Variability of caffeine metabolism by CYP1A2 polymorphism in different populations

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Research Article

Keywords: caffeine, metabolism, CYP1A2, polymorphic gene, slow and fast metabolizers caffeine, metabolism, CYP1A2, polymorphic gene, slow and fast metabolizers.

Posted Date: June 27th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3090935/v1

Abstract

In 2015, the European Food and Safety Authority (EFSA) evaluated the worldwide consumption of coffee to verify the potential use and abuse of caffeine by the population, with the aim to identify potential adverse effects on the human health. The conclusion of the survey was the following: single doses of caffeine up to 200/400 mg did not give to any concern in the population.

Objectives: In 2015, the European Food and Safety Authority (EFSA) evaluated the worldwide consumption of coffee to verify the potential use and abuse of caffeine by the population, with the aim to identify potential adverse effects on the human health. The conclusion of the survey was the following: single doses of caffeine up to 200/400 mg wer not dangerous for the consumers.

Methods: Caffeine is one of the most widely consumed substance and beverage in the world, showing not only benefits, as excellent source of antioxidants, but also offering to prevent inflammatory and oxidative stress-related diseases, including obesity, metabolic syndrome and type 2 diabetes. In the elderly people with several comorbidities, caffeine contributed to reduce several neurological disorders, such as senile dementia, Alzheimer's and Parkinson's disease, contributing to alleviate tremors and helping the memory loss in elderly subjects.

Results: It is widely known CYP1A2 polymorphic enzyme (AA) (AC) (CC) is responsible for different levels in the caffeine metabolism, leading to a distinction in separate categories where CYP1A2*1A allele (AA) are "rapid" caffeine metabolizers, in contrast to carriers of the variant CYP1A2*1F who are "slow" caffeine metabolizers (AC-CC). In the absence of biological matrix, such as blood and urine, we performed *in silico*analysis of the genetic polymorphism CYP1A2*1A rs762551 distributed into five different ethnic groups of 210 subjects, including Caucasian, Africans, Americans, South Asians and East Asians.

Conclusions: The goal of this study is to identify potential significant difference in metabolism of caffeine to verify the most susceptible individuals in five ethnic groups.

Structured abstract

Coffee is one of the most widely consumed beverage in the world although it is not free from various effects and in 2015 the exposure to caffeine and the intake of daily coffee has been regulated by EFSA. Guidelines and EFSA results demonstrated caffeine is easily metabolized in the majority of subjects, although fast metabolizers are advantaged in contrast to other individuals with a slow metabolism.

Introduction

Caffeine (*i.e.*1,3,7-trimethylxanthine) is one of the most widely consumed substance and beverage in the world. It shows many benefits, as excellent source of antioxidants, contributing to prevent inflammatory and oxidative stress-related diseases, including obesity, metabolic syndrome and type 2 diabetes (Barrea et al. 2023) Coffee consumption has been associated to a decreased risk of developing senile conditions

in the elderly people, since epidemiological studies observed that regular coffee consumption is associated with a lower risk of neurodegenerative diseases (Ruggiero et al. 2022). In the elderly people with several comorbidities, comprising neurological disorders such as senile dementia, Alzheimer's and Parkinson's disease, coffee drinking may help to reduce the frequency of tremors and memory loss (Eskelinen and Kivipelto 2010; Ren and Chen 2020; Gongora-Alfaro 2010; Wierzejska 2016). In a further study, coffee consumption seemed to contribute with a lower incidence of several types of cancer with a reduction in the risk of all-cause mortality, concluding that moderate coffee use is associated with a lower all-cause and cancer mortality after a long follow-up period, finding absence of significant association between coffee consumption and cardiovascular mortality (CVD). (Torres-Collado et al. 2021).

Coffee Market

The largest coffee production is concentrated in developing Countries particularly in Brazil, Vietnam and Colombia, while the European Union and the United States of America are the largest consuming and importing markets globally by Food and Agriculture Organization of the United Nations (FAO). The coffee production increased from about 8.5 million tonnes in 2008 to 10.7 million tonnes in 2020, according to (International Institute for Sustainable Development 2022). Brazil, Vietnam, and Colombia are the highest-producing Countries and largest exporters since 2016, with 33 million, 29 million, and 14 million 60-kg bags, respectively, in the years 2021/2022. The European Union (EU), United States, and Japan represents the largest importers with about 43 million, 26 million, and 7 million 60-kg bags, respectively, in 2021/2022. Although the global coffee supply and demand have remained fairly stable over the last 5 years, the coffe demands is expected to drop, mostly due to unfavourable weather conditions (Herforth et al. 2022). Although this sector is in expansion, recurrent and detrimental market imbalances and asymmetric income distribution among market buyers can threaten the livelihood of millions of small holder producers (International Institute for Sustainable Development 2022). Finally, the consumption of up to 400 mg/day (1–4 cups per day) of caffeine is safe, however its impact on health outcomes and adverse effects have been clarified from more scientific resource and data.

Coffee consumption and human health

In the year 2015, due the worldwide consumption of coffee at different levels in the population, the public and the scientific community engaged the European Food and Safety Authority (EFSA) to express an interest in the potential use and abuse of caffeine by the population, due to the potential concern and adverse effects on the human health. The request came upstream from the European Commission, leading to the conclusion that for the healthy adult population, single doses of caffeine up to 200/400 mg (about 3 mg/kg bw for a 70-kg adult) do not give rise to safety concerns. Several benefits were attributed to caffeine including physical endurance, reduction of fatigue, enhancement of mental alertness and concentration (Wierzejska 2012). Caffeine-common ingredient in a diet and its influence on human health). An important and extensive study on this topic was published in the review from Nawrot P & coworkers (2003), concluding that moderate daily caffeine intake at a dose level up to 400 mg, equivalent to 6 mg kg(-1) body weight day(-1) in a 65-kg person) was not associated with adverse effects.

The main role of EFSA evaluation was to analyze the potential bad effects in the fragile categories, such as adolescents, elderly people, pregnant and breastfeeding women as well as adults, to conclude that permissive doses of caffeine could be assumed in the appropriate amount of caffeine for each group. According to the published paper (Turnbull et al. 2017), agreed that in the coffee drinker populations, typical moderate caffeine intake is not associated with increased risks of several diseases, such as cardiovascular, arrhythmia, heart failure and hypertension. According to Vester and Koenig (2018), the data revealed that mean total daily caffeine intake in children, adolescents, and adults was below caffeine intakeirecommendations such as those stated by Health Canada and by the European Food Safety Authority, confirming that caffeine consumption was not detrimental at the permissive and proposed caffeine doses. In most of the survey the predominant source of caffeine for adults was coffee, accounting for between 40% and 94% of the total intake. In Ireland and the United Kingdom, tea was the main source, accounting for 59% of total caffeine intake in the first country and 57% in the second respectively (Caldwell et al. 2018).

Positive and negative effects of caffeine consumption

Seventy percent of the coffee consumption by people has been estimated around the mornig 6:00–9:00 AM and after lunch 13:00–15:00. Caffeine is known to have several positive actions on the brain exerting its effects by blocking adenosine receptors. It increases alertness and well-being, help concentration, improve the mood and limit depression. In few people caffeine may disturb sleep, while other individuals may suffer from anxiety, varying from subjects. Following low moderate ∼300 mg dose, caffeine increases alertness, vigilance, intensification of reaction time and attention but less consistent effects are observed on memory. Although caffeine does not seem to experience dependence, there are people who undergo withdrawal symptoms. A less known effect of caffeine is the intensification on analgesic drugs in headache and migraine, depending also on the genotype (Nehlig 2016; Cornelis 2006).

Caffeine and pregnancy

Pregnancy and medications including oral contraceptives, antidepressants, cardiovascular drugs and antibiotics, slow caffeine removal from the bloodstream, while cigarette smoking increases the rate of caffeine removal from the bloodstream, depending on the gene polymorphism of the individual. It has been known that short-term adverse effects on adults and children may include central nervous system disorders including disrupted sleep, anxiety, and behavioral changes. In the long term, excessive caffeine consumption has been associated with cardiovascular disease and in pregnant women may reduce fetal development. Furtermore excessive exposure to caffeine during sensitive windows of pregnancy may induce epigenetic changes in the developing fetus or even the germ cells to cause adult-onset diseases in subsequent generations (Qian et al. 2020) while it has been recently demonstrated that caffeine consumption in pregnancy is associated with reduced birth size, although potential associations with childhood growth are still unclear (Gleason et al. 2022). Since higher caffeine intake in pregnancy is associated with lower infant birth weight, the caffeine consumption should not exceed 200 mg per day.

Caffeine Metabolism

Coffee is a source of complex organic compounds with many beneficial. The P450 system in the liver has a key role in coffee metabolism. The caffeine intake spreads throughout the body, reaches the liver where it is metabolised by cytochrome P450, namely the CYP1A2*1A enzyme. The compounds, including paraxanthin, theophylline and theobromine are then metabolized into uric acid and excreted in urine. CYP1A2*1A is the enzyme responsible for the metabolism of caffeine and also other drugs. In this context the polymorphic CYP1A2*1A alleles are “rapid” caffeine metabolizers, whereas carriers of the variant CYP1A2*1F gene are “slow” caffeine metabolizers. The rs762551(AA) CYP1A2*1A (C-163A) codes for the "high inducibility" form of the enzyme, characterized by higher activity in the presence of an inducer such as smoking or heavy coffee consumption. Caffeine, is the most well-known constituent that stimulates the central nervous system, as a source of complex organic compounds with beneficial anti-oxidant and endocrine properties. (Nehlig and Debry 1994) Most of the biological effects of caffeine including those on the brain and the central nervous system are mediated through antagonism of the adenosine receptors (Fredholm et al. 1999). The metabolism of caffeine by the CYP1A2 enzyme shows substantial variation between people, because of both genetic and environmental factors (Gu et al. 1992). There is some evidence, although not significant, that polymorphisms in the gene are known to moderate the association between coffee consumption and hypertension (Palatini et al. 2009) and myocardial infarction. No association has been found between variants in CYP1A2 and caffeine consumption, (Cornelis, El-Sohemy, and Campos 2007) but a single-nucleotide polymorphism (SNP) in this gene (rs762551) has been shown to be associated with high inducibility of the CYP1A2 enzyme in smokers. (Sachse et al. 1999). Cornelis and coworkers analyzed the individual susceptibility in gene polymorphism exposed to caffeine to determine whether CYP1A2 genotype modifies the association between coffee consumption and risk of acute nonfatal myocardial infarction (Cornelis et al. 2006). The results demonstrated coffee intake was associated with an increased risk of nonfatal MI only among individuals with slow caffeine metabolism, suggesting that caffeine plays a role in this association. In non-smokers, there was no significant difference in CYP1A2 activity between the genotypes, while in smokers, the A/A homozygotes had 1.6 times higher CYP1A2 activity respective to A/C and C/C genotypes.

Caffeine habits consumption and health

There are large differences between Countries in the contribution of different food sources to the total caffeine intake. According to the EFSA Journal, in the year 2015 (European Food Safety Authority 2015) chocolate was the number one source in six surveys, while coffee was in four surveys, cola drinks in three, and tea in two. In most countries, chocolate was the main source of caffeine for children aged 3 to 10, followed by tea and cola drinks. One reason for the differences in levels of consumption, apart from cultural habits, was the variable concentration of caffeine found in some food products. The concentrations in coffee-based beverages depend on the production process, the variety of coffee beans used and the methods of preparation (e.g. filter coffee, espresso). A short publication (Walter 2022) was released by Kristin Walter on the JAMA journal, who contributed to analyze the beneficial effects and medical use of caffeine, highlighting the common, good and negative effects of this substance. Briefly, the caffeine metabolism varies among individuals, depending on the gene polymorphisms involved in the caffeine metabolism and duration of action was estimated typically between 2.5 and 4.5 hours. Caffeine

consumption in moderate doses from 40 to 200 mg acts within the brain to decrease fatigue, increase alertness, and decrease the reaction time. Caffeine may also decrease appetite and slightly reduce weight gain although perceptions remains unclear. (Schubert et al. 2017). In moderate doses, caffeine has been associated with decreased risk of depression and suicide as found in different studies. (Cappelletti, Piacentino, and Cialella 2021; Centers for Disease Control and Prevention 2022). Also, few reports have shown that coffee decreased the risk of Endometrial Cancer. (Lafranconi et al. 2011; Je et al. 2011). In contrast, cigarette smoke increases the rate of caffeine removal from the bloodstream. In higher doses, caffeine can produce anxiety and have difficulty falling asleep if coffee is assumed late in the day. Futhtermore excess of caffeine (more than 1200 mg) and overuse of supplement caffeine may cause adverse effects such as agitation, severe anxiety, elevated blood pressure and palpitations. Although caffeine does not seem to be addictive, abrupt cessation in regular users may result in withdrawal symptoms, which typically peak at 1 to 2 days and include headache, fatigue, and depressed mood.

Methods: Statistical analysis

The object of this special report has been focused to substitute the traditional genetic polymorphism of CYP1A2*1A made in the laboratory, with the in silico analysis obtained in the five ethnic groups i.e. Caucasian, Africans, Americans, South Asians and East Asians, including men and women to identify a significant difference in the five populations. Two hundreds and ten individual genotypes in each ethnic group have been downloaded from the Ensembl project of genome database for vertebrates and other eukaryotic species (Ensembl GRch37 2023).

All statistical analyses were performed using the software R (version 4.2.0, R Foundation for Statistical Computing, Vienna, Austria). A significance criterion $p < 0.05$ was conventionally adopted. All the probabilities were adjusted for multiple comparison with the Bonferroni criterion. The Pearson chi square test was used to test the statistical significance of the difference between the ethnic groups in caffeine metabolizing efficiency. The heterozygous AC and homozygous CC variants were separately compared to the wild-type variant AA, considered as the fast metabolizer genotype. The incidence of the variant AC or the variant CC (AC + CC) was compared to the wild-type (WT) and finally the incidence of the wild type or the heterozygous variant (WT + AC) was compared to the homozygous variant CC. All the possible comparisons were performed between the ethnic groups. In this analysis the data coming from male and female groups were summed together. The significance of the gender difference was also tested in the different ethnic groups

Results

The maximum incidence of fast metabolizer genotype was found in the Americans ethnic group, in this group a percentage of 72% of wild – type individuals was found. The second group for percentage of fast metabolizers is the Caucasians (62%). In the Africans the percentage of fast metabolizers was of 41% and finally the same percentage of 38% of wild - type genotype was found in South and East Asians. The results of the comparisons between the different ethnic groups are summarized in Table I

Table 1

		Caucasians	Africans	South asians	East asians	Americans
WT – versus heterozygous variant AC	**Caucasians**		4.021E-05	2.864E-07	4.027E-07	n.s.
	Africans	4.021E-04		n.s.	n.s.	1.199E-06
	South asians	2.864E-06	n.s.		n.s.	1.830E-09
	East asians	4.027E-06	n.s.	n.s.		2.739E-09
	Americans	n.s.	1.199E-06	1.830E-09	2.739E-09	
		Caucasians	**Africans**	**South asians**	**East asians**	**Americans**
WT – versus homorozygous variant CC	**Caucasians**		6.627E-05	5.726E-06	2.599E-05	n.s.
	Africans	6.627E-05		n.s.	n.s.	1.451E-12
	South asians	5.726E-06	n.s.		n.s.	3.190E-14
	East asians	2.599E-05	n.s.	n.s.		3.242E-13
	Americans	n.s.	1.451E-12	3.190E-14	3.242E-13	
		Caucasians	**Africans**	**South asians**	**East asians**	**Americans**
WT – versus homozygous + heterozygous variant AC + CC	**Caucasians**		1.384E-06	6.113E-09	2.136E-08	n.s.
	Africans	1.384E-06		n.s.	n.s.	1.364E-13
	South asians	6.113E-09	n.s.		n.s.	5.155E-17
	East asians	2.136E-08	n.s.	n.s.		2.850E-16
	Americans	n.s.	1.364E-13	5.155E-17	2.850E-16	
		Caucasians	**Africans**	**South asians**	**East asians**	**Americans**
WT + homozygous AC versus heterozygous variant CC	**Caucasians**		7.618E-03	5.142E-03	1.400E-02	n.s.
	Africans	7.618E-03		n.s.	n.s.	7.726E-09

		Caucasians	Africans	South asians	East asians	Americans
	South asians	5.142E-03	n.s.		n.s.	3.524E-09
	East asians	1.400E-02	n.s.	n.s.		1.944E-08
	Americans	n.s.	7.726E-09	3.524E-09	1.944E-08	

No significant differences was found in the risk of Caucasians with respect to the Americans. A significantly increased risk was found in the ethnic groups, Africans, South and East Asians when compared to the Americans or to the Caucasian both for the homozygous and heterozygous variants compared to the wild – type and for the AC + CC compared to the WT. Also the comparison between the WT + AC versus the homozygous variant CC was found significantly disadvantageous in the Africans, South and East Asian with respect to the Americans or the Caucasians.No significant differences were found in the groups of Africans, South or East Asians when compared among them. As regards the comparison between males and females within the same ethnic group, the only significant differences were found in the group of Caucasians. In this group the males were found more susceptible ($p = 0.05$) with respect to the females for the homozygous variant and when the WT + AC was compared to the homozygous variant CC ($p = 0.04$).

Conclusions

This paper identified the slow and rapid caffeine metabolizers with the homozygous and heterozygous variant AC and CC with respect to the AA wild-type genotype of the gene CYP1A2*1A. The comparison between the five ethnic groups showed the maximum incidence in the Americans followed by Caucasians of fast caffeine metabolizers. These two groups were found not significantly different. However, when the Africans, South Asians and East Asians were compared to the Americans or Caucasians, a significant risk increase was found. Our in silico results allowed to assess a relative risk evaluation for three etnic groups due to the slow caffeine metabolism. This result can be useful to evaluate the metabolic burden in the different ethnic groups and could help in the diet optimization at preventive purposes. The methodological approach can be extended to other substances present in the diet or as xenobiotics at workplace or in the environmental life**.** When there is no access to genotyping tests or in the absence of informed consent from volunteers or workers,as decribed by the authors in a previous study the use of in silico database may allow to obtain useful results (Chiarella et al. 2019; Westra and de Beaufort 2015). In the last years the availability to enrole numerous subjects to evaluate specific exposures such as in the case of caffeine has become limitant for several reasons. The production of in silico data may represent a valid alternative and an opportunity for researchers, offering the advantage to recruit open data by having full access to several databases. This paper provided useful data related to the susceptibility risk in five different ethnic group samples with slow and fast metabolism, despite the poor numerosity of available subjects. Here the in silico study performed on caffeine concentration patterns has been able to

identify the groups with the highest and lowest risk in metabolizing this substance, leading to identification of the most susceptible subjects. Due to difficulty to recruit volunteers in the absence of experimental results, the only choice for reserchers is to use valid and reliable prediction models.

Declarations

Disclosure statement of interest

No potential conflict of interest was reported by the authors.

Funding

No fundings have been used to write this paper.

Authors'contributions

All the authors contributed to the elaboration of this manuscript. P.Ch. (Pieranna Chiarella) conceptualization, investigation and writing of the original manuscript; P.C. (Pasquale Capone) selection of appropriate scientific literature, correction of manuscript and contribution to bibliography. R.S. (Renata Sisto) statistical analysis, results, data production, contribution to the manuscript and correction, English editing and final supervision of the paper.

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Figures

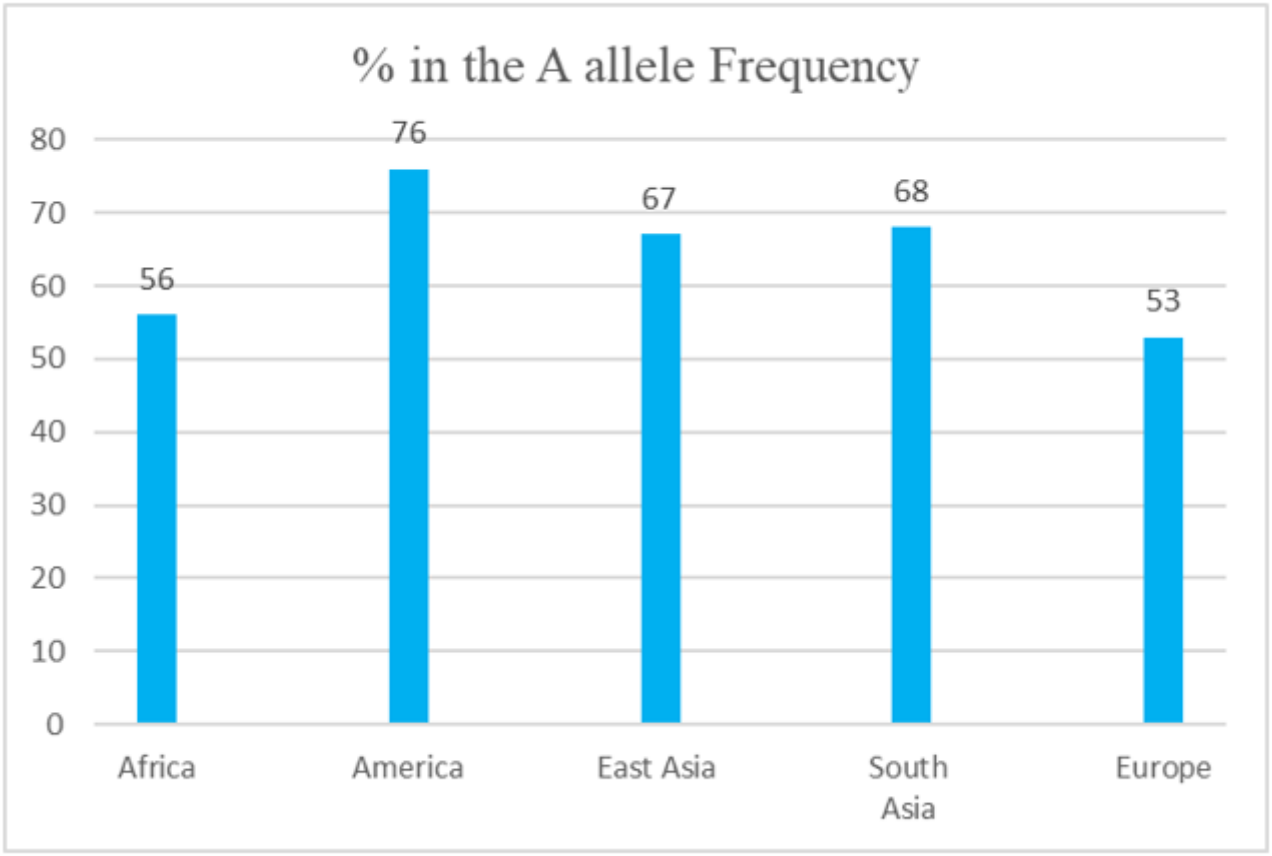

Figure 1

Difference in percentage of the allele frequency in the five ethnicities

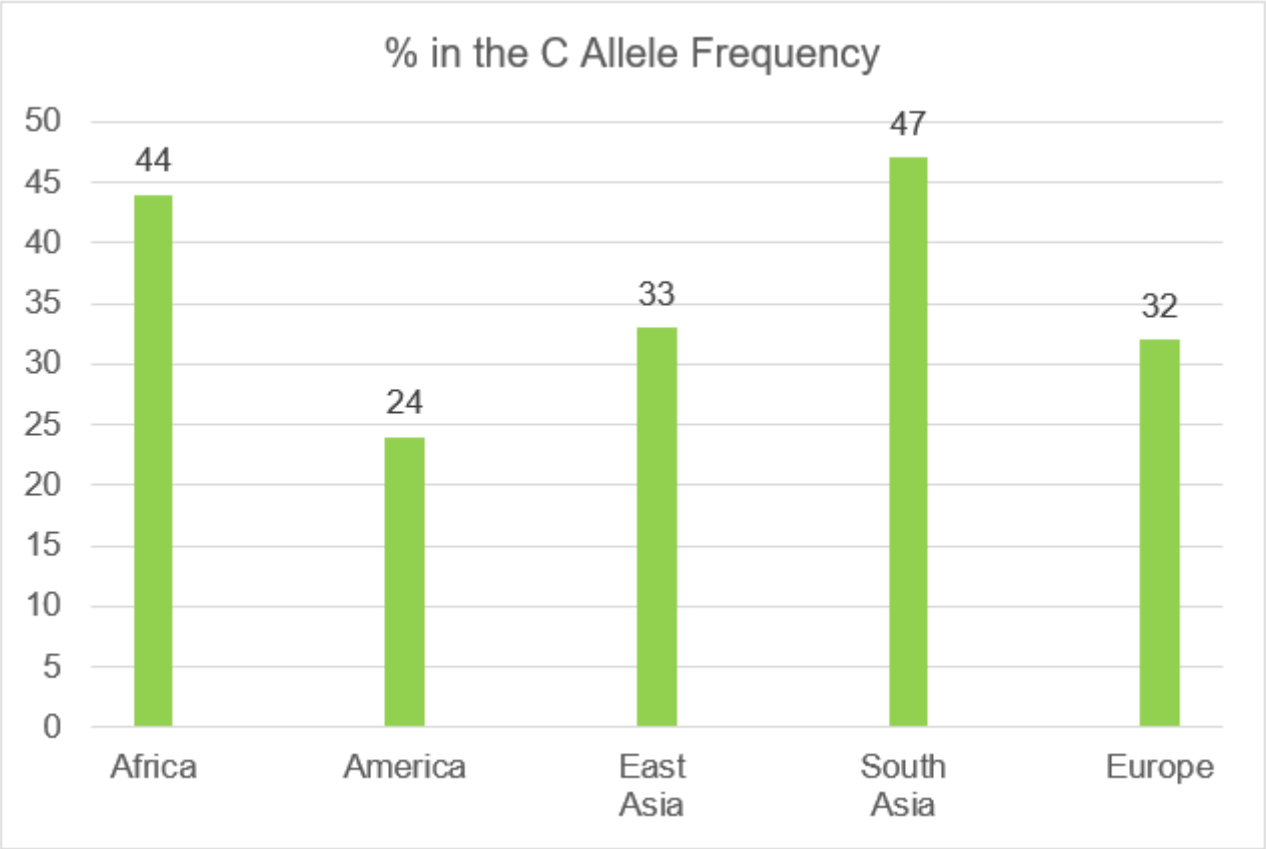

Figure 2

Difference in percentage of the allele frequency in the five ethnicities