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The Association between Single Nucleotide Polymorphisms rs1042522 and rs1642785 in the *TP53* gene and Acute Myeloid leukemia in a sample of the Baghdad/ Iraq population

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Abstract

Acute myeloid leukemia (AML) represents the most prevalent type of acute leukemia in adults and is responsible for approximately 80% of all cases .The tumor suppressor gene (*TP53*) is a gene that has been frequently studied in cancer, and mutations in this gene account for about 50% of human cancers. This study aims to evaluate the correlation between two single nucleotide polymorphisms (SNPs) in the gene: rs1042522 and rs1642785, and a group of Iraqi patients suffering from pre-diagnostic acute myeloid leukemia (AML). Blood samples were collected from sixty patients (26 males and 34 females) and sixty controls (26 males and 34 females); these subjects were matched in gender, age, and ethnicity. Genomic DNA has been extracted from whole frozen blood samples by using the Easy Pure® Blood Genomic Kit, and then the purity and concentration have been measured by using the Nano drop NAS-99 spectrophotometer. Nano Drop readings ranged between 7-55ng/µl for the concentration and between 1.78-1.9 for the purity. High resolution melt (HRM) real-time PCR was used in the detection of these two SNPs. *TP53* genotype frequencies have been in accordance with Hardy–Weinberg equilibrium (HWE), with statistically significant differences $p \leq 0.05$ between the genotypes of the control and patient groups. The rs1042522 genotype frequency was significantly different between patients and controls $p = 0.0001$, and participants with the GA genotype were more likely to develop AML OR = 7.8, 95% CI 3.2–18.4, $p = 0.0001$. In addition, the genotype frequency of rs1642785 was significantly different between patients and controls $p = 0.002$, and participants with the GA genotype were more likely to develop AML OR = 3.5, 95% CI 1.5–8.12, $p = 0.002$.

Keywords: Acute myeloid leukemia, HRM-qPCR, rs1042522, rs1642785, Single Nucleotide Polymorphisms, Tumor protein 53 (*TP53*).

Introduction

Acute myeloid leukemia (AML) is a disease distinguished by the rapid growth of abnormal white blood cells (blasts) and the formation of leukemia-immature cells in the bone marrow and finally in the bloodstream. This disease is caused by a series of recurring hematopoietic stem cell genetic changes that accumulate with age [1, 2]. The pathogenesis of AML represents a multiple-step process including mutagenesis, epigenetics, and genetic variation [3]. In the Iraqi population, leukemia is considered one of the most common cancer types after breast cancer, lung cancer, and colorectal cancer. The annual

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incidence of leukemia is 13.98 per 100.000 people, with 2027 new cases 6% for both sexes (Ministry of Health, Iraqi Cancer Board)[4].

Tumor protein 53 (*TP53* gene) is found on the short arm of chromosome 17 (17p13). *TP53* gene encodes the p53 protein, which has tumor suppression as its main biological function [5]. The mutation rate of *TP53* in all human cancers is between 25% and 40%; therefore, it is one of the most frequently mutated genes in human cancers [6]. *TP53* is essential for regulating the tumor cell cycle, DNA repair, and apoptosis. The stimulation of *TP53*-dependent pathways by external or internal cellular stress signals influences metastasis, progression, cancer cell genesis, and preventing the growth of damaged cells with oncogenic ability. Furthermore, *TP53*, as a transcription factor, can activate a wide range of genes to promote these tumor suppressing processes [7]. Genetic studies employing polymorphisms that can assist in demonstrating associations between some molecules and diseases. The *TP53* gene contains high-frequency, functional single-nucleotide polymorphisms (SNPs) that can change the function of the p53 protein [8]. The *TP53* gene has more than 200 single nucleotide polymorphisms (SNPs). In *TP53* gene, several SNPs have been investigated and found to be associated with the high risk of several types of human cancer [9]. One of the most widely studied polymorphisms in *TP53* gene is rs1042522, which converts the amino acid at codon 72 from arginine to proline. The substitution of this amino acid affects the structure and function of the p53 protein by causing structural modifications [10]. The rs1042522 SNP was investigated for its role in disease risk for the vast majority of common types of cancer, including prostate, breast, and lung cancers [11-13]. Another SNP, rs1642785, is found on intron 2 of the *TP53* gene and is associated with an increased cancer risk [14]. This study aims to see if there is a relationship between two *TP53* polymorphisms (rs1042522 and rs1642785) and the risk of evolving acute myeloid leukemia in some Iraqi patients.

Materials and Methods

Subjects

This study has been designed and performed according to the institutional bioethical guidelines established by the Ethical Committee in the College of Science/University of Baghdad. Sixty patients (26 males and 34 females) and sixty controls (26 males and 34 females) have been matched in gender and age, all with an age range of 15-65. From February 2021 to August 2021, patients were chosen from the Baghdad teaching hospital in the medical city.

Blood Samples

About 3 ml of venous blood from all patients and the control group have been collected by vein puncture using a 5 ml syringe. A volume of 2 ml has been transferred into an EDTA tube and then stored at 4 °C until the extraction of DNA has been carried out.

Genomic Genotyping of *TP53* rs1042522 and rs1642785 SNPs

The human *TP53* gene is located on chromosome 17 and is composed of 10 introns and 11 exons. *TP53* rs1042522 is located on chromosome 17:7676154bp in exon 4. *TP53* rs1642785 is located on chromosome 17:7676483bp in intron 2. Genomic DNA has been extracted from the whole frozen blood that was collected in EDTA tube by using the commercial Easy Pure® blood Genomic kit followed by concentration and purity measurements. *TP53* rs1042522 and rs1642785 SNP primers have been designed using Beacon Designer 8 and provided by Bioneer Company (Korea). Table 1 shows the forward and reverse sequences of these primers. Real time PCR amplification has been carried out with a total volume of 20µl, including the following: the master mix 10µl, forward and reverse primers 1µl each, DNA template 3µl and nuclease free water 5µl. For rs1042522, the real-time PCR conditions have been as follows: one cycle of initial denaturation at 94 °C for 1 minute, followed by 40 cycles of denaturation at 94 °C for 5 seconds, annealing at 52 °C for 15 seconds, extension at 72 °C for 20 seconds, and one cycle of HRM analysis at 60 °C to 95 °C for 2 seconds. And as follows for rs1642785: one cycle of initial denaturation at 94 °C for 1 minute, followed by 40 cycles of denaturation at 94 °C for 5 seconds, annealing at 56 °C for 15 seconds, extension at 72 °C

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for 20 seconds, and one cycle of HRM analysis at 60-95 °C for 2 seconds.

Table 1. Sequences and Information of Primers used in the Study

TP53 SNPs	Sequences of primers (F: Forward R: Reverse) Sequence (5′→3′ direction)	bp	Annealing °C	HRM °C
	F: 5`-TGTAGGAGCTGCTGGTG-3`	17	52	Wild 82.5
rs1042522	R: 5`- CGGACGATATTGAACAATGGT-3`	21		Mutant 82.1
	F: 5`-TTTCGCTTCCCACAGGTCTC-3`	20	56	Wild 82.6
rs1642785	R: 5`-ACCTATGGAAACTGTGAGTGGAT-3`	23		Mutant 82.1

Statistical Analysis

One-way ANOVA analyses have been done using GraphPad Prism for Windows and IBM SPSS 66 Statistics for comparison percentages. The differences are considered significant if *p* values ≤0.05. Genotype and allele frequencies have been presented as percentage frequencies after using Hardy-Weinberg equilibrium (HWE), and differences have been assessed by Pearson's Chi-square test. The association between *TP53* SNPs and AML was detected as an odds ratio (OR) with a confidence interval (CI) estimate of 95% [15, 16].

Results and Discussion

The results of nanodrop indicated that the genomic DNA was variable in concentration as it ranged from 7-55ng/µl. The purity ranged from 1.78- 1.9 these results depended on white blood cells count and blood sample freshness.

Genotyping of *TP53* gene by using HRM Real Time PCR

The closed tube technique called high-resolution melting (HRM) analysis, was used to evaluate an intercalating dye's fluorescence reduction in a double-strand DNA dissociation process. Because of its simplicity, adaptability, nondestructive nature, exceptional sensitivity, and precision, this technique has gained popularity over the past decade. The HRM analysis gives sequence-associated melting profiles and can show single-nucleotide-level changes in genotype[17].

Detection of the *TP53* gene (G>A rs1042522) by using HRM Real Time PCR

The SNP *TP53* (G>A rs1042522) located on chromosome 17 (exon 4) has been found in three genotypes GA, AA, and GG and two alleles *G* and *A* in both control and patient subjects. Melt and fluoresce difference curves have been obtained by HRM assays for the rs1042522 SNP of the *TP53* gene that has a basic relationship with AML. Figs. 1. A and B, Shows the output curve of HRM for heterozygous, homozygous and wild type rs1042522 SNP of the *TP53* gene by real time PCR depending on melting temperature.

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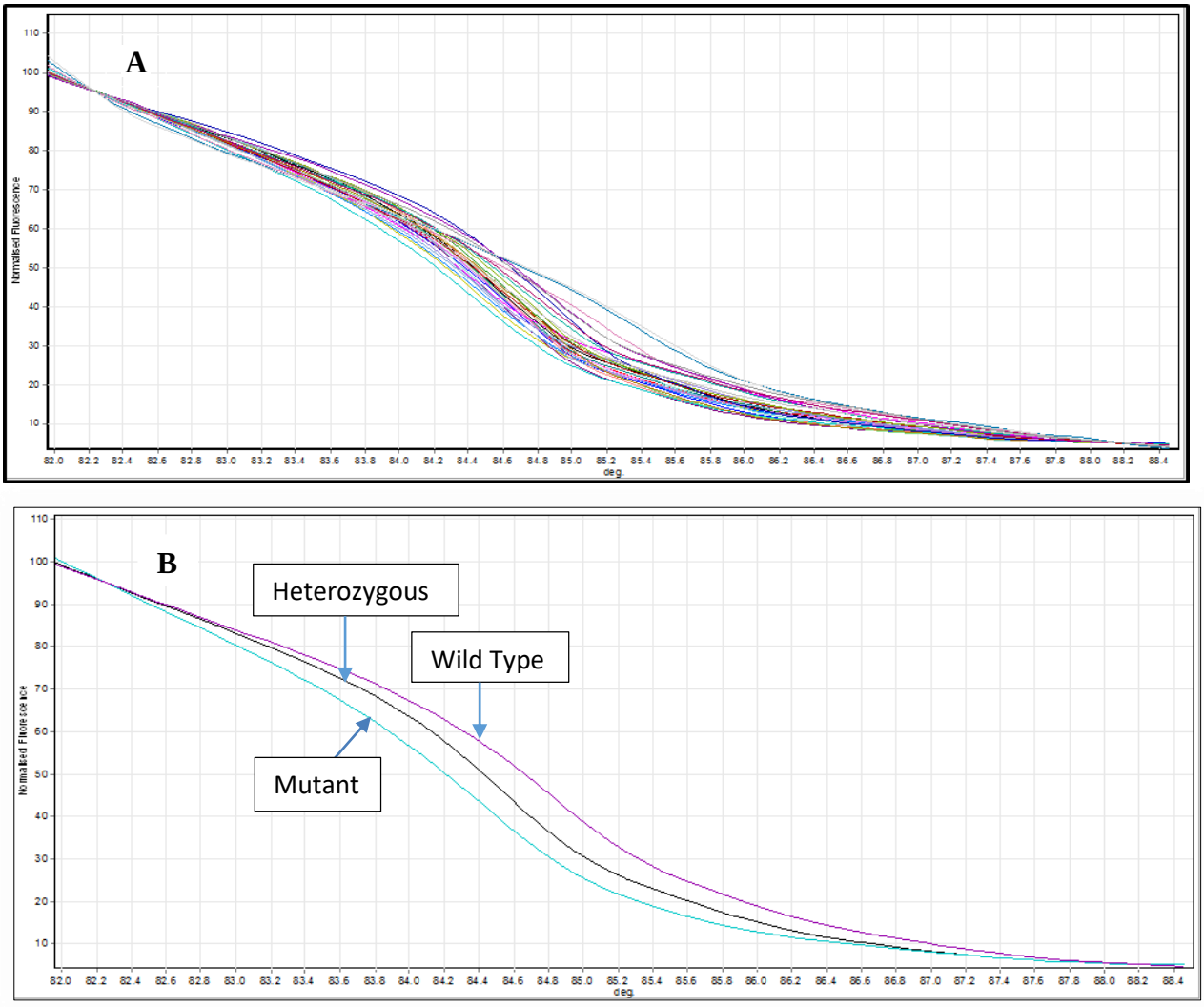

Figure 1. A and B. The results output curves of HRM for heterozygous, homozygous and wild type in *TP53* SNP rs1042522 by real time PCR.

Hardy–Weinberg equilibrium (HWE) analysis in the control group has shown that genotypes were not compatible with equilibrium and there was significant differences p = 0.003 have appeared between the expected and observed genotype in the control group that due to small size of sample, whereas the variation in the AML patient group was compatible and non-significant difference with p = 0.086 as shown in Table 2.

Table 2. Number and percentage frequencies of rs1042522 G/A genotypes and their Hardy-Weinberg equilibrium in the patient and control groups.

Genotype rs1042522	**Patient group N (%)**		**Control group N (%)**	
	Observed	Expected	Observed	Expected
Wild GG	16 (26.66%)	19.27 (32.11%)	42 (70%)	38.4 (64%)
Hetero GA	36 (60%)	29.47 (49.11%)	12 (20%)	19.2 (32%)
Mutant AA	8 (13.33%)	11.27 (18.78%)	6 (10%)	2.4 (4%)
Total	60 (100%)	60 (100%)	60 (100%)	60 (100%)
***p*-value**	0.086**		0.003	
	Non-Significant		Significant	

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The genotypes distribution of the G>A rs1042522 SNP in the patient group was 26.66%, 60% and 13.33% for homozygous wild type, heterozygous, and another homozygous variant, respectively, while genotypes in the control group were 70%, 20%, and 10% for homozygous wild type, heterozygous, and homozygous variant, respectively. Inspecting *TP53* gene genotypes and allele frequencies in the control and patient groups revealed that there was significant variation between these frequencies, with an increase in the *A* alleles 43.33% vs. 20% and a decrease in the frequencies of the *G* allele 56.67% vs. 80. As shown in Table 3, the GA genotype represents risk factor (OR, 7.8; CI, 3.2-18.4; p=0.0001), the AA genotype represents risk factor (OR, 3.5; CI, 1.1-10.2; p=0.04), and the allele *A* represent risk factor (OR, 3.0; CI, 1.7-5.4; p=0.0001). In this study, it has been demonstrated, according to qPCR results, that the rs1042522 SNP was found in the examined sample; therefore, this SNP can be considered a risk factor for acute myeloid leukemia, which is consistent with the findings of other researchers [18]. Who assert a connection between the risk of AML and rs1042522. The main function of the *TP53* tumor suppressor gene is to protect the genome from destruction. Polymorphisms have become an interesting topic in cancer studies [19]. The rs1042522 SNP is a common *TP53* SNP that has been found on codon 72 and encodes for two alleles with different functional properties via transversion mutation [20]. *TP53* Pro72Arg (rs1042522), located in proline rich domain of p53, is essential in the normal function of p53. The variant allele of rs1042522 has been reported to decrease apoptotic activity. Studies demonstrated that the arginine (Arg) variant is able to induce apoptosis faster and more efficiently than proline (Pro), while the Pro variant is better for inducing cycle arrest due to the fact that the Pro amino acid of p53 protein is weaker for apoptosis induction and also for suppressing cellular transformation compared to Arg amino acid. It has been reported that rs1042522 in *TP53* gene can increase risk of cancers (including leukemia), and be associated with poor overall survival (OS) in patients with AML. As a result, the *TP53* variant genotypes (rs1042522) could theoretically be risk factors for cancer progression and/or development [21, 22]. The distribution of *TP53* (rs1042522) genotypes in Iraqi patients with acute myeloid leukemia and control groups was studied, and the results show that this SNP plays a vital role in the progression of AML.

Table 3. Genotype and allele frequencies of *TP53* gene polymorphism rs1042522 SNP between patient and control groups.

Genotype rs1042522	Patient group N (%)	Control group N (%)	*p*-value	OR	CI 95%
GG	16 (26.66%)	42(70%)	--	1.00	(Reference)
GA	36 (60%)	12 (20%)	0.0001**	7.8	3.2-18.4
AA	8 (13.33%)	6 (10%)	0.04*	3.5	1.1-10.2
Total	60 (100%)	60 (100%)	--	--	--
Allele Frequency					
G	68 (56.67%)	96 (80%)	--	1.00	(Reference)
A	52 (43.33%)	24 (20%)	0.0001**	3.0	1.7-5.4

Detection of the *TP53* gene (G>A rs1642785) by using HRM Real Time PCR

The SNP *TP53* G>A rs1642785 located on chromosome 17 (intron 2) has been found in three genotypes GA, AA, and GG and two alleles G and A in both control and patient subjects. Melt and fluoresce difference curves have been obtained by HRM assays for the rs1642785 SNP of the *TP53* gene that has a basic relationship with AML. Fig.2. A and B Shows the output curve of HRM for heterozygous, homozygous and wild type for rs1642785 SNP of *TP53* gene by real time PCR depending on melting temperature.

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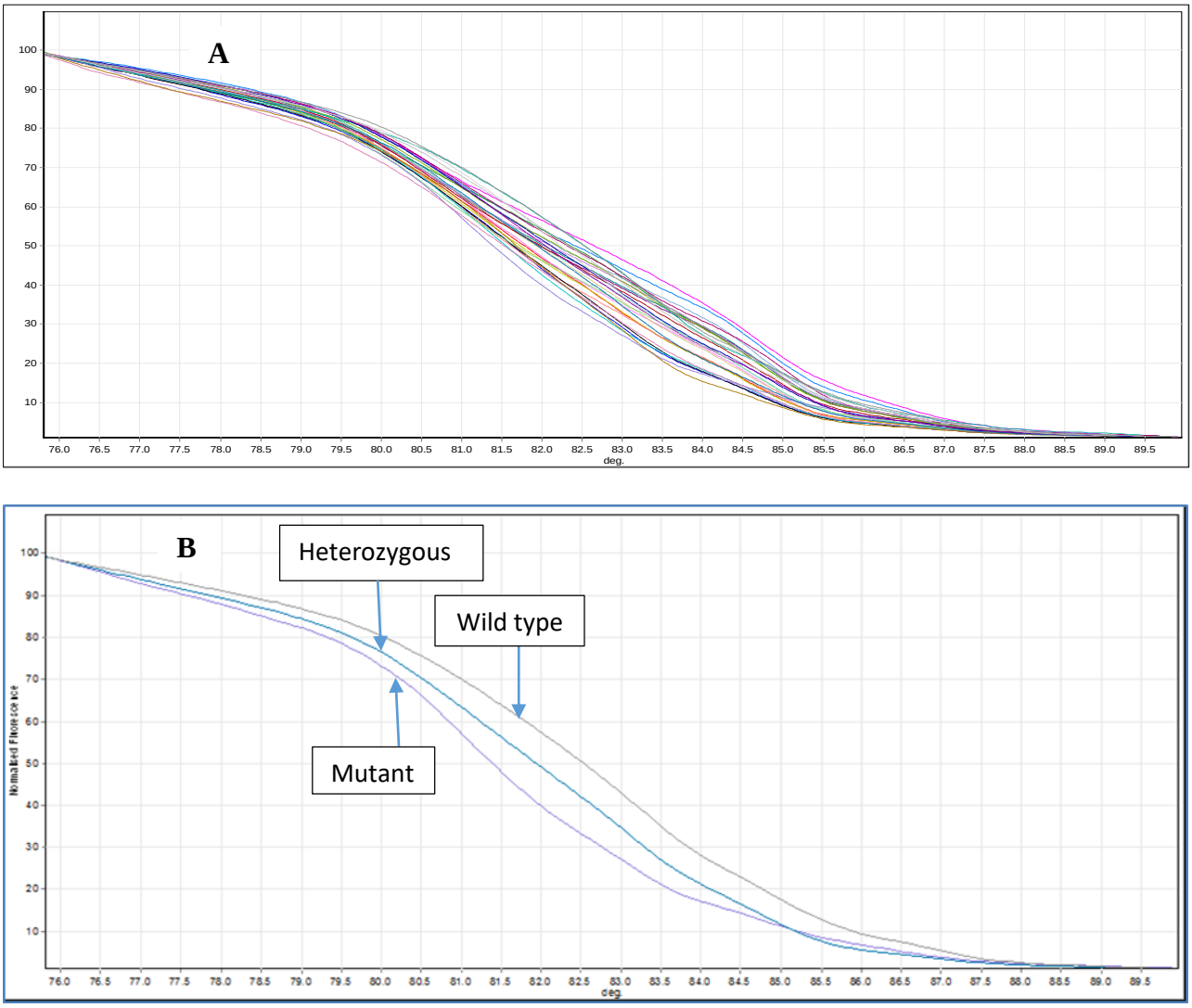

Figure 2. A and B. The results output curves of HRM for heterozygous, homozygous and wild type in *TP53* SNP rs1642785 by real time PCR.

Hardy–Weinberg equilibrium (HWE) analysis in the control and patient groups has shown that genotypes were compatible with equilibrium and that non-significant differences $p = 0.087$ have appeared between the observed and expected genotype in the control group, but the variation in the AML patient group was non-significant with $p = 0.40$ as shown in Table 4.

Table 4. Number and percentage frequencies of rs1642785 G/A genotypes and their Hardy-Weinberg equilibrium (HWE) in the patient and control groups

Genotype rs1642785	Patient group N (%)		Control group N (%)	
	Observed	Expected	Observed	Expected
Wild GG	22 (36.66%)	20.42 (34.03%)	42 (70%)	40.02 (66.69%)
Hetero GA	26 (43.33%)	29.17 (48.61%)	14 (23.33%)	17.97 (29.94%)
Mutant AA	12 (20%)	10.42 (17.36%)	4 (6.66%)	2.02 (3.36%)
Total	60 (100%)	60 (100%)	60 (100%)	60 (100%)
p-value	0.40		0.087	
	Non-Significant		Non-Significant	

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The genotypic distribution of the (G>A rs1642785) SNP in the patient group was 36.66% homozygous wild type, 43.33% heterozygous, and 20% rare homozygous variant, while genotypes in the control group were 70%, 23.33%, and 6.66% for homozygous wild type, heterozygous, and homozygous variant, respectively. Inspecting *TP53* gene genotypes and allele frequencies in the control and patient groups revealed that there was significant variation between these frequencies. The results showed an increase in *A* allele frequency 41.67% vs. 18.33% and a decrease in *G* allele frequencies 58.33% vs. 81.67%. As shown in Table 5, the GA genotype represents risk factor (OR, 3.5; CI, 1.5-8.12; *p*=0.002), the AA genotype represents risk factor (OR, 5.7; CI, 1.6-19.5; *p*=0.005), and the allele *A* represent risk factor (OR, 3.1; CI, 1.7-5.7; *p*=0.0001). In this study, it has been demonstrated, according to qPCR results that the rs1642785 SNP was found in the examined sample; therefore, this SNP can be considered a risk factor for acute myeloid leukemia, which is consistent with the findings of other researchers [23], who indicated that there was an association between rs1642785 and AML risk. Several studies investigated the relationship between rs1642785 genotypes and cancer. SNP rs1642785 is found on intron-2 of the *TP53* gene. Introns are often involved in the regulation of gene expression and DNA-protein interactions and mutations in intron sequences may affect these functions. Therefore, *TP53* mutations in the intronic region may initiate aberrant pre-messenger mRNA splicing, producing an mRNA that may be translated into defective p53 protein, which increases the likelihood of a deleterious phenotype that inhibits the apoptotic pathway and prolongs cell survival [24-26]. The distribution of *TP53* rs1642785 genotypes in Iraqi patients with acute myeloid leukemia and control groups was studied, and the results show that this SNP plays a vital role in the progression of AML.

Table 5. Genotype and allele frequencies of *TP53* gene polymorphism rs1642785 SNP between patient and control groups.

Genotype rs1642785	Patient group N (%)	Control group N (%)	*p*-value	OR	CI 95%
GG	22 (36.66%)	42(70%)	--	1.00	(Reference)
GA	26 (43.33%)	14 (23.33%)	0.002**	3.5	1.5-8.12
AA	12 (20%)	4 (6.66%)	0.005**	5.7	1.6-19.5
Total	60 (100%)	60 (100%)	--	--	--
Allele Frequency					
G	70 (58.33%)	98 (81.67%)	--	1.00	(Reference)
A	50 (41.67%)	22 (18.33%)	0.0001**	3.1	1.7-5.7

Conclusion

In conclusion, this case-control pioneer study showed that there was an association between the SNPs (rs1042522 and rs1642785) in the *TP53* gene (exon 4, intron 2) with AML, which could be risk factors for AML in the Iraqi population.

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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.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Authors' Contribution Statement

The work was done in collaboration between the authors. H. H. D. collected the blood samples, doing the practical work, analysis of data and wrote of manuscript. R. K. M. read and approved final manuscript.

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الأرتباط بين تعدد اشكال النيوكليوتيدات المفردة rs1042522 and rs1642785 في جين *TP53* وسرطان الدم النخاعي الحاد في عينة من سكان بغداد / العراق

هديل حميد داود، رنا كاظم محمد

قسم التقنيات الإحيائية، كلية العلوم، جامعة بغداد، بغداد، العراق.

الخلاصة

يمثل سرطان الدم النخاعي الحاد (AML) أكثر أنواع سرطان الدم الحاد انتشارًا بين البالغين تصل نسبته 80% من جميع الحالات. الجين المثبط للورم *TP53* هو جين تمت دراسته بشكل متكرر في مرض السرطان. والطفرات في هذا الجين تسبب ما يقارب 50% من الامراض السرطانية. هدفت هذه الدراسة إلى تقييم العلاقة بين اثنين من تعدد أشكال النوكليوتيدات المفردة في جين *TP53*: rs1042522، rs1642785 ومجموعة من المرضى العراقيين الذين يعانون من التشخيص الاولي لسرطان الدم النخاعي الحاد. جمعت عينات الدم من ستين مريضاً 26 ذكور و 34 أناث وستين عينة سيطرة 26 ذكور و 34 أناث متوافقين في الجنس والعمر والعرق. تم استخلاص الحمض النووي الجيني من عينات الدم المجمدة بالكامل باستخدام Easy Pure® Blood Genomic Kit. ثم تم قياس النقاوة والتركيز باستخدام مقياس الطيف الضوئي Nano drop NAS-99. حيث تراوحت قراءات التركيز بين (7-55 نانوغرام / ميكرولتر) وتراوحت النقاوة بين 1.78 - 1.9 تم استخدام تقنية High resolution melt (HRM) real time PCR للكشف عن تعدد اشكال النيوكليوتيدات المفردة و كانت تكرارات النمط الجيني لجين *TP53* متوافقة مع توازن هاردي-واينبرغ مع وجود فروق معنوية ذات دلالة إحصائية $p \leq 0.05$ بين الأنماط الجينية لمجموعة السيطرة والمرضى. كان تكرار النمط الجيني rs1042522 مختلفًا بشكل كبير بين المرضى وافراد السيطرة $p = 0.0001$، وكان المشاركون الذين لديهم النمط الوراثي GA أكثر عرضة للإصابة بسرطان الدم النخاعي الحاد $p = 0.0001$, 95% CI 3.2–18.4, OR=7.8. بالإضافة الى تكرار النمط الجيني rs1642785 مختلفًا بشكل كبير بين المرضى و افراد السيطرة p=0.002 والذين يحملون النمط الجيني GA أكثر عرضة للإصابة بسرطان الدم النخاعي الحاد p=0.002, 95% CI 1.5–8.12, OR=3.5.

الكلمات المفتاحية: سرطان الدم النخاعي الحاد، HRM-qPCR، rs1042522، rs1642785، تعدد اشكال النيوكليوتيدة المفردة، البروتين الورمي *TP53*.