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The role of the *APE1* Asp148Glu polymorphism on the risk of acute myeloid leukemia in Iraqi patients

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Abstract

Acute myeloid leukemia is the most common hematological malignancy in adults. The uncontrolled proliferation of non-differentiating myeloid progenitors is a hallmark of this illness. Mutant cells form when DNA damage cannot be repaired by the cell's repair mechanisms. One of the DNA repair mechanisms, the base excision repair pathway. The study involved 70 patients with acute myeloid leukemia (37 females and 33 males) as well as 30 apparently healthy individuals as a control group. The gSYNCTM DNA Extraction Kit from Geneaid/Taiwan was used to extract DNA from entire blood samples from the study groups. The Restriction Fragment Length Polymorphism-PCR method was used to identify the *APE1* gene's (rs1130409; Aspl48Glu, T/G in Exon 5) polymorphism. In genetic analysis, it was shown that an increase in the T/ T genotype and the T allele in the *APE1* codon 148 polymorphisms play a protective role in AML, and that an increase in the G/G genotype and G allele could be associated with acute myeloid leukemia risk. The polymorphism of *APE1* gene at rs1130409 revealed TG genotype and G allele as the most frequent and higher significant (P<0.05) in AML patients compared to the control group. The sequence of the studied region showed that the restriction site of the restriction enzyme is indicated by a site of diversity that is present in the GATC sequencing and transitions to the GAGC sequencing when a nucleotide change (T to G) actually occurs. Our findings suggest that the *APE1* rs1130409 polymorphism may be associated with acute myeloid leukemia susceptibility in Iraqi patients. It was discovered that the polymorphic marker 148 Glu> Asp of the *APE1* gene was associated with the development of AML. Allele T and genotype T/T carriers have a lower risk of developing AML, whereas allele carriers G have an increased risk.

Keywords: Acute Myeloid Leukemia, *APE1*, Base excision repair, Polymorphism, Single nucleotide polymorphism.

Introduction

The most prevalent adult hematological cancer is acute myeloid leukemia (AML)[1]. This disease is characterized by the unregulated proliferation of non-differentiating myeloid progenitors. Eukaryotic cells have a wide range of enzyme systems that can repair DNA damage. When DNA damage cannot be repaired by the cell's repair systems, the cell develops into a mutant cell [2-4]. The Base excision

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repair (BER) pathway, one of the DNA repair systems, is in charge of fixing minor lesions such as oxidative damage, alkylation, or methylation[5-7]. By hydrolyzing the phosphodiester backbone right next to the AP site, AP endonuclease 1 (APE1), also known as APE, APEX, HAP1, and REF-1, plays a crucial part in the BER pathway[8]. In order to start the repair of DNA single strand breaks, which are either directly caused by reactive oxygen species (ROS) or indirectly caused by the enzymatic removal of damaged nucleobases, APE1 can also function as a 3-phosphodiesterase[9].

The human apurinic/apyrimidinic endonuclease 1 (*APE1*) gene is important in the repair of DNA damage for either pathways bases or single-stranded DNA breaks caused by a variety of factors such as oxidation or alkylation[10,11]. The *APE1* gene consists of five exons, has a size range of about 2.5–3 kb of DNA, and is placed on chromosome 14q11.2 [12]. The *APE1* endonuclease takes away basic sites from damaged DNA and is the main enzyme that recognizes damaged sites in the genome. There are about 18 single nucleotide polymorphisms (SNPs) in *APE1*[13]. However, 1349 T>G (rs 1130409) Aspl48Glu is the most polymorphic in Exon 5. Many studies have investigated the association between the *APE1* 1349 T>G polymorphism and the risk of various cancers [14]. The *APE1* Asp148Glu polymorphism has been investigated in relation to breast, bladder, and lung cancer, among other cancer types. While some research indicates that people with the variant allele (Glu/Glu) have a higher chance of acquiring certain cancers, other research indicates that the variant allele (Glu/Glu) may even be beneficial in other groups[15].

It's important to note that thepresent understanding does not fully explain how APE1 polymorphisms m ay affect cancer risk. According to certain research, specific *APE1* polymorphisms may have an impact on the APE1 enzyme's activity, decreasing its capac ity to repair DNA and increasing its sensitivity to D NA damage and mutations [16,17]. According to other studies, *APE1* SNPs may impact the protein's redox signaling or transcriptional control, which could indirectly influence the development of cancer[18].

The main study aims to determine the most common SNP in a gene of DNA base excision repair pathway: the apurinic/apyrimidinic (AP) endonuclease (*APE1*) gene; Aspl48Glu (rs1130409; Aspl48Glu, T/G in Exon 5) polymorphism in acute myeloid leukemia patients and controls in Iraqi patients by polymerase chain reaction restriction fragment length polymorphism and analyzed by DNA sequencing technique to confirm the presence of mutations in this gene.

Materials and Methods

The current study was carried out from March 2022 to July 2022 at the Department of Hematology, Baghdad Teaching Hospital, Medical City, there were 70 patients with acute myeloid leukemia, were diagnosed in the hematology department , thirty seven females and thirty three males, and 30 healthy individuals, 12 females and 18 males, who served as the control group. The age range of the patients and the control group was 15–82. The patient group included all of the patients with AML without any exclusion criteria, while the control group included apparently healthy individuals without any hematology symptoms. The study has received ethics approval and patient consent based on the Iraqi Ministry of Health document.

DNA isolation and Polymerase Chain Reaction (PCR)

Genomic DNA was isolated from nucleated cells in an aseptic environment. The gSYNCTM DNA Extraction Kit from Geneaid/Taiwan was used to extract DNA from entire blood samples taken from the study groups.

Asp148 The *APE1* gene's Glu polymorphism was identified by Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using the following primers: The sense sequence is 5′-CTGTTTCATTTCTATAGGCTA-3′, and the antisense sequence is 5′-AGGAACTTGCGAAAGGCTTC-3′[19]. In the RFLP-PCR technique, the restriction enzyme *Bfa*I act in the GATC sequence, which is used to digest

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the PCR product. A PCR PreMix Reaction Mixture in a 25 µL tube was used for amplification (AccuPower PCR Premix, Bioneer/ Korean company). In order to execute the amplification, a thermal cycler (Cleaver Scientific Ltd./UK) configured for 35 cycles of denaturation at 94°C for 30 seconds, annealing at 55°C for 30 seconds, and extension at 72°C for 1 minute was used, preceded by an initial denaturation of 5 minutes at 95°C. The final extension lasted 5 minutes at 72 °C [20]. Finally, the gel electrophoresis method was done according to Sambrook and Russell, and 5 µL of each sample was loaded onto a 2% Agarose gel.

Sequencing of amplified APE1 gene

The DNA purity range was between 1.65-1.9 for all samples. In order to check up the genetic variation in a rs 1130409; Aspl48Glu, T/G in exon 5 *APE1* gene. The DNA sequencing analysis was done to confirm the PCR-RFLP results; samples from patients were selected randomly with different genetic variations in Iraqi patients with AML compared with apparently healthy control. Six samples for PCR amplification product were sequenced at Bioneer sequencing company, Korea, using the automated sequencer by dideoxynucleotide chain termination reaction with the same primer set used for PCR amplification .The complete nucleotide sequence is examined, and the results are illustrated in Fig. 3, Fig. 4, Fig. 5 and Fig. 6.

Through the current study of the sequential sequence of the region we studied, it was found that there is a site of diversity located between the GATC and GAGC where a change in nucleotides (T to G) ,which represents the restriction site of the restriction enzyme, leads to an amino acid change (Aspartate GAT to Glutamate GAG) and this means that the enzyme is cut in the case of the presence of T in the target site of a segment and not cut in the case of the presence of the base G, when compared to the source reference (Sequence ID: D13370.1, or comparison between patient samples as shown in Fig. 3.

Various genetic analysis methods were used to investigate the presence of genetic diversity or mutations in the region, and the results were compared with what was published on the Gene Bank website, which is part of the American National Center for Biotechnology Information (NCBI). https://www.ncbi.nlm.nih.gov/nuccore/LC738867.1

Statistical Analysis:

All results were statistically analyzed using the SPSS version 26 program. For each polymorphism, using odds ratios (ORs) and 95% confidence intervals, a measure of the polymorphic sites' connection with AML was also calculated (CIs). *P*-values under 0.05 were regarded as significant[21]. The sequences and aligning samples by using the computerized BioEdit program.

Results

A single nucleotide polymorphism (SNP) in codon 148 of exon 5 (rs1130409), where a change from T to G results in an amino acid change from Aspartate (Asp) to Glutamine (Gln), has been connected to an *APE1* variant with reduced capacity to repair DNA breaks. The gel electrophoresis for PCR product of *APE1* gene was 164bp as shown in Fig. 1.The occurrence of *APE1* gene polymorphisms was revealed by the RFLP-PCR technique. By the restriction enzyme *Bfa*I obtained three genotypes, TT (144 bp, 20 bp), GG (164 bp) and TG (164bp, 144 bp 20 bp.) as shown in Fig. 2 [14]. The results revealed that the TG heterozygous genotype relative frequency was found to be 54% and 37% in the AML patients and control group, respectively. Additionally, the homozygous genes revealed important differences: 9% of AML patients had the GG homozygous genotype, but 0% of healthy adults reported. The TT homozygous genotype was present in 63 % of the controls, whereas it was 37 % in the AML patients' as shown in Table 2. The results showed that the "T" allele Showed highly significant frequency in control, which was at 81% compared to the AML patients' 64 %, whereas the relative frequency of the "G" allele was at 36 % in the AML patients and 19 % in controls, as shown in

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Table 1. Sequencing was performed to determine the genetic variation in Iraqi patients with AML compared with the apparently healthy control. The complete nucleotide sequence is examined and the results were illustrated in Fig. 3, Fig. 4, Fig. 5 and Fig. 6.

Table 1. Comparative analysis of the distribution of allele frequencies of polymorphism of rs1130409 among patients with AML and in the control group.

Alleles	Cases	Controls	χ^2	*P*-value	*OR*	
	n = 70	n = 30			value	95% CI
Allele T	90(64%)	49(81%)	5.99	0.01**	0.40	0.19 – 0.85
Allele G	50(36%)	11(19%)			2.47	1.18 – 5.19

*** (*P*<0.05), ** (*P*<0.01), NS: Non-significant.**

Table 2. Comparative analysis of the distribution of genotype frequencies of polymorphism of rs1130409 among patients with AML and in the control group.

Genotypes	Cases	Controls	χ^2	*P*-value	OR	
	n = 70	n = 30			value	95% CI
Genotype T/T	26(37%)	19 (63%)	7.09	0.008**	0.34	0.14 – 0.83
Genotype T/G	38 (54%)	11(37%)			2.05	0.85 – 4.94
Genotype G/G	6(9%)	0(0%)			6.15	0.34 – 112.68

*** (*P*<0.05), ** (*P*<0.01), NS: Non-significant.**

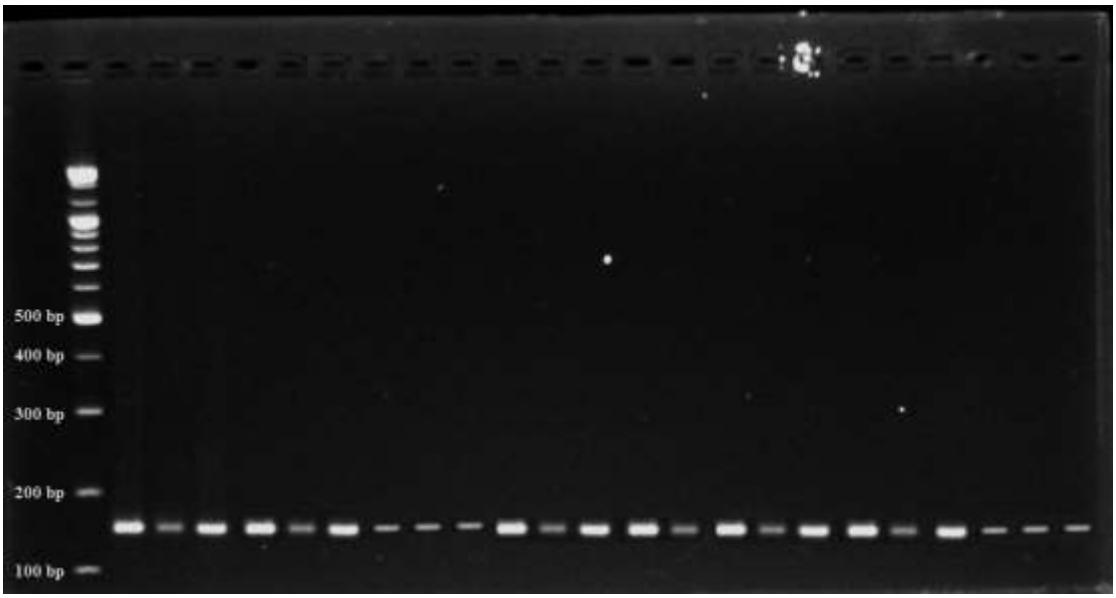

Figure 1. Gel electrophoresis for PCR product of *APE1* gene (164bp) with DNA ladder molecular weight marker on agarose gel (2%) (100v, 1 hour).

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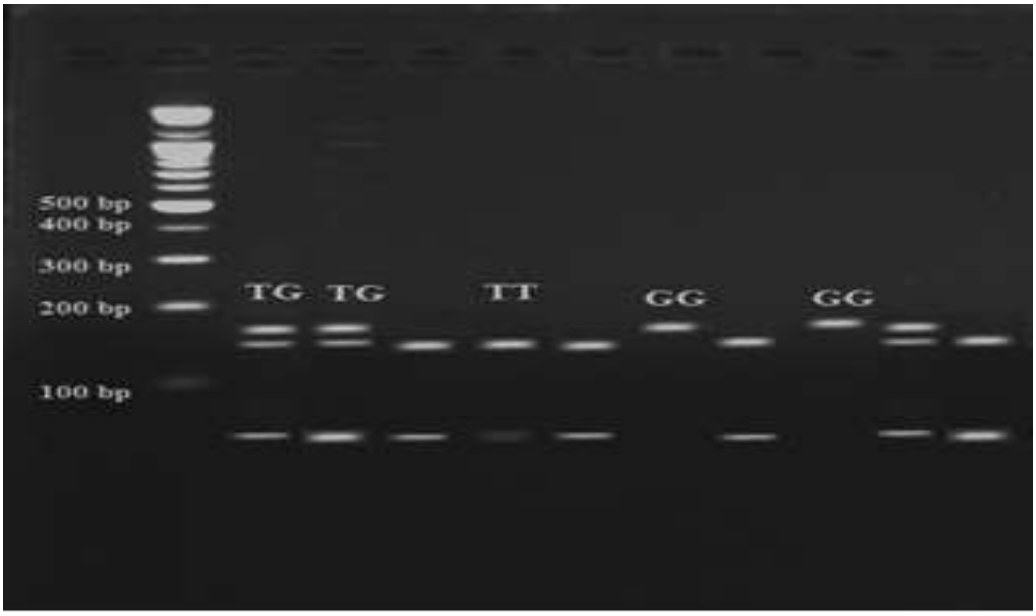

Figure 2. Ethidium bromide-stained agarose gel of PCR-RFLP product of APE1 gene. Show: DNA molecular size marker (100bp Ladder), : The restriction process shows three genotypes, TT (144 bp , 20 bp), GG (164 bp) and TG (164bp , 144 bp 20 bp.).

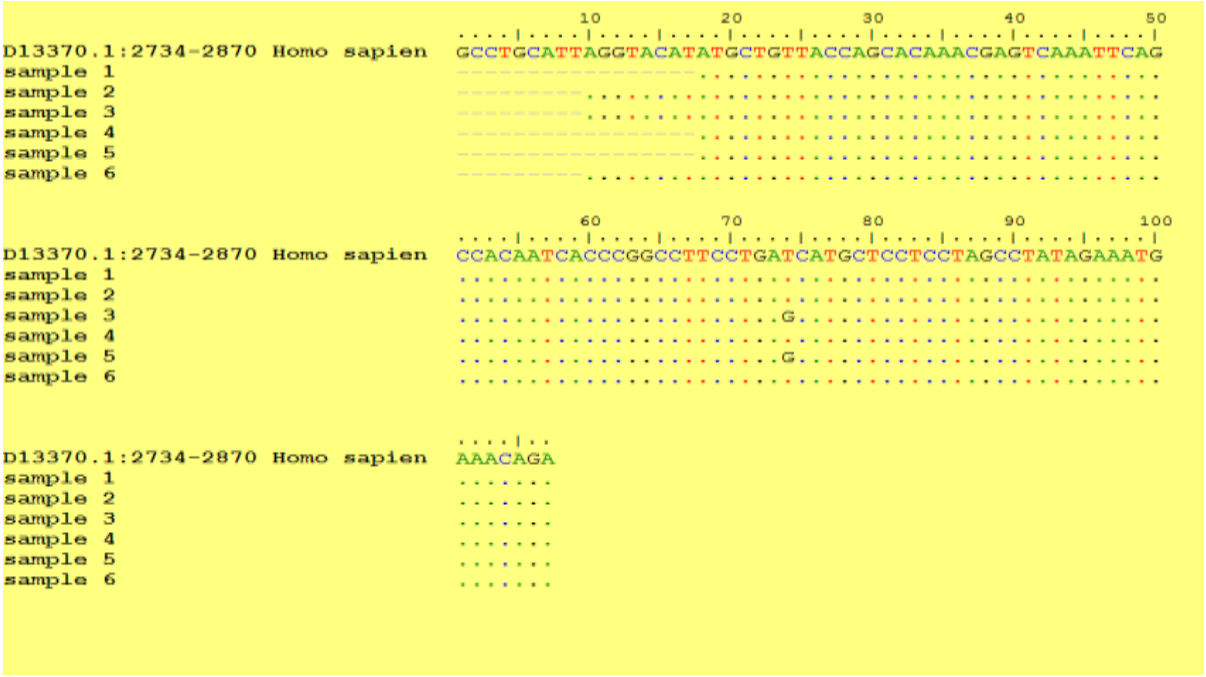

Figure 3. Comparison of the alignment of nucleotide in patient samples of a fragment of DNA from the APE1 gene, the difference site in one of the nucleotide, which is the same as the restriction site of the enzyme.

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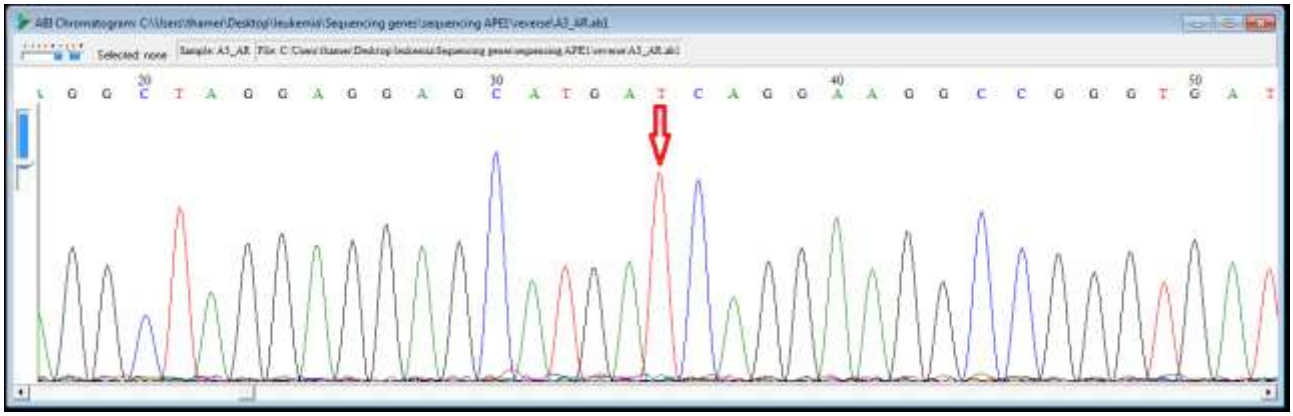

Figure 4. Sequencing map view of TT genotype at rs1130409

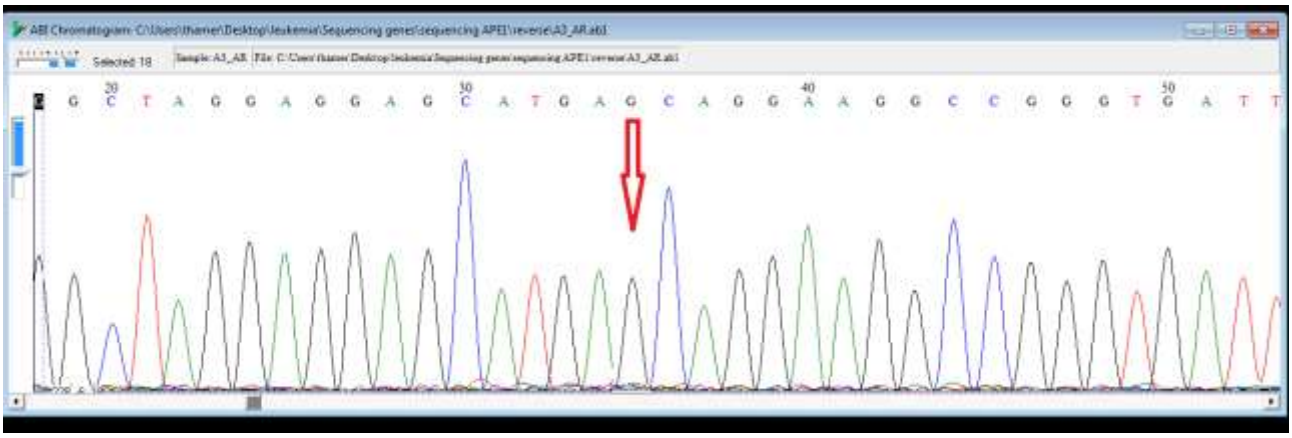

Figure 5. Sequencing map view of GG genotype at rs1130409

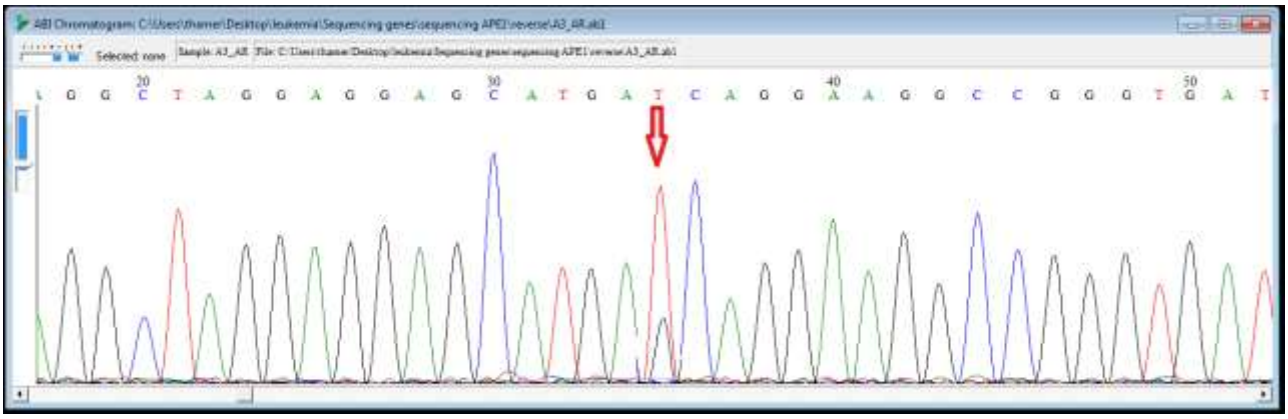

Figure 6. Sequencing map view of TG genotype at rs1130409

Discussion

The *APE1* gene includes a genetic variation called *APE1* polymorphism, which has been associated with a higher risk of developing leukemia[21]. *APE1* is a DNA repair and base excision repair pathway enzyme that is produced by the apurinic/apyrimidinic endonuclease 1 (*APE1*) gene. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia are more likely to occur in individuals with specific APE1 polymorphisms, according to studies. The importance of *APE1* Asp148Glu in a wide range of biological activities, including gene transcription and DNA repair, it is scientifically probable that the polymorphism may influence the chance of developing different types of cancer[22]. The endonuclease domain includes this polymorphism, which leads to reduced

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endonuclease activity[23]. Furthermore, the allele result to Glu of the *APE1* gene is associated with an enhanced mitotic delay after exposure to ionizing radiation. Moreover, some researchers have hypothesized that *APE1* polymorphisms may be linked to increased sensitivity to specific chemotherapeutic drugs, including cytarabine and daunorubicin[24]. Leukemia risk has been investigated in relation to the *APE1* Asp148Glu polymorphism. The *APE1* gene, which is involved in DNA repair and redox control, contains this polymorphism in its 3' repair domain. Previous studies have revealed that this polymorphism's Glu148 variation is linked to a higher risk of both acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL)[25].
Our study revealed that the G allele, TG and GG genotypes in AML patients were over than the controls, and observed that individuals with the GG genotypes had a higher risk for developing AML disease. In contrast, the "T" allele, and TT genotype have a rather preventive role. This may indicate that the "T" allele may be protective. A significant association between polymorphism of *APE1*gene; Asp 148 Glu and AML, overall data analysis revealed that *APE1*gene; Asp 148 Glu may be significantly correlated with elevated leukemia risk. We discovered a strong correlation between the polymorphism Asp 148 Glu with the risk of developing AML (P-value = 0.01, OR = 2.47; 95% CI =1.18 – 5.19 for the G allele). In the case of Asp 148 Glu, individuals with AML were more likely to have combined heterozygous genotypes than controls (OR =2.05; 95% CI =0.85 – 4.94; P –value = 0.008). This was also detected when the G/G genotype was examined (OR = 6.15; 95% CI =0.34 – 112.68). In this study, showed that an increase in the T / T genotype and the T allele in the APE1 codon 148 polymorphisms may play a protective role in AML OR = 0.34, 95% CI = 0.14 – 0.83, and an increase in G/G genotype in acute leukemia was associated with early relapse.

Although a number of studies have found a link between *APE1* polymorphisms and the risk of certain types of cancers, many researchers have mentioned that the variant 148 Glu allele is associated with an increased risk of cancers. Ionizing radiation sensitivity may increase in those who carry the Glu allele. Hu et al [26] .A strong connection has been shown by other studies. Confirmed the findings of Ruyck et al[27].Who discovered a relationship between the Asp/Glu genotype and lung cancer risk in Caucasians, and observed a significant association between the Asp148Glu heterozygous genotype with risk of lung cancer. Among smokers there was an association between the APE1 148 Glu allele and an increased risk of lung cancer discovered in a Chinese study of severely smoking males Shen H. et al [28].
Amit et al.[29] study revealed there was a significant statically positive correlation between the *APE1* gene and the incidence of breast cancer in north Indian women. *APE1* risk genotypes are becoming more prevalent among Caucasians, and Tasha et al.[30] showed significant changes in breast cancer risk. These findings imply that combined SNPs in several DNA repair pathways may affect breast cancer risk; hence, larger investigations are required to further assess polygenic models of DNA repair in breast cancer risk.
Another study by Canbay et al.[31] hypothesized that in a Turkish population, the *APE1* Asp148Glu polymorphisms would be associated with a greater risk of colorectal cancer. The study suggests that, without decreasing enzyme activity, the *APE1* Asp148Glu variation may have a significant effect on colorectal cancer risk. It's interesting to observe that there may be a correlation between the observed significantly increased risks for colorectal cancer among individuals with the Glu allele of the *APE1* Asp148Glu gene polymorphisms. In view of the overlapping pathologic characteristics of colorectal cancer, these findings further indicate that the distribution of DNA repair gene polymorphisms is significant.
Xiahong et al.[32] ovarian cancer risk was significantly increased by the APE1 gene polymorphism. The G allele and the TG/GG genotype were linked to a lower risk of ovarian cancer. The results suggest that the *APE1* gene polymorphism may link with ovarian cancer risk in a Han Chinese population.
The *APE1* Asp148Glu polymorphism may be associated with an increased risk of lung cancer development in Iraqi patients, according to Mustafa MA.[33] and the Asp/Glu genotype contributed to the disease's increased predisposal by playing a significant role in increased gene activity as a result

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of the polymorphism, whereas the Asp/Asp genotype may have a protective effect.
Other studies, disagreed with our results, since did not consider the *APE1* genetic variants to be risk factors for leukemia because they demonstrated that the presence of the *APE1* Asp/Asp genotype increases the risk of AML, whereas *APE1* Glu/Glu genotype reduces the risk in the development of AML (Atsushi, Iwasaki. et al.[34]).

According to Ana et al.[35] the *APE1* deficiency reduced the risk of developing prostate cancer, and this finding is explained by the simultaneous reduction of important DNA repair pathways. As a result, prostatic tissue is likely protected from the spread of potentially cancerous clones and prostatic cells have probably died. In southern Brazilian men, the relationship between SNPs and clinical and epidemiological data was thought to have no association with *APE1* susceptibility to disease.

Conclusion

Our findings suggest that the *APE1* rs1130409 polymorphism may be associated with acute myeloid leukemia susceptibility in Iraqi patients. It was discovered that the polymorphic marker 148 Glu> Asp of the *APE1* gene was associated with the development of AML. Allele T and genotype T/T carriers have a lower risk of developing AML, whereas allele G carriers have an increased risk.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- The author has signed an animal welfare statement.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee in University of Iraqi Ministry of health.

Authors' Contribution Statement

This work was carried out in collaboration between all authors "Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing and writing original draft preparation, Th. M. J. and R. M. A. Al. review and editing, visualization, supervision and project administration, R. M. A. Al. All authors have read and agreed to the published version of the manuscript.

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دور تعدد الأشكال لجين *APE1* Asp148Glu على خطر الإصابة بسرطان الدم النخاعي الحاد في المرضى العراقيين

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الخلاصة

ابيضاض الدم النخاعي الحاد هو أكثر أنواع امراض الدم الخبيثة شيوعًا عند البالغين. يعد انتشار الخلايا الطافرة الغير مسيطر عليها للأسلاف النخاعية الغير متمايزة سمة مميزة لهذا المرض. يمكن إصلاح تلف الحمض النووي عن طريق مجموعة متنوعة من الأنظمة الأنزيمية الموجودة في الخلايا حقيقية النواة. تتشكل الخلايا الطافرة عندما لا يمكن إصلاح تلف الحمض النووي بواسطة آليات إصلاح الخلية. إحدى آليات إصلاح الحمض النووي هي مسار إصلاح استئصال القاعدة ، التي تكون المسئولة عن تصحيح الأضرار الصغيرة الناتجة عن التلف ألتأكسدي أو والقلوية أو المثيلة.

اشتملت الدراسة على 70 مريضًا مصابًا بسرطان الدم النخاعي الحاد - 37 أنثى و 33 ذكرًا - بالإضافة إلى 30 فردًا سليمًا كمجموعة سيطرة. تم استخدام مجموعة استخلاص الحمض النووي gSYNCTM لاستخراج الحمض النووي من عينات الدم الكاملة من مجموعات الدراسة. تم استخدام طريقة PCR-RFLP لتحديد تعدد الأشكال Asp148 Glu للجين *APE1*

في التحليل الجيني ، تبين أن الزيادة في النمط الجيني T/T وأليل T في تعدد الأشكال في كودون 148 *APE1* يلعب دورًا وقائيًا في مرض ابيضاض الدم النخاعي الحاد AML، وأن الزيادة في النمط الجيني G / G يمكن أن تترافق مع خطر الإصابة بسرطان الدم الحاد. . أظهرت النتائج أن النمط الجيني المتغاير لجين*APE1* ، (T / G) Asp 148 Glu وأليل G كانت أعلى بشكل ملحوظ (P <0.05)في مرضى AML مقارنة بمجموعة السيطرة . في تسلسل المنطقة التي تم دراستها ، وجد أن هناك موقعًا للتغاير يقع بين GATCو GAGC ، حيث يمثل التغيير في النيوكليوتيدات T إلى G موقع تقييد الإنزيم القاطع.

حيث ارتبط النمط الجيني متعدد الأشكال Asp 148 <Glu من جين *APE1* مع تطور AML في المرضى العراقيين. أثبتت الدراسة أن حاملي النمط الجيني T / T لديهم مخاطر أقل لتطور مرض ابيضاض الدم النخاعي الحاد AML، في حين أن حاملي الأليلات G لديهم مخاطر متزايدة.

الكلمات المفتاحية: ابيضاض الدم النخاعي الحاد , مسار إصلاح استئصال القاعدة , جين*APE1* ,تعدد الاشكال , تعدد الاشكال النيوكليويدة المفردة.