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Screening for TKD mutation in fms-like tyrosine kinase 3 (*FLT3*) gene in Iraqi patients with acute myeloid leukemia

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Abstract: Acute myeloid leukemia (AML) is a destructive hematological tumor illness marked via uncontrolled proliferations of myeloid progenitor cells in the bone marrows. One of the most common genetic variations in AML is the mutations in the *FLT3* gene. This study aimed to discover the mutations in the tyrosine kinase domain (TKD) of the *FLT3* gene. This study consisted of two groups, the control group included 50 apparently healthy subjects and 50 newly diagnosed Individuals with AML. Blood samples were collected for DNA extraction used in the RFLP to detect the TKD mutation. The Eco RV enzyme was used to detect the TKD. The wild-type fragments were 80 bp, 51 bp, and 20 bp, while the mutant-type fragments were 131 bp and 20 bp. The findings indicated that the ratio of the TKD mutation was significantly ($p<0.05$) greater in males than in females. All the TKD mutations detected in the present study were heterozygous. The TKD mutation ratio was 8 % in Iraqi Individuals with AML. According to the FAB classification, the mutant cases were 3 in the M5 and 1 in the M7. WBC was significantly ($P=<0.01$) greater in Individuals with AML than in the healthy controls (HCs). No significant variations were noted between the wild-type and the mutant-type related to the WBC count and peripheral blast cell in patients.

Keywords: AML, *FLT3* gene, TKD mutation, FAB.

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Introduction

The abnormal and uncontrolled growth of bone marrow's myeloid blast cells and peripheral blood is the hallmark of a blood cancer, acute myeloid leukemia (AML) (1). The etiology of AML is largely unknown, but some risk factors including ionizing radiation, exposure to benzene, smoking, and earlier cytotoxic chemotherapy may have function in the AML pathogenesis (2). The AML diagnosis can be happened in all ages, and it mostly occurs in adults (3). It is critical to detecting AML genetic markers for risk stratification, optimizing treatment choices, and improving illness management (4). Feline McDonough sarcoma-like type 3 (*FLT3*) is a transmembrane receptor that has an important function in the management of differentiation, survival, and proliferation of cells via several signaling transduction pathways (5). About 30% of Individuals with AML harbor FLT3 mutation and the most common type of this mutation is the internal tandem duplications (*FLT3*-ITD) which is about ~25%, while about 5-10 % is a missense

mutation in tyrosine kinase domain (*FLT3*-TKD). Leukemogenesis is aided by these mutations, which are constitutively active and overexpressed in leukemic cells (6,7 and 8). Classically, *FLT3* is related to lesser responses to chemotherapeutic regime and poor prediction (9). The most common alteration in these mutations is the changing of aspartic acid into tyrosine in the codon location of D835 at the kinase domain's active loop. Nevertheless, other substitutes such as Asp835His, Asp835Val, Asp835Asn, and Asp835Glu have also been described (10,11). These TKD point mutations cause a constant open configuration of the activation loop, resulting in constitutive signaling of the FLT3 receptor (12). Patients can impact the responses into specific treatments as mutations of *FLT3*-TKD are related to a low destructive illness in contrast to that of *FLT3*-ITD (13). The purpose of the work was to assess the distributing of the *FLT3*-TKD (D835) gene mutation incidence in a sample of Iraqi patients who were newly diagnosed with AML and their association with leukocyte, peripheral blast cell ratio, gender, and AML FAB subtype.

Material and Methods

The work includes fifty a new diagnosed Iraqi patients with AML of both sexes and different ages who were referred to the Hematology Center at Medical City Complex in Baghdad between March (2023) and May (2024). In addition to these fifty Individuals with AML, fifty apparently healthy participants were also included in this investigation. All participants were informed before the study's establishment, and written consent was obtained from all participants. The blood samples were obtained from apparently healthy individuals who had no previous medical conditions. The ages and the sexes of the healthy volunteers chosen for this investigation were the same as those of Individuals with AML. For both Individuals with AML and the HCs, peripheral blood samples were collected in tubes of EDTA and, then reserved in a deep freeze (-20°C) till the DNA extraction day. The flow cytometry reports were documented from the patient's records in the Hematology Center at Medical City Complex to determine the FAB subtype of the Individuals with AML. Genomic DNA was obtained from peripheral blood samples via utilization of the Purification Kit of Wizard Genomic DNA (Promega, USA) according to the constructer's recommendations. Utilizing a Nanodrop spectrophotometer device, the genomic DNA concentration was ascertained.

FLT3-TKD Detection

The LeukoStrat® *FLT3* Mutation kit (Invivoscribe Technologies, Inc., CA, USA),was used to detection of *FLT3*-TKD mutation in exon 20 according to manufacturer's instructions. The *FLT3*-TKD master mix contained dNTPs, the forward (5′TET_GTAAAACGACGGCCAGCC GCCAGGAACGTGCTTG-3′) and reverse (5′-GGGGCAATGTGAGGCTGATATCG **TCATAG**CTGTTTCCTG -3′) primers. Assay of PCR-RFLP was carried out for the mutation of D835 due to the codons I836 and D835 were coded via the nucleotides sequence GAT-ATC respectively, which forms a restriction site for the Eco RV enzyme, moreover, the reverse primer contains an additional Eco RV recognition digest site located among the primer *M13R* sequence and the coding, this engineered recognition site acts as an internal control for the inclusiveness of cutting of restriction enzyme. The PCR reactions were carried out in a final

volume of 50 µL. To prepare the PCR mix for the *FLT3*-D835 assay, the master mix and Taq DNA polymerase were combined based on the number of samples being processed, with additional volume included to account for pipetting errors. For each sample, 45 µL of *FLT3*-D835 master mix and 0.25 µL of Taq DNA polymerase were prepared. Then, 45µL of the PCR mix was aliquoted into individual 0.25 µL PCR tubes, and 5 µL of gDNA (5 ng) was added to each corresponding tube. Samples were amplified via utilization of the conditions of PCR: 95°C for 7 min; 35 cycles at 95°C for 30 s, 56°C for 1 min, 72°C for 2 min, with a final extension at 72°C for 7 min) which produced a 151 bp product. The PCR products obtained by conventional PCR (Applied Biosystems) were restricted with the Eco RV enzyme, the digestion of Eco RV of PCR product results of wild-type in three fragments on 3% agarose gel , 80 bp and 51 bp, and 20 bp (resulting from the digestion of both recognition sites in the amplified product), while in the mutant–type PCR product that harbors the point mutation the recognition site disappears in the allele resulting in two fragments due to a cut in the other restriction site at the reverse primer; 131 bp and 20 bp (the 20 bp fragment cannot be detected by the gel electrophoresis due to the small size).

Statistical Analysis

To identify the impact of the two groups (control and patients) on the study's parameters, the Statistical Analysis System-SAS (2018) application was used. When comparing probabilities of 0.05 and 0.01 by ratio, a chi-square test was used. Values for the study's estimated correlation coefficients.

Results

Our study was conducted on 50 AML newly diagnosed patients and 50 healthy subjects as a HCs. The average age ranges for the HCs and the individuals with AML are presented in Table (1).

Table (1): Distributing of sample study based on ages in Individuals with AML and HCss.

Age range (year)	Control	AML patient	$\chi 2$	P-value
Less than 20	6 (12%)	7 (14%)	0.077	NS
20-39 yr.	16(32%)	15 (30%)	0.032	NS
40-59 yr.	18 (36%)	18 (36%)	0.00	NS
More than 59	10 (20%)	10 (20%)	0.00	NS
Total	50 (100%)	50 (100%)	--	--
NS: Non-Significant.				

No significant variations were noted between the two groups. Our results revel that AML is more common in elderly subjects. *FLT3*-TKD (D835) mutation was detected only in 4 patients (8%), and **Figure (1**) demonstrates fragments of the TKD mutation and the wild-type using gel electrophoresis before and after digestion by Eco RV enzyme. The fragments were 131 bp, 20 bp for the mutant allele, and 80 bp, 51 bp, and 20 bp for the wild-type**.** The findings of the TKD mutation ratio in the FLT 3 gene (wild-type and mutant–type) between males and females of Individuals with AML are shown in **Table (2)**. The findings indicated that the ratio of the TKD mutation was significantly ($p<0.05$) greater in males than in females (16% versus 0%, respectively, $X^2=3.72$, OR=0.86). The fragment sizes after digestion with Eco RV enzyme for the homozygous mutant-type, heterozygous mutant-type

and wild-type in the apparently healthy subjects *versus* the Individuals with AML are presented in **Table (3)**. All the TKD mutations detected in the present study were heterozygous. No homozygous mutants were found in the Individuals with AML in our study.

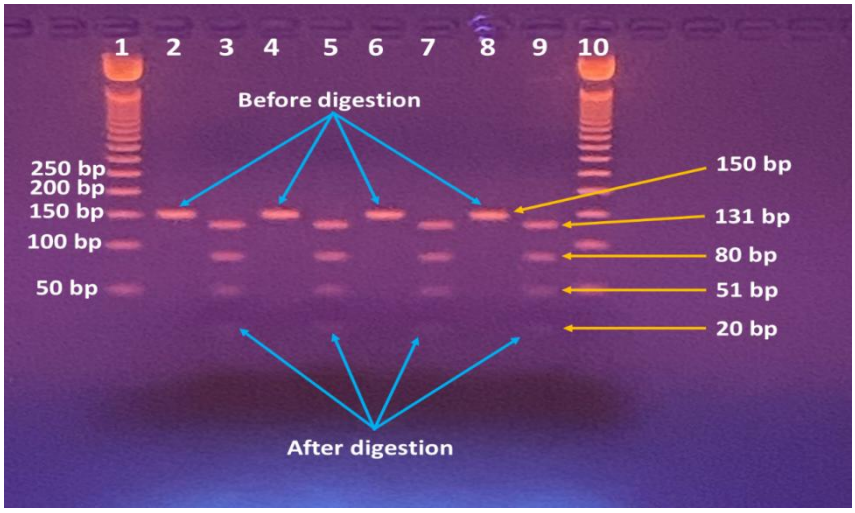

Figure (1): A 3% agarose gel image with Et Br-stained indicating *FLT3*-TKD mutations. Lanes 1 and 10 are 50 pb marker. Lanes 2-9 are patients' samples positive for the *FLT3*-TKD mutation. Lanes 2,4,6 and 8 were the samples before digestion via Eco RV and showing 150 bp band (undigested product). Lanes 3, 5,7and 9 were the samples after digestion by Eco RV showing products sizing at 131 bp, 80 bp, and 51 pb (Heterozygous mutation).

Table (2): Distributing of AML samples study based on TKD mutation in FLT 3 gene and gender.

TKD mutation in FLT 3 gene	Individuals with AML				
	Male	Female	χ2	OR (CI)	P-value
Wild Type	21 (84%)	25 (100%)	0.347 NS	0.319 (0.18-0.79)	0.556
Mutant Type	4 (16%)	0 (0%)	3.72 *	0.861 (0.47-1.59)	0.0419
Total	25 (100%)	25 (100%)	--	--	--
* (P≤0.05), NS: Non-Significant.					

Table (3): TKD genotype in patients and HCss.

TKD genotype	Fragments size	Control	Patient	χ2	OR (CI)	P-value
Wild type GG	20bp + 51bp+80bp	50 (100%)	46 (92%)	0.167 NS	0.152 (0.09-0.42)	0.683
Heterozygous mutation	20bp + 51bp+80bp+131bp	0 (0%)	4 (8%)	3.72 *	0.86 (0.47-1.59)	0.0419
Homozygous mutation	20bp +131bp	0 (0%)	0(0%)	0.00NS	--	0.00
NS: Non-Significant; ** (P≤0.05).						

The FAB classification in the wild-type versus the mutant-type in the AML patients is presented in Table (4). As shown from the findings, the most common AML subtype according to FAB classification was M5 which constitute about 18 (39.1 %) of the patients with normal wild type for *FLT 3*-TKD, followed by M4 in 10 (21.7%), while in *FLT3*-TKD (D835) patients, M5 was also the most prevalent at 3 (75%) of the patients, followed by M7 in 1 (25%) of the patients.

Table (4): Distribution of *FLT3*-TKD samples according to FAB classification.

FAB n (100%)	Wild type	Mutant type	χ2	OR (CI)	P-value
M0	4 (8.7%)	0 (0%)	3.72 *	0.86 (0.47-1.59)	0.0419
M1	0 (0%)	0 (0%)	0.00 NS	--	0
M2	4 (8.7%)	0 (0%)	3.72 *	0.861 (0.47-1.59)	0.0419
M3	5 (11%)	0 (0%)	3.91 *	1.07 (0.72-1.64)	0.0397
M4	10 (21.7%)	0 (0%)	8.750 **	1.853 (0.91-2.46)	0.0002
M5	18 (39.1%)	3 (75%)	10.71 **	2.05 (106-2.57)	0.0011
M6	2 (4.3%)	0 (0%)	1.081 NS	0.531 (0.27-0.87)	0.169
M7	3 (6.5%)	1 (25%)	1.00 NS	0.294 (0.17-0.63)	0.317
Total	46 (100%)	4 (100%)	--	--	--
NS: Non-Significant; ** (P≤0.01); * (P≤0.05)					

The findings of the count of white blood cells (WBCs) in the HCs versus the AML patients are presented in Table (5). As shown from the findings the WBC was significantly ($p<0.01$) greater than that in the HCs (29.09 ±6.12 $\times10^9$/L versus 7.29 ±0.24 $\times10^9$/L) respectively. Regarding the relationship of the hematological parameters between the individuals with AML carrying *FLT3*-TKD and other AML individuals without mutations (wild-type) that enrolled in the recent work, Table (6) reveled no significant variations among the wild-type and the mutant-type as related with the WBC and peripheral blast cell.

Table (5): Comparison between Individuals with AML and HCss in WBC.

Parameter	Mean ±SE		P-value
	Individuals with AML	Control	
WBC count $\times10^9$/L	29.09 ±6.12	7.29 ±0.24	0.0006 **
NS: Non-Significant; ** (P≤0.01)			

Table (6): Relationship among TKD mutation in *FLT 3* gene and hematological parameters.

TKD mutation in FLT 3 gene	Mean ±SE	
	WBC count $\times10^9$/L	Peripheral blast cell (%)
Wild type	29.09 ±2.67	49.72 ±4.19
Mutant type	28.00 ±1.91	45.80 ±2.76
P-value	0.866 NS	0.279 NS
NS: Non-Significant.		

Discussion

In aggressive hematology malignancies like acute myeloid leukemia (AML), normal hematopoiesis is suppressed due to the aberrant proliferation of hematopoietic

progenitor cells in the bone marrow (14, 15). Our investigation shows that AML is more common in elderly subjects and this result in agree with Mohammed *et al*. (16). The high incidence of AML in adults may be due to exposure to different environmental mutagens such as ionizing radiation, benzene, and smoking. Among the most prominent genetic variants associated with AML are mutations in the *FLT3* gene. This gene is crucial for hematological homeostasis and hematopoiesis (17). Approximately one-third of Individuals with AML have mutations in the *FLT3* gene; these mutations are often linked to a poor prognosis and a diminished impact of chemotherapy treatment (18, 19, 20). Codon I836 deletions, primarily point mutations in codon D835 or small mutations in the activation loop, are the most common mutations within *FLT3*-TKD. Assumedly gain-of-function mutations, these changes cause receptor tyrosine kinase activation by constitutive tyrosine phosphorylation (21). Since there were two distinct generations of FLT3 inhibitors obtainable according to their selectivity, determining the kind of *FlT3* mutation is crucial. While second-generation Type I inhibitors are more effective when both the mutations of TKD and *FLT3*-ITD are present, type II inhibitors are exclusive to the *FLT3*-ITD mutation. Therefore, it is critical for patient care to detect *FLT3* mutations in order to find suitable targeted treatments (22). *FLT3*-TKD (D835) mutation in the present study was detected in 4 out of 50 AML patients with an incidence of 8 %, in regional research conducted by Fahad, *et al*. (23), who investigated 50 AML Iraqi patients the incident was 4% which is lower than our findings. In another study on a sample of AML patients from Baghdad conducted by Alswaili, *et al*. (24), who also investigated 50 Individuals with AML the incident was 6%, which is slightly lower than our result. Conversely, Qiu *et al*. (25) have shown that 17.7% of their research population have *FLT3*-TKD, and they demonstrated the defect in the *FLT 3* gene has an association with response to treatment. Males were predominating regarding this mutation, all the mutations were detected in 4 males, and no females were harboring the *FLT 3*-TKD mutation. This finding was contrary to the result obtained by Fahad, *et al*. (23), which found that females were the predominant, while in another study conducted by Sarojam, *et al*. (26), they found the males showed a slight predominance compared to females with incidence of 58% and 42 % respectively for the *FLT3* -TKD mutation. The exact reason for this variance is unclear, it could be the sample size used in our study, or it could imply the prospective role of hormonal variations in revising illness biology influences, or it could be the environmental stresses that can influence this variation. According to the current study, *FLT3*-TKD mutations were more frequently distributed in the FAB M5 subtype. The mutation was found in only four patient samples; three of them expressed the M5 subtype, and the other patient expressed M7 subtype. In an Indonesian study conducted on 20 newly AML patients, they found only one patient with the *FLT3*-TKD mutation with the subtype M5. (27). Our results were in contrast to those obtained by Naseem, *et al*. (28), who found that the commonest subtype was M3. Owing to the minimal rate of the *FLT 3*-TKD mutation and studied patients, we cannot precisely determine the correlation between this mutation and FAB subtypes.

Conclusion

In our investigation, we examined the *FLT 3*-TKD mutation in a sample of newly diagnosed Iraqi patients with AML. The *FLT3*-TKD mutation frequency reported in this study is 8% which is a slightly higher than in other regional studies. The pattern of the *FLT3*-TKD was heterozygous mutations. Our data show that *FLT3*-TKD mutation in this study occurs predominantly in the males,

there was a significant difference in the prognostic factor (sex) in the patients with *FLT3*-TKD mutation versus *FLT3* wild-type, and the males were predominant, with their proportion being 100% of patients with *FLT3*-TKD mutation compared to 0% of female. *FLT3*-TKD mutation was mostly found in the FAB M5 subtype. The WBC was in AML patients significantly greater than that of the HCs. No significant variations were noted between the wild-type and the mutant-type as related with WBC count and peripheral blood blast cell.

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