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Study the rs2069154005 and rs6928 *MAPK1* Gene Polymorphism in a Sample of Iraqi Patients with Chronic Myeloid Leukemia

[1]Noor T. Naeem, [2]Basima Q. Hasan ALsaadi

[1]Department of Forensic Biology, Higher Institute of Forensic Sciences, Al-Nahrain University, Baghdad, Iraq.
[2]Institute of Genetic Engineering and Biotechnology for Postgraduate Studies, University of Baghdad.

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Abstract: Chronic myeloid leukemia (CML), is characterized by a startling excess of immature and mature granulocytes. In 90–95% of cases of CML, the Philadelphia (Ph) chromosome is present results from reciprocal translocation of chromosomes 9 and 22. The aim of study was the association between the polymorphisms of the *MAPK1* gene rs2069154005 and rs6928 in susceptibility to develop CML. This study consists of three groups, first group includes fifty newly diagnosed CML patients (females 22, males 28), second group consisted of fifty CML patients treated with tyrosine kinase inhibitor (TKI) (female 25, male 25). Third group included another fifty apparently healthy volunteers (female 20, male 30). The patients were admitted from the National Center of Hematology/ Mustansiriyah University. All patients diagnosed according to complete blood count (CBC), a bone marrow examination, and a BCR-ABL gene test. The result suggests that heterozygous genotype GA of rs2069154005 shows significant differences P≤ 0.05 it was (18%) in chronic CML patient while (4%) in control with OR= (5.1), Homozygous mutant AA genotype of rs2069154005 was 45% in CML patients (Newly diagnosed) and 4% in Control and OR= 345. Homozygous mutant AA genotype frequency of rs6928 was 38% in CML patients (chronic phase) and 0% in Control and shows significant differences with P ≤ 0.05 and OR= 12. AA genotypes are associated with increase the risk of having the disease polymorphisms were related with a risk for CML.

Keywords: (CML) chronic myeloid leukemia, (*MAPK1*) Mitogen-activated protein kinase, (HRM) high resolution melting.

Corresponding author: (Email: noortarek8@gmail.com).

Introduction

A myeloproliferative disease called chronic myeloid leukemia (CML) is defined by an excessive build-up of myeloid cells that appear to be normal (1). Results from the malignant transformation of hematopoietic stem cells (HSCs)2. The median age of the CML onset 50–60-year (3). CML caused by reciprocal chromosome translocation t (9;22) (q34; q11)4. There are three stages to CML chronic phase, accelerated phase and blast (crisis) phase. Tyrosine kinase inhibitors (TKI) use has prevent the disease from progressing to blast crisis (5). Mitogen-activated protein kinases MAPKs are protein Ser/Thr kinases that mediate a variety of cellular responses in response to extracellular stimuli (6).

BCR/ABL gene produces atypical tyrosine kinase – BCR/ABL which activates MAPK pathway and induces cell proliferation, blocks apoptosis and leads to genome instability resulting in further development of the disease and induction of leukemogenesis(7). MAPK pathway is an important downstream signaling cascade in several types of cancer, the MAPK signaling cascade plays a central role in CML (8). CML progression may be related to single nucleotide polymorphisms (SNPs) (9). Therefore, the location of the SNPs determines the changes in gene expression and how they affect a person's risk of developing cancer (10). The exonal SNPs affect cancer susceptibility by suppressing gene transcription and translation (11). SNPs in intron regions cause splice variants in transcripts and can either enhance or impair long non-coding RNA binding and function) (Minotti *et al*;2018)12. SNPs in the 5′-UTR affect translation, whereas SNPs in the 3′-UTR affect microRNA (miRNA) binding (13).

There are many studies in Iraq to predictive biomarker for CML progression and development (14, 15, 16, 17, 18, 19) respectively.

Materials and methods

This study consists of three groups of Iraqi patients with CML. The patients' ages ranged from 35 to 62, first group include 50 individuals (50) newly diagnosed CML patients (male 28, female 22), second group consist fifty (50) CML patients treated with tyrosine kinase inhibitor (TKI) were with the complete molecular response (p210 BCR-ABL transcript levels ≤ 0.1% IS) (male 25, female 25). Third group include Fifty (50) apparently healthy volunteers (male 30, female 20). The personal information`s such as age, sex, duration of disease, RT-qPCR result for BCR-ABL1 IS (%) were also included. All patients diagnosed according to (CBC), a bone marrow examination, and a BCR-ABL gene test.

The samples were admitting from the National Center of Hematology/ Mustansiriyah-University, this study was conducted in Baghdad during the period of March 2023 to december2023.

The study's design was accepted by the Institute of Genetic Engineering and Biotechnology for Postgraduate Studies/ University of Baghdad. Writing informed consents were obtained from all patients and apparently healthy control group.

Patients exclusion criteria

Patients age < 18 years' old, patient suffering from liver or kidney disease along with those who suffer from Hepatitis B and C and patient with (HIV) were also excluded.

Blood sample collection

Three ml from peripheral blood was obtained from each individual in each group by venipuncture using disposable syringes directly into EDTA anticoagulant tubes for complete blood count (CBC) and molecular test, DNA extraction for detection two (SNPs) rs 2069154005 and rs9628 by High-Resolution Melting (HRM) analysis.

Genomic DNA isolation

Deoxyribonucleic acid extraction was done by EasyPure® Genomic DNA Kit (TransGen, biotech. EE101-01).

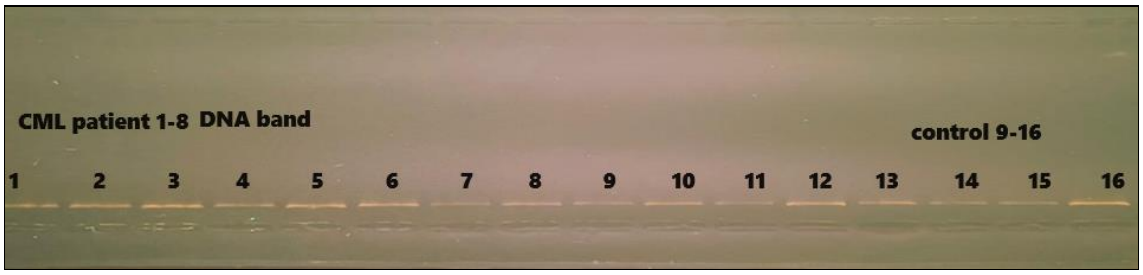

Figure (1): Genomic DNA integrity in agarose gel with a concentration of 1% for 70 min and 70 volts. Genomic DNA extracted from blood samples, visualized under UV light after staining with Ethidium Bromide

DNA concentration and purity assessment

By using a ONEc Nano drop spectrophotometer (Thermo Fisher Scientific, USA) The concentration was in the range of 75-110 ng/µl. the absorbance of sample was read at two wavelengths (260 and 280nm). The A260/A280 ratio was within the range 1.7-1.9, which is suggestive that the DNA sample was pure.

Genotyping by high-resolution melting analysis

Two genetic variants of the MAPK1 gene were selected in order to study their associations with CML Iraqi patents. High-Resolution Melting analysis real-time PCR was used to detect these SNPs (MAPK rs2069154005 G>A and *MAPK1* rs6928 C>A).

Table (1): Shows the primer sequences for and *MAPK* rs2069154005 and *MAPK1*rs6928.

Primer	Sequence (5′→3′ direction)	primer size bp	Product size bp	Ta °C
	(SNP Genotyping) MAPK12069154005			
Forward	TGGTTGGTGCTCGAATAATG	20	89	60
Reverse	CCAGAGAACCCTGAGGGAGA	20		
	(SNP Genotyping) MAPK1rs6928			
Forward	AAGCAGATACAAAGCAGTTTCAGA	24	72	59
Reverse	TGTTGCCTTTTCTTGTGCTG	20		

***bp: base pair, *Ta: annealing temperature**

ARotor gene Q Real-time PCR System (QIAGEN) was used to perform qPCR-HRM, followed by an HRM analysis with 0.2 °C scaling from 55 to 95 °C. *2xTransStart*® Tip Green qPCR Super Mix Synthetic SNP sequences were evaluated using duplicates.

MAPK1 gene (rs2069154005 and rs6928) SNPs genotyping by using HRM real-time PCR

This study includes two SNPs of *MAPK1* gene for evaluation, rs2069154005 located on Chromosome 22 (exon 2) affecting protein-coding sequences and rs6928 is located on chromosome 22 on 3 UTR Variant regulate mRNA-based processes, such as mRNA localization, mRNA stability, and translation.

Table (2): Characteristics of *MAPK1* Gene SNPs Investigated in this study According to National Center for Biotechnology Information (NCBI) Reference SNP (rs) Reports[#]

SNPs	Position/ Location	Alleles	Global Frequency*		Type	Alternate residues
			Reference allele	Alternative allele		
rs2069154005	chr22:21807728 Exon 2	G>A	None	None	Missense variant	His 80 Trp
rs6928	chr22:21760715 3' UTR	C>A	C=0.49873	G=0.50127	Missense variant	Non

 # Reference SNP (rs) reports released in September 21, 2022.

Table (3): The HRM SNPs experiment uses quantitative real-time PCR components.

Components	20 µl rxn
***2xTransStart*® Tip Green qPCR Super Mix**	10
Nuclease free water	4
Forward Primer (10 µM)	1
Reverse Primer (10 µM)	1
DNA	4

The cycling protocol was programmed for the following optimized cycles, as given in Table (4).

Table (4): The thermal profile of HRM genotyping

Step	Temperature (°C)	Time (sec.)	Cycles
Enzyme activation	94	30	1
Denaturation	94	5	40
Annealing	50	15	
Extension	72	20	
HRM	55-95	0.2sec for 1 degree	

*** Ta: Annealing temperature, for *MAPK1* rs2069154005 60°C and rs6928 59 °C.**

Statistical analysis

The results used one-way ANOVA, Haplotype and linkage disequilibrium (LD) analysis were done by SHEsisPlus online based platform (Shen *et al* ;2016)20. The distribution of haplotype combination between patients and control were compared using chia secure test, OR and 95% CI.

Results and discussion

Genotype and Allele Frequency of *MAPK1*Gene rs2069154005 SNP G>A

Genotyping of *MAPK1* gene rs2069154005 SNP was done by (HRM-qPCR). The resulting output of qPCR machine (Rotor-Gene® Q) of the analysis process for His 80 Trp SNP (rs2069154005) of *MAPK1*gene by HRM-qPCR is shown in the (Figure 1).

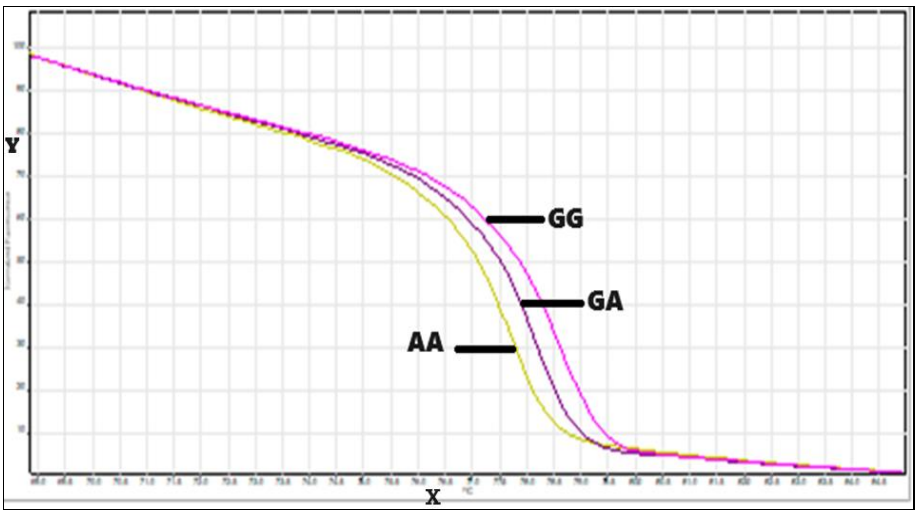

Figure (2): The Result Output of HRM -qPCR for the three genotypes (GG Wild, GA Heterozygous and AA Mutant) of SNP (rs2069154005) of *MAPK1* gene. Images captured using Qiagen Rotor Gene Q qPCR Machine. X: number of cycles, Y: florescent.

The genotype and allele frequency in (rs2069154005 G>A) of *MAPK1* gene was presented with three genotype GG, GA, AA that were corresponding to two alleles (G and A). In apparently healthy subjects (controls group) versus CML patients are presented in table (5, 6). Homozygous wild genotype GG was Ref. and the highest percentage were in apparently healthy control 98% and 80% in chronic phase CML patients'. Heterozygous genotype GA shows significant differences P≤ 0.05 with OR= (5.1), the Homozygous mutant genotype AA shows no significant differences with P value ≥0.05 with OR= (0.5). The result suggest genotype AG is associated with increased the risk of the disease. The odds ratio was >1 for GA genotypes, this indicates that genotypes act as risk factors for CML patent. While the wild genotype (GG) represents the protective factor. The frequency of the G allele was lower in Chronic CML patients compared to Control, the result suggests the protective effect of the G allele 89% versus 97%, whereas the frequency of the A allele was higher in Chronic CML patients compared to Control.

Table (5): Genotype and Allele Frequency among patient groups (chronic phase) compared with the healthy group of *MAPK1*Gene rs2069154005 SNP G>A.

rs2069154005	Frequencies (%)		Odd ratio (95% CI)	P value
	Chronic Patients (n= 50)	Control (n= 50)		
Genotype frequency				
GG	40 (80%)	46 (98%)	1.00 (Reference)	---
GA	9 (18%)	2 (4%)	5.1 (1.05 to 25.36)	0.04*
AA	1 (2%)	2 (4%)	0.5 (0.05 to 6.58)	0.6
Allele frequency				
G	89 (89%)	97 (97%)	1.00 (Reference)	---
A	11 (11%)	3 (3%)	3.9 (1.0797 to 14.790)	0.02*

1: chronic myeloid leukemia patients (chronic phase), 2 controls: apparently healthy subjects, OR (95% CI): odd ratio (95% confidence interval), NS: Non- significant, * and ** means significant at 0.05 and 0.01 levels respectively.

Distribution of genotype and allele frequencies of *MAPK1* rs2069154005 G>A between CML patient groups (Newly diagnosed) compared with the healthy group listed in Table (6). According to genotype frequencies homozygous wild type GG genotype was Ref and the highest percentage 98 % in apparently healthy control and (6%) in CML patient group (Newly diagnosed), heterozygous genotype GA shows no significant differences Odds ratio was 15.3 for GA genotype and 3.9 for A allele this indicates that there is a A allele -related risk factor for CML, Homozygous mutant AA genotype frequency was 90% in CML patients (Newly diagnosed) and 4% in Control and shows high significant differences with $P \leq 0.01$ with OR= 345. The result suggest that homozygous mutant AA genotypes are associated with increase the risk of having the disease in the population by AA genotype. on the other side, GG genotype and G allele have a protective effect.

The result suggests that the presence of the A allele (mutant allele) might increase the risk of having the disease. Disease-associated SNPs that result in amino acid substitutions at the protein sequence level since they can alter protein stability, interfere with protein-protein interaction properties, eliminate catalytic activity, affect protein folding, or lead to aggregation (21).A missense mutation involving the substitution of histidine (His) with tryptophan (Trp) can impact the proteins structure and function.

Table (6): Genotype and Allele Frequency among CML patient groups (Newly diagnosed) compared with the healthy group of *MAPK1*Gene rs2069154005 SNP G>A.

rs2069154005	Frequencies (%)		Odd ratio (95% CI)	P value
	Newly (n= 50)	Control (n= 50)		
Genotype frequency				
GG	3 (6%)	46 (98%)	1.00 (Reference)	---
GA	2 (4%)	2 (4%)	15.3 (1.5659 to 150.14)	0.01**
AA	45 (90%)	2 (4%)	345 (55.0218 to 2163.232)	0.0001**
Allele frequency				
G	8 (8%)	94 (94%)	1.00 (Reference)	---
A	92 (92%)	6 (6%)	3.9 (1.0797 to 14.790)	0.0001**

1: chronic myeloid leukemia patients (Newly diagnosed), 2 controls: apparently healthy subjects, OR (95% CI): odd ratio (95% confidence interval), NS: Non- significant, * and ** means significant at 0.05 and 0.01 levels respectively.

According to genotype frequencies Homozygous wild CC genotype was Ref and the highest percentage was in apparently healthy control 48% and 18% in CML patients (chronic phase), The frequency of the heterozygous CA genotype was 44% in CML patients (chronic phase) and 52% in apparently healthy control gives no significant differences P value = 0.09, OR = 2.2. Homozygous mutant AA genotype frequency was 38% in CML patients (chronic phase) and 0% in Control and shows significant differences with $P \leq 0.05$ and OR= 12. The result suggest that homozygous mutant AA genotypes are associated with increase the risk of

having the disease in the population by AA genotype.

The frequency of the C allele was lower in CML patients (chronic phase) compared to apparently healthy control, 40% versus 74%, whereas the frequency of the A allele was higher in CML patients (chronic phase) compared to apparently healthy control, 60% versus 26%. The result suggests that the presence of the C allele (normal allele) is associated with decreased risk of the diseases and the presence of A allele (mutant allele) might increase the risk of having the disease for 2.3 time in people carrying the A allele than the persons do not have.

Table (7): Genotype and Allele Frequency among patient groups (chronic phase) compared with the healthy group of MAPK1Gene rs6928SNP C >A.

rs6928	Frequencies (%)		Odd ratio (95% CI)	P value
	Chronic Patients (n= 50)	Control (n= 50)		
Genotype frequency				
CC	9 (18%)	24(48%)	1.00 (Reference)	---
CA	22 (44%)	26 (52%)	2.2 (0.8695 to 5.855)	0.09
AA	19 (38%)	0	12 (2.3056 to 62.4579)	0.003**
Allele				
C	0.4 (40)	0.74 (74)	1.00 (Reference)	---
A	0.6 (60)	0.26 (26)	4.1 (2.3435 to 7.7773)	0.0001**

1: chronic myeloid leukemia patients (chronic phase), 2 controls: apparently healthy subjects, OR (95% CI): odd ratio (95% confidence interval), NS: Non- significant, * and ** means significant at 0.05 and 0.01 levels respectively.

Distribution of genotype and allele frequencies of *MAPK1* rs6928 C>A between CML patient groups (Newly diagnosed) compared with the healthy group listed in table (8). According to genotype frequencies homozygous wild type CC genotype was Ref and the highest percentage 78% in CML patient groups (Newly diagnosed) and 48% in Control group, while the frequency of heterozygous genotype (CA) was higher in apparently healthy than CML patients (Newly diagnosed) subjects (52%, 22%). Homozygous mutant AA genotype frequency was not detecting in any group. The frequency of the C allele was lower in apparently healthy control 74% compared to CML patient groups (Newly diagnosed) 89%. the frequency of the A allele was higher in apparently healthy control 26% compared to CML patients (Newly diagnosed) 11%. in patient suffering from depressed.

Santos *et al* (22) found *MAPK1* gene rs6928 polymorphisms was associated with disease relapse in patient have antidepressant treatment 22.

In patients with lung adenocarcinoma, *ERK2* rs6928 and rs5999521 SNPs contributed to brain metastasis risk, the rs6928 GG and CG genotypes were associated with 2.033-fold (P=0.033) and 1.910-fold (P=0.012) increases in the risk of developing BM compared with the CC genotype (23).

Table (8): Genotype and Allele Frequency among patient groups (Newly diagnosed) compared with the healthy group of *MAPK1*Gene rs6928 SNP C>A.

rs6928	Frequencies (%)		Odd ratio (95% CI)	P value
	Newly (n= 50)	Control (n= 50)		
Genotype frequency				
CC	39 (78%)	24(48%)	1.00 (Reference)	---
CA	11 (22%)	26 (52%)	0.2 (0.1092 to 0.6210)	0.002**
AA	0	0	0.6 (0.0119 to 32.2864)	0.8
Allele				
C	89 (89%)	74 (74%)	1.00 (Reference)	---
A	11 (11%)	26 (26%)	0.3 (0.1630 to 0.7593)	0.0007**

1: chronic myeloid leukemia patients (Newly diagnosed), 2 controls: apparently healthy subjects, OR (95% CI): odd ratio (95% confidence interval), NS: Non- significant, * and ** means significant at 0.05 and 0.01 levels respectively.

Genetic variations, localized in the 3′ untranslated region (UTR) in mitogen-activated protein kinase (MAPK) pathway-related genes, may alter the transcription and impact the pathogenesis of laryngeal squamous cell carcinoma (24).

3′UTR SNP in the *MAPK1* gene may contribute to the identifications of patients at higher risk of CML development.

SNP in 3′UTR of the gene, where the miRNA binds directly. This binding then induces transcript cleavage or translational repression depending on the level of complementarity between the miRNA and mRNA transcript. Polymorphisms in this region may affect miRNA regulation, either by disrupting or creating a miRNA binding site, and cause transcription changes (25).

The results revealed that *MAPK1* polymorphisms are associated with clinic pathological features of CML.

This finding may consider the guess that this SNPs change miRNA and mRNA binding sites complementary, causing increased transcription activity and Ras/Raf/MEK/ERK1/2 cascade hyperactivation, which promotes carcinogenesis (24). *MAPK1*rs6928 showed the strongest association with coronary artery disease risk factors (26).

SNPs in *MAPK1* gene were significantly associated with high grade rash using an allelic test namely: rs6928 (3’ UTR), rs9607340 (upstream of the gene), rs9340 (3’ UTR), and rs13943 (3’ UTR). These 4 SNPs were in LD (27).

Li *et al.* (23) suggest association of genetic variations in *MAPK* with the risk of CML in patients (23).

Haplotype analysis of *MAPK1* gene SNPs rs2069154005 and rs6928

The results of haplotype frequency of *MAPK1*gene SNPs rs2069154005 G>A and rs6928 C>A SNPs was performed by using SHESIS plus software to investigate their association with CML risk in Iraqi patients and apparently healthy control Table (9) and table (10) summarize *MAPK1* gene SNPs haplotypes frequencies and risk association to CML chronic phase and CML newly diagnose.

Table (9): The frequency of haplotypes rs2069154005and rs6928 in *MAPK1* gene in chronic CML patients.

Haplotypes	Frequency		χ^2	P- value	Odds Ratio [CI 95%]
	Chronic CML (50)	Control (50)			
A A	11.00 (0.110)	0.47 (0.005)	9.318	0.002278	25.960 [3.194~211.027]
G A	48.00 (0.480)	25.53 (0.255)	10.362	0.000129	2.637 [1.451~4.793]
G C	41.00 (0.410)	72.47 .(0.725)	21.529	0.00035	0.249 [0.137~0.454]

Haplotype analysis revealed a high significant increased frequency (p<0.01) of the haplotype AA and GA in chronic CML patients 11% and 48% compared to controls 0.47% and 25.53% with odd ratio (95%CI) =25.960 [3.194~211.027] and (95%CI) = 2.637 [1.451~4.793] respectively, this result suggests strong association with the disease and this haplotype increase the risk for the persons who carrying this haplotype to have the disease. Haplotype analysis highly significant increased frequency of the haplotype GC in apparently healthy control group decrees the risk of having disease (41.00 versus 72.47) with odd ratio (95%CI) =0.249 [0.137~0.454].

Table (10): The frequency of haplotypes rs2069154005 and rs6928 in *MAPK1* gene in CML patients newly diagnosed.

Haplotypes	Frequency		χ^2	P- value	Odds Ratio [CI 95%]
	Patients Newly (50)	Control (50)			
A A	10.00 (0.100)	0.47 (0.005)	8.403	0.003757	23.707 [2.895~194.124]
A C	82.00 (0.820)	1.53 (0.015)	133.106	0.00093	29.25 [5.45~156.11]
G A	1.00 (0.010)	25.53 (0.255)	26.154	0.00035	0.029 [0.004~0.222]
G C	7.00(0.070)	72.47(0.725)	89.490	0.0038	0.029 [0.012~0.069]

In (Table10) Haplotype analysis revealed a high significant increased frequency (p<0.01) for AA and AC haplotype in newly diagnosed CML patients 10% and 82% compared to controls 0.47% and 1.53 with odd ratio (95%CI) =23.707 [2.895~194.124] and 29.25 [5.45~156.11] respectively. This result suggests association with the disease and this haplotypes may increase the risk for the persons who carrying this haplotype to have the disease. while GA and GC Haplotypes were higher in apparently healthy control 25.53 and 72.47 compared to newly diagnosed CML patients 1.00 and 7.00 respectively, GA and GC Haplotypes may decree the risk of having disease. This outcome supported the genotype result, which suggested that the variant allele for both rs2069154005(A) and rs6928(A) have a risk effect, these results give a reasonable cause to explore such SNPs to be used as a biomarker in prediction the response to IM treatment before getting started (28).

Linkage disequilibrium test

Linkage disequilibrium analysis of *MAPK1* gene SNPs, rs2069154005and rs6928 revealed a strong LD with (D' = 0.8 and r^2 = 0.06) among CML patients (chronic phase) and controls, as shown in figure (3). While the two variants (rs2069154005 and rs6928) have weak LD with a D' of

(0.41) among CML patients (newly diagnose) and control, and the correlation coefficient value (r) was weak.

Table (11): Linkage disequilibrium analysis of MAPK1 gene SNPs, rs2069154005 and rs6928 in patient (chronic phase) and control.

Linkage disequilibrium (chronic with control)	Rs05	Rs28	
Rs05	-	D′	0.832
		r^2	0.065
Rs28		-	

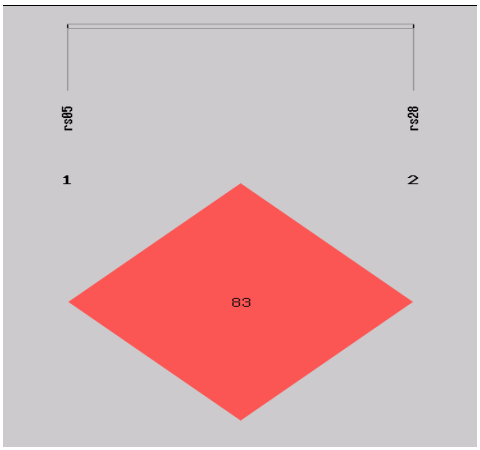

Figure (3): Linkage Disequilibrium Map of *MAPK1* Gene SNPs (rs2069154005 and rs6928) Among CML chronic phase and Controls.

Table (12): Linkage disequilibrium analysis of MAPK1 gene SNPs, rs2069154005 and rs6928 in patient (newly diagnose) and control.

Linkage disequilibrium (Newly with control)	Rs05	Rs28	
Rs05	-	D′	0.41
		r^2	0.03
Rs28		-	

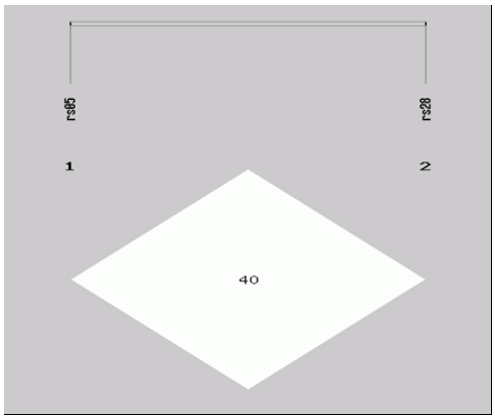

Figure (4): Linkage Disequilibrium Map of *MAPK1* Gene SNPs (rs2069154005 and rs6928) Among CML newly diagnose and Controls.

Conclusion

According to genotype and allele frequency for *MAPK1*gene rs2069154005 suggest that homozygous mutant AA genotypes are associated with increase the risk of having the disease in the population. A allele (mutant allele) might increase the risk of having the disease, the Linkage disequilibrium analysis of *MAPK1* gene SNPs, rs2069154005and rs6928 was strong among CML patients (chronic phase) and controls. Haplotype analysis revealed a high significant increased frequency (p<0.01) of the haplotype AA, GA and AC in CML patients compared to controls, this result suggests strong association with the disease.

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