Genetic polymorphism of the adenosine A_{2A} receptor is associated with habitual caffeine consumption[1–3]

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ABSTRACT

Background: Caffeine is the most widely consumed stimulant in the world, and individual differences in response to its stimulating effects may explain some of the variability in caffeine consumption within a population.

Objective: We examined whether genetic variability in caffeine metabolism [cytochrome P450 1A2 (*CYP1A2*) −163A→C] or the main target of caffeine action in the nervous system [adenosine A_{2A} receptor (*ADORA2A*) 1083C→T] is associated with habitual caffeine consumption.

Design: Subjects (n = 2735) were participants from a study of gene-diet interactions and risk of myocardial infarction who did not have a history of hypertension. Genotype frequencies were examined among persons who were categorized according to their self-reported daily caffeine intake, as assessed with a validated food-frequency questionnaire.

Results: The *ADORA2A*, but not the *CYP1A2*, genotype was associated with different amounts of caffeine intake. Compared with persons consuming <100 mg caffeine/d, the odds ratios for having the *ADORA2A TT* genotype were 0.74 (95% CI: 0.53, 1.03), 0.63 (95% CI: 0.48, 0.83), and 0.57 (95% CI: 0.42, 0.77) for those consuming 100–200, >200–400, and >400 mg caffeine/d, respectively. The association was more pronounced among current smokers than among nonsmokers (P for interaction = 0.07). Persons with the *ADORA2A TT* genotype also were significantly more likely to consume less caffeine (ie, <100 mg/d) than were carriers of the *C* allele [P = 0.011 (nonsmokers), P = 0.008 (smokers)].

Conclusion: Our findings show that the probability of having the *ADORA2A* 1083*TT* genotype decreases as habitual caffeine consumption increases. This observation provides a biologic basis for caffeine consumption behavior and suggests that persons with this genotype may be less vulnerable to caffeine dependence. *Am J Clin Nutr* 2007;86:240–4.

KEY WORDS Caffeine, *ADORA2A*, adenosine A_{2A} receptor gene, *CYP1A2*, cytochrome P450 1A2, genotype, epidemiology, dependence

INTRODUCTION

Caffeine is the most widely consumed stimulant in the world with an estimated 80–90% of adults reporting regular consumption of caffeine-containing beverages and foods (1). Caffeine intakes vary widely from country to country and from person to person (2, 3). The pleasurable and reinforcing effects of caffeine have led to some concern that it is a potential drug of dependence (1, 4, 5). However, some persons experience anxiety, tachycardia, nervousness. or other adverse effects with low-to-moderate intakes of caffeine (4). These differences in response to caffeine may explain some of the variability in caffeine intake within a population (1, 6, 7). Although demographic, psychosocial, health-related, and environmental factors such as smoking have been linked to habitual caffeine consumption (8–11), there is some evidence that genetic factors are also important (12–15). Twin studies report heritability estimates of up to 77% for caffeine use, toxicity, tolerance, and withdrawal symptoms (12–15), but the specific genes involved are not yet identified.

Caffeine is metabolized primarily by cytochrome P450 1A2 (CYP1A2) in the liver through an initial N^3-demethylation (16, 17). CYP1A2 accounts for ≈95% of caffeine metabolism and shows wide variability in enzyme activity between persons (17–19). An A to C substitution at position −163 (rs762551) in the *CYP1A2* gene decreases enzyme inducibility as measured by plasma or urinary caffeine-to-metabolite ratios after a dose of caffeine (20). Carriers of the −163*C* allele can be considered slow caffeine metabolizers, whereas persons who are homozygous for the −163*A* allele are more rapid caffeine metabolizers (20). It is not clear, however, whether *CYP1A2* genotype alters caffeine consumption.

In amounts typically consumed from dietary sources, caffeine antagonizes the actions of adenosine at the adenosine A_{2A} receptor (1), which was shown to play an important role in the stimulating and reinforcing properties of caffeine (21, 22). $A_{2A}R$ knockout mice have been found to have less of an appetite for caffeine than do their wild-type littermates (23). A C-to-T substitution at nucleotide position 1083 (rs5751876) (also referred to as 1976C→T) in the *ADORA2A* gene, which codes for the A_{2A}

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receptor, was associated with caffeine-induced anxiety among nonhabitual caffeine consumers (24). Persons who were homozygous for the 1083*T* allele experienced greater anxiety after consuming 150 mg caffeine (24). However, it is not known whether persons with that genotype limit their habitual caffeine intake because of such adverse physiologic effects. The purpose of the present study was to examine whether genetic variability in caffeine metabolism (ie, *CYP1A2*) or the major target of caffeine action in the central nervous system (CNS) (ie, *ADORA2A*) is associated with habitual caffeine consumption in a free-living population.

SUBJECTS AND METHODS

Study design and participants

Details of the study design (case-control study) and participants were reported previously (25). Subjects were self-described Hispanic Americans living in Costa Rica and participating in a study of gene-diet interactions and risk of myocardial infarction (MI). Eligible cases were men and women who were survivors of a first acute MI between 1994 and 2004. Cases were ineligible if they died during hospitalization, were ≥75 y old on the day of their first MI, were physically or mentally unable to answer the questionnaire, or had a previous hospital admission related to cardiovascular disease. One control for each case, matched for age (±5 y), sex, and area of residence (county), was randomly selected with the use of information available at the National Census and Statistics Bureau of Costa Rica. Because of the comprehensive social services provided in Costa Rica, all persons living in the catchment areas had access to medical care without regard to income. Controls were ineligible if they were physically or mentally unable to answer the questionnaires or if they had a previous hospital admission related to MI or other cardiovascular disease. Participation for eligible cases and controls was 98% and 88%, respectively. For the current study, all subjects reporting a history of hypertension were excluded because these persons may have reduced their caffeine intake on the advice of their physician. Indeed, a significantly ($P < 0.001$) smaller proportion of persons with a history of hypertension (14%) than of persons with no history of hypertension (21%) reported consuming >400 mg caffeine/d. All subjects were visited at their homes for the collection of information on diet and medical history, for anthropometric measurements, and collection of biologic specimens.

Cases and controls gave written informed consent. The study was approved by the ethics committees of the Harvard School of Public Health and the University of Costa Rica, the Office of Protection from Research Risk at the National Institutes of Health, and the ethics review committee at the University of Toronto.

All data were collected during an interview with trained fieldworkers who used 2 questionnaires. The questionnaires consisted of closed-ended questions about smoking, sociodemographic characteristics, socioeconomic status, physical activity, diet, and medical history, including use of medication and personal history of diabetes and hypertension. Dietary intake was collected with the use of a 135-item semiquantitative food-frequency questionnaire specifically developed and validated to assess dietary intake during the previous year in the Costa Rican population (26). For cases, average intake represented the year preceding their MI. Included in the food-frequency questionnaire were questions about the consumption of caffeinated coffee, tea, cola beverages, and chocolate. Total caffeine intake was calculated with the use of the US Department of Agriculture food-composition data file. Subjects were categorized into 4 groups with self-reported caffeine intakes of <100, 100–200, >200–400, or >400 mg/d.

Genotyping

Blood samples were collected in the morning at the subject's home after an overnight fast and were centrifuged at 1430 × *g* for 4 min at 20 °C to separate the plasma and leukocytes for DNA isolation by standard procedures. The *CYP1A2* −163A→C (rs762551) and *ADORA2A* 1083C→T (rs5751876) polymorphisms were detected by restriction-fragment length polymorphism–polymerase chain reaction as described previously (27, 28). Genotype distributions among subjects did not deviate from Hardy-Weinberg equilibrium ($P > 0.05$).

Statistical analysis

All data were analyzed with the use of SAS software (version 8.2; SAS Institute, Cary, NC). DNA was available from 2873 subjects with no history of hypertension. Because caffeine consumption data were based on the year before incidence of MI, cases with nonfatal MI as well as population-based controls were included in the analyses. Nine subjects with missing data on caffeine intake and smoking status and 129 who could not be genotyped for either *CYP1A2* or *ADORA2A* were also excluded from the study. These exclusions left a total sample size of 2735 for the final analyses.

Significant differences in the distribution of lifestyle characteristics by *CYP1A2* and *ADORA2A* genotype were tested with the use of Pearson's chi-square test (categorical variables) or *t* tests (continuous variables). Analyses were conducted with the use of a dominant *CYP1A2 C* allele model with *AC* and *CC* genotypes (slow metabolizers) combined, because the 2 groups have a similar rate of caffeine metabolism (20). For *ADORA2A*, results are presented with the use of a recessive *ADORA2A T* allele model with *CC* and *CT* genotypes combined because no differences in caffeine-induced anxiety were reported between persons with the *CC* or *CT* genotype (24). Odds ratios and 95% CIs were estimated by unconditional logistic regression to determine the relation between caffeine consumption and the risk of having the *CYP1A2 C* allele or *ADORA2A TT* genotype with the lowest caffeine intake (<100 mg/d) as the reference group. A test for linear trend was calculated across categories of caffeine intake for each polymorphism by treating caffeine intake as an ordinal variable. Pearson's chi-square test with 1 df was used to compare the proportion of light caffeine consumers (ie, persons consuming <100 mg caffeine/d) among each genotype. Nonsmokers (never or past smokers) and current smokers were examined separately because smokers metabolize caffeine more rapidly than nonsmokers, and smokers may respond differently to the stimulating effects of caffeine as a result of the interaction of the A_{2A} receptor with the dopamine D_2 receptor, which plays a role in the behavioral effects of both caffeine and nicotine (1). Caffeine-smoking interactions were tested by comparing −2 log (likelihood) ratios from a model with caffeine intakes and smoking as main effects only and from another that included their interaction term. All statistical analysis were 2-sided, and *P* values < 0.05 were considered significant.

TABLE 1
Subject characteristics by cytochrome P4501A2 (*CYP1A2*) and adenosine A_{2A} receptor (*ADORA2A*) genotype[1]

Characteristic	*CYP1A2* − 163A → C			*ADORA2A* 1083C → T		
	AA (n = 1241)	*AC* (n = 1214)	*CC* (n = 280)	*CC* (n = 611)	*CT* (n = 1288)	*TT* (n = 836)
Age (y)	57.0 ± 11.22[2]	56.8 ± 11.7	56.3 ± 10.9	57.4 ± 11.5	56.6 ± 11.3	56.7 ± 11.6
Male (%)	79	81	84	80	81	79
Urban residence (%)	74	74	72	75	74	73
Waist-to-hip ratio						
Men	0.98 ± 0.06	0.98 ± 0.06	0.98 ± 0.05	0.98 ± 0.61	0.98 ± 0.06	0.98 ± 0.06
Women	0.88 ± 0.06	0.88 ± 0.06	0.87 ± 0.08	0.88 ± 0.07	0.88 ± 0.06	0.88 ± 0.06
Smoking status (%)						
Never or past smoker	65	63	67	61	67	64
1–9 cigarettes/d	10	9	9	10	9	10
≥10 cigarettes/d	25	28	24	29	24	26
Current alcohol consumption (%)	52	56	58	51	54	57
Income (US$/mo)	528 ± 401	543 ± 405	577 ± 404	513 ± 399	546 ± 393	550 ± 421
Secondary education or higher (%)	39	41	43	37	42	41
Physical activity (METs)	1.58 ± 0.76	1.62 ± 0.75	1.49 ± 0.70	1.58 ± 0.76	1.60 ± 0.76	1.58 ± 0.71
History of diabetes (%)	13	12	11	12	13	11

[1] METs, metabolic equivalent tasks. No significant differences were observed between genotypes for any characteristics based on Pearson's chi-square test (categorical variables) or *t* tests (continuous variables).
[2] $\bar{x}$ ± SD (all such values).

RESULTS

Subject characteristics based on *CYP1A2* and *ADORA2A* genotype are presented in **Table 1**. *CYP1A2* genotype frequencies did not differ significantly across categories of caffeine intake (**Table 2**). Compared with persons consuming <100 mg caffeine/d, the odds ratios of carrying the *CYP1A2* −163*C* allele were 0.88 (95% CI: 0.53, 1.47), 0.84 (0.55, 1.29), and 1.06 (0.66, 1.68) in those consuming 100–200, >200–400, and >400 mg caffeine/d, respectively (P for trend = 0.38). Similar results were observed among current smokers and nonsmokers. We next examined whether persons consuming different amounts of caffeine varied genetically at the A_{2A} receptor, the main target of caffeine action in the CNS. Compared with persons consuming <100 mg caffeine/d, the odds ratios of having the *ADORA2A* 1083*TT* genotype were 0.74 (0.53, 1.03), 0.63 (0.48, 0.83), and 0.57 (0.42, 0.77) in those consuming 100–200, >200–400, and >400 mg caffeine/d, respectively (P for trend < 0.001; **Table 3**). This association was more pronounced among current smokers than among nonsmokers (P = 0.07 for caffeine-smoking interaction). Among smokers, the odds ratios of having the *ADORA2A* 1083*TT* genotype were 0.77 (0.37, 1.66), 0.47 (0.25, 0.86), and 0.37 (0.12, 0.70) in those consuming 100–200, >200–400, and >400 mg caffeine/d, respectively. We next examined whether those with the *ADORA2A* 1083*TT* genotype limit their caffeine intake; we found that persons with this genotype were significantly (P = 0.0007) more likely to consume <100 mg caffeine/d than were carriers of the *ADORA2A* 1083*C* allele (**Figure 1**).

TABLE 2
Odds ratio of having the cytochrome P4501A2 (*CYP1A2*) − 163*C* allele for caffeine intake among nonsmokers and current smokers[1]

Caffeine intake	*CYP1A2* genotype		Odds ratio (95% CI)
	AA	*AC* + *CC*	
	n (%)		
All subjects			
<100 mg/d	108 (43)	142 (57)	1.00
100–200 mg/d	190 (49)	200 (51)	0.88 (0.53, 1.03)
>200–400 mg/d	694 (46)	814 (54)	0.84 (0.55, 1.29)
>400 mg/d	249 (42)	338 (58)	1.06 (0.66, 1.68)
P for trend			0.38
Nonsmokers			
<100 mg/d	91 (44)	114 (56)	1.00
100–200 mg/d	146 (47)	166 (53)	1.03 (0.59, 1.80)
>200–400 mg/d	472 (47)	533 (53)	0.85 (0.52, 1.37)
>400 mg/d	104 (42)	141 (58)	1.19 (0.67, 2.11)
P for trend			0.80
Current smokers			
<100 mg/d	17 (38)	28 (62)	1.00
100–200 mg/d	44 (56)	34 (44)	0.32 (0.07, 1.41)
>200–400 mg/d	222 (44)	281 (56)	0.83 (0.31, 2.19)
>400 mg/d	145 (42)	197 (58)	0.97 (0.36, 2.61)
P for trend			0.40

[1] Results were determined by unconditional logistic regression.

DISCUSSION

Although caffeine is the most widely consumed stimulant in the world, there is large interindividual variability in its consumption (1–3). This variability may, in part, be due to individual differences in response to the stimulating effects of caffeine (1, 6, 7). Twin studies have suggested that genetic factors play an important role in determining habitual caffeine consumption and response to caffeine (12–15). However, the specific genes involved are not yet identified. In the present study, we examined whether genetic polymorphisms affecting caffeine metabolism or the main site of caffeine action influence habitual caffeine consumption in a free-living population. Our findings show that the probability of having the *ADORA2A* 1083*TT* genotype decreases as the caffeine intake increases in a population, and that persons with that genotype are more likely to limit their caffeine

TABLE 3
Odds ratio of having the adenosine A_{2A} receptor (*ADORA2A*) 1083*TT* genotype for caffeine intake among nonsmokers and current smokers[1]

Caffeine intake	*ADORA2A* genotype		Odds ratio (95% CI)
	CC + CT	*TT*	
	n (%)		
All subjects			
<100 mg/d	150 (60)	100 (40)	1.00
100–200 mg/d	261 (67)	129 (33)	0.74 (0.53, 1.03)
>200–400 mg/d	1062 (70)	446 (30)	0.63 (0.48, 0.83)
>400 mg/d	426 (73)	161 (27)	0.57 (0.42, 0.77)
P for trend			<0.001
Nonsmokers			
<100 mg/d	127 (62)	78 (38)	1.00
100–200 mg/d	216 (69)	96 (31)	0.72 (0.50, 1.05)
>200–400 mg/d	714 (71)	291 (29)	0.66 (0.49, 0.91)
>400 mg/d	174 (71)	71 (29)	0.66 (0.45, 0.99)
P for trend			0.03
Current smokers			
<100 mg/d	23 (51)	22 (49)	1.00
100–200 mg/d	45 (58)	33 (42)	0.77 (0.37, 1.66)
>200–400 mg/d	348 (69)	155 (31)	0.47 (0.25, 0.86)
>400 mg/d	252 (74)	90 (26)	0.37 (0.12, 0.70)
P for trend			<0.001

[1] Results were determined by unconditional logistic regression. $P = 0.07$ for caffeine × smoking interaction was determined by the −2log ratio test.

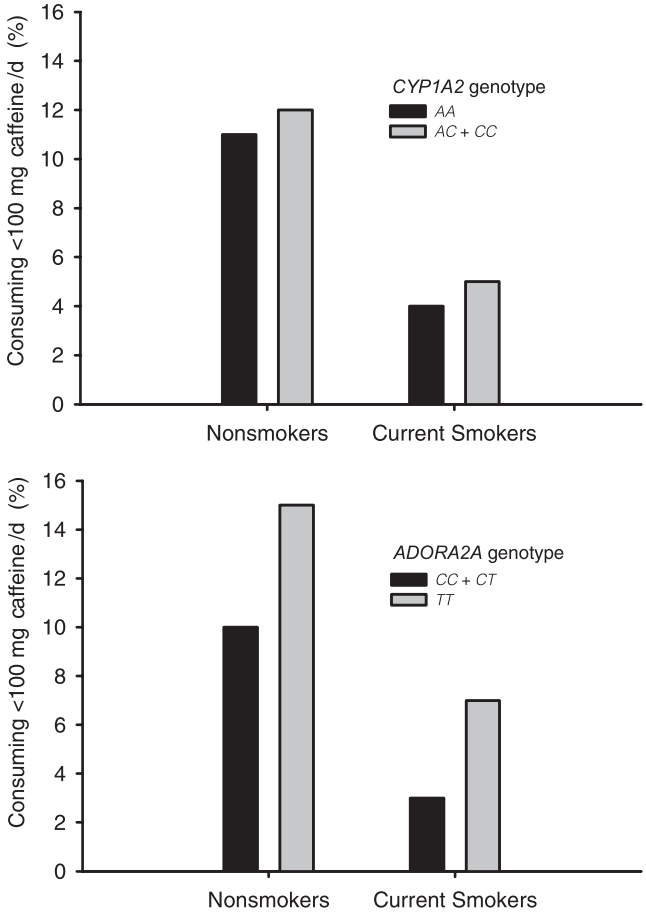

FIGURE 1. Frequency of nonsmokers and current smokers consuming <100 mg caffeine/d by cytochrome P4501A2 (*CYP1A2*) genotype [$P = 0.62$ for nonsmokers (11.1% compared with 12.0%) and $P = 0.32$ for current smokers (4.0% compared with 5.2%)] and adenosine A_{2A} receptor (*ADORA2A*) genotype [$P = 0.011$ for nonsmokers (10.3% compared with 14.6%) and $P = 0.008$ for current smokers (3.4% compared with 7.3%)]. Results are from Pearson's chi-square test with 1 df. The *ADORA2A* × smoking interaction was not significant for either genotype.

intake. However, we found no association between the *CYP1A2* −163A→C polymorphism and caffeine intake. This is consistent with our previous study showing no differences in *CYP1A2* genotype frequencies across categories of coffee intake (25). Although coffee is the main source of caffeine in this population (>90% of total caffeine intake), our previous study included subjects with a history of hypertension who may have been avoiding caffeine because of its link with high blood pressure (29). These observations suggest that, for caffeine consumption behavior, persons may not be sensitive to differences in the rate of caffeine metabolism, but they appear to be sensitive to differences in the interaction between caffeine and the adenosinergic system.

Previous studies have identified numerous environmental factors that are associated with caffeine consumption, many of which have been accounted for in observational studies of caffeinated beverage consumption and various health outcomes. Because our findings suggest that the *ADORA2A* 1083C→T polymorphism is associated with caffeine consumption within a population, this polymorphism may be a potential genetic confounder in these observational studies.

A_{2A} receptor–mediated adenosinergic neuromodulation was implicated in the development of various neurologic disorders, such as Parkinson's disease, schizophrenia, and panic disorder. Studies have examined the association between the *ADORA2A* 1083C→T polymorphism and the risk of these disorders (30, 31), but findings have been inconsistent. On the basis of Mendel's principle of independent inheritance, these studies reasonably assume that the *ADORA2A* 1083C→T polymorphism is a marker of A_{2A} receptor function, which is unlikely to be associated with diet or other lifestyle characteristics (32). Therefore, any difference in risk should provide evidence for the role of the A_{2A} receptor in the development of these disorders. Although *ADORA2A* genotype may reflect A_{2A} receptor function, our findings show that it is also associated with caffeine consumption, thereby violating the assumption of independence. As a result, caffeine consumption may be a confounder in studies examining the main effect of *ADORA2A* genotype on various health outcomes.

Debate is ongoing as to whether caffeine is a potential drug of dependence (1, 4). The 10th edition of the *International Statistical Classification of Diseases and Related Health Problems* from the World Health Organization recognizes a diagnosis of substance dependence due to caffeine, but the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* from the American Psychiatric Association does not. Caffeine elicits pleasurable and reinforcing effects in some persons that may lead to dependence (1, 4, 5). Other persons, however, experience anxiety, tachycardia, nervousness, or other adverse effects with low-to-moderate intakes of caffeine, and they are unlikely to develop dependence (1, 4). A polymorphism of the *ADORA2A* gene was previously associated with caffeine-induced anxiety (24), and we now show that persons with this genotype limit their

caffeine intake. This observation provides a biological basis for caffeine consumption behavior and suggests that persons with this genotype may be less vulnerable to caffeine dependence.

Our results are consistent with evidence showing the important role that behavioral responses to caffeine play in habitual caffeine consumption (1, 6, 7). However, the role of other genetic or environmental factors affecting caffeine consumption cannot be excluded. For example, genetic differences in taste were shown to affect how persons rate the bitter taste of caffeine, which may in turn affect their preference for caffeinated beverages (33). We excluded persons with a history of hypertension, but some persons may avoid caffeinated beverages because of other perceived adverse health effects. Finally, the social context in which caffeinated beverages are consumed could also contribute to habitual caffeine consumption. These factors, however, would have attenuated the effect of *ADORA2A* genotype on caffeine consumption.

In summary, genetic variation in the A_{2A} receptor, the main target of caffeine action in the CNS, is associated with caffeine consumption in a free-living population. The association between *ADORA2A* genotype and caffeine consumption suggests that this genetic variant might be a confounder in observational studies that relate caffeine intake to certain health outcomes. Variation in the adenosinergic system also may be an important factor in studies of a genetic predisposition to caffeine dependence, a subject of ongoing debate (1, 5).

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