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

Farnoush Farokhian Msc[1], Nader Cohan PhD [1], Mani Ramzi MD[1], Elham Abedi PhD[1], Farzaneh Fakhraei BSc[1], Shirin Parand MA[1], Reyhane Khademi PhD[2], Mohamad Moghadam Msc [1*]

1. Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
2. Thalassemia & Hemoglobinopathy Research Center, Health research institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
*Corresponding author: Mohamad Moghadam, Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. Email: mohammad.moghaddam@hotmail.com. ORCID ID: 0000-0001-8354-8423.

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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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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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