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# FAT1 Gene Expression in Iranian Acute Lymphoid and Myeloid Leukemia Patients

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**ABSTRACT**

**Background:** FAT atypical cadherin 1 (FAT1) is a member of the cadherin superfamily whose loss or gain is associated with the initiation and/or progression of different cancers. FAT1 overexpression has been reported in hematological malignancies. This research intended to investigate FAT1 gene expression in adult Iranian acute leukemia patients, compared to normal mobilized peripheral blood CD34+ cells.

**Materials and Methods:** The peripheral blast (peripheral blood mononuclear cells) cells of 22 acute myeloid leukemia (AML), 14 acute lymphoid leukemia (ALL) patients, and mobilized peripheral blood CD34+ cells of 12 healthy volunteer stem cell donors were collected. Then, quantitative real-time polymerase chain reaction (qPCR) was used to compare FAT1 gene expression.

**Results:** Overall, there were no significant differences in FAT1 expression between AML and ALL patients ($p>0.2$). Nonetheless, the mean expression level of FAT1 was significantly higher in leukemic patients (AML and ALL) than in normal CD34+ cells ($p=0.029$). Additionally, the FAT1 expression levels were significantly higher in both CD34+ and CD34- leukemic patients than in normal CD34+ cells ($p=0.028$).

**Conclusion:** No significant differences were found between FAT1 expression in CD34+ and CD34- leukemic samples ($p> 0.3$). Thus, higher FAT1 expression was evident in ALL and AML leukemia cells but this appeared unrelated to CD34 expression. This suggests in a proportion of adult acute leukemia, FAT1 expression may prove to be a suitable target for therapeutic strategies.

**Keywords**: FAT1; Cadherin; Acute Myeloid Leukemia (AML); Acute lymphoid leukemia **(**ALL); Leukemia

## INTRODUCTION

Leukemias are cancers of white blood cells divided into either acute or chronic subgroups according to their pathophysiology. Acute lymphoblastic leukemia (ALL) is a malignancy of lymphoid progenitor cells characterized by multiple

cytogenetic and molecular abnormalities[1]. ALL is an important cause of mortality and the most common malignancy in children. The disease is more prevalent in males, both in 2–50year-old children and adults over 50 years[2]. Conversely, acute myeloid leukemia (AML) is a heterogeneous malignancy classified by abnormal growth of myeloid cells [3]. AML is the most common type of leukemia in adults (25%), with lowest survival rate of all leukemia. AML incidence shows two peaks in early childhood and later adulthood and has a slightly male predominance in adults [4].

Worldwide, there is a trend of increasing leukemia incidence in Western countries[6,7,8]. In Iran, hematological malignancies are also steadily growing in both males and females, with ALL and AML together accounting for about half of total cases (50%). However, the presentation of this disease is different, where for example, ALL is as prevalent as AML in Iran[5], while in the USA, AML is 2.5-fold more prevalent than ALL[8]. Both environmental and genetic factors are known to contribute to leukemia development[1], but the cause of this discrepancy remains unknown.

Knowledge of the molecular mechanisms underlying acute leukemias has been advanced by genome-wide studies. Traditional methods together with microarray analysis and next generation sequencing can be used to characterize myeloid and lymphoid leukemias through chromosome rearrangements, sub-microscopic DNA copy number aberrations, and gene mutations[9]. With increasing recognition of newly identified molecular features of acute leukemias, new perspectives about prognostic and diagnostic markers have been achieved, providing novel insights into the pathobiology of these diseases. For example, CD34 expression, the most widely used marker of hematopoietic stem cells, is related to drug resistance and worse outcomes in both AML and ALL [10-12]. Additionally, for therapeutic and prognostic purposes, AML is classified into subtypes, which includes acute promyelocytic leukemia (APL) in the World Health Organization (WHO) classification [13], which is equal to M3 subtype in the French-American-British (FAB) classification[14]. This subtype is clinically most important since it is linked with the highest incidence of early death [15].

Amongst the diversity of mechanisms involved in the pathogenesis of leukemia, the identification of genes and proteins that are commonly altered may be useful as either diagnostic or treatment markers. Calcium-dependent adherins (cadherins) are known to support homeostasis in adult tissues as well as play significant roles in differentiation during development, epithelial cell-cell adhesion, and morphogenesis[16]. Amongst the more than 250 cadherin genes are the FAT family genes (FAT1, FAT2, FAT3 and FAT4), each encoding giant 500–600 kDa proteins [17, 18].

The first identified FAT family member, FAT1, consists of 27 exons located on chromosome 4q34–35 which regulates processes such as neuronal differentiation, cell polarity, migration, and growth control [17, 19, 20]. FAT1 has been most closely studied in the context of human diseases albeit with conflicting roles reported in cancer[20]. Some studies have indicated that FAT1 mRNA expression increases in malignancies showing its possible oncogenic role[20-23], while others have indicated a tumor suppressor effect linked with its mutational loss[17,20,24]. Overexpression of FAT1 is evident in breast cancer, glioma, hepatocellular carcinoma, and pancreatic cancer [22, 23, 25, 26] along with reports showing its expression in subsets of both childhood and adult acute leukemias [21, 27]. In this regard, Gawdat et al. showed high expression levels of FAT1 in the pediatric T-cell ALL and claimed that FAT1 expression may help in distinguishing high-risk adult chronic and acute myeloid lymphoma [28].

The purpose of this study was to evaluate FAT1 gene expression in an Iranian cohort of lymphoid and myeloid leukemias. Previous studies did not detect FAT1 expression in mature blood cells; we purified mobilized CD34+ cells to compare FAT1 expression between normal and malignant blasts.

## MTERIALS AND METHODS

### Case selection and sampling

Among the 48 volunteer participants, 22 and 14 were AML and ALL patients, respectively, along with 12 healthy volunteer stem cell donors categorized as the normal (control) group. The criteria for the study participants included active leukemia either newly diagnosed or relapsed before receiving

chemotherapy. The demographic data of all participants are summarized in Table 2.

Among AML cases, 86.4% (19 of 22) were newly diagnosed patients, while the remaining three (12.6%) were relapsed patients. For ALL, 42.8% (6 of 14) and 57.2 represent newly diagnosed and relapse patients respectively. Although patients were selected at random, the mean ages were calculated as 39, 26, and 24 years for AML, ALL, and controls, respectively. Table 3 lists the age distribution of the participants.

The blood samples were incubated at 4°C for up to two hours prior to laboratory procedures.

All subjects including normal controls willingly participated in the study, providing signed written consent for the procedure. The entire patient identification information was kept confidential and no interventions were made in the clinical management of the cases. The ethical committee of TUMS approved the study (IRB approval number: 86-7143). Diagnoses were confirmed by morphological FAB criteria, cytochemistry and immunophenotype, flow cytometric immunophenotyping, as well as molecular and cytogenetic studies.

**Cell isolation**

**RNA Extraction and cDNA Synthesis**

Samples of 5 mL of peripheral venous blood were separated to yield mononuclear cells fraction by the standard Ficoll solution protocol (Sigma-Aldrich; Cat. No. H4153). Thereafter, the separated cells were studied via flow cytometry to confirm purity was > 95%. Furthermore, the normal (control) samples were apheresis products of granulocyte colony-stimulating factor (G-CSF) mobilized normal stem cell donors (n=12), whose CD34+ cells were isolated using a Dynabead protocol (Invitrogen; Cat. No.113.01D). Flow cytometric analyses confirmed their CD34+ purity >60%. The isolated samples were preserved using the RNA protect reagent (Qiagen; Cat.No.130176139). The total RNA pool extraction was performed by the RNA extraction kit (Qiagen, RNeasy PlusMini Kits, Cat. No. 74134) with yield and quality of the isolated RNA assessed by spectrophotometry and agarose gel electrophoresis, respectively. DNase-1 was used to eliminate co-purified DNA and the RNA samples stored at -80°C prior to analysis. Complementary DNA synthesis was performed by cDNA synthesis kit (Fermentase cat. No.K1622) and products were stored at -80 °C.

*Amplification primers and qRT-PCR*

The cDNA samples were subjected to qRT-PCR measurements to measure FAT1 mRNA expression with an endogenous housekeeping control, glucuronidase beta (GUSB), used to normalize gene expression. The amplification primers of FAT1 and GUSB genes plus their specifications are presented in Table 1. Prior to analysis of the entire cohort, the amplified products of the primers were sequenced to confirm the appropriate targets were being amplified.

qRT-PCR reactions were performed using an Applied Biosystems StepOne Plus™ Real-Time PCR System (Applied Biosystem, USA) and Power SYBR Green I PCR Master Mix (Applied Biosystems P/N: 4367659, USA) according to the manufacturer's protocol. The qRT-PCR was initiated by a preliminary denaturing stage at 95 °C for 10 min followed by 35 cycles of denaturation at 95 °C for 15 sec, annealing at 60 °C for 1 minute, and extension at 72 °C for 20 sec.

**Statistical analyses**

The differences of mean Ct (triple tests for each sample) of FAT1 and GUSB genes (endogenous control) for each sample, defined as ΔCT, and the fold change of gene expression between cases and controls were studied according to 2-ΔΔCt method (29). As the distribution of FAT1 expression was not compatible with Gaussian distribution both graphically and statistically, we described it as median with inter-quartile range (IQR) and performed data analysis with non-parametric statistical tests. The Kruskal-Wallis test was employed to find statistical differences in FAT1 expression between the study groups. The analysis was performed by SPSS (IBM Corp. Released 2012).

IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.), and p-value <0.05 was considered statistically significant.

**Table 1. Primers used for qrt-pcr analysis**

| Genes | | Primer sequence | Primer length (bp) | *Product length (bp) |
|---|---|---|---|---|
| FAT1 | F | 5'-GTGTGATTCGGGTTTTAGGG-3' | 20 | 132 |
| | R | 5'-CTGTACTCGTGGCTGCAGTT-3' | 20 | |
| GUSB | F | 5'-GCCAATGAAACCAGGTATCCC-3' | 21 | 71 |
| | R | 5'-GCTCAAGTAAACAGGCTGTTTTCC-3' | 24 | |

* High primer amplification efficiency was empirically determined for these primer sets.

**Table 2. Diagnosis and gender of participants**

| | Cases | | | Normal | Total participants |
|---|---|---|---|---|---|
| | AML | ALL | Total | | |
| Male | 10 | 8 | 18 | 7 | 25 |
| Female | 12 | 6 | 18 | 5 | 23 |
| Total | 22 | 14 | 36 | 12 | 48 |

**Table 3.** The age distribution of participants

| AML | | | ALL | | | Controls | | |
|---|---|---|---|---|---|---|---|---|
| Age groups | Number | Percent | Age groups | Number | Percent | Age groups | Number | Percent |
| <20 | 2 | 9.09 | 18< | 4 | 28.57 | <14 | 4 | 33.33 |
| 20-30 | 5 | 22.73 | 18-25 | 3 | 21.43 | 14-20 | 3 | 25 |
| 30-50 | 6 | 27.27 | 25-35 | 5 | 35.72 | 20-30 | 3 | 25 |
| 50-60 | 8 | 36.36 | 35< | 2 | 14.28 | 30< | 2 | 16.67 |
| 60< | 1 | 4.55 | - | - | - | - | - | - |
| Total | 22 | 100 | | 14 | 100 | | 12 | 100 |

## RESULTS

Flow cytometric analysis of CD34 expression in the AML and ALL blasts revealed most ALLs were CD34+, while there was a higher proportion of CD34- cases for AML. The differences were statistically significant, likely because of the acute promyelocytic leukemia (APL) subgroup. Amongst the 22 AML patients, ten were APL, all being CD34-. However, amongst the 12 non-M3 cases, nine were CD34+ (Table 4).

**Table 4.** CD34 expression in AML and ALL cells

| | | CD34+ | CD34- | Total | p |
|---|---|---|---|---|---|
| | | Number (%) | Number (%) | Number (%) | |
| ALL Blasts | | 11 (78.6) | 3 (21.4) | 14 (100) | 0.029 |
| AML Blasts | APL (M3) | 0 | 10 (45.4) | 22 (100) | |
| | Non-M3 | 9 (41) | 13 (59) | | |
| Total | | 20 (55.55) | 16 (44.45) | 36 (100) | |

With respect to FAT1, it was found 11 of 14 ALL patients had detectable FAT1 mRNA expression. Notably all of the APL as well as 9 of 12 non-M3 AML cells also displayed FAT1 expression. On the other hand, only 3 of 12 normal (CD34+) cell samples expressed detectable FAT1. Regardless of CD34 expression status, the FAT1 expression level was higher in the leukemic groups (AML and ALL) compared to normal CD34+ cells; however, statistically significant differences were only recorded between APL and normal stem cells (p-value=0.005). This means 17.00 (IQR=5.23), 13.11 (IQR=15.32), and 12.03 (IQR=7.22) for M3, non-M3 AML, and ALL, respectively, compared to 0.00 (IQR=11.86) for the control group (Figure 1). Furthermore, FAT1 expression was not significantly different between APL (M3) and non-M3 AML blasts (p-value=0.20).

Notably, analyses conducted based on CD34 expression also indicated the FAT1 expression levels were significantly higher in CD34- (median=15.74, IQR=5.23) compared with both leukemic CD34+ (median=11.82, IQR=13.58) and normal CD34+ cells (median=0.00, IQR=11.86) (Figure 2). There were no significant differences between FAT1 expression in normal and leukemic CD34+ cells (p-value=0.97).

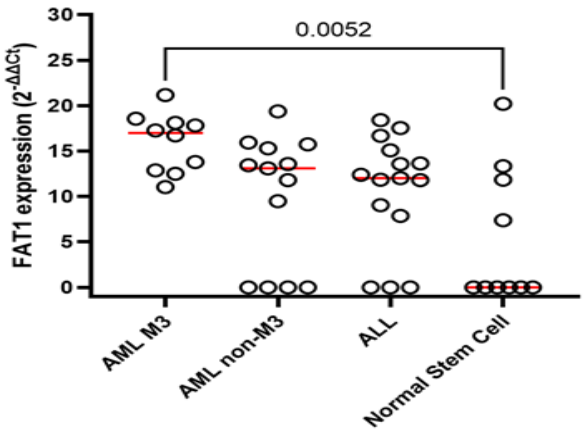


Figure 1. *FAT1* mRNA expression in AML and ALL blasts versus normal CD34+ apheresis cells

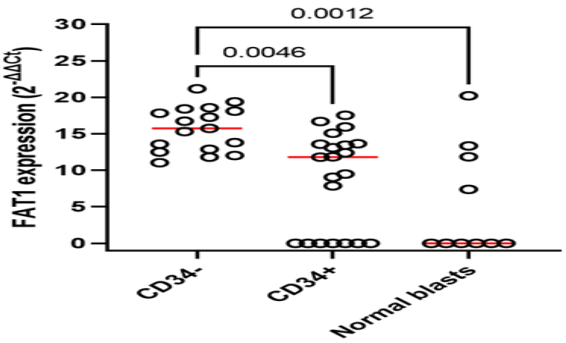


Figure 2. *FAT1* mRNA expression in CD34+, CD34- AML or ALL cells versus normal CD34+ apheresis cells

**DISCUSSION**

In this study, we evaluated differences in FAT1 expression between leukemia (AML and ALL) and normal CD34+ stem cells across an Iranian cohort. The work was initiated based on previous reports showing that FAT1 is overexpressed in acute leukemias [28] together with other reports suggesting implication of FAT1 in some solid malignancies, especially in its aberrant form [22-26]. Under normal conditions, FAT1 plays important regulatory roles in cell growth and development, affecting processes including differentiation, morphogenesis, cell polarity, and migration [16-19.] In leukemia, there is a general concordance that in some cases significantly higher expression level of FAT1 occurs is most subtypes, denoting a potential oncogenic function[30]. Although FAT1 may be a biomarker for acute leukemia and its expression may indicate poor prognosis, its function in this setting remains unknown.

FAT1 was initially cloned from a T-cell ALL cell line[31] with later reports showing its expression in different types of acute leukemias isolated from patients. In childhood ALL samples, 1 of 3 B-cell and 2 of 3 T-cell ALL cases expressed FAT1, while only 1 of 10 AML cases revealed expression [21]. The high expression of FAT1 in T-ALL was later confirmed in half of adult patients, though FAT1 was mutated in 15% of T-ALL cases and mutation often led to lack of FAT1 expression [27]. This study also found aberrant FAT1 expressed in 23% of AML and 32% of B-ALL patients[27], which is similar to childhood cases for B-ALL, but it has been reported to be twice as prevalent compared to childhood AML[21]. In a more recent study, Gawdat et al. also showed FAT1 mRNA was detected in 66% of pediatric ALLs overall and 50% of adult AML cases [28]. Interestingly, a recent NGS-based study indicated that FAT1 is among the five most frequently related mutated genes in patient samples of AML [32]. Thus, while most studies concur that FAT1 is aberrantly expressed in leukemia, the rate of positivity has been reported to vary, especially in adult AML cases.

Here, we demonstrated FAT1 expression in the majority of acute leukemia samples (30/36, 83% of cases). Division of this into subtypes revealed 11/14 ALL (78%) and 19/22 AML (86%) were FAT1 positive, with all nine APL cases being positive. It is interesting to note that our results, using qRT-PCR, are more in line with Gawdat et al. [28], who also detected FAT1 mRNA using this technology, whereas other reports relied upon microarrays[21,27]. While the high percentage of FAT1 expression in T-ALL is a recurring theme throughout, the available data suggest that earlier reports may have under-represented the expression of FAT1 in AML. Regardless, our data suggest a very high rate of positivity, which is a promising feature if FAT1 is to be considered a marker for acute leukemias. For example, Ardjmand et al. reported FAT1 may be a useful treatment target and/or MRD marker [33, 34]. The expression and mutation profile of FAT1 could therefore make it an interesting MRD marker for patients' follow up and risk stratification, especially when there are no other suitable markers such as PML/RAR-α, Wilms tumor 1 hyper expression, and BCR-ABL. Nevertheless, there is a caveat to this conclusion.

Most developmental studies have detected high FAT1 expression during embryonic development and with low or negligible expression in few adulthood tissues. The idea that certain malignant disorders express high levels of FAT1 suggests its potential as a therapeutic target for immunotherapy, chemotherapy, and even personalized therapy [21, 27, 28, 33-36]. In this study, we found 3/12 normal (CD34+) cell populations expressed detectable FAT1 expression which was low. Neumann et al. reported that unselected bone marrow (BM), CD34pos progenitors, peripheral blood, and CD3pos T cells from healthy donors lacked FAT1 expression, while FAT1 expression was highly expressed in BM-derived mesenchymal stromal cells (BMSC) from healthy donors [27]. De Bock and coworkers [21] also analyzed early hematopoietic cell progenitors isolated from either umbilical cord blood or the BM, where one out of four cases of BM cells enriched for CD34pos CD38neg CD33neg Rhohigh had expression of the FAT1 transcript. Thus, the implication that some patient's normal cells express FAT1 should be considered in testing for FAT1 and especially if FAT1 is to be employed as a treatment target. Nevertheless, considering this overall significantly higher expression levels of FAT1 in ALL and AML subtypes compared to normal CD34+ cells, its

expression in normal cells of some normal samples can be neglected[37].

Beyond FAT1 being a biomarker per se, interest in this molecule in leukemia arose from the report that FAT1 was as an independent predictive or prognostic indicator in pediatric ALL[28]. Conversely, it was also demonstrated that in patients with peripheral T-cell lymphoma not otherwise specified, recurrent mutations of FAT1 were associated with lower survival compared to those with wild-type FAT1 [38]. Furthermore, a truncated FAT1 protein expressed in T-ALL was reported to be regulated independently of wildtype FAT1 and act as a cooperating oncogene with mutated NOTCH [30]. Irrespective of whether gain or loss, or potentially both, are important to the oncogenic role of FAT1, what are the mechanisms involved? In addition to classical cadherin functions in regulating cell-cell adhesion, other potential oncogenic mechanisms involving FAT1 include Wnt[39] and hippo signaling[19] together with regulating mitochondrial function[40]. Nevertheless, the interaction between leukemic cells and their microenvironment seems the most probable starting point of investigation [27, 30].

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