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Original article

Association of genetic predisposition studies in *CYP1A1* polymorphism studies in acute myeloid leukemia

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ABSTRACT

Cytochrome P450 Family 1 Subfamily A Member 1 (CYP1A1) gene is one of the sub-members of CYP450 family member and it encodes with the families of drug metabolizing enzyme families along with the cancers and leukemias. Among leukemias, AML is considered to be one of the important leukemia which attack the older adults. The aim of this study is to explore the role of A4889G polymorphism in CYP1A1 gene in acute myeloid leukemia (AML) in the Saudi population. This study was designed as an experimental case-control study in which 100 AML cases and 100 controls were selected. This in vivo study was carried out using genomic DNA extraction, polymerase chain reaction and agarose gel electrophoresis and then BsrDI restriction enzyme to digest the A4889G polymorphism of the PCR products. In this study, 200 subjects were digested and based on the appearance of the bands, genotypes were categorized. The attained data was used to calculate the clinical details as well as genotype analysis. The study results confirmed AG genotype (OR = 3.23, CI = 1.60–6.55, p = 0.0008), AG + GG (OR = 3.47, CI = 1.76–6.86, p = 0.0002) and GG + AA (OR = 12.47, CI = 6.18–15.17, p < 0.0001) and G vs A (OR = 3.15, CI = 1.71–5.81, p = 0.0001) were associated in AML cases. In conclusion, we confirm that A4889G polymorphism is associated with AML in the Saudi population.

1. Introduction

In this era, cancers and leukemias are exploring in the worldwide population. Among leukemias, acute myeloid leukemia (AML) is documented as an aggressive hematologic malignancy characterized as recurrent abnormalities in both cytogenetic and molecular patterns which results in varied hematopoietic precursors (Lachowiez et al., 2023). In majority of AML patients, somatic mutations exist in which 50 % of them were large genomic rearrangements, structural variants and copy no variants (Levy et al., 2023). The treatment is still challenging among AML patients with survival rate of 30 % patients during the half-decades (Naldini et al., 2023). Blood, bone marrow, and, if necessary, cerebrospinal fluid must undergo a variety of laboratory examinations, including morphological, immunophenotypic, and genetic assessment, in order to arrive at a definitive diagnosis of AML (Mehta et al., 2023). Classification of AML is an ongoing endeavor necessary for effective disease treatment (McCarter et al., 2023). The majority of cases of AML occurred in the elderly, with a median age at diagnosis ranging from 68 to 71 years old (Chen et al., 2023). The average patient with AML is above the age of 65, while the median age of diagnosis is 68. About 20,240 people in the United States were diagnosed with AML in 2021. The overall 5-year survival rate for people diagnosed with AML was estimated to be 29.5 % in the most recent available data (2011–2017) (Daver et al., 2023). About half of those diagnosed with AML had intermediate-risk karyotypes. Due to the heterogeneity of this group, the use of new molecular markers is becoming more important for determining prognosis and guiding therapy (Hussein et al., 2023). The increasing number of cases of cancer in children and young adults may be traced to a combination of causes. Pollutants, radiation, and chemicals are just some of the environmental carcinogens that may play a role. Cancer risk may also be influenced by dietary and lifestyle variables including obesity and inactivity (Usenova et al., 2023). A 40 % of leukemia cases in the West are diagnosed as AML, making it the most common form of acute leukemia in adults. It is predicted that there are 3.5 new instances per 100,000 people each year, with the rate increasing with age to 12.6 % per 100,000 people among those over the age of 65. Patients are typically between the ages of 60 and 75 when they are first diagnosed, with a median age of 64 years (Alarcón-Payer et al., 2022). The prevalence of AML cases diagnosed in the Saudi population was found to be 17 % and 25 % in male and female population (Alahmari

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et al., 2021). There has been an abundance of research into the causes of this condition, but scientists still don't fully understand the biochemical processes at play here (Ahadi et al., 2022). Humans have many genetic variations, the most frequent of which are single nucleotide polymorphisms (SNPs), which are being shown to have an increasingly essential role in human diseases (Wu et al., 2023). Numerous SNPs in a broad variety of genes have been linked to an increased risk of AML by genome-wide association studies (GWAS). Genomic changes in AML patients are said to differ significantly from those in adults with the disease (Deng et al., 2023).

Xenobiotics are non-biological chemicals which include medications, environmental agents, carcinogens, and natural substances. Xenobiotic side effects are caused by covalent interactions between intermediate metabolites and genetic materials or proteins and their metabolites. The principal enzyme systems catalyzing phase I oxidative metabolism are those belonging to the cytochrome P450 (CYP) superfamily. Phase II enzymes may be involved in the detoxification of hazardous compounds produced during these processes (Taspinar et al., 2008). The CYP1A1 gene is a member of the CYP family, which is important for the metabolism of polycyclic aromatic hydrocarbons (Abd El Wahab et al., 2017). The CYP1A1 gene is a polymorphic gene that normally codes for drug metabolism and the conversion of some exogenous procarcinogens have been transformed into extremely reactive electrophilic carcinogens chemicals. Both of these processes depend on the CYP1A1 gene, which is polymorphic and encodes for a crucial phase-translational enzyme aryl hydrocarbon hydroxylase I XME (Indulski and Lutz, 2000). One of the commonly studied polymorphisms are A4889G (rs1048943), which is present at 7th exon region (Oliveira et al., 2015). Full fledge studies were not recorded in the Saudi Arabia among the case-control population-based studies in AML. Only, few studied were studied among AML in the Saudi population (Al-Amer et al., 2019, Farasani 2019, Farasani 2019, Al-Tamimi et al., 2022, Farasani, 2022, Farasani 2023, Farasani 2023, Farasani 2023). The exon region-based polymorphisms are considered to be playing a major role in the human diseases especially leukemias and cancers and in this study, we aimed to explore the A4889G polymorphism present in *CYP1A1* gene among AML patients diagnosed in the Saudi population.

2. Materials and methods

AML cases and controls

We have collected 200 blood samples used for this study. The 100 AML patients has confirmed as cases in this study and these 100 AML cases were compared with 100 controls. All the 200 samples were collected from one of the major laboratories in the Saudi Arabia which is known as Riyadh Regional Laboratories (RRL) in the capital city i.e., Riyadh city. The inclusion and exclusion criteria of AML cases and controls were described in our prior studies (Farasani 2023). The patients who were confirmed with other cancers and leukemia's are excluded from cases and controls of this study and additionally none of the controls were developed or had any type of family history of cancers or leukemia's. Both the cytogenetics and histopathological tests were confirmed in AML patients in their specific labs of RRL. Flow cytometry, a full blood count, and bone marrow tests all pointed to AML. Cytogenetic and FISH analysis further confirmed the results of AML. Ethical approval was received for this study, participants (n = 200) has signed the patient consent form and this study was designed as the declaration of Helsinki. The AML patients has not documented any other diseases involved in this study. From each patient, 2 ml of EDTA blood was collected (Alshammary et al., 2023) and processed for the protocol of DNA isolation analysis.

DNA analysis studies

All 200 patients of the venous blood were collected in an EDTA vacutainer and was used to isolate the genomic DNA using genomic DNA purification kit. The DNA isolation was carried out as per the given kit from the company. The completion of DNA isolation further will take place to check the quality of the DNA through the instrument using NanoDrop spectrophotometer which can be used to quantify the DNA quality. After successful completion of verifying all the qualities of DNA, further we have proceeded to conduct the PCR analysis for CYP1A1*2C SNP. This includes both forward and the reverse primer sequences such as F: CTGTCTCCCTCTGGTTACAGGAAGC and the R: TTCCACCCGTTGCAGCAGGATAGCC; which is finally converted into 10pmoles. Genotyping was carried out using 50ul reactions which includes the combination of 10pmoles of both the sequences of the primers as shown below. Furthermore, we have added the master mix, DNA templates and finally PCR reaction was made up to 50ul reaction. In this study, denaturation, annealing at 62 °C and extension was applied to make-up the 35-cycle reaction and holds at 4 °C after the completion of the experiment. The primer sequence consists of 204 bp of PCR sequence. A well-known restriction enzyme i.e., BsrDI was used to digest the PCR products into149 and 55 bp respectively. The protocol of the digestion was carried out based on the recent study (Alsobaie et al., 2023). PCR and BsrDI was run on 2 % agarose gel stained with ethidium bromide liquid.

Statistical analysis

In this case-control study, the t-tests were used to measure basic information present in the Table 1. HWE analysis was studied in the control population. The Table 2 in this study defines the genotype and allele frequencies and in Table 3, both the genotype and allele frequencies were calculated using odds ratios (ORs), 95 % confidence intervals (95 %CIs) and the p values using different genetic models. Overall, p value was considered as < 0.05 as a positive association in this study (Khan et al., 2019).

3. Results

Demographic details

Based on the research's design, 100 AML patients and 100 controls were chosen for this study. Table 1 displays age and gender information. In this study, the age range of 200 subjects was in between 18 and 82 years of the age in which control subjects were found to be 18–63 years and cases were found to be 19–82 years of the age. The mean age of the AML cases and controls were shown as 38.91 ± 15.10 and 39.92 ± 12.06 years of the age. In this study, 61 % of male and 39 % of the females were present in the AML cases, while, 54 % of male and 46 % of the females were present. However, age calculated between AML cases and controls and found to be non-significant association (p = 0.60). We did not calculate the gender and age ranges as it was not applicable for calculating t-tests. The HWE-analysis was calculated towards the control population and variant allele frequency was found to be 0.08, while χ^2 was 0.24 and p value is 0.62 which indicates HWE was found to be consistent towards designing this study.

Genetic association studies

The genotype and allele distribution between AML cases and controls were showed in Table 2. In this study, AA genotype was considered to be Isoleucine (Ile)/Ile, AG was considered to be Ile/Valine (Val) and GG was considered to be Val/Val. Ile/Ile are digested with two alleles and indicated as +/+ and termed as homozygous extensive mobilizer, while, +/- are digested with only one allele and is termed as heterozygous extensive mobilizer. Finally, -/- was not digested with any of the alleles and confirmed to be poor metabolizers of this study. Overall, AA/AG/GG is defined as Ile/Ile, Ile/Val, Val/Val as well as homozygous/

Table 1
Age and gender details information for AML cases and control subjects.

	AML cases (n = 100)	Controls (n = 100)	P value
Age (Years)	38.91 ± 15.10	39.92 ± 12.06	0.60
Age Ranges	19–82 years of age	18–63 years of age	NA
Male (Gender)	061 (061 %)	054 (054 %)	NA
Female (Gender)	039 (039 %)	046 (046 %)	NA

Table 2
Genotype and allele frequencies present in AML cases and controls.

CYP1A1*2C	Controls (n = 100)	Cases (n = 100)
AA genotype	85 (85 %)	62 (62 %)
AG genotype	14 (14 %)	33 (33 %)
GG genotype	01 (01 %)	05 (05 %)
A allele	184 (0.92 %)	157 (78.5 %)
G allele	16 (0.08 %)	43 (21.5 %)

Table 3
Calculation of genotype, genetic models and allele frequencies in AML cases and controls.

A4889G	Odds ratios (ORs)	95 % Confidence intervals	P values
AA	1.00	1.00	1.00
AG	3.23	1.60–6.55	0.0008
GG	6.86	0.78–60.15	0.04
AG + GG vs AA	3.47	1.76–6.86	0.0002
GG + AA vs AG	12.47	6.18–15.17	<0.0001
AG + AA vs GG	5.21	0.60–45.42	0.09
A allele	1.00	1.00	1.00
G allele	3.15	1.71–5.81	0.0001

heterozygous/poor extensive metabolizers. In this study, the control women were found to have 85 %, 14 %, and 1 % of AA, AG and GG genotypes and AML cases were found to have 62 %, 33 % and 5 %. The details were shown in Table 2. The AA genotype was found to be high in controls and both the AG and GG genotypes was high in AML cases. However, statistical association was shown in Table 3 and it was calculated between AML cases versus controls. In this study, AG genotype (OR = 3.23, CI = 1.60–6.55, p = 0.0008), AG + GG (OR = 3.47, CI = 1.76–6.86, p = 0.0002) and GG + AA (OR = 12.47, CI = 6.18–15.17, p < 0.0001) genotype distributions was approximately significant higher in AML cases when studied with the control subjects. The allele frequencies were 92 %, 8 % and 78.5 %, 21.5 % in controls and AML cases of A and G alleles and positive impact was found on it (OR = 3.15, CI = 1.71–5.81, p = 0.0001).

4. Discussion

This study aimed to execute the molecular association based studied in A4889G polymorphism in *CYP1A1* gene in the Saudi patients diagnosed with AML disease. In this case-control study, 100 AML and 100 control population samples were selected and A4889G polymorphism was studied. The mean age of the controls was found to be high in compared towards AML cases i.e., 39.92 ± 12.06 and 38.91 ± 15.10 years. The AA genotype was found to be high in controls, while AG and GG genotypes was found to high in AML cases. Genetic association was found in AG (AG vs AA: OR = 3.23, CI = 1.60–6.55, p = 0.0008) and additionally in different genetic models i.e., AG + GG (OR = 3.47, CI = 1.76–6.86, p = 0.0002) and GG + AA (OR = 12.47, CI = 6.18–15.17, p < 0.0001). The A allele was high in controls, while G allele was high in AML cases i.e., (OR = 3.15, CI = 1.71–5.81, p = 0.0001). This study was found to be in agreement with HWE analysis.

The A4889G is one of the polymorphisms in CYP1A1 gene is considered to be drug metabolizing enzymes which is contributing to the susceptibility of human diseases precisely in leukemias and cancers. Previous studies have contributed towards cancers (Oliveira et al., 2012, Cardoso-Filho et al., 2013, Li et al., 2013, Oliveira et al., 2013, Oliveira et al., 2015) as well as leukemias (Krajinovic et al., 2002, Barragan et al., 2007, Yamaguti et al., 2010, Swinney et al., 2011, Cardoso-Filho et al., 2013, Lakkireddy et al., 2015, Zou et al., 2015, Zou et al., 2016). However, a *meta*-analysis study was documented studied between A4889G polymorphism and AML (Vijayakrishnan and Houlston, 2010). This similar polymorphism was studied with overall risks of cancer in the form of *meta*-analysis studies (Wu et al., 2013). Both AG and GG genotypes were found to be causing a disease susceptibility locus for developing AML in the studied population. However, age and gender factors cannot be considered in this restricted case-control study as we have opted 100 AML cases and 100 controls based on the previous study towards the sample size enrollment (Alkudmani et al., 2023). In control population of this study, the frequencies of AG and GG genotypes were found to be low when compared with AML cases. This could be one of the major factors for developing AG and GG genotypes in AML cases and low in control subjects. We have selected both the AML cases and controls with almost similar age criteria and there was no elevation in the gender population between AML cases and controls. Our study was found to be similar and supportive towards the Taspinar et al (Taspinar et al., 2008) studies as this study showed the AG and GG genotypes high in AML cases vs controls and their control population was found to be low. But this study was carried out in CML cases and our study carried out in AML cases. This is the one of the differences between our study and Taspinar et al (Taspinar et al., 2008) studies. Based on the documented studies, we confirm that polymorphisms play a huge role in cancers and leukemias specifically, AML in the children. It is envisaged that the therapeutic response would contribute in the development of fresh, alternative therapeutic techniques for the treatment of AML, strategies that may be effective on their own or in tandem with current medications. New methods are making it possible to collect an individual's whole genomic sequence, which would allow for the detection of polymorphisms in the genome and the consequent prediction of cancer susceptibility (Lakkireddy et al., 2015).

In this study, one of the limitations of this study can be documented as studying only one polymorphism. Missing of validation can be another limitations of this study. The final limitations could be restricted to limited sample size.

5. Conclusion

This current study confirms A4889G polymorphism is associated with AML patients in the Saudi population. This study recommends to update the *meta*-analysis studied between AML and A4889G polymorphism as the previous study was documented in 2010 (Vijayakrishnan and Houlston, 2010).

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