Denden *et al.*
Bulletin of the National Research Centre (2023) 47:20
https://doi.org/10.1186/s42269-023-00978-2

Bulletin of the National Research Centre

RESEARCH

Open Access

Beverage preference (coffee vs. tea) according to *CYP1A2* gene rs2470893 SNP genotypes in the Tunisian population

Sabri Denden[1,2*], Mohamed Hichem Sellami[3], Ridha Kibech[3], Amel Haj Khelil[1] and Mohamed Hédi Hamdaoui[2,4]

Abstract

Background Caffeine intake has been positively or negatively associated with the risk of chronic disease. Genome-wide association studies identified single-nucleotide polymorphisms (rs2472297 and rs2470893) in Cytochrome P450 1A2 (CYP1A2) gene that are involved in habitual caffeine intake. In this study, we investigated the association of common *CYP1A2* SNPs (rs762551, rs2472297 and rs2470893) with most consumed caffeinated beverages intake (coffee and tea) in the Tunisian population. Five hundred and twenty healthy blood donors were enrolled. Coffee and tea intake data were extracted from dietary questionnaires of the participants. Genotyping was performed using PCR–RFLP. $p < 0.05$ was considered as statistically significant.

Results There were no significant genetic effects of rs762551 and rs2472297 SNPs on coffee ($p = 0.083$ and $p = 0.70$) or tea ($p = 0.49$ and $p = 0.49$) consumption, respectively. However, rs2470893 SNP A carriers displayed higher coffee consumption [$p = 0.001$, OR (95% CI) 1.46 (1.16–1.86)] and lower tea consumption [$p = 0.001$, OR (95% CI) 0.80 (0.70–0.97)]. After stratification by confounding factors, the genetic effect was observed in women (1.2% of variation in coffee intake and 9.6% of variation in tea intake), subjects ≤ 35 years (1.5% of variation in coffee intake) and nonsmokers (1.4% of variation in tea intake).

Conclusions Our data are consistent with a beverage preference (coffee vs. tea) according to rs2470893 SNP genotypes (A carriers vs. GG). Furthermore, genetic variation is significant at the condition of lower CYP1A2 enzyme activity (among women, nonsmokers and younger age groups).

Keywords Coffee, Tea, Habitual consumption, *CYP1A2* SNPs

Background

There is a particular interest in the potential effects of caffeine consumption on health, as long-term caffeine intake has been associated with cardiovascular diseases, diabetes, neurodegenerative diseases and cancers (Rodak et al. 2021). Indeed, caffeine consumption has gained more attention from the public as fears of possible negative consequences of coffee drinking have been increasing. The most commonly consumed forms of caffeine are tea and coffee. In Tunisia, these beverages are the most consumed drinks after water. Indeed, national studies stated that individual consumption is

*Correspondence:
Sabri Denden
denden_sabri@yahoo.fr
[1] Laboratory of Human Genome and Multifactorial Diseases (LR12ES07), Faculty of Pharmacy of Monastir, University of Monastir, Monastir, Tunisia
[2] High School for Health Sciences and Technicals, University of Tunis El Manar, Bab-Souika, B.P. 176, 1006 Tunis, Tunisia
[3] Blood Transfusion Department, National Blood Transfusion Center of Tunis, University of Tunis El Manar, Tunis, Tunisia
[4] Research Unit on the Antioxidant Compounds, Oxidative Stress, Trace Elements and Metabolic Diseases, High School for Health Sciences and Technicals, University of Tunis El Manar, Tunis, Tunisia

at an average of 0.8 kg of coffee and 1 kg of tea per year (National Institute of Statistics 2013). Coffee is a predominant drink in Europe, both in North and South America, and Algeria. Whereas tea is the most preferred in Great Britain, Asia and Morocco (Euromonitor International report 2017). Although historical, cultural and psychosocial factors are relevant for such preference, it was reported that liking a particular source of caffeine (from tea or coffee) could also be due to a specific genetic background (Cornelis and van Dam 2021). Several external factors (such as smoking (Treur et al. 2016)) may additionally influence habitual caffeine consumption, but twin studies have evidenced that there are genetic determinants linked to habitual caffeine intake (Vink et al. 2009). Recent studies reported single-nucleotide polymorphisms (SNPs) at different loci (*CD8*, *AHR*, *CYP1A2,* and *CYP2A6*) that were associated with caffeine metabolites (Cornelis et al. 2016). However, it is well known that more than 95% of caffeine is metabolized by the CYP1A2 enzyme (Thorn et al. 2012). An SNP in the *CYP1A2* gene, rs762551, was first described as altering enzyme activity, as C allele carriers showed reduced activity of the enzyme (Sachse et al. 1999). However, the relationship between rs762551 SNP and high caffeine consumption is not established, owing to controversial data obtained from GWAS (Amin et al. 2012; Sulem et al. 2011; Rodenburg et al. 2012), candidate gene association studies (Cornelis et al. 2007) and meta-analyses (Denden et al. 2016). Genome-wide association studies (GWAS) on habitual coffee intake (Amin et al. 2012; Sulem et al. 2011; Cornelis et al. 2011, 2015) reported other *CYP1A2* gene SNPs reaching GWAS significance, rs2472297 and rs2470893, located at the *CYP1A1-CYP1A2* genes junction. In the present study, we investigated the association between common *CYP1A2* SNPs (rs762551, rs2472297 and rs2470893) and caffeinated beverages (coffee and tea) intake in the Tunisian population and examined the genetic association modification by age, gender or smoking status as these factors have been shown to influence habitual caffeine intake. Furthermore, we analyzed the evidence for any coffee or tea preference according to SNPs genotypes.

Methods

Study design and participants

The individuals enrolled in this study were 520 healthy blood donors who attended the National Blood Transfusion Center of Tunis between 2016 and 2017. Subjects were excluded if they reported suffering from any chronic disease (hypertension and diabetes). Information on demographic and lifestyle factors was provided through questionnaires. Participants were 405 males and 115 females aged 18–61 years. The categories of smoking status were never-smokers (37.86%), former smokers (11.65%) and smokers (50.48%). Pack years mean (SD) was 7.80 (10.66) ranging from 0 to 46. The study was approved by the Ethics Committee of the National Blood Transfusion Center of Tunis and informed consents were obtained from the participants.

Assessment of coffee, tea and caffeine intake

Coffee and tea intake data were extracted from dietary questionnaires of participants, asked about how many cups of drink/day/week they had consumed during the previous year. We estimated that the caffeine content was 100 mg/cup of coffee (per 50 mL serving) and 174 mg/cup of tea (per 100 mL serving) according to published data on espresso (the most consumed coffee form) caffeine content (Hammad et al. 2015) and our previous study on green tea decoction (the most consumed tea form) caffeine content (Hamdaoui et al. 2016). The total caffeine intake was calculated as follows: Total caffeine (mg/day) = (Number of coffee cups/day × 100 mg/cup) + (Number of tea cups/day × 174 mg/cup).

Genotyping

Blood samples were collected and DNA was extracted by using the standard salting-out method.

Genotyping for rs762551, rs2472297 and rs2470893 SNPs was performed by RFLP-PCR. rs762551 SNP genotyping was conducted as previously described (Cornelis et al. 2004). For rs2472297 and rs2470893 SNPs genotyping, DNA was amplified using the primer pairs: (5′-AGA GCTTCTGGACTGACCCT-3′ and 5′-ACACTTCTA GGAGCACTTGGC-3′ for rs2472297 SNP) and (5′-CCT CACATAATCCGTACGCCT-3′ and 5′-TCCCATTCC GGTCAT ATGCG-3′ for rs2470893 SNP). PCR products were then digested with *Alw26I* and *HhaI* restriction enzymes, respectively.

Statistical analyses

Data analysis was performed with SPSS software version 24 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered as statistically significant. Genotype distributions for each SNP were tested for the deviation from Hardy–Weinberg equilibrium by Pearson's chi-square test. Subject characteristics were compared between groups by using Student's t-test or Pearson's chi-square test where appropriate. Coffee and tea intakes were compared according to smoking status (never plus former smokers (nonsmokers) vs. current smokers (smokers)), age (≤ mean age (35 years) vs. > mean age) and gender (men vs women) by using Student t test. Dominant rs2472297, rs2470893 and rs762551 minor allele models and a

recessive rs762551 minor allele model were assumed for SNPs effects. *p* values were calculated by using linear regression where the number of cups or the total caffeine intake was the dependent variable and the SNP genotype as the independent variable. Gender, age and smoking status were used as covariates. ORs, 95% CIs and effect sizes (partial eta squared, η^2_p) were given for significant effects. Sensitivity analysis was conducted using stratification by smoking status, mean age and gender, in order to investigate evidence for confounding variables genetic effect modification. Main effect and two-way interaction models were used to evaluate main and interactions effects of genotype, smoking status, age and gender on drink consumption. Beverage preference according to genotypes was further analyzed by calculating chi-square test ORs of drinking only coffee compared to drinking only tea and drinks consumption correlation in the whole sample and according to genotypes using Pearson's correlation test.

Results

All genotypes were distributed according to Hardy–Weinberg equilibrium (Table 1). Subject characteristics according to SNPs genotypes are presented in Table 2. Carriers of the rs2470893 A allele showed higher mean age ($p=0.005$) as compared to rs2470893 GG carriers, but there was no significant difference in gender distribution between genotypes. In addition, rs2470893 A allele carriers were almost nonsmokers ($p=0.026$) with lower pack years mean ($p=0.020$). rs762551CC genotype carriers did not show any relationships with smoking status ($p=0.11$) although they were almost the heaviest smokers (pack years mean of 16.40 as compared to A carriers, 7.54; $p=0.007$).

Table 1 Allelic and genotypic frequencies of rs2470893, rs2472297 and rs762551 SNPs

SNP	Major allele (1) (frequency)	Minor allele (2) (frequency)	Genotype (11) *N*(frequency)	Genotype (12) *N*(frequency)	Genotype (22) *N*(frequency)	*p**
rs2470893	G (0.894)	A (0.106)	415 (0.798)	100 (0.192)	5 (0.009)	0.70
rs2472297	C (0.955)	T (0.045)	475 (0.913)	43(0.082)	2 (0.003)	0.34
rs762551	A (0.684)	C (0.315)	236 (0.453)	240 (0.461)	44 (0.084)	0.11

**p*: Hardy–Weinberg Equilibrium p of Pearson's chi-square test

Table 2 Subject characteristics according to SNPs genotypes

SNP genotype	Age Mean (SD)	Gender Male/female	Smoking status NS (*N*)/S (*N*)*	Pack years Mean (SD)
rs2470893 G > A				
GG (*N* = 415)	35.16 (10.56)	325/90	197/218	8.29 (11.09)
GA + AA (*N* = 105)	38.63 (11.63)	80/25	63/42	5.90 (8.55)
P	0.005[a]	0.69[b]	0.022[b]	0.020[a]
rs2472297 C > T				
CC (*N* = 475)	35.80 (10.59)	365/110	242/233	8.32 (10.95)
CT + TT (*N* = 45)	36.37 (13.54)	40/5	18/27	1.87 (2.11)
P	0.79[a]	0.063[b]	0.16[b]	0.000[a]
rs762551 A > C				
AA (*N* = 236)	35.58 (10.35)	193/43	106/130	6.97 (10.46)
AC + CC (*N* = 284)	36.48 (11.75)	212/72	154/130	8.91 (11.17)
p	0.39[a]	0.065[b]	0.034[b]	0.59[a]
rs762551 A > C				
AA + AC (*N* = 476)	35.80 (10.94)	370/106	243/233	7.54 (10.43)
CC (*N* = 44)	40.00 (13.23)	35/9	17/27	16.40 (14.74)
p	0.10[a]	0.78[b]	0.11[b]	0.007[a]

*NS (Nonsmoker) versus S (Smoker)

[a] Student *t* test

[b] Pearson chi-square test

Table 3 The effect of SNP genotypes on beverage and total caffeine intake

SNP genotype	Beverage intake		Total caffeine (mg/day) Mean (SD)
	Number of coffee cups/day mean (SD)	Number of tea cups/day mean (SD)	
rs2470893 A > G			
GG (*N* = 415)	1.40 (1.19)	0.34 (0.63)	201.25 (156.68)
*GA + AA (*N* = 105)	1.70 (1.17)	0.16 (0.31)	199.62 (116.55)
p	0.025	0.006	0.92
OR (95% CI)	1.33 (1.03–1.72)	0.83 (0.73–0.94)	–
η^2_p	0.010	0.015	–
p^a	0.001	0.001	–
OR (95% CI)	1.46 (1.16–1.86)	0.80 (0.71–0.97)	–
η^2_p	0.022	0.024	–
rs2472297 C > T			
CC (*N* = 475)	1.46 (1.21)	0.31 (0.60)	201.26 (152.86)
*CT + TT (*N* = 45)	1.53 (0.96)	0.25 (0.41)	197.33 (106.52)
p	0.70	0.49	0.86
rs762551 A > C			
AA (*N* = 236)	1.49 (1.14)	0.23 (0.49)	191.30 (134.72)
*AC + CC (*N* = 284)	1.47 (1.24)	0.31 (0.60)	202.56 (162.21)
p	0.81	0.11	0.41
rs762551 A > C			
AA + AC (*N* = 476)	1.43 (1.16)	0.28 (0.59)	193.65 (149.22)
*CC (*N* = 44)	2.16 (1.45)	0.21 (0.37)	253.93 (158.24)
p	0.001	0.49	0.033
OR (95% CI)	2.06 (1.33–3.21)	–	6.68 (5.16–115.58)
η^2_p	0.022	–	0.010
p^a	0.083	–	0.55
OR (95% CI)	–	–	–
η^2_p	–	–	–

*Risk genotype

[a] Adjusted for age, gender and smoking status

Association of CYP1A2 genotypes with beverage and total caffeine intakes

The effect of SNP genotypes on beverage and total caffeine intakes is summarized in Table 3. Coffee intake was 0.30 cups/day higher in rs2470893 A allele carriers [*p* value adjusted for age, gender and smoking status $p^a = 0.001$, OR (95% CI) 1.46 (1.16–1.86)], whereas no significant effect on coffee intake was detected for rs2472297 SNP ($p = 0.70$). rs762551 CC carriers showed significantly increased coffee consumption in univariate analysis [$p = 0.001$, OR (95% CI) 2.06 (1.33–3.21)] but not in multivariate analysis ($p^a = 0.083$). Tea consumption, also, did not show any relationships with rs762551 ($p = 0.49$) and rs2472297 ($p = 0.49$) genotypes, but, interestingly, it was − 0.18 cups/day lower in rs2470893 A allele carriers [$p^a = 0.001$, OR (95% CI) 0.80 (0.70–0.97)]. The analysis, conducted for total caffeine intake, showed significant effect only in rs762551 CC carriers [$p = 0.033$, OR (95% CI) 6.68 (5.16–115.58)], but not at the multivariate level ($p^a = 0.55$).

Gender, age and smoking effects on beverage intake

The univariate analysis showed that coffee intake was higher by 1.24 cups/day in smokers ($p = 0.000$) and by 0.39 cups/day in men ($p = 0.002$) but it did not differ between age groups ($p = 0.88$). Tea intake increased in women (+ 0.17 cups/day, $p = 0.008$), subjects older than 35 years (+ 0.24 cups/day, $p = 0.000$) but declined by smoking (− 0.12 cups/day, $p = 0.018$). Gender, age and smoking main effects on beverage intake are shown in Table 4. Linear regression yielded a gender ($F = 23.27$, $p = 0.000$, $\eta^2_p = 0.048$) and smoking status ($F = 120.73$, $p = 0.000$, $\eta^2_p = 0.209$) main effects on coffee intake, but no main effect was found for age ($F = 3.11$, $p = 0.078$, $\eta^2_p = 0.007$). For tea intake, there was a significant main effect for age ($F = 118.97$, $p = 0.000$, $\eta^2_p = 0.208$) and

Table 4 rs2470893 SNP genotypes, age, gender, and smoking status main effects and interactions on coffee and tea drinking

rs2470893 SNP GG versus GA + AA	Coffee drinking				Tea drinking			
	df	*F*	*p*	η^2_p	*df*	*F*	*p*	η^2_p
Genotype	1	10.02	0.002	0.021	1	63.35	0.000	0.122
Mean age	1	3.11	0.078	0.007	1	118.97	0.000	0.208
gender	1	23.27	0.000	0.048	1	8.19	0.004	0.018
Smoking status	1	120.73	0.000	0.209	1	0.117	0.46	0.001
Genotype × mean age	1	7.06	0.008	0.015	1	1.98	0.15	0.004
Genotype × gender	1	5.70	0.017	0.012	1	48.32	0.000	0.096
Genotype × Smoking status	1	1.61	0.204	0.004	1	6.67	0.01	0.014

gender ($F=8.19$, $p=0.004$, $\eta^2_p=0.018$) but not for smoking status ($F=0.117$, $p=0.46$, $\eta^2_p=0.001$).

Genetic effect modification, main effect and interactions

The *CYP1A2* rs2470893 SNP GA + AA genotype showed a significant main effect on coffee intake ($F=10.02$, $p=0.002$, $\eta^2_p=0.021$) (Table 4). After stratification (Table 5), the p values were $p=0.000$ for nonsmokers and $p=0.017$ for smokers ($p=0.204$ for genotype × smoking status), $p=0.009$ for subjects ≤ 35 years and $p=0.38$ for subjects > 35 years ($p=0.008$ for genotype × mean age), $p=0.001$ for women and $p=0.67$ for men ($p=0.017$ for genotype × gender). The main effect of rs2470893 SNP GA + AA genotype on tea intake was also significant ($F=63.35$, $p=0.000$, $\eta^2_p=0.122$) (Table 4). The association differed after stratification by smoking status [nonsmokers ($p=0.002$) vs. smokers ($p=0.12$), $p=0.01$ for genotype × smoking status], mean age [subjects ≤ 35 years ($p=0.32$) vs. subjects > 35 years ($p=0.033$), $p=0.15$ for genotype × mean age] and gender [men ($p=0.05$) vs. women ($p=0.045$), $p=0.000$ for genotype × gender]. For rs762551 SNP, there was no significant main effect on coffee consumption ($F=0.210$, $p=0.64$, $\eta^2_p=0.001$). Sensitivity analysis showed significantly higher coffee consumption in rs762551 CC carriers that were smokers (+0.73 cups/day, $p=0.011$), of younger age (+1.09 cups/day, p = 0.001) and of male gender (+1.12 cups/day, $p=0.000$) (Table 5), but interaction effects were not significant.

Beverage preference according to rs2470893 SNP genotypes

In our sample, there were 375 persons of coffee only drinkers, 45 of tea only drinkers, and 100 of both tea and coffee drinkers. rs2470893 SNP A allele carriers were higher coffee only drinkers [OR (95% CI) 1.30 (0.79–2.13)] and lower tea only drinkers [OR (95% CI) 0.46 (0.18–1.21)], but significance was not reached ($p=0.29$ and $p=0.12$, respectively) (Table 6). Correlation analysis in the whole sample showed that coffee and tea consumption were inversely correlated ($r=-0.97$, $p=0.027$). However, no significant correlation was observed in rs2470893 GG carriers ($r=-0.70$, $p=0.158$) instead of a stronger inverse correlation detected in rs2470893 A allele carriers ($r=-2.41$, $p=0.013$; Table 6).

Discussion

The habitual consumption of a beverage can vary widely among human populations according to historical, cultural and genetic factors. *CYP1A2* gene SNPs association with habitual caffeine consumption was replicated in GWAS on populations of European ancestry. Therefore, it would be interesting to replicate associations in geographically, culturally and genetically different populations. In this candidate gene study, we investigated *CYP1A2* gene SNPs association with habitual coffee and tea intake in the Tunisian population, a functional SNP, rs762551 (Sachse et al. 1999), and two SNPs showing significant association with coffee intake in GWAS, rs2472297 and rs2470893 (Amin et al. 2012; Cornelis et al. 2011, 2015; Sulem et al. 2011).

CC carriers of rs762551 SNP showed significantly increased coffee consumption in univariate analysis, but not in multivariate analysis. Smoking and gender effects (responsible for 26.9% and 7.9% of variation in coffee intake, respectively) may explain the observed association in rs762551 CC carriers, as increased coffee intake was observed among CC carriers that were smokers ($p=0.000$) and of the male gender ($p=0.000$); (Table 5). For tea intake, there was no significant association with the rs762551 CC genotype. Early studies on coffee intake genetics looked to rs762551 SNP, as C allele carriers showed decreased activity of the enzyme (Sachse et al. 1999). However, its association with coffee consumption remains controversial. Previous GWAS for habitual coffee drinking reported only nominal significance for rs762551 SNP [($p=0.003$) (Amin et al. 2012) and ($p=0.008$) (Sulem et al. 2011)]. However, other data showed a stronger relationship

Table 5 The effect of rs2470893 and rs762551 SNPs genotypes on beverage intake after stratification by smoking status, age and gender

rs2470893 SNP genotype	Number of coffee cups/day mean (SD)	Number of tea cups/day mean (SD)	rs762551 SNP genotype	Number of coffee cups/day mean (SD)
Nonsmokers				
GG ($N=197$)	0.73 (0.73)	0.44 (0.81)	AA + AC ($N=243$)	0.95(0.84)
*GA + AA ($N=63$)	1.22 (0.92)	0.11 (0.19)	*CC ($N=17$)	0.99(0.83)
p	0.000	0.002	p	0.83
OR (95% CI)	1.64 (1.30–2.06)	0.72 (0.58–0.89)	OR (95% CI)	–
η^2_p	0.068	0.036	η^2_p	–
p^a	0.000	0.000	p^a	–
OR (95% CI)	1.64 (1.25–2.14)	0.62 (0.50–0.78)	OR (95% CI)	–
η^2_p	0.055	0.070	η^2_p	–
Smokers				
GG ($N=218$)	2.00 (1.21)	0.24 (0.38)	AA + AC ($N=233$)	2.02 (1.20)
*GA + AA ($N=42$)	2.50 (0.96)	0.14 (0.33)	*CC ($N=27$)	2.75 (1.28)
p	0.017	0.12	p	0.011
OR (95% CI)	1.63 (1.09–2.44)	–	OR (95% CI)	2.07 (1.18–3.62)
η^2_p	0.022	–	η^2_p	0.028
p^a	0.098	–	p^a	0.000
OR (95% CI)	–	–	OR (95% CI)	2.50 (1.50–4.16)
η^2_p	–	–	η^2_p	0.055
Age ≤ 35				
GG ($N=225$)	1.38 (1.24)	0.19 (0.41)	AA + AC ($N=250$)	1.41 (1.18)
*GA + AA ($N=50$)	1.90 (0.88)	0.12 (0.31)	*CC ($N=20$)	2.5 (0.42)
p	0.009	0.32	p	0.001
OR (95% CI)	1.67 (1.14–2.46)	–	OR (95% CI)	2.95 (1.60–5.42)
η^2_p	0.027	–	η^2_p	0.051
p^a	0.003	–	p^a	0.15
OR (95% CI)	1.63 (1.18–2.25)	–	OR (95% CI)	–
η^2_p	0.035	–	η^2_p	–
Age > 35				
GG ($N=190$)	1.49 (1.17)	0.47 (0.73)	AA + AC ($N=226$)	1.48 (1.04)
*GA + AA ($N=55$)	1.34 (0.82)	0.24 (0.32)	*CC ($N=24$)	1.83 (1.99)
p	0.38	0.033	p	0.25
OR (95% CI)	–	0.79 (0.64–0.98)	OR (95% CI)	–
η^2_p	–	0.020	η^2_p	–
p^a	–	0.000	p^a	–
OR (95% CI)	–	0.64 (0.52–0.79)	OR (95% CI)	–
η^2_p	–	0.071	η^2_p	–
Gender (F)				
GG ($N=90$)	0.92 (1.36)	0.53 (1.02)	AA + AC ($N=106$)	1.28 (1.56)
*GA + AA ($N=25$)	2.02 (1.67)	0.11 (0.16)	*CC ($N=9$)	0.00 (0.00)
p	0.001	0.045	p	0.069
OR (95% CI)	3.01 (1.58–5.73)	0.65 (0.43–0.99)	OR (95% CI)	–
η^2_p	0.093	0.035	η^2_p	–
p^a	0.000	0.000	p^a	–
OR (95% CI)	3.38 (1.92–5.94)	0.34 (0.20–0.59)	OR (95% CI)	–
η^2_p	0.168	0.141	η^2_p	–
Gender (M)				
GG ($N=325$)	1.54 (1.10)	0.29 (0.46)	AA + AC ($N=370$)	1.48 (1.02)

Table 5 (continued)

rs2470893 SNP genotype	Number of coffee cups/day mean (SD)	Number of tea cups/day mean (SD)	rs762551 SNP genotype	Number of coffee cups/day mean (SD)
*GA + AA (*N* = 80)	1.59 (0.95)	0.18 (0.34)	*CC (*N* = 35)	2.60 (1.18)
p	0.67	0.05	*p*	0.000
OR (95% CI)	–	0.89 (0.80–0.99)	OR (95% CI)	3.05 (2.00–4.65)
η^2_p	–	0.010	η^2_p	0.068
p^a	–	0.002	p^a	0.000
OR (95% CI)	–	0.84 (0.75–0.93)	OR (95% CI)	2.07 (1.37–3.12)
η^2_p	–	0.025	η^2_p	0.034

*Risk genotype

[a] Adjusted for age, gender and smoking status

Table 6 Beverage preference according to rs2470893 SNP genotypes

Parameters	rs2470893 genotypes		OR (95% CI)	*p*
	AA + GA*	GG		
Only coffee (*N*)/total (*N*)	80/105	295/415	1.30 (0.79–2.13)	0.29
Only tea (*N*)/total (*N*)	5/105	40/415	0.46 (0.18–1.21)	0.12
Coffee intake versus tea intake correlation				
r	− 2.41	− 0.70		
p	0.013	0.158		

*Risk genotype

between rs762551 SNP and coffee intake ($p < 0.0002$) (Rodenburg et al. 2012).

On the other hand, we did not detect any significant effect of rs2472297 SNP on coffee or tea intakes, but rs2470893 A carriers were higher coffee consumers, with a significant main effect ($\eta^2_p = 0.021$). Despite its association with coffee intake in previous GWAS (Amin et al. 2012; Cornelis et al. 2011, 2015; Josse et al. 2012), rs2472297 SNP seems not to have any effect in the Tunisian population, probably in relation with its minor allele (*T*) low frequency ($f = 0.045$) as compared to rs2470893 SNP ($f(A) = 0.106$). Furthermore, the 2 SNPs were weakly linked ($R^2 = 0.4$), even rs2472297 SNP T mutation occurred on an ancestral rs2470893 SNP A allele carrying haplotype ($D' = 1$). A GWAS on coffee consumption performed on the Icelandic population showed significant effects for both rs2472297 and rs2470893 SNPs, as they were in strong LD ($R^2 = 0.85$) (Sulem et al. 2011). But in another candidate gene study on the Costa Rican population, where the authors reported a R^2 value of 0.70 for rs2472297 and rs2470893 SNPs, they found significant association only for rs2472297 SNP (Josse et al. 2012).

The effect of rs2470893 SNP on caffeine intake was estimated mainly based on coffee drink assumptions (Cornelis et al. 2011, 2015; Amin et al. 2012). However, few studies have investigated its relationship with tea, or caffeine from tea intake. Previous data in the US population showed a stronger association between the rs2470893 A allele and coffee intake, as compared to total caffeine intake (from coffee, tea, soft drinks and chocolate) suggesting a closer relationship to coffee than tea (Cornelis et al. 2011). A recent study, conducted on a sample from the UK Biobank (Taylor et al. 2018), and in line with a previous report from the same research group (McMahon et al. 2014) showed that a 2 SNP (rs4410790 (G allele) from *AHR* gene and rs2470893 (A allele) from *CYP1A2* gene) genetic risk score was associated with coffee and tea intakes [OR (95% CI) 1.12 (1.10–1.14) and 1.15 (1.13–1.17), respectively]. Interestingly, this association was observed with black tea (the most consumed tea type in the UK) but not with green tea [OR (95% CI) 0.98 (0.94–1.02)]. In the present study, we found that tea intake was − 0.18 cups/day lower in rs2470893 A carriers, with green tea as the most consumed tea type (86% of tea consumers). The lack of association with herbal tea intake in the UK Biobank study was attributed to that it was not consumed in high quantities (as black tea, containing more caffeine than green tea, is the regular tea beverage in the UK). A possible explanation of our finding of coffee preference instead of tea in rs2470893 SNP A allele carriers could be the automatic limitation of consuming other drinks among habitual coffee consumers (rs2470893 SNP A carriers), as a person has to consume only a certain number of drinks per day. However, the strong inverse correlation between the two beverages intake observed in rs2470893 A allele carriers disappeared when analyzing rs2470893 GG genotype carriers, suggesting another direct link between the genotype and beverage preference. Nevertheless, the preference

could not be attributed to the higher caffeine content of coffee, as a cup of green tea decoction contains more caffeine than a cup of coffee (Hammad et al. 2015; Hamdaoui et al. 2016). Other issues should be explored to explain such beverage preference according to *CYP1A2* rs2470893 SNP genotypes, related to caffeine metabolism rate, or bitter taste perception. Indeed, the inducing effect of coffee on CYP1A2 activity is more pronounced than that of heavy tea consumption, through the other coffee components (such as polycyclic aromatic hydrocarbons) (Perera et al. 2012), which suggests a faster caffeine metabolism rate after coffee ingestion. In the study of Masi et al. (2016), the authors showed that the preference for stronger coffee flavor is consequent to regular coffee consumption, which induces faster caffeine metabolism and lower sensitivity to bitter taste. Similarly, this situation of a higher coffee intake in addition to the faster caffeine metabolism rate that would occur in rs2470893 SNP A allele carriers, could explain the observed coffee preference instead of tea.

The study of the main effect of genotypes, demographic, and lifestyle factors on beverage intake demonstrated that smoking was responsible for 20.9% of the variation in coffee intake, followed by gender (4.8%) and genotype (2.1%). Additionally, age accounted for 20.8% of the variation in tea intake, followed by genotype (12.2%) and gender (1.8%). For demographic variables, our data align with a previous report on Australian twins (Luciano et al. 2005) suggesting that gender and age had a significant effect on the consumption rate of both beverages, except for a nonsignificant age effect on coffee intake in our study. In both data, age was positively correlated with tea intake; furthermore, in the data of our study, females consumed more tea than males, but males consumed more coffee in comparison. On the other hand, sensitivity and interaction analyzes showed that women who were carriers of the allele rs2470893 SNP A were higher coffee drinkers (1.2% of variation) and lower tea drinkers (9.6% of variation) whereas no significant genetic effect was observed in men. This data is consistent with the report of the Australian twins' study (Luciano et al. 2005) that determined that tea and coffee intakes were influenced by different genes in men, whereas genes that increased tea consumption decreased coffee consumption (and vice versa) in women. Regarding age, the interaction with rs2470893 SNP GA + AA genotype on coffee drinking was significant (1.5% variation) as the association was only observed in subjects ≤ 35 years ($p = 0.009$). However, the interaction effect on tea intake was not significant ($p = 0.15$). Regarding smoking, although the difference between rs2470893 SNP genotypes, in terms of coffee intake, was more pronounced in smokers ($p = 0.000$), compared to nonsmokers ($p = 0.017$), there was no significant genotype-smoking status interaction ($p = 0.204$). However, there was a significant interaction on tea drinking ($p = 0.01$) with the lowest intake observed in nonsmokers who were carriers of the rs2470893 SNP A allele. According to all these data, there is evidence for genetic variation in beverage liking at the condition of lower CYP1A2 enzymatic activity (that would be observed in women (Gunes and Dahl 2008), nonsmokers (Backman et al. 2008), and younger subjects (although controversial (Gunes et al. 2009; Simon et al. 2001)).

Finally, there are some limitations to this analysis that should be considered. First, this study had a relatively small sample size, which limited the statistical power. Also, caffeine use utilizes self-report measures of daily consumption, but this information can be biased by differences in terms of coffee amount used, tea brewing time, brands used, size of cup, etc. In addition, information about other caffeinated food uses like cola and chocolate (although not consumed as much as coffee and tea) and alcohol consumption (as a possible covariate for caffeinated foods intake) was not available in this study.

Conclusions

In this study from the Tunisian population, we showed that CYP1A2 rs2470893 SNP was associated with caffeinated beverages intake. Interestingly, an opposite genetic effect of rs2470893 SNP GA + AA genotype on coffee and tea intakes was observed, suggesting a beverage preference according to genotype. Furthermore, we observed that genetic variation was significant at the condition of lower CYP1A2 enzyme activity (women, nonsmoker and younger age).

Abbreviations

CYP1A1	Cytochrome P450, family 1, subfamily A, member 1
CYP1A2	Cytochrome P450, family 1, subfamily A, member 2
DNA	Deoxyribonucleic acid
GWAS	Genome-wide association study
PCR	Polymerase chain reaction
RFLP	Restriction fragment length polymorphism
SNP	Single-nucleotide polymorphism

Acknowledgements

This work was supported by the Tunisian Ministry of Higher Education and Scientific Research and the Tunisian Ministry of Health. We thank all technicians from the National Blood Transfusion Center of Tunis for their valuable technical assistance.

Author contributions

SD designed the study, did the laboratory work, performed data analysis and drafted the paper. MHS and RK were involved in blood donors selections, consent signature and data collection. AHK supervised the study process and participated in data analysis. MHH was the main supervisor of the research, revised and edited the final manuscript. All authors have read and approved the final manuscript.

Funding

No specific fund was secured for this study.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
To participate in this study, written consent was obtained from all participants according to a protocol approved by the Ethical Committee for Scientific and Medical Research of the National Blood Transfusion Center of Tunis (Tunisia). The committee's reference number is not available.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 17 June 2021 Accepted: 31 December 2022
Published online: 13 February 2023

References

Amin N, Byrne E, Johnson J, Chenevix-Trench G, Walter S, Nolte IM et al (2012) Genome-wide association analysis of coffee drinking suggests association with CYP1A1/CYP1A2 and NRCAM. Mol Psychiatry 17:1116–1129
Backman JT, Schröder MT, Neuvonen PJ (2008) Effects of gender and moderate smoking on the pharmacokinetics and effects of the CYP1A2 substrate tizanidine. Eur J Clin Pharmacol 64:17–24
Coffee and Caffeine Genetics Consortium, Cornelis MC, Byrne EM, Esko T, Nalls MA, Ganna A, Paynter N et al (2015) Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. Mol Psychiatry 20(5):647–656
Cornelis MC, El-Sohemy A, Campos H (2004) Genetic polymorphism of CYP1A2 increases risk of myocardial infarction. J Med Genet 41:758–762
Cornelis MC, El-Sohemy A, Campos H (2007) Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. Am J Clin Nutr 86:240–244
Cornelis MC, Kacprowski T, Menni C, Gustafsson S, Pivin E, Adamski J et al (2016) Genome-wide association study of caffeine metabolites provides new insights to caffeine metabolism and dietary caffeine-consumption behavior. Hum Mol Genet 25(24):5472–5482
Cornelis MC, Monda KL, Yu K, Paynter N, Azzato EM, Bennett SN et al (2011) Genome-wide meta-analysis identifies regions on 7p21 (AHR) and 15q24 (CYP1A2) as determinants of habitual caffeine consumption. PLoS Genet 7:e1002033
Cornelis MC, van Dam RM (2021) Genetic determinants of liking and intake of coffee and other bitter foods and beverages. Sci Rep 11:23845
Denden S, Bouden B, Haj Khelil A, Ben Chibani J, Hamdaoui MH (2016) Gender and ethnicity modify the association between the CYP1A2 rs762551 polymorphism and habitual coffee intake: evidence from a meta-analysis. Genet Mol Res 15(2):gmr.15027487
Euromonitor International report (2017) Hot drinks: quarterly statement Q2 2017. http://www.euromonitor.com/hot-drinks-quarterly-statement-q2-2017/report. Accessed 4 May 2018
Gunes A, Dahl ML (2008) Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms. Pharmacogenomics 9:625–637
Gunes A, Ozbey G, Vural EH, Uluoglu C, Scordo MG, Zengil H, Dahl ML (2009) Influence of genetic polymorphisms, smoking, gender and age on CYP1A2 activity in a Turkish population. Pharmacogenomics 10:769–778
Hamdaoui MH, Snoussi C, Dhaouadi K, Fattouch S, Ducroc R, Le Gall M et al (2016) Tea decoctions prevent body weight gain in rats fed high-fat diet; black tea being more efficient than green tea. J Nutr Intermed Metab 6:33–40
Hammad S, Tyyem R, Musaiger AO (2015) Caffeine content in beverages commonly consumed in Jordan. Pakistan J Nutr 14:447–452
Josse AR, Da Costa LA, Campos H, El-Sohemy A (2012) Associations between polymorphisms in the AHR and CYP1A1-CYP1A2 gene regions and habitual caffeine consumption. Am J Clin Nutr 96:665–671
Luciano M, Kirk KM, Heath AC, Martin NG (2005) The genetics of tea and coffee drinking and preference for source of caffeine in a large community sample of Australian twins. Addiction 100:1510–1517
Masi C, Dinnella C, Pirastu N, Prescott J, Monteleone E (2016) Caffeine metabolism rate influences coffee perception, preferences and intake. Food Qual Prefer 53:97–104
McMahon G, Taylor AE, Davey Smith G, Munafò MR (2014) Phenotype refinement strengthens the association of AHR and CYP1A1 genotype with caffeine consumption. PLoS ONE 9(7):e103448
National Institute of Statistics (2013) National survey on expenditure, consumption and household living standards for the year 2010. http://www.ins.tn/sites/default/files/publication/pdf/consb_2010.pdf. Accessed 01 Apr 2017
Perera V, Gross AS, McLachlan AJ (2012) Influence of environmental and genetic factors on CYP1A2 activity in individuals of South Asian and European ancestry. Clin Pharmacol Ther 92(4):511–519
Rodak K, Kokot I, Kratz EM (2021) Caffeine as a factor influencing the functioning of the human body—friend or foe? Nutrients 13:3088
Rodenburg EM, Eijgelsheim M, Geleijnse JM, Amin N, Van Duijn CM, Hofman A et al (2012) CYP1A2 and coffee intake and the modifying effect of sex, age, and smoking. Am J Clin Nutr 96:182–187
Sachse C, Brockmöller J, Bauer S, Roots I (1999) Functional significance of a C–>A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. Br J Clin Pharmacol 47:445–449
Simon T, Becquemont L, Hamon B, Nouyrigat E, Chodjania Y, Poirier JM et al (2001) Variability of cytochrome P450 1A2 activity over time in young and elderly healthy volunteers. Br J Clin Pharmacol 52:601–604
Sulem P, Gudbjartsson DF, Geller F, Prokopenko I, Feenstra B, Aben KK et al (2011) Sequence variants at CYP1A1-CYP1A2 and AHR associate with coffee consumption. Hum Mol Genet 20:2071–2077
Taylor AE, Davey Smith G, Munafò MR (2018) Associations of coffee genetic risk scores with consumption of coffee, tea and other beverages in the UK Biobank. Addiction 113(1):148–157
Thorn CF, Aklillu E, McDonagh EM, Klein TE, Altman RB (2012) PharmGKB summary: caffeine pathway. Pharmacogenet Genom 22:389
Treur JL, Taylor AE, Ware JJ, McMahon G, Hottenga JJ, Baselmans BML et al (2016) Associations between smoking and caffeine consumption in two European cohorts. Addiction 111(6):1059–1068
Vink JM, Staphorsius AS, Boomsma DI (2009) A genetic analysis of coffee consumption in a sample of Dutch twins. Twin Res Hum Genet 12:127–131

Publisher's Note