ORIGINAL ARTICLE

The Impact of Genetic Polymorphisms of Cytochrome P450 (CYP1A1&2D6) Gene in the Incidence of Acute Myeloid Leukaemia

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ABSTRACT

Background: A combination of risk factors effecting of genetic susceptibility and environmental exposure may explain the multi-step process of carcinogenesis/leukemogenesis of acute myeloid leukemia (AML).

Objectives: The study objective is to evaluate the role of genetic polymorphisms of human cytochrome P450, namely CYP1A1 & CYP2D6 enzymes, involved in the transformation of chemical and cellular metabolism of drugs and carcinogenic agents as risk factors for AML Sudanese patients.

Methods/design: A case control study was conducted between June 2016and June 2018 at the Radiation and Isotope Center Khartoum (RIKA), Sudan. A total of 265 blood specimens (200AML patients and 65 controls) were investigated for allele frequency and genotypes of CYP1A1*2C and CYP2D6*4. The DNA was extracted from all blood specimens, using Qiagen DNA extraction kit. Standard polymerase chain reaction and Restriction fragment length polymorphism analysis (PCR -RFLP) methods were used for genotyping.

Results: Although no significant variations were evident for CYP1A1 AG genotype, the GG genotype showed significant differences. We also found no difference in frequencies of alleles A and G of gene CYP1A1 between patients. While, there is evidence of increased frequency when compared with control G allele. The genotype of the CYP2D6*4 allele revealed no significant differences between IM (heterozygous) and the mutant homozygous (PM) genotype. The PM allele for the CYP 2D6 gene was high in both patients and controls.

Conclusions: Our findings illustrate that the genetic polymorphisms for xenobiotic metabolizing enzymes CYP1A1 heterozygous AG reveal no significant association with AML, where homozygous GG shows a protective effect. CYP2D6 suggests no association with the risk of AML for both heterozygous IM and the mutant homozygous PM.

Key words: Cytochrome P450, CYP1A1, CYP 2D6 & AML

INTRODUCTION

The frequency of cancer and hematological malignancies is increased universally. Annually there were 57 thousand cases of leukemia discovered all around the world; acute myeloid leukemia (AML) comprises the common type, which constitutes the theme of this research. The causes of different types of leukemia are still unclear some factors like ionizing radiation, chemicals long exposure such as benzene, have association with this disease[1].

There was a positive impact of awareness and advancement of diagnostic tools at the cancer incidence level. The published information for both incidences of leukemia and factors which may predispose populations to leukemia is largely unknown[2].

Human cytochrome P450 (CYP) is a metabolically active enzyme which have a vital cellular metabolic role in biotransformation of chemical agents and drugs from status of harmless chemical “procarcinogenic” agents into active carcinogenic agents (genotoxic intermediates). Recent studies, using CYP450 phenotyping on carcinogenesis and risk identification demonstrate a strong relationship between the activity of human CYP P450 enzymes and cancer development[3].

The carcinogenesis of AML can be explained by the concept of multi-step process and accumulated mutations, resulting from failure of DNA repair & detoxification mechanisms and permanent DNA lesions[4]. The usual carcinogenic triggers are variable, including different acquired environmental factors and a few inherited genetic defects[4]. The disruptions of the cellular repair mechanism as a result of exposure to different hazards will lead to genomic chromosomal instability, insensitivity to anti-growth signals and evasion of apoptosis[5]. AML susceptibility may be explained by different studies that focus on polymorphisms in genes , which are altering cellular metabolism and negatively affect enzymatic activities of DNA repair mechanisms and detoxification [4].

Some genes are defined as AML risk factors, such as cytochrome P450 genes (CYP2D6, CYP1A1) which act as detoxification genes by encoding for antioxidant enzymes[6]. Polymorphisms in these protein-coding genes have appropriate penetrance that dramatically modify its

phenotype, expression and function as well as possibly altering its enzymatic activity[7].

Cytochrome P450 enzymes (CYPs), are considered as one of the important superfamilies of phase I enzymes which are responsible of endogenous and exogenous (xenobiotic) materials, such as dibenzanthracene, polycyclic aromatic hydrocarbons (PAHs), benzo[a]pyrene, 6-aminochryse, styrene, nicotine, and vinyl chloride. CYPs superfamily enzymes are key factors on the cellular level that confer proper protection against different cellular oxidative stress and prevent further injuries and damage[8].

On the other hand, CYP1A1 polymorphisms can interact with DNA and contribute to DNA adduct formation[9]. The expression of the CYP1 gene family will be manifested as remarkable uncontrolled excessive proliferation of "immature" lymphoblastic and myeloblastic cell lines. This is in addition to its important role in detoxification of environmental factors[10]. To date, approximately twenty variant alleles of CYP1A1 have been identified[10, 11]. The CYP1A1 enzyme plays a great role in hematopoietic cells carcinogenesis. Moreover, recent studies specifically demonstrate strong association of cancer risks and susceptibility with single nucleotide variation in the polymorphisms of CYP1A1[10, 12].

CYP1A1*2A and CYP1A1*2C are well-known polymorphisms of CYP1A1gene, exhibiting changing sequence within protein non-coding gene. The T6235C change is found in specific genetic region of CYP1A1*2A, rs464690 and the A2455G (CYP1A1*2C), has been proposed to have strong association with cancer susceptibility [9, 10, 13].

The single nucleotide polymorphism (SNP) results in the substitution of isoleucine (Ile) by valine (Val) in an exon7 at a codon 462 (i.e. Ile462Val or CYP1A1*2C polymorphism, rs1048943). Therefore, the restriction site polymorphism of Exon7 leads to three genotypes: Ile/Ile form which is a predominant homozygous, Ile/Val which is the heterozygote state and Val/Val which is a rare homozygous state[14]. A2455G change in the heme-binding occurs in the domain of exon 7 (CYP1A1*2C)[9].

Cytochrome 2D6 is one of the human Cytochrome P450 enzymes that are encoded by CYP2D6 gene, which is highly polymorphic, as over catalogued alleles have been evident [15]. The Cytochrome 2D6 has an important role in the body by metabolism of exogenous (xenobiotics) compounds metabolism. The main metabolic function of CYP2D6 is elimination of approximately 25% of prescribed medicines, by the boosting of certain functional groups specifically dealkylation, demethylation, and hydroxylation [16].

Recent published data described 105 allelic variants of CYP2D6. These alleles have been divided into three entities, poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs) and ultra-rapid metabolizers[17].

The main cause of the CYP2D6- PMs phenotype is the CYP2D6*4 polymorphism (position 1934), due to alteration of the splice position at the 3rd intron and 4th exon junction. This genetic polymorphism will directly affect CYP2D6 protein activity and may lead to reduction or absent of encoded protein and resulting in the PMs[18].

To our knowledge, there are a limited number of reported studies to date analyzing the ethnography of genetic polymorphisms of Cytochrome P450 (CYP1A1&2D6) among the Sudanese populations, whose lifestyle is unique and characteristic. Therefore, they might be different from the other population. This will improve information and debunk myths about leukemia cause and identification of individuals at higher risk of having leukemia.

METHODS

Setting: The study was carried out at Radiation and Isotope Khartoum Centre (RIKA), Khartoum, Sudan, which is a national referral hospital, specializing in Oncology supporting all states hospitals in Sudan.

The analytical tasks of this study achieved in collaboration with the Khartoum-Flowcytometery centers, National Center of Neurological Sciences and Institute of Endemic Disease- Khartoum University (Sudan), because of the availability of needed supporting facilities.

Study design & population: This is a retrospective case-control study to detect the impact of genetic polymorphisms of Cytochrome P450 (CYP1A1&2D6) gene in the incidence of AML among Sudanese patients with AML.

Two hundreds Sudanese patients with AML were enrolled in this study (male 102, female 98).; with mean age 34.43 and 65 apparently healthy controls(male 35, female 30) . A total of 65 control subjects, with mean age 40 who have no an evidence of any personal or family background of hematological malignancies or other diseases. Three ml of venous blood was taken from all studied population in Ethylenediaminetetra-acetic acid (EDTA) container.

The total duration including data and samples collection was two years (from June 2016 to June 2018), including further analysis and processing.

Data collection and handling: A pretested, well-designed preformed questionnaire was used to collect data for assessing the role of genetic polymorphisms of Cytochrome P450 (CYP1A1&2D6) gene in the incidence of acute myeloid leukaemia (AML) among different ethnicities of Sudanese population.

Molecular analysis: The DNeasy Blood & Tissue Kit (250) from QIAGEN Kit had been used for DNA extraction according to manufacture procedure, Qiagen, 2006.

Standard polymerase chain reaction method PCR and restriction fragment length polymorphism (RFLP) analysis was used for genotyping.

Statistical Analysis:-All the data was entered and done, using the Statistical Package for Social Science (SPSS) software version 21 and statistical analysis was done. Differences between the two groups for categorical variables will be analyzed by Chi Square test, odds ratios and 95% CI was calculated.

Ethical considerations: The study was approved by the Central Institutional Review Board, Al Neelein University. The participation consent from the participant was assured. They were briefed about the objective of the study before sample collection. They were also informed that all the information was kept purely confidential and was used only for the purpose of statistical analysis.

RESULTS

This case-control study designed to evaluate the impact of genetic polymorphisms of human cytochrome P450 CYP1A1 and & CYP2D6 enzymes involved in the transformation of chemical and cellular metabolism of carcinogenic agents among 200 of Sudanese patients with AML and 65 healthy controls. All participants agreed to fill out the questionnaire as explained to them. All the patients and controls were successfully genotyped by the PCR-RFLP.

Table-1 summarizes the allele and genotype frequencies of the polymorphic cytochrome P450 genes (CYP1A1&2D6) of those subjects. The most frequent genotype observed for CYP1A1 gene among AML patients was heterozygous AG (99%), when we compared with control group (35.38%).Whereas the homozygous GG showed remarkably lower frequency in AML patients (0.5%) with obvious high frequency noted in the controls (63.08%).

However, no statistically significant differences were observed for CYP1A1 AG(OR=8.609, 95% CI: 0.521–14.231, p value = 0.133) in both patients and healthy controls, while significant differences was seen when compared to the GG genotype (OR = 0.024, 95% CI: 0.001–0.737, p value = 0.033).

Table1. Allele and genotype frequencies of the polymorphic cytochrome P450 genes (CYP1A1&2D6) in the Sudanese AML patients.

Genotype/Allele		Case		Exp (B)	95%CI		P-value
		Control N (%)	Patient N (%)		Lower	Upper	
CYP1A1	AA	1 (1.54%)	1 (0.5%)	Ref			
	AG	23 (35.38%)	198 (99%)	8.609	0.521	14.231	0.133
	GG	41 (63.08%)	1 (0.5%)	0.024	0.001	0.737	0.033
	A allele	25 (19.2%)	200 (50%)	-	-	-	-
	G allele	105 (80.8%)	200 (50%)	-	-	-	-
CYP2D6	Wild type E (EM)	1 (1.5%)	1 (0.5%)	Ref.			
	Heterozygous (IM)	13 (20%)	120 (60%)	1.538	0.088	26.821	0.768
	Homozygous (PM)	51 (78.00%)	79 (39.5%)	1.55	0.95	25.32	0.759
	E allele	15 (11.5%)	122 (30.5%)	-	-	-	-
	P allele	115 (88.5%)	278 (69.5%)	-	-	-	-

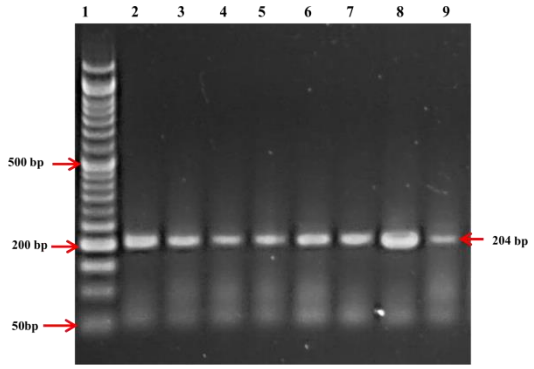

Figure 1. Agarose gel electrophoresis image for CYP1A1gene
Lane 1= 50 bp ladder; lanes 2 – 8 show 204 before digestion by BsrDI.

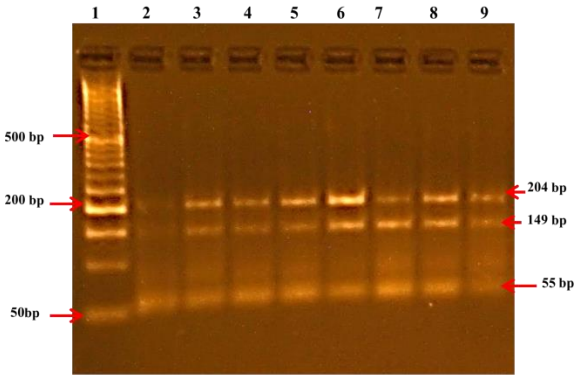

Figure 2. CYP1A1 gene mutation- Heterozygous form
An agarose gel electrophoresis of PCR-RFLP patterns of CYP1A1 gene with BsrDI (Fragments). Lane 1= 50 bp ladder; lanes 2 – 8 show AG (Ile/Val, heterozygous genotype) 204, 149 and 55 bp bands.

Interestingly, there were similar allele frequencies of the CYP1A1 genes for A & G alleles were predominantly seen in both patients and controls (50%). However, the frequency of G alleles is remarkably increased as noted in the control group (80.8%), while the estimation of the frequency of A allele was only (19.2%) in the control as presented in Table-1.

Careful analysis of CYP2D6 showed that the most frequent genotypes in patients was the Heterozygous IM (60%), followed by the Homozygous PM (39.5). On the other hand, the allele frequency result of the wild type EM genotype was significantly lower in AML patients (0.5%), with similar findings in controls (1.5%). In addition, we noticed that the most frequent genotypes obtained in the control group was Homozygous PM (78%), followed by the Heterozygous IM (20%) shown in Table-1.

The observed results for CYP2D6 genotype showed statistically no significant differences for both IM (heterozygous) (OR = 1.538, 95% CI: 0.088–26.821, P = 0.768) and the mutant homozygous (PM) genotype (OR = 1.55, 95% CI: 0.95–25.32, P = 0.759). However, the most frequent alleles noticed for CYP2D6 genotypes was the P allele in patients(69.5%) as well as in controls (88.5%), while lower frequency was obtained in E allele (30.5%) in patients and in controls (11.5%) (Table-1).

DISCUSSION

Cancer is the second leading cause of death in the world - following cardiovascular disease - and in 2015 was responsible for approximately $8.7x10^6$ mortalities[19].

Many reports have been published to clarifying the pathogenic significance of certain genetic polymorphisms encoding carcinogen-metabolizing enzymes (Cytochrome P450), that are actively involved in the development of various cancer forms such as AML[8, 9, 17]. The roles of the

CYP1A1 and CYP2D6 genotypes in susceptibility to leukemia have been discussed by some investigators in different populations, but no consistent conclusions have yet been made on the impact of these polymorphisms in the progression and development of leukemia[10, 12, 14, 20].

In this study, after an analysis and stratification of data, we found that most of the patients assessed for CYP1A1 gene were of heterozygous (AG) form. Furthermore, our reports on the CYP1A1 gene frequencies calculated no significant differences were observed for CYP1A1 AG (p vale = 0.133), whereas higher significant differences were observed for the CYP1A1 GG genotype (P = 0.033 OR = 0.024, 95% CI = 0.001–0.737), which may indicate a protective effect of CYP1A1 GG on AML, as shown in Table 1. These results are in the same line with a previous study on CYP1A1 gene published by Balta et al in Turkish AML patients[20].

Our study reflects no differences in allele frequencies of A and G of CYP1A1 gene observed in all AML patients, they repeated equally (50%) for each; however, allele G occurred significantly more frequently in controls (80.8%). By contrast, the frequencies of polymorphic genes in one population are reported different across various ethnic groups. Additionally, intra-ethnic variations have been established[10, 21]. The CYP1A1 genetic polymorphism were dissimilar in different areas as well as varied ethnic groups [22].

In Maxico population, the prevalence of CYP1A1 Val allele was 6% and 16% in the healthy individuals and ALL patients respectively[23], whereas, people of Turkish appears to have higher prevalence for CYP1A1 (heterozygous mutant), than the individuals of other Western countries (9.8%)[24].

Interestingly, there has been a surprising lack of scientific consensus among a few studies; including reports conducted by Aydin-sayitoglu et al and meta-analysis done by Zhuo et al. found that the CYP1A1 Ile462Val may have a marked correlation with high acute leukemia risk[14, 25] . Also another study conducted in Italy concluded that the presence of CYP1A1 polymorphic xenobiotic-metabolism genes, including CYP1A1*4 may increase the risk of adult AML[26]. Conversely, few studies concluded that no obvious significant association of CYP1A1 polymorphisms with risk of leukemia[21].

In a study done on other variants of CYP1A1 also lack of consensus[27]. A meta-analysis study failed to reveal a significant association between CYP1A1 MspI variation and childhood acute leukemia[28]. Also another study found no association of CYP1A1 *2A or *2B with AML[27]. However, the CYP1A1*2A CYP1A1 m1 alleles were found to be highly inducible and strongly associated with high enzymatic activity and greater risk of developing ALL[9, 26].

In other hematological disorders like ALL, there was an elevated prevalence of the CYP1A1 Val/Val genotype[29] and also ALL subjects that carry at least one variant allele of both CYP1A1m1 and m218. Other findings demonstrated association between polymorphic alleles of CYP1A1 and risk of developing CLL[30]. The rapid metabolizer alleles *2A and *2B have not been associated with lymphomas[3].

The reasons behind the inconsistent findings regarding the CYP1A1 polymorphisms are unknown, but clearly the ethnic variation in enzyme activity and an association between this polymorphism and environmental factors could contribute to factors that influence the leukemia[31]. Therefore, polymorphism of CYP1A1 might play different roles in different cancers including hematological malignancies.

Furthermore, genetic and statistical analysis of the CYP2D6 gene reveals a higher frequency of the heterozygous polymorphic gene in cases over controls (60% in cases and 20% in controls), as demonstrated in Table 1. While no significant variations were observed for both intermediate metabolizer (IM) (heterozygous) (OR = 1.538, 95% CI: 0.0858–26.821, P = 0.768) and the mutant homozygous poor metabolizer (PM) genotype (OR = 1.55, 95% CI: 0.95–25.32, p value = 0.759). This means no association found between CYP2D6 genotype and the risk of AML.

Additionally, the results of this study also showed higher frequency level of the P allele homozygous PM (poor metabolizer) in both AML patients (69.5%), and a control population (88.5%). It was hypothesized that PM individuals were at increased risk of developing different hematological neoplasia, because of the subsequent impaired detoxification of a hypothetical, as yet unidentified chemical (32). However, other studies suggested a merely protective relationship between the PM allele carriers and leukemia development[18]. However, a few authors found no significant association ascertained[25].

In contrast, the prevalence of CYP2D6*4 varies across different ethnicities, and frequencies of 36.6, 28.6, 28.0, 13.8, 13.8, 7.3 and 0.2% have been documented in Iranians[19], Malaysian Indians[32], Turks[33], Spanish subjects[34], Brazilians[35]. Similar studies in Africans and African Americans have observed almost 50% of CYP2D6 allele frequencies have reduced function and enzymatic activity. In the Ethiopian population study showed absence of alleles CYP2D6*4[36]. Some studies conclude that black populations may also carry higher levels of SNPs associated with reduced 2D6 enzymatic activity[37].

Our result matches and are comparable to studies published by Lemos et al calculated a higher frequency of CYP2D6*4 in the leukemia group[38]. Similarly, phenotyping studies show an elevated risk of acute leukamia in adults with CYP2D6 PM phenotype among Indian population[39]. Also, it was proven by Liu et al significant association of the CYP2E1*5 variant genotype (cytochrome P450 isoforms) with an elevation risk for developing acute leukemias including both ALL and AML[22]. Furthermore, a different study showed significant correlation between CYP2E1 and CYP2D6 genes and the etiology of acute leukemias[40].

The reasons for the inconsistency in findings for both CYP1A1 and CYP2D6 gene polymorphisms, can be explained by the contradictory data obtained from published reports on the association of leukemia risks and gene polymorphisms could be due to several factors e.g. ethnicity differences (inter-individual variations), lifestyle factors, geographical differences and different environmental carcinogens exposure. Accumulating clinical evidence demonstrates that the combinations of susceptibility variants or number of patients may have great effect on results differences. This is true especially of

CYP450 enzyme genes, which may influence carcinogenesis pathways, and where environmental factors make such comparisons more complex.

CONCLUSION

Our findings illustrated that the genetic polymorphisms in genes for xenobiotic metabolizing enzymes CYP1A1 heterozygous AG reveal no significant association with AML, where homozygous GG shows a protective effect. CYP2D6 suggests no association with the risk of AML for both heterozygous IM and the mutant homozygous PM.

Recommendation: In spite of the above, further studies are still needed, especially for further elucidation of the roles played by other genes, in gene-gene and gene-environment interaction, and phenotypic studies to clarify their exact role in disease development.

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Data and Materials: Availability: The data underlying the findings of this study is available from the last author, on request.

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