G1359A Variant of the Cannabinoid Receptor Gene (rs1049353) and Obesity-Related Traits and Related Endophenotypes: A Meta-Analysis

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Keywords

Cannabinoid receptor gene · Polymorphism · Leptin · Body mass index · Dietary intake

Abstract

Background: This study aimed to investigate the comparison of G1359A variant of cannabinoid receptor gene (rs1049353) with obesity-related traits including body mass index (BMI), fat mass (FM), fat-free mass (FFM), food-related traits, and leptin among healthy and non-healthy adults. **Methods:** We searched PubMed, Cochrane, Scopus, Web of Science, and EMBASE until December 2016 for observational studies assessing each of the anthropometric measurements, food-related traits, and leptin of 1359 G/A polymorphism of *CNR1* gene. A total of 22 studies were included in the meta-analysis comparing mean and SD differences of the anthropometric measurements, leptin, and dietary intake between GA/AA and GG genotypes. **Results:** The results showed that subjects with GA/AA genotype had significantly lower BMI (weighted mean difference = -0.59 kg/m^2 , $p < 0.001$) compared to those with the GG genotype. Dietary intake of fat, carbohydrate, and protein as well as serum levels of leptin was not significantly different between GA/AA and GG genotypes. **Conclusion:** It was revealed that subjects

with mutant polymorphism (GA/AA) of *CNR1*, compared to the wild-type group (GG), had lower BMI (although there was unexplained heterogeneity).

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Introduction

The endocannabinoid system contributes to energy homeostasis and is involved in controlling appetite and body weight [1]. This system consists of endogenous ligands and 2 G-protein coupled cannabinoid receptors (CNRs): cannabinoid type-1 (CB1) receptor is located mainly in the central nervous system and a variety of peripheral tissues including adipose tissue and CB2 receptor are found in the immune system [2]. A silent intragenic biallelic polymorphism in codon 435 of the cannabinoid receptor 1 (*CNR1*) gene, substitution of G to A at nucleotide position 1359 (1359 G/A rs1049353), was reported to be associated with several disorders like obesity [3], type 2 diabetes mellitus [4], and metabolic syndrome [5]. It is a common polymorphism among different populations, as the frequency of the rare allele (A) carriers was reported to be 24–32% in German [6] and 48.1% in Spanish [7] populations. Earlier studies reported an association of A-

allele (mutant allele) with better anthropometric measurements [8], metabolic profile [3, 7] and adipokines [9] compared to non-A allele carriers (wild type allele). However, other studies failed to find such associations [10–12]. Mixed results have been recently reported considering the association between dietary intake and different genotypes. While the intake of cholesterol and saturated fat was significantly different between genotypes [13], no significant changes in calorie and macronutrient intakes were detected [10]. Findings from clinical trials showed that hypocaloric diets resulted in different outcomes of body weight and metabolic improvement in the polymorphism groups of 1359 G/A of *CNR1* gene [14, 15]. Moreover, different study designs along with different health conditions of participants have failed to provide conclusive evidence. This study is the first meta-analysis investigating the comparison of 1359 G/A polymorphism with obesity-related traits, food-related traits, and serum leptin.

Methods

Search Strategy

Using suggested meta-analysis guidelines [16], we performed a systematic search of human studies in PubMed, Cochrane, Scopus, Web of Science, and Embase until December 2016. The following search criteria were used: (“G1359” or “1359 G/A” or “rs1049353”) and (“body mass index [BMI]” or “Quetelet index” or “fat mass [FM]” or “leptin”). To identify other relevant articles, we also reviewed reference lists of each study. No restrictions were applied for time and language. The protocol has been registered with PROSPERO (registration number CRD42017054204).

Selection Criteria

We included studies that reported distinct information according to 1359 G/A polymorphism genotype in the dominant model (G1359A and A1359A genotypes with rare allele (A) as the mutant-type group, versus G1359G as the wild-type group) for; (1) obesity-related traits including BMI, waist circumference (WC), FM and FFM; (2) food-related traits including intake of energy, carbohydrate, protein, fat, saturated fatty acid (SFA), polyunsaturated fatty acid (PUFA), monounsaturated fatty acid (MUFA), and fiber; (3) serum levels of leptin. The dominant model was used in most of the studies related to this topic, and we did not have data to assess recessive or additive models. For clinical trials and cohort studies, only baseline measurements were extracted. In effect, clinical trials were extracted as 2 separate studies according to the reported baseline data for the intervention and control groups. Since 12 out of 22 studies included in the current meta-analysis have been published by the same investigator, the absence of sample overlap in the 12 papers was verified by the author via email.

Data Extraction

Two reviewers, independently, extracted the following key data: first authors' last name, publication date, study design, research location, participants' age and gender, sample size, number of cases with

different genotypes, subjects' race and health condition, SNP detection method, mean and SD for BMI, FFM, FM, WC, leptin, and dietary intake of energy, carbohydrate, protein, fat, SFA, PUFA, MUFA, and fiber reported distinctly for mutant and wild-type groups.

Quality Assessment of Studies

Newcastle-Ottawa scale was employed to score the quality of studies included in this meta-analysis [17]. Each study received a maximum of 9 scores. The rationale behind the scores was based on the selection of study groups (mutant versus wild genotypes), comparability of groups, and the substantiation of exposure.

Statistical Analysis

The statistical analysis for calculating weighted mean difference (WMD) was performed on the mean difference and SD of the abovementioned parameters in the polymorphism groups. The relationship between variables and genotypes was presented as WMD with 95% CIs. To pool the effect sizes, the fixed effects model was used. When there was heterogeneity among data, the random effects model was used to ensure the power of the chosen model. To find the source of heterogeneity, subgroup analysis was performed. Cochran's Q test and I^2 metric were employed to evaluate between-study heterogeneity [18]. Heterogeneity was considered statistically significant if the p value was less than 0.01 or $I^2 > 50\%$. To add robustness, we conducted sensitivity analysis by omitting individual study from the model and analyze the influence of each study on the pooled effect size. The visual inspection of funnel plot and formal analysis of Egger's and Begg's test were, in turn, used to assess publication bias. Data synthesis was performed by Stata software (version 12.0; StataCorp, College Station, TX, USA). Since we evaluated 13 variables, we applied the Bonferroni correction for multiple testing; therefore, we rejected null hypothesis if the p value was <0.003 .

Results

Description of Studies

We identified 108 references from our initial search. After a 2-step screening by 2 different investigators, 22 articles met the inclusion criteria, including 10 cross-sectional [3, 7–10, 12, 13, 19–21], 4 case-control [4, 5, 22, 23], 1 cohort [24], and 7 clinical trial [14, 15, 25–29] studies (Fig. 1). Two studies were excluded as they did not illustrate the information for different genotypes [11, 30], while another study was eliminated, as it was reportedly based on the recessive model [31]. The total number of participants with GG and GA/AA genotypes was 5,133 (62.93) and 3,024 (37.07%), respectively, with the age range of 29–69. Except 2 studies that were carried out on the Asian population [5, 23], other studies were carried out on Caucasians. While most of the studies were conducted in Spain, some were conducted in Germany, Italy, China, Denmark, and Poland. The quality score of the studies ranged from 3 to 10, with a median of 7. We con-

Fig. 1. The flow diagram of the study selection process.

sidered studies with the score of 7 or greater as high-quality studies and those with the score of lower than 7 as low-quality studies (Table 1).

Pooled Analyses

Obesity-Related Traits

The meta-analysis of 27 point estimates from 22 studies was conducted on mean BMI among subjects with wild and mutant genotypes. Subjects with AA/AG genotype (mutant-type) had significantly lower BMI compared to those with GG genotype (wild-type; WMD = -0.59 ; 95% CI -1.1 to -0.075 ; $p < 0.001$; Table 2), with a significant heterogeneity ($I^2 = 73.7\%$, $p < 0.001$; Fig. 2). No single study altered the overall findings as determined by sensitivity analysis (Fig. 3).

Data combination of 16 estimates from 12 studies did not show a significant difference for FM between subjects

with wild genotype compared to those with mutant genotype (WMD = -0.23 ; 95% CI -0.87 to 0.41 ; $p = 0.48$). There was also no significant difference for fat-free mass (FFM; WMD = -0.62 ; 95% CI -1.76 to 0.53 ; $p = 0.29$). No significant heterogeneity was observed for FM or FFM either.

There were 18 effect sizes from 14 studies for mean differences included in the meta-analysis of waist circumference. No significant difference was found in mutant-type subjects compared to the wild type group (WMD = -0.55 ; 95% CI -1.54 to 0.45 ; $p = 0.28$), with no significant heterogeneity.

Food-Related Traits

The overall estimate of 6 publications reporting energy intake showed that there was no significant

Table 1. Characteristics of studies included in the meta-analysis

Fist author	Year	Country	Ethnicity	Detection method of SNP	Study design	Sample size	M/F	GG, n	GA/AA, n	BMI, kg/m ²		Quality score
										GG	GA/AA	
Gazzerro [3]	2007	Italy	Caucasian	Multiplex PCR	Cross-sectional	176	94/82	116	60	28.6±5.5	27.09±5.5	10
Aberle [30]	2008	Germany	Caucasian	PCR-RFLP	RCT	1,721	NR	1,308	413	30.1±8.9	24.8±11.8	6
De Luis [19]	2009	Spain	Caucasian	Molecular beacon	Cross-sectional	66	17/49	38	28	45.4±4.7	43.3±3.4	5
Hu [5]	2010	China	Asian	TaqMan	Case-control	382	209/173	345	37	27.25±3.55	25.98±2.35	4
de Luis [12]	2010	Spain	Caucasian	Molecular beacon	cross-sectional	60	14/46	35	25	37.8±6.9	38.1±5.9	6
de Luis [26]	2010	Spain	Caucasian	Molecular beacon	RCT	66	15/51	39	27	48.3±6.5	48.9±7.6	5
Storr [22]	2010	Germany	Caucasian	Multiplex PCR	Case-control	215	105/110	114	101	23.9±4	22.09±3.9	7
Storr [22]	2010	Germany	Caucasian	Multiplex PCR	Case-control	166	83/83	97	69	23.8±3.7	24.6±4.8	7
Frost [8]	2010	Denmark	Caucasian	TaqMan	Cross-sectional	774	774/0	377	397	24.5±2.9	24.2±3.1	9
de Luis [10]	2011	Spain	Caucasian	Molecular beacon	Cross-sectional	290	0/290	159	131	35.9±6.9	35.4±6.1	7
Wang [23]	2011	China	Asian	PCR-RFLP	Case-control	450	NR	393	57	25.61±3.83	24.44±2.83	3
de Luis [9]	2011	Spain	Caucasian	Molecular beacon	Cross-sectional	458	NR	251	207	37.2±6.5	37.1±7.2	6
de Luis [9]	2011	Spain	Caucasian	Molecular beacon	Cross-sectional	469	NR	207	262	35.6±5.7	35.1±7.3	6
De Luis [15]	2011	Spain	Caucasian	Molecular beacon	RCT	94	24/70	47	47	33.9±5.3	34.5±4.5	7
de Luis [14]	2012	Spain	Caucasian	Molecular beacon	RCT	122	NR	68	54	35.1±5.3	35.4±6.5	8
de Luis [14]	2012	Spain	Caucasian	Molecular beacon	RCT	127	NR	75	52	36.2±7.8	35.7±5.3	8
Caruso [13]	2012	Italy	Caucasian	Multiplex PCR	Cross-sectional	118	60/58	75	43	28.9±5.7	27.8±6.4	10
Aller [21]	2012	Spain	Caucasian	Multiplex PCR	Cross-sectional	70	47/23	41	29	34.4±10.3	31.5±9.3	7
De Luis [27]	2013	Spain	Caucasian	Molecular beacon	RCT	125	NR	83	42	36.8±6.6	37.8±4.5	8
De Luis [27]	2013	Spain	Caucasian	Molecular beacon	RCT	133	NR	82	51	37.7±4.8	37.4±8.2	8
Buraczynska [4]	2014	Poland	Caucasian	PCR-RFLP	Case-control	667	330/337	402	265	28.9±5.3	29.6±6.3	5
de Luis [28]	2014	Spain	Caucasian	Molecular beacon	RCT	86	44/42	51	35	34.1±6.9	31.8±5.1	7
De Luis [29]	2015	Spain	Caucasian	Molecular beacon	RCT	92	NR	46	46	35.3±4.9	35.5±4.1	8
Suarez-Pimilla [24]	2015	Spain	Caucasian	SNPLex	Cohort	65	44/21	36	29	22.53±2.16	23.48±3.07	6
de Luis [7]	2016	Spain	Caucasian	Molecular beacon	Cross-sectional	341	120/208	177	164	37.1±6.1	37.2±6.1	8
de Luis [20]	2016	Spain	Caucasian	Molecular beacon	Cross-sectional	796	0/796	454	342	37.1±6.6	36.7±6.6	4
M/F, male/female; BMI, body mass index; RCT, randomized clinical trial.												

Table 2. Results of meta-analyses

Outcome or subgroup title	No. of effect sizes	Sample size	References	WMD (95% CI)	<i>p</i> value	<i>I</i> ² , %	<i>p</i> heterogeneity
BMI, kg/m ²	27	8,227	[3–5, 7–10, 12–15, 19–29]	–0.59 (–0.11 to –0.075)	<0.001	73.7	<0.001
FM, kg	16	4,131	[7–10, 12, 14, 15, 19, 20, 27–29]	–0.23 (–0.87 to 0.41)	0.48	4.6	0.40
FFM, kg	7	1,120	[7, 10, 12, 14, 15, 28]	–0.62 (–1.76 to 0.53)	0.29	0	0.93
WC, cm	18	3,875	[5, 7, 9, 10, 12, 14, 15, 19–21, 26–29]	–0.55 (–1.54 to 0.45)	0.28	12.2	0.31
Energy, kcal/day	6	1,424	[10, 12, 13, 15, 19, 20]	–33.02 (–132.45 to 66.41)	0.52	52.9	0.06
Fat, g/day	6	1,424	[10, 12, 13, 19, 20]	–4.60 (–7.91 to –1.29)	0.006	0	0.70
SFA, g/day	5	1,330	[10, 12, 13, 19, 20]	–2.42 (–6.70 to 1.86)	0.27	91.3	<0.001
PUFA, g/day	5	1,330	[10, 12, 13, 19, 20]	–0.44 (–0.87 to –0.001)	0.05	0	0.68
MUFA, g/day	5	1,330	[10, 12, 13, 19, 20]	–0.96 (–2.38 to 0.47)	0.19	0	0.80
Carbohydrate, g/day	6	1,424	[10, 12, 13, 15, 19, 20]	–2.45 (–9.31 to 4.41)	0.49	0	0.87
Protein, g/day	6	1,424	[10, 12, 13, 15, 19, 20]	–0.60 (–2.94 to 1.75)	0.62	0	0.74
Fiber, g/day	5	1,330	[10, 12, 13, 19, 20]	–0.26 (–0.81 to 0.30)	0.37	0	0.82
Leptin, ng/mL	13	2,204	[9, 10, 12, 14, 15, 19, 21, 27, 29]	2.65 (–2.05 to 7.35)	0.27	16.95	0.15

Fig. 2. Mean difference of BMI among patients with GA/AA compared with those with GG genotype.

difference between energy intake of subjects with GA/AA genotype compared to those with GG genotype (WMD = –33.02; 95% CI –132.45 to –66.41; *p* = 0.52). No evidence of heterogeneity was found. Also, sensitivity analysis did not lead to a significant alteration in the

corresponding pooled WMD or did it provide additional information.

The combined estimate of the total fat intake from 6 studies was –4.60 g/day (95% CI –7.91 to –1.29; *p* = 0.006), with no significant heterogeneity (Fig. 4). Com-

Fig. 3. Sensitivity analysis for the mean difference of BMI among patients with GA/AA compared with those with GG genotype. BMI, body mass index.

Fig. 4. Mean difference of total dietary fat intake among patients with GA/AA compared with those with GG genotype.

pared to the mutant-type group, subjects with wild genotype consumed 4.6 g/day more dietary fat; however, this difference was not statistically significant.

When we pooled 5 studies for a meta-analysis of dietary SFA, no significant difference was observed among GA/AA genotypes compared to the GG genotype (WMD = -2.42; 95% CI -6.70 to 1.86; $p = 0.27$), with a moderate heteroge-

neity between studies ($I^2 = 45.97\%$, $p < 0.001$). A series of sensitivity analyses did not change these results (Fig. 5).

Data from 5 publications were included in the meta-analysis for mean differences of PUFA intake. There was no significant difference between GA/AA genotypes compared to the GG genotype (WMD = -0.44; 95% CI -0.87 to -0.001; $p = 0.05$).

Fig. 5. Sensitivity analysis for the mean difference of SFA among patients with GA/AA compared with those with GG genotype.

The pooled effect size for mean difference of MUFA intake estimated from 6 studies was found to be -0.96 (95% CI -2.38 to 0.47 ; $p = 0.19$).

The pooled analysis of studies reporting data on the comparison of mean dietary carbohydrate (WMD = -2.45 ; 95% CI -9.31 to 4.41 ; $p = 0.49$), protein (WMD = -0.60 ; 95% CI -2.94 to 1.75 ; $p = 0.62$), and fiber (WMD = -0.26 ; 95% CI -0.81 to 0.30 ; $p = 0.37$) showed no significant difference among the mutant genotype compared to the wild genotype group.

Serum Levels of Leptin

Findings from meta-analysis on point estimates of serum concentrations of leptin also showed no significant difference among participants with GA/AA and GG genotypes (WMD = 2.65 ; 95% CI -2.05 to 7.35 ; $p = 0.27$).

Subgroup Analysis

The subgroup analysis was done based on the quality score (measured by the Newcastle-Ottawa score) and BMI category (BMI <30 , BMI ≥ 30) when heterogeneity was significant. There were no significant results in the subgroup analysis.

Publication Bias

No significant publication biases were observed through funnel plots and Begg's test; BMI ($p = 0.82$; Fig. 6), FM ($p = 0.53$), FFM ($p = 0.18$), WC ($p = 0.97$), dietary energy ($p = 1.0$), carbohydrate ($p = 0.13$), protein

($p = 0.71$), fat ($p = 0.81$), SFA ($p = 0.81$), MUFA ($p = 0.81$), PUFA ($p = 0.46$), fiber ($p = 0.46$), and serum levels of leptin ($p = 0.54$).

Discussion

It was found that subjects with GA/AA genotype had lower BMI compared to the GG genotype group, but no significant difference was observed for FFM, FM, and WC. There were also no significant differences for consumption of total energy, fat, protein, and carbohydrate as well as dietary fiber, SFA, and PUFA. Besides, serum concentrations of leptin were not significantly different among wild and mutant genotypes.

Our findings showed that people with GA/AA genotype had lower BMI than those of the GG genotype group. Compared to lean controls, the expression of cannabinoid 1 receptors has been suggested to be higher in adipocytes of obese animals [32]. Moreover, there is a body of evidence suggesting that the mesolimbic dopaminergic system is modulated by the endocannabinoid system [33], and BMI is increased as a result of treatment with dopamine receptor agonists [34]. In addition, an increased desire to eat was attributed to cannabinoids as their contribution to enhanced reward or hedonic properties of food [35]. However, it is not clear how the G1359A polymorphic variant affects BMI, and no evidence of amino acid substitution or levels of protein ex-

Fig. 6. Funnel plot for the mean difference of BMI among patients with GA/AA compared with those with GG genotype. WMD, weighted mean difference.

pression in mutant subjects was found to contribute to these mechanisms.

Unlike BMI, no significant difference was found for important body composition indicators. One possibility to declare this inconsistency is the presence of other polymorphism in the *CNR1* gene. Total body fat and abdominal obesity were observed to be much more in patients with 3813G (rs12720071) polymorphism [36]. Researchers attempted to identify factors influencing body composition including gender. Several data detected higher levels of FM among women and larger WC among men [37], and the visceral FM was reported to increase by age in both genders [38]. Since the data could not be stratified by gender and age, it is possible that the difference in the observed BMI is partially related to age and gender differences between the groups. This might also help to explain why no differences were observed in any other parameters related to body weight or composition.

Obesity is accompanied by the loss of leptin's ability to reduce appetite and increase energy expenditure [39]. Selective CB1-receptor blockade with Rimonabant attenuates hyperleptinemia in obese subjects [40]. Since hyperleptinemia is required for the development of leptin resistance [41], a decrease in the leptin resistance contributes to the antiobesity effect of CB1 blockade. We could not find any significant difference in the serum levels of leptin among different genotypes of G1359A polymorphism. A theoretical explanation may be the fact that the participants of most studies had a mean BMI of more than 35

and, as we know, circulating concentrations of leptin are closely related to FM and BMI [42].

We included all available data on the comparison of obesity-related traits, food-related traits, and serum concentrations of leptin between G1359A variants for both healthy and non-healthy adults. Particular strengths of our study are the explanatory approach and the absence of publication bias. However, some limitations should be acknowledged for the present meta-analysis. The diversity of studies did not facilitate the performance of subgroup analysis by the participants' health condition and ethnicity. The observational approach of the meta-analysis also makes it difficult to decide about the causality. OR values were not reported in almost any of the studies to analyze the association of the G1359A polymorphism of *CNR1* with health conditions including type 2 diabetes mellitus and coronary heart diseases.

Since dietary recommendations based on whole foods are growing, future studies may focus on the genetic-based dietary advice with emphasis on dietary patterns. It is recommended that studies targeting obesity provide data for G1359A polymorphism of *CNR1*. This information would help to provide insights into which aspect(s) of obesity is influenced by the genetic variant. Future interventions and mechanistic studies in humans are required to better understand the putative relationship between G1359A and macronutrient intake.

In conclusion, the results of the present meta-analysis study showed that compared to the wild genotype group, subjects with mutant polymorphism had lower BMI.

Disclosure Statement

None of the authors had any personal or financial conflicts of interest to disclose.

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