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The minor C-allele of the rs2014355 variant in ACADS gene is associated with exercise-induced increase in HDL cholesterol levels in Taiwanese adults

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Abstract

We investigated the association between high-density lipoprotein cholesterol (HDL-C) and rs2014355 variant in the gene, short-chain acyl-coenzyme A dehydrogenase (*ACADS*) based on exercise habits.

Data collected between 2008 and 2015 for individuals aged 30 to 70 years were available in the Taiwan Biobank (TWB) database. Backward stepwise linear regression was used to evaluate the associations of rs2014355 and exercise with HDL-C levels.

We analyzed data of 5515 physically active and 4169 inactive biobank participants. The HDL-C concentrations were higher in the exercise compared to no exercise group (beta value, β = 1.79856; $P < .0001$). We observed that the test for interaction was significant for the *ACADS* rs2014355 variant and exercise (P for interaction =.0412). Multivariate analyses showed significant association between TC+CC genotype and HDL-C in the exercise ($\beta = 1.09785$; P value = .0146) compared to the no-exercise group ($\beta = -0.03754$, $P = .9154$).

In summary, the association between HDL-C and exercise differed significantly with respect to *ACADS* rs2014355 genotypes. Compared to the TT genotype, the TC+CC genotype together with exercise was associated with higher levels of HDL-C.

Abbreviations: ACADS = short-chain acyl-coenzyme A dehydrogenase, β = beta coefficient, BMI = body mass index, CI = confidence interval, HWE = Hardy-Weinberg equilibrium, MOST = Ministry of Science and Technology, SNP = single nucleotide polymorphisms, TWB = Taiwan Biobank.

Keywords: ACADS gene, exercise, HDL-C, SNP

1. Introduction

Short-chain acyl-coenzyme A dehydrogenase is a homotetrameric flavoenzyme that catalyzes the initial step of the mitochondrial fatty acid beta-oxidation pathway.[1] It cuts long-chain free fatty acids (FFA) into short-chains (C3/C4) when they are inside the mitochondria.[1] This pathway plays an important role in energy metabolism especially during a physiological response to tissue energy depletion during periods of fasting, illnesses, and increased muscular activity. Mutations of the *ACADS* gene are associated with deficiency of the short-chain acyl-coenzyme A dehydrogenase protein (SCADD) which is marked by an increased amount of fatty acids, and the presence of increased butyrylcarnitine (C4) in blood plasma, and increased ethylmalonic acid (EMA) concentrations in urine.[2,8,17]

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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It is well known that HDL-C has a strong correlation with the risk of coronary atherosclerosis.[3,11,14] There is much evidence to show that exercise and diet are important in improving serum HDL-C levels, hence minimizing the risk of cardiovascular disease.[5,10,12] It has also been reported that regular endurance exercise training may increase HDL-C levels.[13] ACADS is one of the quantitative effectors of HDL-C.[15] An experiment on *ACADS* gene deletion in mice (Balb/cBy) showed higher levels of HDL regardless of gender or diet.[15] The mechanism underlying the relationship between HDL and ACADS is still unclear. Another research in ACADS-deficient mice also showed this gene protects mice against diet-induced obesity and insulin resistance.[2] Triglycerides, free fatty acids, cholesterol, glucose, and hepatic lipid were found to be lower in Balb/cBy mice.[17]

The *ACADS* gene is approximately 13 kb in length and has 10 exons at chromosome 12 (12q24.31).[18] Several single nucleotide polymorphisms (SNPs) of this gene have been reported.[8,18] In a genome-wide association study (GWAS), an association was found between *ACADS* rs2014355 SNP and the ratio between the short-chain acylcarnitines C3 and C4.[9] Mirkov et al also found that *ACADS* SNPs affect serum metabolomics traits: mRNA of *ACADS* in liver tissue of people with rs2014355 TC/CC than in those with TT genotype.[16] The minor C-allele of rs2014355 in the *ACADS* gene affects insulin release following oral glucose load.[4] The above data imply that *ACADS* rs2014355 genotypes will affect glucose and lipid metabolism.

However, studies that explore the effects of exercise and *ACADS* on HDL-C are limited. The purpose of this study was to investigate the association of exercise and *ACADS* rs2014355 genotypes with HDL-C.

2. Material and methods

The entire data used in this study were retrieved from the TWB database (2008–2015). Enrollment in the Taiwan biobank is restricted to Taiwanese adults between the ages of 30 and 70 with no personal history of cancer. In our study, data were available for 9684 participants (that is, 5515 physically inactive and 4169 active participants). Baseline characteristics included exercise, rs2014355 (TT, TC+CC genotypes), sex (women/men), age, smoking habits (never/former/current), drinking habits (never/former/current), BMI (normal/underweight/overweight/obese), vegetarian (no/yes), coffee-drinking habits (no/yes), and disease (coronary heart disease, hyperlipidemia, diabetes, and hypertension) status (yes/no). We obtained exercise data through TWB questionnaires and defined exercise as participating in any exercise activity for over 30 minutes per session (at least 3 times per week) for the last 3 months. Other lifestyle variables used in our analysis have been previously described.[6] Disease conditions including hyperlipidemia and coronary heart disease were determined using self-answered TWB questionnaires. Diabetes was determined by self-answered questionnaires and confirmed by a fasting blood glucose of over 126 mm Hg or HbA1c of over 6.5. Hypertension was also determined through questionnaires and confirmed by SBP and DBP of over 140 mm Hg and 90 mm Hg, respectively. All eligible TWB participants signed informed consent prior to data collection. The Institutional Review Board of Chung Shan Medical University Hospital approved this study (CS2–16114 and CS1-20009).

2.1. Statistical analysis

We performed statistical analyses using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and Plink 1.9. The rs2014355 SNP passed quality control (i.e., HWE P value $\geq$.001, minor allele frequency = 0.12, and call rate = 0.999). HDL-C levels across different exercise groups were compared using the Student t-test. Differences between categorical variables were tested using the chi-square test. Backward stepwise linear regression was used to assess the associations of rs2014355 genotypes and exercise with HDL-C levels.

3. Results

Overall, 9,684 participants were enrolled in this study (Table 1). There were 5515 physically active (exercise group) and 4169 inactive individuals (no exercise group). HDL-C levels were significantly different between the exercise and no exercise group ($P < .0001$). The mean HDL-C concentration was 52.63 mg/dl for no exercise and 54.68 mg/dl for the exercise group. Of the participants in the no-exercise group, 76.63% were those with the rs2014355 TT genotype while 23.37% were those with the TC+CC genotype. Among those in the exercise group, 78% were

Table 1

Basic characteristics of the study participants.

Variables	No exercise n = 5515	Exercise n = 4169	*P* value
HDL-C	52.6272 ± 0.1759	54.6781 ± 0.2111	<.0001
rs2014355			.1097
TT	4226 (76.63)	3252 (78.00)	
TC+CC	1289 (23.37)	917 (22.00)	
Sex			.1105
Women	2937 (53.25)	2152 (51.62)	
Men	2578 (46.75)	2017 (48.38)	
Age	46.8711 ± 0.1394	54.6006 ± 0.1579	<.0001
Cigarette smoking habit			<.0001
No	4167 (75.56)	3260 (78.20)	
Former	599 (10.86)	617 (14.80)	
Current	749 (13.58)	292 (7.00)	
Alcohol drinking habit			<.0001
No	4905 (88.94)	3698 (88.70)	
Former	149 (2.70)	176 (4.22)	
Current	461 (8.36)	295 (7.08)	
BMI			<.0001
Normal	2486 (45.08)	2072 (49.70)	
Underweight	180 (3.26)	74 (1.78)	
Overweight	1660 (30.10)	1278 (30.65)	
Obese	1189 (21.56)	745 (17.87)	
Vegetarian			.1686
No	5230 (94.83)	3979 (95.44)	
Yes	285 (5.17)	190 (4.56)	
Coffee drinking habit			.0901
No	3529 (63.99)	2737 (65.65)	
Yes	1986 (36.01)	1432 (34.35)	
Coronary heart disease			.0024
No	5464 (99.08)	4102 (98.39)	
Yes	51 (0.92)	67 (1.61)	
Hyperlipidemia			<.0001
No	5209 (94.45)	3853 (92.42)	
Yes	306 (5.55)	316 (7.58)	
Diabetes			<.0001
No	4993 (90.53)	3642 (87.36)	
Yes	522 (9.47)	527 (12.64)	
Hypertension			<.0001
No	4529 (82.12)	3088 (74.07)	
Yes	986 (17.88)	1081 (25.93)	

Continuous variables are presented as mean ± standard error and categorical variables as n (%).

Table 2

Multiple linear regression showing the association of ACADS rs2014355 and exercise with HDL-C levels.

Variables	β	*P* value
rs2014355 (ref: TT)		
TC+CC	0.45517	.1024
Exercise (ref: no)		
Yes	1.79856	<.0001
Sex (ref: Women)		
Men	−7.68782	<.0001
Age	0.04148	.0007
Cigarette smoking habit (ref: No)		
Former	−0.73999	.0600
Current	−3.29346	<.0001
Alcohol drinking habit (ref: No)		
Former	−0.73943	.2713
Current	3.34271	<.0001
BMI (ref: Normal)		
Underweight	7.43222	<.0001
Overweight	−5.14607	<.0001
Obese	−8.12695	<.0001
Vegetarian (ref: No)		
Yes	−6.18723	<.0001
Coffee drinking habit (ref: No)		
Yes	1.05275	<.0001
Coronary heart disease (ref: No)		
Yes	−2.22465	.0398
Hyperlipidemia (ref: No)		
Yes	−1.67701	.0007
Diabetes (ref: No)		
Yes	−3.92351	<.0001
Hypertension (ref: No)		
Yes	−0.95193	.0022

Table 3

Association between HDL-C and rs2014355 based on exercise habits.

	No exercise		Exercise	
Variables	β	*P* value	β	*P* value
rs2014355 (ref: TT)				
TC+CC	−0.03754	.9154	1.09785	.0146
Sex (ref: Women)				
Men	−7.87164	<.0001	−7.39905	<.0001
Age	0.05524	.0004	0.01946	.3193
Cigarette smoking habit (ref: No)				
Former	−0.50632	.3390	−1.06173	.0736
Current	−3.26175	<.0001	−3.25918	<.0001
Alcohol drinking habit (ref: No)				
Former	−0.60034	.5295	−0.92207	<.0001
Current	3.48232	<.0001	3.08553	<.0001
BMI (ref: Normal)				
Underweight	6.80027	<.0001	8.95338	<.0001
Overweight	−5.57660	<.0001	−4.63021	<.0001
Obese	−8.15255	<.0001	−8.24442	<.0001
Vegetarian (ref: No)				
Yes	−5.79936	<.0001	−6.79596	<.0001
Coffee drinking habit (ref: No)				
Yes	1.12684	.0003	0.94829	.0165
Coronary heart disease (ref: No)				
Yes	−3.17466	.0455	−1.50048	.3187
Hyperlipidemia (ref: No)				
Yes	−2.05037	.0025	−1.32929	.0682
Diabetes (ref: No)				
Yes	−3.73565	<.0001	−4.13118	<.0001
Hypertension (ref: No)				
Yes	−0.68059	.1116	−1.15985	.0109
Interaction (rs2014355*exercise)	*P* value = .0412			

those with the TT genotype while 22% were those with the TC +CC genotype. There was no significant difference in HDL-C concentrations of those with TT+CC and those with the TT genotype ($P=.1024$) (Table 2). However, HDL-C levels were significantly higher among individuals in the exercise, compared to no exercise group (β=1.79856; $P<.0001$). There was a significant interaction between *ACADS* rs2014355 and exercise on HDL-C concentration ($P=.0412$). Regression analysis showed a significant association between TC+CC genotype and HDL-C only in the exercise group (i.e., $\beta=1.09785$; *P* value = .0146). The β-value was −0.03754 ($P=.9154$) in the no-exercise group (Table 3). When no exercise and TT genotype was used as the reference group (Table 4), the β value was −0.02881, ($P=.9372$), for the TC+CC/no exercise group, 1.53846 ($P<.0001$) for the TT/exercise group, and 2.66237 ($P<.0001$) for the TC+CC/exercise group (Table 4).

4. Discussion

To our knowledge, this is the first study to examine the relationship between ACADS rs2014355 genotypes and HDL based on exercise habits. We found that the association between HDL-C and exercise differed with respect to the rs2014355 genotypes. Compared with the TT genotype, the TC+CC genotype together with exercise was more effective in improving HDL-C levels (that is, there was a 2.7 mg/dl increase in HDL-C levels of those with the TC+CC genotype compared to just 1.6 mg/dl among those with the TT genotype). In the absence of exercise, HDL-C concentrations were low and there were no differences regardless of the genotype.

A genome-wide GWAS carried out in Germany in 2010 pointed out that the metabolic capacity of the *ACADS* rs2014355 C allele is stronger than that of the TT genotype.[9] This is consistent with our study. Genes mRNA levels and their regulations/expressions are different in different tissues. Mirkov et al reported that the ACADS mRNA levels in liver tissues were higher among TC+CC (rs2014355) than in TT individuals.[16] ACADS is highly expressed in the small intestine, colon, and liver, but there is no data to show its expression in white blood cells.[7] In Taiwan biobank, DNA was extracted from white blood cells.

So far, it is well known that exercise can improve the performance of *ACADS*, HDL-C, and insulin sensitivity. Our results suggest that this phenomenon could be more pronounced in those with the minor C allele. Besides, studies by Hornbak et al in 2011 showed that the minor C-allele of rs2014355 was associated with reduced glucose-stimulated insulin released during an oral glucose tolerance test (OGTT) and may be mediated through an impaired β-oxidation of fatty acids.[4] This study also indicated that levels of HDL-C under OGTT did not differ between people with TT or TC+CC genotypes. In contrast, the studies cited above did not include exercise in their study design, as we have done. Of note, exercise plays a major role in the regulation of *ACADS*.

Our study was limited in that information on the intensity and frequency of exercise was not available in the Taiwan Biobank

Table 4

Association of HDL-C based on exercise habits and rs2014355 genotypes.

Variables	β	*P* value
Exercise, rs2014355 (ref: No exercise, TT)		
No exercise, TC+CC	−0.02881	.9372
Exercise, TT	1.53846	<.0001
Exercise, TC+CC	2.66237	<.0001
Sex (ref:Women)		
Men	−7.68390	<.0001
Age	0.04146	.0007
Cigarette smoking habit (ref: No)		
Former	−0.74611	.0579
Current	−3.29365	<.0001
Alcohol drinking habit (ref: No)		
Former	−0.75567	.2609
Current	3.35266	<.0001
BMI (ref: Normal)		
Underweight	7.42941	<.0001
Overweight	−5.15605	<.0001
Obese	−8.12641	<.0001
Vegetarian (ref: No)		
Yes	−6.19380	<.0001
Coffee drinking habit (ref: No)		
Yes	1.05097	<.0001
Coronary heart disease (ref: No)		
Yes	−2.21828	.0404
Hyperlipidemia (ref: No)		
Yes	−1.70297	.0006
Diabetes (ref: No)		
Yes	−3.92081	<.0001
Hypertension (ref: No)		
Yes	−0.93990	.0025

dataset. Further investigations in this area are recommended. HDL-C levels might be influenced by exercise type and intensity. This study adds more knowledge on exercise-related HDL-C elevation to improve cardiovascular disease.

5. Conclusions

The association between HDL-C and exercise differed based on the *ACADS* rs2014355 genotypes. Compared to the TT genotype, the TC+CC genotype in combination with exercise was associated with higher levels of HDL-C. These results suggest that people with the rs2014355 TT genotype may improve their HDL-C levels by increasing their physical activity. This might in turn help to reduce the risk of cardiovascular disease.

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