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Gene Polymorphism of CYP2B6 and Susceptibility to Acute Myeloid Leukemia in Egypt

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ABSTRACT

Background: Acute myeloid leukemia (AML) is a diverse hematologic neoplasm that is distinguished by aberrant myeloid progenitor cell growth. Genetic factors, including polymorphisms in drug-metabolizing enzymes, such as CYP2B6, have been implicated in AML susceptibility and treatment outcomes. Understanding the association between CYP2B6 gene polymorphisms and AML risk can offer insights into personalized treatment strategies and prognosis.

Objective: To ascertain the relationship between CYP2B6 gene polymorphism (rs3745274) and vulnerability to AML in the Egyptian population. Additionally, the study aimed to explore the potential connections between this genetic variation and clinical outcomes, as well as patients' survival.

Patients and methods: In the current study, a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique using BseNI restriction enzyme was used to investigate the CYP2B6 rs3745274 gene polymorphism in the peripheral blood and/or bone marrow of 105 AML patients and 111 healthy controls. **Results:** Based on the study's findings, there was a notable increase in GT, GT+TT genotypes, and T alleles observed in AML patients in contrast to the control group. The statistical analysis indicated that the differences in these polymorphic variants were significant with P-values of 0.018, 0.011, and 0.015, respectively. However, these genetic variations were not associated with any specific FAB subtypes, clinical outcomes, or patients' survival.

Conclusion: CYP2B6 rs3745274 gene polymorphism may potentially assist in the emergence of AML.

Keywords: AML; SNP; CYP2B6 rs3745274.

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous disease that results from the uncontrolled proliferation of clonal hematopoietic cells. It is the most prevalent form of acute leukemia in adults, with diagnosis typically occurring at a median age of 68 years. Despite its prevalence and the identification of various risk factors, the precise pathogenesis of AML remains incompletely comprehended. It is worth noting that exposure to certain genotoxic xenobiotics, such as chemotherapeutic alkylating agents, benzene, ethylene oxides, and herbicides, can lead to a higher chance of acquiring AML [1,2]. The process of carcinogenesis caused by genotoxic xenobiotics is intricate and multi-stage process. The efficacy of these stages is influenced by gene polymorphisms in phase I and phase II detoxification enzymes, which are responsible for the metabolic activation and detoxification of carcinogens [3].

Cytochrome P450 (CYP450) superfamily belongs to phase I detoxification enzymes that shield cells from several exogenous and endogenous genotoxic compounds [4,5], by inserting an atom of molecular oxygen into these substrates, serving as mono-oxygenases, oxidases and peroxidises [3]. Thirty-seven unique star-alleles, or gene haplotypes with a unique variation amino acid sequence or proven functional impact, are mentioned on CYP alleles website. More than thirty single-nucleotide polymorphisms (SNPs) vary in amino acid and can occur singly or in combination has many more SNPs that haven't been linked to specific haplotypes yet, along with more non-coding variations [6,7]. Belonging to this family is CYP2B6, whose gene located in the CYP2 gene cluster on the long arm of chromosome 19 [8]. CYP2B6 is primarily expressed in the liver, accounting for approximately 1-10% of the total CYP P450 pool [9]. In addition to the liver, CYP2B6 exhibits consistent expression in various sections of the digestive, respiratory systems, skin, and kidneys; nevertheless, the precise role of CYP2B6 in these extra hepatic tissues is not yet understood [10-12]. The CYP2B6 enzyme is essential for the metabolism of many different substances, including prescription medications, noxious agents found in the environment like pesticides, and substances found naturally in the body such steroid sex hormones. Because of this, it is essential to the body's processes of drug metabolism and detoxification [13].

The expression and enzymatic activity of CYP2B6 exhibit a wide range of inter-individual and ethnic variance. This variation can be attributed to the widespread genetic polymorphism present, as well as the presence of potent inducers and inhibitors that impact its expression [6]. The CYP2B6 gene is known to have a specific SNP called rs3745274. This SNP is characterized by a substitution of guanine to thymine at nucleotide 516 in exon 4 (c.516G>T), concluding in a replacement of glutamine to histidine at amino acid position 172 (Gln172His). Accordingly, this variant is associated with a notable decrease, approximately 50-75%, in enzyme levels, which is caused by improper mRNA splicing and lower expression of functional mRNA [14]. Additionally, this inactivating polymorphism has been reportedly associated with various hematologic malignancies, including acute leukemia, myelodysplastic syndromes, and breast cancer

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[3,15-18]. Furthermore, it affects the response to fludarabine plus cyclophosphamide chemotherapy in chronic lymphocytic leukemia (CLL) [19]. While previous studies investigated the correlation of this polymorphism to AML risk, but none examined the relationship between it and clinical outcome or survival [16,17]. The current study set out to examine any possible correlation between our population's risk of AML and polymorphism variants of the CYP2B6 gene. We further investigated the possible connections between these genetic variations and clinical outcomes and patients' survival.

PATIENTS AND METHODS

Study Population

Retrospective case-control research was done on 105 AML patients and 111 healthy control subjects. The patients received their diagnoses at the Haematology Unit of Mansoura University's Oncology Centre between January 2011 and June 2015. The WHO classification of acute leukemias and myeloid neoplasms was used to make the diagnosis [20,21]. Patients without any structural or numerical abnormalities and with normal karyotypes were included in the study. The study specifically excluded patients with therapy-related AML (t-AML) and acute promyelocytic leukaemia (APL).

Genotype Analysis

The bone marrow and/or peripheral blood of AML patients, and 5 ml of control participants' peripheral blood (on EDTA), were used to extract the genomic DNA. Following the manufacturer's guidelines, the QIAamp DNA Blood Mini Kit from Qiagen (Hilden, Germany) a well-known worldwide supplier of molecular biology products, was utilised for the extraction procedure. After that, genotypic analysis was conducted using the isolated DNA as a template.

The genotyping of CYP2B6 rs3745274 was conducted utilizing a conventional PCR-RFLP approach on both AML and control samples. The gene amplification process was initiated via the forward primer (5'-AGGTGACAGCCTGATGTTCC-) and the reverse primer (5'-TTTCTCGTGTGTTCTGGGTG-3'. In a 50 µl total reaction volume, the amplification mixture contained the following final concentrations: 4 µM of both forward and reverse primers, 200 µMdNTPs (Roche), 4U FastStart Taq polymerase (Roche), 10X Buffer (MgCl2, 25 mM) (Roche), 5 µl of DNA template, and nuclease-free water (Qiagen).

The polymerase chain reaction (PCR) amplification process was carried out under carefully controlled cycling conditions. To be more precise, the procedure involved three minutes of initial denaturation at 94°C, succeeded by 35 cycles of denaturation at 94°C for two minutes each. Annealing at 55°C and extension at 72°C for two minutes each came right after these. The procedure was finished with a final extension phase that lasted ten minutes at 72°C. UV transillumination was used to visualise the amplified PCR products on a 1 % agarose gel that had been previously ethidium bromide-stained. The DNA samples were subjected to digestion using the restriction enzyme BseNI, as per the manufacturer's guidelines. Subsequently, the digested products were subjected to electrophoresis on a 1% agarose gel, and the resulting genotypes were classified into three distinct patterns: homozygous wild (GG), heterozygous (GT), and homozygous mutant (TT).

Ethical consideration:

The study was carried out following permission from Mansoura University's Research Ethics Committee (Approval number: R.24.04.2595). Each patient gave written, informed consent. The consent form explicitly stated that the participants accepted to publish their data in medical studies and that the provided data would be kept private and confidential. The study was executed per the World Medical Association's Code of Ethics for research involving human participants (Declaration of Helsinki).

Statistical Analysis

SPSS (Statistical Package for the Social Science) program version 20, developed by SPSS, Inc. Chicago, USA and Microsoft Office 2013 Excel were utilized for the statistical analysis of data.

Mean, standard deviation (SD), median, and range were displayed for quantitative data. Frequency and percentage were used to represent qualitative data. The χ^2 test was utilized to contrast the observed and anticipated frequencies of genetic variants in order to confirm that the genotype and allele distributions in the analysed groups fit the Hardy-Weinberg equilibrium. The relationships between the CYP2B6 rs3745274 genotype and AML were estimated using logistic regression analysis, and the ORs and their 95 % CI were calculated. The Kaplan-Meier test was utilized to examine the survival data, and log-rank test was performed to determine the statistical significance of the discrepancies between the curves. If p-value is < 0.05 at a 95% CI, it was deemed significant.

RESULTS

Clinical Characteristics of the studied population:

The 111 healthy participants in the control group, whose mean age was 45.5±13.1 years and who were divided 64% into males and 36% into females, participated in the study. In contrast, the patient group included 105 AML patients with a mean age of 44.2±14.2 years, 71 (67.6%) males and 34 (32.4%) females. With 31.4% of cases among the patients, M4 was the most prevalent FAB subtype. Complete remission (CR) has been accomplished in 60% of the patients, while induction death occurred in 25.7% of the patients during the research period, 14.3% of patients were resistant to treatment, 12.4% experienced relapses, and 34.3% died during the research as illustrated in table (1).

Table (1): The patients' clinical characteristics and outcome.

		AML (N=105)
Age (years); mean ±SD		44.2±14.2
Males; N (%)		71 (67.6)
Females; N (%)		34 (32.4)
Fever /infection; N (%)		78 (74.3)
Pallor; N (%)		96 (91.4)
Bleeding tendency; N (%)		74 (70.5)
Splenomegaly; N (%)		61 (58.1)
Hepatomegaly; N (%)		74 (70.5)
Lymphadenopathy; N (%)		54 (51.4)
Total leucocytic count ($X10^9$/L); median (range)		18 (0.9-213)
Hemoglobin concentration (g/dL); median (range)		8 (4.2-13.4)
Platelets count ($X10^9$/L); median (range)		41 (6-335)
Peripheral blasts (%); median (range)		80 (9-95)
Bone marrow blasts (%); median (range)		79 (22-95)
LDH (IU/L); median (range)		638 (190-2546)
FAB; N (%)	**M0**	3 (2.9)
	M1	20 (19)
	M2	22 (21)
	M4	33 (31.4)
	M5	15 (14.3)
	M6	9 (8.6)
	M7	3 (2.9)
Complete remission; N (%)		63 (60)
Induction death; N (%)		27 (25.7)
Refractory; N (%)		15 (14.3)
Relapse; N (%)		13 (12.4)
Total mortality; N (%)		36 (34.3)

AML: Acute Myeloid Leukemia, FAB: French-American-British (Classification system for AML subtypes).

CYP2B6 rs3745274 genotyping and risk of AML:

The Dakahlia Governorate's research population was chosen randomly, and they were unconnected. CYP2B6 rs3745274 genotypes in AML cases and control subjects were independent, indicating they were in Hardy-Weinberg equation (HWE). No evidence suggested rejection of HWE assumption in the sample.

The CYP2B6 rs3745274 genotype analysis using RFLP revealed four different restriction patterns. The homozygous mutant (TT) showed one fragment of 289 bp, while the homozygous wild (GG) showed two fragments of 196 bp and 93bp. The GT heterozygous group was found to exhibit either three or four fragments. Table 2 displays the frequency of alleles and genotypes in both groups. A comparison of the genotypic and allele frequencies between the two groups revealed a significant difference. AML patients showed a greater occurrence of the T allele, GT, and GT+TT genotypes in contrast to the control group.

Table (2): Distribution of CYP2B6 rs3745274 alleles and genotypes in AML patients and control group.

Genotypes and alleles	Control (n=111)		AML (n=105)		*P*	OR (95%CI)
	No	%	No	%		
GG	68	61.3	46	43.8	-	Reference
GT	40	36.0	53	50.5	0.018	1.959 (1.124-3.413)
TT	3	2.7	6	5.7	0.139	2.957 (.704-12.423)
GT+TT	43	38.7	59	56.2	0.011	2.028 (1.179-3.490)
G	176	79.3	145	69.0	0.015	1.715 (1.108-2.655)
T	46	20.7	65	31.0		

AML: Acute Myeloid Leukemia, OR: Odds Ratio, CI: Confidence Interval.

Correlation of CYP2B6 rs3745274 genotypes to patients' characteristics, outcome and survival:

The data presented in table 3 reveals no discernible variations between the CYP2B6 and rs3745274 genotypes regarding FAB subtypes, laboratory data, demographic data, or clinical outcomes. Moreover, the overall survival (OS) and disease-free survival (DFS) rates across different genotypes were examined, and no significant differences were seen, as shown in table 4 and Figures 1 and 2.

Table (3): CYP2B6 rs3745274 genotypes according to patients' characteristics and outcome

	***CYP2B6* rs3745274**						***p***
	GG (n=46)		**GT (n=53)**		**TT (n=6)**		
Age (years); mean ±SD	44.1	13.9	44.8	14.7	44.2	14.2	0.741
Males; N (%)	30	65.2	36	67.9	5	83.3	0.793
Females; N (%)	16	34.8	17	32.1	1	16.7	
Fever /infection; N (%)	32	69.6	41	77.4	5	83.3	0.664
Pallor; N (%)	45	97.8	46	86.8	5	83.3	0.067
Bleeding tendency; N (%)	31	67.4	38	71.7	5	83.3	0.782
Splenomegaly; N (%)	28	60.9	28	52.8	5	83.3	0.345
Hepatomegaly; N (%)	30	65.2	39	73.6	5	83.3	0.601
Lymphadenopathy; N (%)	26	56.5	26	49.1	2	33.3	0.507
Total leucocytic count (x10^9/L); median (range)	17	0.9-213	18	2-213	19	0.9-91	0.919
Hemoglobin concentration (g/dL); median (range)	8.9	4.2-12.5	7.5	4.2-13.4	8.6	7.4-10	0.303
Platelets count (x10^9/L); median (range)	39	6-335	44	7-303	41.5	20-142	0.771
Peripheral blasts (%); median (range)	83	9-95	70	30-95	47	9-80	0.226
Bone marrow blasts (%); median (range)	64	22-95	80	22-95	80	22-90	0.102
LDH (IU/L)	638	190-2546	638	190-2546	882.5	565-1200	0.958
M0	3	6.5	0	0	0	0	0.241
M1	10	21.7	9	17.0	1	16.7	0.842
M2	9	19.6	11	20.8	2	33.3	0.735
M4	13	28.3	17	32.1	3	50.0	0.553
M5	5	10.9	10	18.9	0	0	0.460
M6	4	8.7	5	9.4	0	0	1
M7	2	4.3	1	1.9	0	0	0.659
Complete remission; N (%)	29	63.0	30	56.6	4	66.7	0.768
Induction death; N (%)	11	23.9	15	28.3	1	16.7	0.879
Refractory; N (%)	6	13.0	8	15.1	1	16.7	1
Relapse; N (%)	5	10.9	8	15.1	0	0	0.631
Total mortality; N (%)	14	30.4	19	35.8	3	50.0	0.564

LDH: Lactate Dehydrogenase.

Table (4): *CYP2B6* rs3745274 genotypes according to survival times.

Survival	*GG*				*GT*				*TT*				*p*
	Cumulative Survival (%)	**Mean *(months)***	**95% CI**		**Cumulative Survival (%)**	**Mean *(months)***	**95% CI**		**Cumulative Survival (%)**	**Mean *(months)***	**95% CI**		
OS	69.1	35.294	29.24	41.385	72.2	30.466	24.012	36.921	41.7	21.194	10.676	31.713	0.556
DFS	69.9	38.097	31.81	44.313	61.0	36.154	29.693	42.614	66.7	28.333	20.065	36.602	0.993

Cumulative Survival: Cumulative proportion surviving at 24 months. CI 95%: Confidence interval at 95%, OS: Overall survival. DFS: Disease free survival.

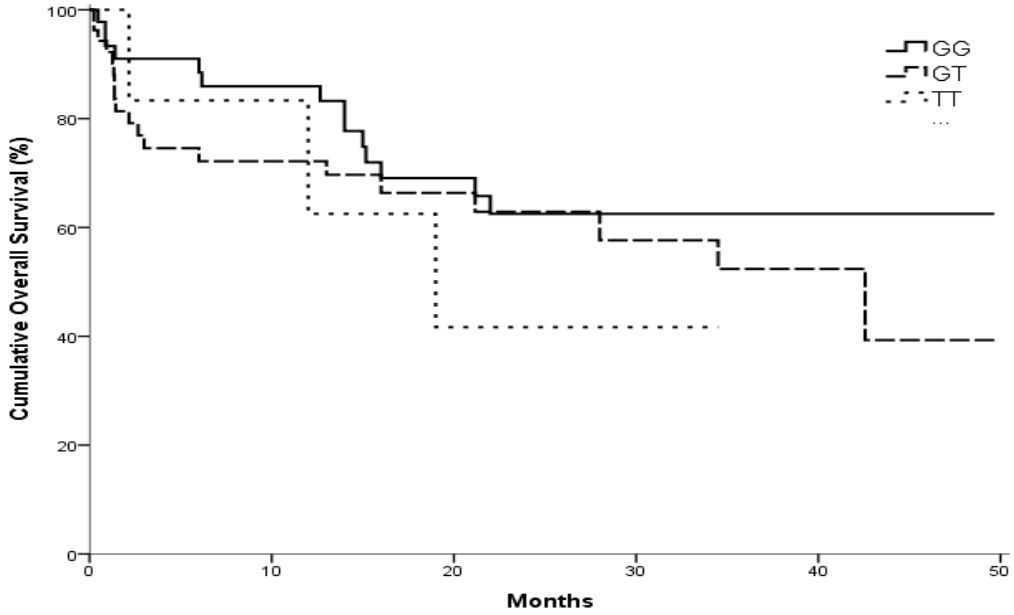

Figure (1): According to CYP2B6 rs3745274 genotypes, overall survival (OS) did not significantly differ between genotypes.

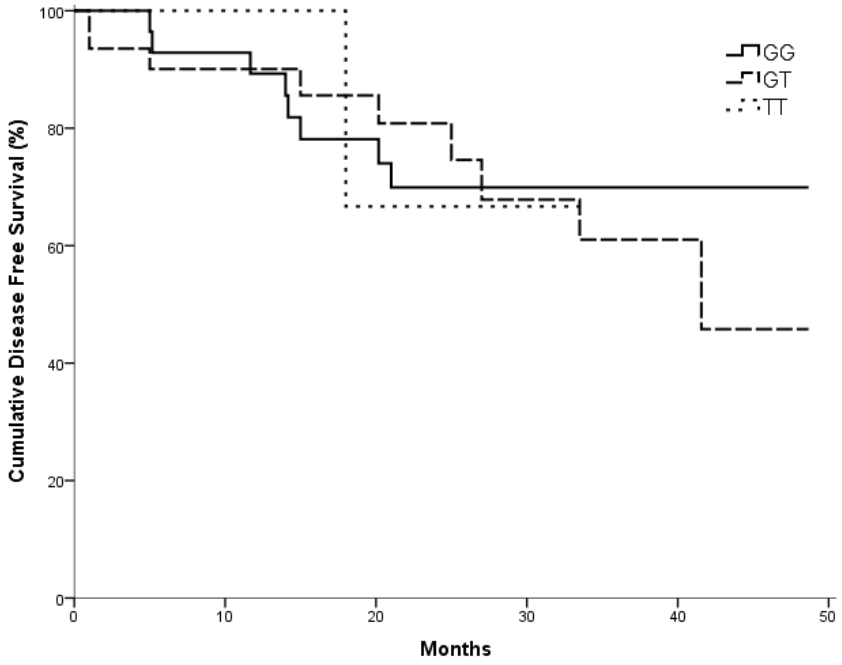

Figure (2): The CYP2B6 rs3745274 genotypes did not significantly differ in disease free survival (DFS).

DISCUSSION

AML is a hematopoietic progenitor cell clonal disorder that results in arrested differentiation. Research indicates that exposure to genotoxic agents can potentially impact AML pathogenesis. Approximately 10–20% of AML cases are therapy-related (t-AML), which occur due to chemo and/or radiotherapy used to treat another primary malignancy [15,22].

DNA is protected from harm by the CYP2B6 enzyme, which is important in the first stage of detoxification of many carcinogens [3]. On the other hand, CYP2B6's inactivating SNP (rs 3745274) may lessen the efficacy of detoxification of carcinogens into harmless substances [23-25]. This biochemical phenomenon could provide a plausible explanation for the observed variability in individual susceptibility to AML.

In this research, we analysed CYP2B6 (rs 3745274) gene polymorphism in adult AML patients and healthy controls utilizing PCR-RFLP. Our results suggest that the frequency of the homozygous mutant genotype (TT) in our control group is comparable to that of other studies conducted on the Caucasian population, which falls within the range of 3% to 6% [17,26,27]. However, we observed a significantly higher frequency of variant genotypes (GT, GT+TT) and T allele in AML patients in contrast to the control group (P value of 0.018, 0.011, and 0.015, respectively), which is consistent with previous studies [16,17,28]. These findings suggest a possible association between CYP2B6 (rs 3745274) gene polymorphism and AML pathogenesis."

Yu and co-authors [29] analyzed The *CYP2B6* gene polymorphism in 126 patients with acute leukemia and 161 healthy controls. Three genotypes (GG, GT, and TT) of the CYP2B6 c.516G>T polymorphism were identified in ALL, AML, and healthy controls. It was demonstrated that there was a correlation between the TT and GT genotypes with the incidence of AML and ALL (OR: 2.638, 2.322, 2.893, and 2.579, respectively; $p < 0.05$). T allele carriers had ORs for ALL and AML of 2.388 and 2.209, respectively, indicating a potential correlation between the T allele and vulnerability to acute leukemia.

A recent investigation of the impact of genetic characteristics on treatment response and survival rates in AML patients was carried out in Egypt. The research used a PCR-based restriction fragment length polymorphism (RFLP) technique to genotype SNPs in the CYP2B6 (G516T) and CYP3A4 (A290G) genes in 50 AML patients and 50 healthy persons. The study's findings demonstrated that those with CYP2B6 gene mutations were more likely to develop AML, with an OR of 3.0 (95 % CI, 1.3-6.9) [30].

Our study's outcomes indicate that there were no significant correlations between CYP2B6 rs3745274 genotypes and variables such as age, sex, or FAB subtypes. However, previous research has shown that certain FAB subtypes are significantly correlated with genotypes. Specifically, **Yuan *et al*** stated that variant genotypes (GT, GT+TT) and the variant T allele were more frequently observed in the AML M5 subtype [17], whereas **Daraki *et al.*** found these to be more common in M2 and M6 subtypes [28]. These discrepancies may be ascribed to racial and genetic variations across different populations. The identification of the specific FAB subtypes that are associated with genotypes represents a meaningful contribution to the ongoing pursuit of a more comprehensive understanding of these genetic associations. Although an earlier investigation revealed a higher frequency of the T allele in females, it was not statistically significant [28].

It is interesting to note that the current study is the first to correlate CYP2B6 rs3745274 genotypes with clinical outcomes and survival in AML patients. According to the outcomes, there were no significant differences noted between different genotypes and clinical outcomes, disease-free survival, or overall survival across different genotypes.

CONCLUSION

In conclusion, the polymorphic genetic variations of the detoxifying enzyme CYP2B6 may be linked to an increased likelihood of acquiring AML. However, it is remarkable that such variants do not seem to have a significant effect on patient survival or outcomes. The research highlights the need for further research that entail recruiting a significant number of patients and examining additional gene polymorphisms to comprehensively identify the precise function of CYP2B6 polymorphism in the pathogenesis and survival of AML patients.

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