, Germany). The ABCG1 gene contained SNP rs1044317 was studied using polymorphism chain reaction-restricted fragment length polymorphism (PCR-RFLP) with these determined primers: Forward: 5'- GCTGGGTTGGATCTTCTCTCC -3' and Reverse: 5' - TGGCTTGCAAAAATGACTTCTCA -3'. The temperature conditions for the polymerase chain reaction (PCR) were set at 94°C with 5 minutes for initial denaturation, 32 cycles at 94°C for denaturation, 51°C for annealing, and 72°C for extension, each step lasting 45 s, with a final extension for 5 min, at 72°C. The amplification products yielded a 359-base pair (bp) fragment, of which the A allele contained a H haI site (234/125 bp). PCR products underwent enzymatic digestion were resolved on 3.0% agarose gel electrophoresis.

Statistical Analysis

All data were analyzed using SPSS software (SPSS ver.21.0, Chicago USA). Fit to the expectation of Hardy-Weinberg Equilibrium (HWE) was tested using X^2 test. For continuous variable, 1-sample Kolmogorov-Smirnov Test was conducted to check the normality of data distribution. Since the data were not distributed normally, the non-parametric analysis was performed. Mann-Whitney Test was performed to see the difference between alleles. The association between alleles and risk factors were analyzed using Spearman's Test. P-value was set as ≤ 0.05 for significant correlation and set based on a two-tailed test.

Results

General Characteristics of the Study Population

Four hundred and thirty-four subjects were included in the analysis. The characteristic in this study were presented in Table 1. The mean age of the sample population was homogenous between genders (range 14.8 years old to 16.1 years old).

Table 1: General Characteristic and metabolic syndrome prevalence in subjects

Parameter (mean±SD)	Total	Male	Female	p-value
	n=434	n=217 (50)	n=217 (50)	
Age (month)	177±4	177±4	177±4	0.180
Weight (kg)	50±10.1	52.2±10.6	47.7±9.1	0.000*
Height (cm)	159.8±7.7	164.4±6.9	155.2±5.3	0.000*
Waist Cir. (cm)	67.5±8	67.5±8	67.4±8	0.850
BMI (kg/cm2)	19.5±3.3	19.2±3.2	19.8±3.3	0.031*
Sistole (mmHg)	106±62	110±9	102±8	0.000*
Diastole (mmHg)	62±6	62±6	61±6	0.275
Cholesterol (mg/dL)	138.4±29.5	132±27	144±31	0.000*
LDL-C (mg/dL)	75.5±19.4	72±18	79±20	0.001*
HDL-C (mg/dL)	39±12	39±11	39±13	0.989
Triglyceride (mg/dL)	104±48	105±55	103±39	0.535
FBS (mg/dL)	91±9	93±9	89±8	0.000*
HbA1c (%)	5.5±0.8	5.6±0.8	5.4±0.7	0.056
IL-6 (pg/mL)	281.6±203	281±200	283±206	0.856

hs-CRP (mg/L)	0.7±1.6	0.8±1.69	0.7±1.58	0.221
TNF-α (pg/mL)	35.12±49.7	39.7±56.4	30.6±41.5	0.424
	Met S Risk Factors n (%)			
MetS, N(%)	17 (3.9)	10 (4.6)	7(3.2)	
Waist Circumference	43 (9,9)	22 (10,1)	21 (9,68)	
Fasting Blood Sugar	59 (13,6)	39 (18)	20 (9,22)	
HDL-Cholesterol	233 (53,7)	114 (52,5)	119 (54,8)	
Triglyceride	61 (14,1)	33 (15,2)	28 (12,9)	
Hypertension	3 (0,69)	3 (1,38)	0 (0)	
Without Risk Factor	159 (36,6)	76 (35)	83 (38,2)	

p< 0.05 is considered to be statistically significant.

Genotype and Allele Frequency Distribution of ABCG1 Polymorphism

Frequencies of ABCG1 genotypes in subjects did not deviate from Hardy Weinberg equilibrium (HWE) ($p > 0.05$). There is a small difference in allele frequency between gender. However, the allele frequency in the present study were similar with data in previous studies[19] (Table 2).

Table 2: Genotype and allele distribution of ABCG1 between subjects

Genotype	Total	Male	Female
	n=434	n= 217	n=217
AA (n/%)	104 (24)	51 (49.0)	53 (51)
AG (n/%)	229 (52,8)	121 (52.8)	108 (47.2)
GG (n/%)	101 (23,7)	45 (44.6)	56 (55.4)
Gallele frequency	0.50	0.51	0.49
HWE p value	0.249	0.087	0.948

HWE p value; Hardy Weinberg equilibrium p-value; HWE p-value, for comparison among genotype in group; p-value for the comparison of genotype frequencies in male and female. *Based on the results of the chi-square test, $p < 0.05$ was considered statistically significant.

The Proportion of Wild Allele and Variant Allele in Each Metabolic Risk Factor

The proportion of wild genotype(AA) and variant genotypes (AG+GG) in each criterion of Met S were showed in Table 3. All data show a similar trend that the frequency of having a criterion of Met S was increased in wild alleles by odd ratio analysis. However, no significant were observed. This table shows that most of the subjects that meet the criteria, had wild alleles, in males and females' groups. Contrary to that, the frequency of female subject who has higher waist circumference found in variant allele. Another interesting point can be highlighted is the percentage of subject with low HDL-c. It appears consistent that more than 50% of the subject in all gender and genotype has lower HDL.

Association of ABCG1 Polymorphism with the Metabolic Syndrome (Met S) Risk Factors Among Control Adolescents

When analyzed the subjects only who were not yet Met S case and cardio-metabolic risk factor or Met S components, there was a trend of higher

inflammatory marker in variant genotypes. IL-6 levels were higher in variant genotypes compared to the wild genotypes in both genders. However, this result was considered significant only in the male group (p-value = 0.036), but not in the female group. FBS seems to be significantly higher in female groups for subjects who posed the variant genotypes (p value = 0.003) (Table 4).

Table 3: The proportion of wild genotype and variant genotypes in each Met S Criteria

Met S Risk Factors	Wild genotype (AA) (n/%)	Variant genotype (AG+GG) (n/%)	Odd ratio	(95% CI)	P-value
Male	**51 (23.5)**	**166 (76.5)**			
High Waist Cir.	7 (12.7)	15 (9.0)	1.602	(0.61-4.17)	0.425
High FBS	11 (21.6)	28(16.9)	1.355	(0.62-2.96)	0.532
Low HDL-C	27 (52.9)	87 (52.4)	1.022	(0.55-1.92)	1.000
High Triglyceride	8 (15.7)	25 (15.1)	1.049	(0.44-2.50)	1.000
Hypertension	0 (0)	3 (1.8)	- a)	-	1.000
Female	**53 (24.8)**	**161 (75.2)**			
High Waist Cir.	3 (5.7)	18 (11)	0.487	(0.13-1.72)	0.422
High FBS	7 (13.2)	13 (7.9)	1.768	(0.67-4.70)	0.276
Low HDL-C	30 (56.6)	89 (54.3)	1.099	(0.59-2.05)	0.874
High Triglyceride	9 (17.0)	19 (11.6)	1.561	(0.66-3.70)	0.347
Hypertension	0 (0)	0 (0)	- a)	-	1.000

a) Test cannot be performed on empty group, *p < 0.05 is considered to be statistically significant.

Table 4: Correlation between the genotype with the MetS risk factor and inflammatory markers in healthy adolescent

Parameter	Wild genotype (AA)	Variant genotype (AG+GG)	*p-value genotype*
Male			
Waist circumference (cm)	63.74±4.5	65.17±3.7	NS
Systole (mmHg)	109±8	110±9	NS
Diastole (mmHg)	61±7	62±6	NS
FBS (mg/dL)	89.81±3.9	88.83±5.8	NS
Triglyceride (mg/dL)	75.8±22.7	84.9±24.3	NS
Total cholesterol	142.2±32.8	134.3±23.6	NS
HDL-C (mg/dL)	49.5±7.4	48.0±6.7	NS
LDL	74.4±20.4	68.5±15.7	NS
IL-6 (pg/mL)	196.0±227.8	293.9±202.7	**0.037**
hCRP	0.37±0.7	0.65±1.6	NS
Female			
Waist circumference (cm)	64.81±3.7	64.81±4.5	NS
Systole (mmHg)	102±8	102.8	NS
Diastole (mmHg)	61±5	61±6	NS
FBS (mg/dL)	85.0±4.6	88.9±5.4	**0.003**
Triglyceride (mg/dL)	83.8±25.6	80.9±19.1	NS

Total cholesterol	153.7±26.2	156.0±29.5	NS
HDL-C (mg/dL)	51.5±12.9	49.5±8.8	NS
LDL	77.6±19.2	81.2±20.7	NS
IL-6 (pg/mL)	251.5±169.2	313.1±214.5	NS
h CRP	0.28±0.3	0.39±1.3	NS

NS = Not Significant, Data are presented as mean – SD. $p < 0.05$ is considered to be statistically significant. The p-value for genotype were calculated by Mann-Whitney Test.

Discussion

ABCG1 is a cholesterol transporter that is known as the inducer of nascent HDL lipidation of and issues commands for redistribution of cholesterol to the outer of plasma membrane that facilitated by HDL. Some of the polymorphism of ABCG1 indicated a significant role in HDL metabolism,[20] and an association with the plasma Lipoprotein Lipase (LPL) which also functions in lipid deposit in macrophage.[8]

The polymorphism of ABCGI rs1044317 is located in the 3'-untranslated regions (UTR) of the chromosome 21. p12. Research regarding this gene has been conducted among some sample populations. Based on the result of this study, there was no correlation in general between the diagnosed of Met S with ABCG1 SNP rs1044317 even though the prevalence of the Met S case was match with the previous study which is 4% in adolescent population.[3]

The recent study showed that this SNP had no correlation with any plasma lipid profile (HDL-c, LDL-c, TG, TC) in the adolescent sample population, even though the adjustment model for gender and specific MetS criteria has been applied. In comparison with previous study held in Spanish Caucasian, the result is coherent. That population showed no significant effect between the Rs1044317 with any postprandial lipid level.[21] In accordance with that, a study in Chinese Han population also concluded deleterious role of this SNP in the risk of any factors related to coronary artery disease.[11] Meanwhile, one research was found conflicting with the recent result. It suggested the association between the rs1044317 with the fasting HDL-c level in subject with intake polyunsaturated fatty acid more than 13.6 g/day.[22]

ABCG1 in conjunction equally with ABCA1 participated to maintain glucose by controlling the secretion and activity of insulin.[23] This is supporting the recent finding about hyperglycemia in female group with variant allele. In one animal study conducted in mice, ABCG1 expression is reduced in later stages of disease similar to beta cell failure which arises after hyperglycemia. This effect generated a positive feedback cycle which causes metabolic dysfunction.[10] This idea supported by a coherence finding that suggested the Loss of beta cell ABCA1 and ABCG1 aggravate glucose intolerance and the dysfunction of b-cell.[9] However, the pathway of down regulation of ABCG1 expression and its SNP by hyperglycemia stage is remain obscure.

Our research suggested that the healthy subjects with variant allele of rs1044317 tend to have a higher degree of inflammation based on the IL-6 level.[24] This finding indirectly indicated that this subject group was prone to a higher risk of Met S. Low-grade inflammation is characterized in obesity within all ages and correlated significantly with Met S.[14] The study that uncovered this relationship is still limited and the mechanism between them is unclear.

Another interesting result of this recent study was more than half population in all gender and genotypes are prone to have low level of HDL. Younger populations have a tendency of a better lipid profile with an optimum reverse cholesterol transport mechanism. Contrary with that, the low physical exercise and hypercaloric eating habit can lead to low HDL-c. Exercise, especially aerobic becomes an important factor to trigger the activation of PPAR that involved in reverse cholesterol transport. The product of this pathway is mature HDL-c.[25] The current generation of Thai adolescent shifted the lifestyle from physically active to sedentary behavior.[26] That explained the finding of low HDL-c in this study.

Currently, this research is the first of a kind in Thailand about ABCG1 SNP rs1044317 conducted in adolescent population. This study is expected to initiate the future research about this topic in Asian population. However, it was limited in several ways especially the study design and the number of subjects participated. Due to the sample population came from one province, the result might be recondite and did not represent the general effect in Thailand population.

This study detected the higher risk of Met S as the effect of rs1044317 in the variant allele. However, that result was only relevant in healthy subject. ABCG1 expression has been found enhance the cholesterol efflux interrelated with ABCA1 performance and other supportive agent[27] and found significantly lower in Met S case.[28] To explain this finding, future study should be undertaken to explore the expression of ABCG1-dependent agent and its pathway, with some SNPs, in variation of many age levels.

Conclusion

Returning to the question posed at the beginning of this study, the findings provide a result that the existence of RS1044317 ABCG1 SNP affected the susceptibility of specific criteria of MetS in Thai adolescence population. However, the correlation appeared significant after modification in gender and Met S related health factors. The subject who possesses the variance allele seems to have a higher risk of Met S. It was shown by the hyperglycemia in the females' group and significant higher level of IL-6 in males' group.

Authors' Contributions

LMGBS, TP and CC participated in investigation. LMGBS wrote the original draft of manuscript. UT, NO, KT and PL performed data analysis and CC reviewed and edited the final draft of the manuscript. All authors provided clarification and guidance on the manuscript. All authors were involved in editing the manuscript and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no competing interests.

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List of Abbreviation

Met S = Metabolic syndrome
WC = Waist circumference
TG = Triglyceride
HDL-c = High-Density Lipoprotein-cholesterol
BP = Blood pressure
FBS = Fasting blood sugar
ABCG1 = ATP Binding Cassette G member 1
SNP = Single nucleotide polymorphism
TC = Total cholesterol
LDL-c = Low-Density Lipoprotein-cholesterol
HPLC =high-performance liquid chromatography
IL-6 = Interleukin-6
TNF- α = Tumor Necrotic Factor- α
ELISA = Enzyme-Linked Immunosorbent Assay
hs-CRP = high sensitivity C-Reactive Protein
HWE = Hardy-Weinberg Equilibrium
LPL = Lipoprotein Lipase
PPAR =Peroxisome proliferator-activated receptor