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# The Gene Expression Levels of *ETS2*, *ADAM28*, and *GPRC5D* Genes in Acute Lymphoblastic Leukemia Patients

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**Abstract**

**Background:** Genetic biomarkers significantly influence the pathological differentiation and proliferation of lymphoid precursor cells, contributing to the development of Acute Lymphoblastic Leukemia (ALL) in children. This case-control study aimed to assess the expression levels of three potential biomarkers: *ETS2*, *ADAM28*, and *GPRC5D*, in patients with ALL.

**Materials and Methods:** In this cross-sectional study, a group of ALL patients (n=65) referred to the hematology-oncology departments of Nemazee Hospital and Amir Hospital in Shiraz, Iran, from May 2018 to May 2021 were selected as the patient group. A control group (n=65) of age- and gender-matched volunteers was also selected.

Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to study the expression profiles of these genes in patients and compare the results to those of a control group. The study included 65 patients with ALL and 65 healthy participants. The Pfaffl method of relative quantification, which compares the threshold cycle of a constitutive gene (*TBP*) with the test gene of each sample in duplicate, was used to determine the relative levels of *ETS2*, *ADAM28*, and *GPRC5D* gene expression. SPSS software version 16 was used for statistical analysis. Nonparametric tests were used to analyze non-normally distributed data, and the Mann-Whitney test was used to compare the medians and ranges and a p-value of 0.05 was considered significant.

**Results:** The patient group showed significantly greater expression of the *ETS2* and *ADAM28* genes compared to the control group. (P <0.0001; fold changes of 2.80 and 2.14, respectively), while *GPRC5D* expression remained unchanged (P >0.05).

**Conclusion:** These genetic biomarkers in patients with ALL may play an oncogenic role in the pathogenesis of the disease and could serve as potential novel biomarkers for ALL.

**Keywords:** Acute Lymphoblastic Leukemia, *ADAM28*, Biomarker, *ETS2*, Pathogenesis

## Introduction

The most common type of childhood cancer is acute lymphoblastic leukemia (ALL), which represents about a third of all pediatric malignancies. In the United States, the incidence is 3 to 4 cases per 100,000 children under 14 years and about one case per 100,000 individuals over 15. Although ALL can affectchildren and adults throughout their lives, it is most commonly diagnosed in children aged 2 to 6 years (1). Also, in Iran, it is assumed that ALL is the sixth most common type of cancer (2). This malignancy is described by the accumulation of immature B and T lymphoblast due to a defect in these cell differentiations. Etiological studies have identified a significant association between environmental factors—such as pesticides, ionizing radiation, and certain infections—and an increased risk of developing ALL.

Additionally, chromosomal and genetic abnormalities, including chromosomal alterations and rearrangements, along with genetic and epigenetic changes like noncoding RNA regulation, histone modifications, and DNA methylation,



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contribute notably to the development of ALL. Gaining insights into the roles of these genetic biomarkers in leukemia may help the patients by facilitating treatment decisions and improving risk assessment (3). The *GPRC5D* gene encodes a G protein-coupled receptor protein with seven transmembrane segments in cell membranes. While information regarding the role of *GPRC5D* in cancer is limited, two studies have reported its presence in the bone marrow of patients with multiple myeloma. The correlation of *GPRC5D* expression levels with factors such as bone marrow plasma cell count, plasma b2-microglobulin levels, the International Staging System (ISS), cytogenetic alterations (including deletion of 13q14 and translocation t (4;14)), and overall survival has made *GPRC5D* a novel prognostic marker in multiple myeloma. Additionally, it has been identified as a potential new cancer antigen as it is upregulated in low-risk myeloma but downregulated in normal tissues (4, 5). *GPRC5D* gene association with ALL has never been investigated before. Human lymphocytes express *ADAM28* in two different forms: membrane (ADAM28m) and short secreted (ADAM28s). The expression of *ADAM28* mRNA serves as a marker for cell proliferation. Additionally, high expression of *ADAM28* has been reported in various human tumors, including lung, breast, gastric, bladder cancers, and in ALL (6-12). Its tissue expression levels have been shown to correlate with cancer metastasis. Research indicates that *ADAM28* influences the proliferation, migration, and invasion of leukemic cells in vitro. Furthermore, elevated levels of *ADAM28* lead to increased degradation of *IGFBP-3* and enhance IGF-I-induced cell proliferation (13). Transcriptional regulation plays a crucial role in maintaining the sequential stages of hematopoiesis as it affects differentiation, proliferation, and lineage commitment through the regulation of lineage-specific gene expression. The V-ets erythroblastosis virus *E26* oncogene homolog 2 (*ETS2*) is a transcription factor that regulates gene expression by binding to various genes containing GGA (A/T) ETS response elements (EREs). The Ras/Raf/MAP kinase pathway and the phosphatidylinositol 3-kinase/Akt pathway both target *ETS2* as a downstream effector, influencing various cellular processes such as proliferation, differentiation, migration, transformation, and apoptosis.(14). Research has demonstrated that *ETS2* exhibits dual roles in cancer, functioning as both an oncogene and a tumor suppressor. For instance, *ETS2* acts as an oncogene in acute myeloid leukemia (AML) patients (15) while it displays tumor-suppressive properties in non-small cell lung cancer. (14). In this study, the *ETS2*, *ADAM28*, and *GPRC5D* gene expression levels in ALL patients were evaluated.

## Materials and Methods

### Patients and control group

In this cross-sectional study, a group of ALL patients referred to the hematology-oncology departments of Nemazee Hospital and Amir Hospital in Shiraz, Iran, from May 2018 to May 2021 were selected as the patient group. The inclusion criteria were newly diagnosed and untreated patients. A control group of age- and gender-matched volunteers was also selected. Subjects with a history of diagnosed cancer or any history of chemotherapy were excluded from the study. The patients were diagnosed using WHO criteria as well as clinical, laboratory, and molecular tests. All participants signed written informed consent forms from the Shiraz University of Medical Sciences Ethics Committee in







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**Total RNA extraction and cDNA synthesis**

Lymphodex (Innotrain) was used to collect peripheral blood granulocyte cells from the patient and control groups. Total RNA was extracted using RiboExTM (GeneAll) according to the manufacturer's instructions. A NanoDrop ND1000 spectrophotometer was used to measure the concentration of RNA at 260 nm. RNA integrity was also assessed using electrophoresis on a 1% agarose gel. The cDNA Kit was used to synthesize cDNA from the total RNA (500 ng) (Thermo Fisher Scientific). Then, the cDNA was used as a template for real-time PCR.

**Real-Time PCR**

Real-time PCR was performed by the set of primers for *ETS2*, *ADAM28*, and *GPRC5D* gene which were designed by Primer3 and AllelId software shown in Table I. Gene expression was normalized to the expression of a housekeeping gene (TATA box binding protein [TBP]). The PCR conditions were 95°C for 10 minutes, then 40 cycles of 95°C for 20 seconds, 60°C for 30 seconds, and 72°C for 20 seconds.

**Statistical analysis**

The Pfaffl method of relative quantification, which compares the threshold cycle of a constitutive gene (*TBP*) with the test gene of each sample in duplicate, was used to determine the relative levels of *ETS2*, *ADAM28*, and *GPRC5D* gene expression. SPSS software version 16 was used for statistical analysis, and a p value of 0.05 was considered significant. Mean and standard deviation were computed for normally distributed data. Nonparametric tests were used to analyze non-normally distributed data, and the Mann-Whitney test was used to compare the medians and ranges.

## Results

This study included 65 ALL patients and 65 healthy individuals matched for age and sex (27 males and 38 females with a mean age of 11±8 years old for the patient's group and 28 males and 37 females with a mean age of 13±6 years old for the control group). The group of patients had an average hemoglobin level of 10.3±2.6 gr/dl, a mean platelet count of 123±35.7 ×103/mm3, and an average WBC count of 23.7±11.8 ×103/mm3. The *ETS2* gene and *ADAM28* gene expression were significantly higher in the patients' group compared to the control group (P<0.0001 with the actual fold-change difference of 0.67 and 0.9868, respectively), whereas *GPRC5D* gene expression did not differ between the two groups ($P > 0.05$). Compared to the control group, the *ETS2* and *ADAM28* genes showed 2.80 and 2.14-fold greater expression, respectively. Figure 1 shows a histogram analysis of the relative expression of the *ETS2 ADAM28* and *GPRC5D* genes in two groups. *ETS2* gene expression was significantly greater in males compared to females; however, the expression level of the two other genes was not different in both genders.

*Table I: Primer sequences and PCR product sizes of genes*

| Gene name | Primer sequence | Product length |
|---|---|---|
| ***GPRC5D*-F** | GCCCGAGACAGTGATGGA | |
| ***GPRC5D*-R** | CAACAGTCTGCGGCTGAATG | 76 bp |
| ***ADAM28*-F** | GGTGGTTGCTATGGTAATC | |
| ***ADAM28*-R** | CTTCATCTGACTCATCTCTTG | 154 bp |
| ***ETS2*-F** | CAGCGGCAGGATGAATGA | |
| ***ETS2*-R** | CCCATCAAAGGTGTCAAAGG | 112 bp |
| ***TBP-F*** | CCCGAAACGCCGAATATAATC | |
| ***TBP-R*** | TCTGGACTGTTCTTCACTCTTG | 134 bp |







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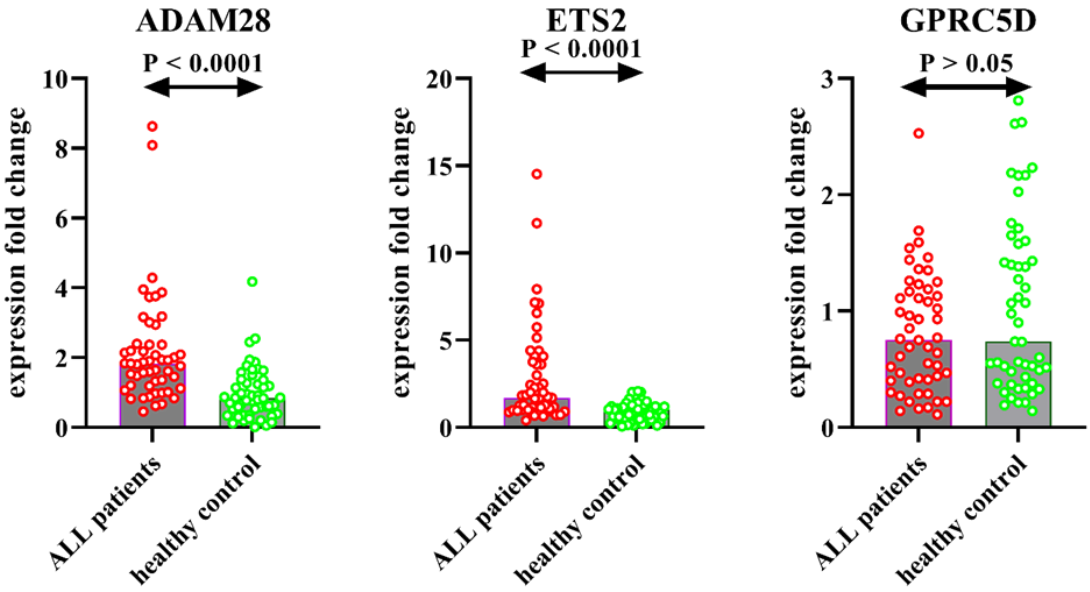


Figure 1. *ETS2*, *ADAM28*, and *GPRC5D* genes' expression fold change in patients and control group

## Discussion

The present study examined the levels of gene expression for *ETS2*, *ADAM28*, and *GPRC5D* in patients with ALL and their matched control specimens using real-time PCR. Identifying biomarkers for ALL is essential for developing innovative targeted therapies and risk-based treatment plans. According to the available data, this research is among the first to investigate the expression levels of these genes in ALL patients. While the results indicated no significant difference in *GPRC5D* expression between the control and patient groups, both *ETS2* and *ADAM28* were significantly upregulated in ALL patients compared to their controls. Although the biological function of *GPRC5D* remains largely unclear, two previous studies have indicated that this gene is overexpressed in multiple myeloma and its expression diminishes in response to antimyeloma treatments (4, 5). Moreover, they showed that *GPRC5D* was overexpressed exclusively in multiple myeloma cells, while most normal and abnormal bone marrow cells exhibited low to moderate levels of expression. These results are in the same line with the findings of their study, which indicated that this gene was expressed only at minimal levels in lymphoblastic leukemia and normal lymphocytes (5). Based on available data, there is a limited number of investigations into *ADAM28* as a biomarker for ALL (16). *ADAM28* is involved in several biological processes, including cell adhesion, proteolysis, and the growth and metastasis of solid tumors, as well as hematological malignancies (17). Research has shown that *ADAM28* is significantly expressed in various human tumors, including chronic lymphocytic leukemia, B-cell ALL, as well as lung, breast, and colorectal cancers (17-20). Tissue expression levels of *ADAM28* are also







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directly related to cancer metastasis (21). Studies have reported that *ADAM28* is specifically overexpressed in advanced stages of human non-small cell lung cancer (NSCLC). Its expression is associated with several factors, including tumor size, cell growth, lymph node metastasis, and overall prognosis for patients with this type of cancer. This suggests that *ADAM28* may play a critical role in the progression and aggressiveness of NSCLC, making it a potential target for therapeutic intervention or a biomarker for disease monitoring (11, 18, 22). Further studies have shown that *ADAM28* facilitates lung metastasis by cleaving and inactivating the pro-apoptotic protein von Willebrand's factor (vWF) in carcinoma cells, likely enhancing the survival of these cells within blood vessels. Additionally, in human breast cancer cells, *ADAM28* has been identified as being overexpressed in its active form. This overexpression promotes cell proliferation by increasing the availability of IGF-I, which is released from the IGF-I/IGFBP-3 complex that *ADAM28* can specifically cleave (16). The upregulation of urinary *ADAM28* in bladder cancer has been identified, suggesting that *ADAM28* could play as a potential biomarker for the disease (10). In a single study examining *ADAM28* in ALL, researchers discovered a direct correlation between *ADAM28* expression levels and relapse rates and prognoses in de novo B-ALL patients. It was demonstrated that the PI3K pathway regulated *ADAM28* expression in B-ALL cells, indicating that modifications to signal transduction pathways could also impact both *ADAM28* transcription and traslation (12). This study demonstrated the overexpression of *ADAM28*, aligning with earlier findings. *ADAM28* is a gene that plays a significant role in immune regulation and inflammation. It is expressed in B lymphocytes and is overexpressed in various immune and inflammatory conditions, as well as in adult B-ALL. Its involvement in B-ALL is likely linked to its role in B lymphocyte function and immune regulation, highlighting its potential significance in the pathology and prognosis of the disease (17). Further research is essential to fully elucidate the mechanisms underlying *ADAM28*'s role in B-ALL and to identify potential therapeutic targets for the disease. Understanding how *ADAM28* contributes to the pathophysiology of B-ALL could lead to new strategies for intervention, potentially improving patient outcomes and guiding the development of targeted therapies. Investigating the signaling pathways and molecular interactions associated with *ADAM28* will be crucial in advancing our understanding and management of this malignancy. *ETS2* is a transcription factor that plays a critical role in regulating a variety of biological processes, including cell division, development, differentiation, apoptosis, and immune modulation. Its function is highly context-dependent; *ETS2* can act as both an activator and an inhibitor of transcription, depending on the specific genes involved and the cellular environment. By modulating the expression of target genes, *ETS2* influences essential processes in both normal physiology and disease states. Understanding its multifaceted role may reveal important insights into the mechanisms of various diseases, including cancers and immune disorders, and could inform the development of targeted therapies (23). The product of this gene serves as a downstream target for the phosphatidylinositol 3-kinase (PI3K) pathway and the Ras/Raf/MAP kinase pathways (24). Multiple researchs indicate that *ETS2* plays dual roles in cancer, acting as both a tumor promoter and a tumor suppressor in different malignancies. For instance, it functions as an oncogene in acute megakaryocytic leukemia, but







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demonstrates tumor-suppressive effects in non-small cell lung cancer (14). *ETS2* overexpression has been observed in hypopharyngeal cancer and is associated with the metastasis stage of this malignancy. Additionally, inhibiting *ETS2* may adversely affect cell viability and colony formation in hypopharyngeal cancer (26). A study found that *ETS2* was highly expressed in tissues and cell lines of renal cell carcinoma, correlating to the clinicopathological characteristics of patients with the disease. Downregulating *ETS2* significantly decreased both in vitro invasion of renal cell carcinoma cells and in vivo metastasis. Moreover, the study revealed that renal carcinoma cells with reduced *ETS2* levels exhibited significantly lower phosphorylation levels of PI3K and Akt. (27). Another study identified *ETS2* as part of a novel signaling pathway. It was found that *ETS2* regulated *MDM2* transcription through the PI3K/mTOR/*ETS2* pathway independently of the *p53* protein. This mechanism may shed light on why *MDM2* is overexpressed in over 50% of cancers when p53 is nonfunctional (28). *ETS2* has been reported in association with a poor prognosis in AML patients (24). Moreover, elevated *ETS2* expression is associated with poor prognosis not only in patients with acute myeloid leukemia (AML) but also in those undergoing allogeneic hematopoietic stem cell transplantation. Consequently, it has the potential to serve as a novel biomarker for AML (15). The findings of this study indicate that *ETS2* gene overexpression is present in patients with ALL as compared to a healthy control group. This observation is consistent with previous reports identifying *ETS2* as an oncogenic factor in various cancer types. Additionally, Bhatia et al. reported comparable results for *ETS2* in a smaller cohort of patients (29).

## Conclusion

The findings of this study suggest that the *ETS2* and *ADAM28* genes may contribute to the oncogenic processes involved in the pathogenesis of ALL. Given that the PI3K pathway has been recognized as a crucial signaling pathway in ALL and a significant target for antileukemic therapies, these genes warrant further investigation. Consequently, these genes may serve as potential biomarkers for ALL. Further research involving larger study populations is recommended to thoroughly assess the roles of these genes in the disease development and prognosis for a more comprehensive evaluation.

## Ethical Considerations

Informed patient consent was obtained for publication of this report. IR.SUMS.REC.1399.450

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## Authors' Contributions

Study design: Nader Cohan and Mani Ramzi; Methodology: Farnoush Farokhian, Mohamad Moghadam and Farzaneh Fakhraei; Data collection and data analysis: Nader Cohan, Elham Abedi and Shirin Parand; Writing–original draft preparation: Nader Cohan and Elham Abedi; Writing – review and editing: Nader Cohan, Mani Ramzi and Elham Abedi. All authors have read and agreed to the published version of the manuscript.

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## Conflict of Interest

None.

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