Erciyes BioGenome

Research Article

Imprint:
Issue: 1
Year: 2025
Page: 11-21

Ecmel Mehmetbeyoglu Duman [a,b]
Ayse UZ[a,b]
Sudenur Sancak [b,c]
Mai R. S. Abusalim [b,c]
Venhar Cinar [a,b]
Serpil Taheri[a,b*]

* Corresponding Author
Serpil Taheri,
serpiltaheri@hotmail.com

[a] Department of Medical Biology, Faculty of Medicine, Erciyes University, Kayseri, Türkiye
[b] Betül Ziya Eren Genome and Stem Cell Center, Erciyes University, Kayseri, Türkiye
[c] Gevher Nesibe Genome and Stem Cell Institute, Erciyes University, Kayseri, Türkiye

Received: 14/11/2025
Accepted: 24/12/2025
Published: 31/12/2025

Citation:
Mehmetbeyoglu Duman E, Uz A, Sancak S, Abusalim MRS., Cinar V, Taheri S (2025). Transcriptional and Proliferative Heterogeneity Among Leukemia Cell Lines: A Baseline Characterization of Epigenetic and DNA-Repair Pathways. *Erciyes BioGenome*, 1, 11-21.

Screened by iThenticate for Authors & Researchers

Except where otherwise noted, content in this article is licensed under a Creative Commons 4.0 International license. Icons by Font Awesome.

Transcriptional and Proliferative Heterogeneity Among Leukemia Cell Lines: A Baseline Characterization of Epigenetic and DNA-Repair Pathways

Abstract

Leukemia comprises biologically diverse hematologic malignancies with subtype-specific molecular characteristics that influence disease behavior and therapeutic response. To establish baseline transcriptional and proliferative profiles across representative leukemia models, we quantified the expression of TRDMT1 (DNMT2), RAD51, TET2, and XPA in six leukemia cell lines (ARH-77, CCRF-SB, HL-60, K-562, Kasumi-1, SUP-T1) and assessed their growth dynamics over a 96-hour period. qPCR analysis revealed significant differences in the baseline expression of all four genes among cell lines. ARH-77 showed the highest expression levels for each gene, while HL-60 and K-562 generally displayed lower expression. Growth assays demonstrated variable proliferation rates, with SUP-T1 and CCRF-SB exhibiting the greatest increases in cell number. To contextualize these findings within clinical disease patterns, expression of the same genes was examined in hematologic malignancies using the BloodSpot dataset (GSE13159). Public transcriptomic data demonstrated heterogeneous subtype-dependent expression ranges for TRDMT1, RAD51, TET2, and XPA, and these patterns aligned with the variability observed across the leukemia cell lines. Together, these results provide a comparative molecular and phenotypic baseline for commonly used leukemia models and establish a reference framework for subsequent functional and therapeutic studies.

Keywords: Leukemia, DNA Repair, Gene Expression

INTRODUCTION

Leukemia represents a heterogeneous group of hematologic malignancies characterized by the uncontrolled proliferation of immature leukocytes that replace normal hematopoietic cells in the bone marrow, resulting in impaired oxygen transport, hemostasis, and immune function (Chennamadhavuni et al., 2023; Malik et al., 2022; Sharma et al., 2025). It affects individuals of all ages: acute lymphoblastic leukemia (ALL) predominates in children under five, whereas acute myeloid (AML), chronic lymphocytic (CLL), and chronic myeloid (CML) leukemias are more common in older adults. Incidence and outcomes vary by age and ethnicity, with over half of leukemia-related deaths occurring after age 60 and lower survival rates reported among Black patients (Yi et al., 2020; Tebbi, 2021; Du et al., 2022; Zhao, 2018). Clinically, leukemias are categorized as acute or chronic according to proliferation rate and as myeloid or lymphoid by lineage origin (Lightfoot et al., 2008; Arber et al., 2016). The main subtypes include AML, CML, ALL, and CLL, while mature B-, T-, and NK-cell leukemias are less frequent.

Leukemogenesis arises from a complex interplay of genetic and environmental factors, including chromosomal rearrangements, ionizing radiation, chemical exposure, viral infection, and inherited

syndromes such as Down or Fanconi anemia (Lightfoot et al., 2008; Figueroa et al., 2010; Bispo et al., 2020). Beyond genetic lesions, epigenetic dysregulation plays a decisive role. Aberrant promoter hypermethylation of tumor-suppressor genes (p15, p57) leads to cell-cycle disruption and blocked differentiation, while recurrent mutations in DNMT3A, TET2, and other chromatin modifiers such as ASXL1, BAP1, RUNX1, and MLL further alter the hematopoietic epigenetic landscape (Quesnel et al., 1998; Shen et al., 2003; Sampath et al., 2021; Schoofs et al., 2014; Abdel-Wahab et al., 2013; Koh et al., 2013). These molecular changes contribute to abnormal differentiation, enhanced proliferation, and adverse prognosis.

Therapeutic success in leukemia is closely linked to DNA-repair competence. Conventional treatments—including chemotherapy, radiotherapy, and targeted agents—induce DNA damage, and the ability of tumor cells to repair such damage determines both efficacy and resistance (Helleday et al., 2008; Li et al., 2021; Wang et al., 2021). Key repair factors include RAD51, which mediates homologous recombination (HR); XPA, a core component of nucleotide-excision repair (NER); and TET2, an epigenetic regulator influencing the transcription of repair-associated genes (Grundy et al., 2020; Pulzová et al., 2020; Maifrede et al., 2021). In addition, TRDMT1 (DNMT2) acts as an RNA methyltransferase that stabilizes tRNA and enhances cellular stress tolerance (Goll et al., 2006; Tuorto & Lyko, 2016). Dysregulated expression of these genes can modify DNA-repair efficiency, genomic stability, and ultimately treatment response.

In the present study, we aimed to establish a baseline molecular framework capturing intrinsic differences in genome maintenance and regulatory states across leukemia subtypes. We selected TRDMT1, RAD51, TET2, and XPA as a focused gene set representing interconnected regulatory processes that collectively influence cellular stability and proliferative behavior in leukemia. We hypothesized that coordinated variation in the basal expression of these genes reflects subtype-specific molecular states that may underlie differences in proliferation kinetics and therapeutic responsiveness. To test this hypothesis, we analyzed the baseline expression of TRDMT1, RAD51, TET2, and XPA together with proliferation kinetics in six leukemia cell lines representing major hematologic subtypes and validated these findings using the BloodSpot (GSE13159) transcriptomic dataset, thereby establishing a comprehensive molecular reference for subsequent therapeutic response studies.

MATERIAL and METHOD

Cell Culture and Growth Assay

Human leukemia/lymphoma cell lines ARH-77, CCRF-SB, HL-60, K562, Kasumi-1, and SUP-T1 were thawed from liquid nitrogen storage and cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (v/v) and 1% penicillin-streptomycin. Standard culture conditions were followed, maintaining the cells at 37°C in a humidified environment with 5% CO_2. All cell lines used in this study were generously provided as a research gift by Dr. Mustafa Burak Acar, Erciyes University,Betül Ziya Eren Genom and Stem Cell Center.

Regarding the growth assay, cells were seeded into 24-well plates at an initial number of 50,000 cells per well. Each cell line was plated in triplicate, and cultures were maintained for four days. Cell numbers were determined every 24 hours using a hemocytometer. To assess cell viability, a trypan blue exclusion assay was performed, with dead cells stained blue and live cells remaining unstained.

Total RNA Isolation

Total RNA was extracted from cells using PureZOL™ Reagent (Bio-Rad, USA; Cat. No: 7326890) according to the manufacturer's protocol. Briefly, cells were washed with phosphate-buffered saline (PBS, pH 7.5) and homogenized in 500 µL PureZOL using a 2 mL syringe. Following homogenization, 200 µL of chloroform was added, and samples were centrifuged at 12,000 x g for 20 minutes at 4°C. The aqueous phase was transferred to new labeled microtubes, mixed with an equal volume of isopropanol, and incubated at -20°C overnight to precipitate RNA. The resulting RNA pellet was washed with 75% ethanol, air-dried, and resuspended in 40 µL nuclease-free water. After RNA

CC: BY-ND-NC

concentration and purity were determined using a NanoDrop spectrophotometer (Thermo Fisher Scientific, USA), they were stored at -20°C until further use.

cDNA Synthesis

Complementary DNA (cDNA) was synthesized from total RNA using the iScript™ High-Fidelity cDNA Synthesis Kit (Bio-Rad Laboratories, USA; Cat. No. 1708891) by preparing a mix of 4 µL reaction buffer, 8 µL nuclease-free water, and 2 µL of reverse transcriptase enzyme with 6 µL of RNA used as a template in a 10 µL total volume per reaction, following the manufacturer's instructions. Cycling conditions started at 25°C for 5 minutes, 46°C for 20 minutes, followed by 95°C for 1 minute, and held at 4°C (Taheri et al., 2022).

Real-Time PCR for Transcript Levels Determination

Transcription levels of the target genes (*DNMT2A*, *RAD51*, *TET2*, and *XPA*) were quantified using the Real-Time PCR on the Roche Light Cycler LC480 system (Roche, Germany). Reactions were carried out using the Syber Green 1 Master Kit (Roche, Cat No: 04707516001, Germany) according to the manufacturer's protocol. Each 20 µL of reaction consisted of a mixture containing 10 µL of Syber Green master mix, 0.5 µL of 10 pM primers, both forward and reverse, with 5 µL of dH2O added to 4 µL of template DNA. The thermal cycling protocol consisted of an initial denaturation at 95°C for 5 minutes, followed by 40 amplification cycles comprising denaturation at 94°C for 20 seconds, annealing at 60°C for 20 seconds, and extension at 72°C for 45 seconds. Melting curve analysis included a brief denaturation at 95°C for 15 seconds, a rapid drop to 67°C for 1 second, and final steps at 95°C and 40°C, each held for 30 seconds. The primer sequences used are provided in Supplementary Table 1.

After using the β-actin gene as the housekeeping gene, the Ct values obtained were normalized using the $2^{-\Delta\Delta Ct}$ method (Livak & Schmittgen, 2001).

Statistical Analysis

All statistical analyses were performed using RStudio (version 2025.05.1). The suitability of the data for normal distribution was assessed using histograms, Q–Q plots, and the Shapiro–Wilk test. Levene's test was applied to evaluate the homogeneity of variances. Differences among multiple cell lines were performed using one-way ANOVA followed by Tukey's post-hoc test. Associations between quantitative variables were examined using Spearman correlation analysis. Statistical significance was set at $p < 0.05$. Data are presented as mean ± standard deviation (SD) unless otherwise specified.

RESULTS

Cell proliferation was monitored in six leukemia cell lines (ARH-77, CCRF-SB, HL-60, K-562, Kasumi-1, and SUP-T1) over 96 hours, and cell numbers were recorded at 0, 24, 48, 72, and 96 hours. All cell lines demonstrated time-dependent increases in cell number in Figure 1. SUP-T1 showed the greatest increase, reaching approximately ~1.2×10^6 cells at 96 hours, followed by CCRF-SB, which reached ~500,000 cells at the same time point. ARH-77 and Kasumi-1 exhibited moderate growth, reaching ~300,000 cells and ~260,000 cells, respectively, at 96 hours. HL-60 and K-562 demonstrated comparatively lower increases in cell number, reaching ~150,000 cells and ~120,000 cells at 96 hours, respectively. Growth differences among the leukemia models were evident throughout the 96 hours, with significant separation becoming more apparent after 48 hours.

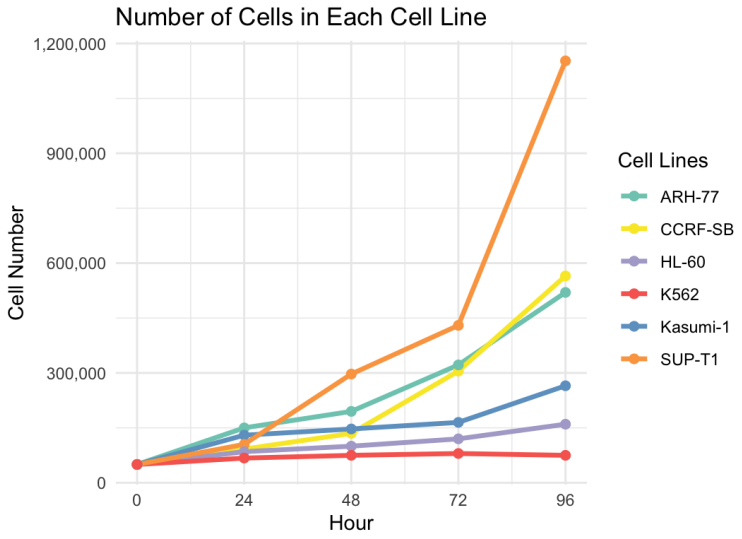


Figure 1: Time-dependent cell proliferation across ARH-77, CCRF-SB, HL-60, K562, Kasumi-1, and SUP-T1 cell lines.

Baseline Transcriptional Landscape of RNA-methylation and DNA-repair Machinery Across Leukemia Subtypes

To characterize intrinsic transcriptional programs associated with leukemia lineage and transformation state, we mapped baseline expression signatures of key genome-maintenance genes, including the RNA methyltransferase TRDMT1 (DNMT2) and canonical DNA-repair regulators (RAD51, TET2, XPA) across a representative panel of hematologic malignancy models: ARH-77 (plasma-cell leukemia), CCRF-SB (B-ALL), SUP-T1 (T-ALL), HL-60 (AML-M2), Kasumi-1 (t(8;21) AML), and K-562 (CML-BCR-ABL1+). These cell lines were chosen to capture both myeloid and lymphoid leukemia, spanning developmental and differentiation stages.

Expression values were normalized to internal controls and are presented as mean ± SEM (standard error of mean) (n = 3) in Figure 2. Among the examined genes, ARH-77 demonstrated the highest expression across all four targets ($p < 0.05$). For TRDMT1, expression was highest in ARH-77, followed by Kasumi-1 and SUP-T1, while lower levels were observed in CCRF-SB, HL-60, and K-562. RAD51 expression was highest in ARH-77, moderate in Kasumi-1, CCRF-SB, and SUP-T1, and lowest in HL-60 and K-562. TET2 expression was highest in ARH-77, with CCRF-SB and SUP-T1 showing intermediate expression, and lower levels were detected in HL-60, K-562, and Kasumi-1. XPA expression was the highest in ARH-77, followed by K-562 and HL-60, whereas CCRF-SB, SUP-T1, and Kasumi-1 exhibited lower levels. One-way ANOVA followed by Tukey's post-hoc test confirmed statistically significant differences among groups for each gene ($p < 0.05$), and distinct statistical groupings are shown in Figure 2.

Alignment of Cell Line Data with BloodSpot Validation

Baseline qPCR expression patterns of TRDMT1, RAD51, TET2, and XPA in leukemia cell lines were compared with transcriptomic profiles from the BloodSpot GSE13159 dataset. Across both datasets, each gene showed variable expression levels among leukemia subtypes. In the cell line panel, all four genes displayed significant expression differences across ARH-77, CCRF-SB, HL-60, K-562, Kasumi-1, and SUP-T1. In parallel, the BloodSpot dataset demonstrated broad transcriptomic variability for each gene across patient-derived hematologic malignancy categories. TRDMT1 values ranged approximately from log2 4.0 to 7.2 with wide distributions in CML, T-ALL, and MDS (Figure 3). RAD51 expression ranged from log2 4.0–8.5 with broader dispersion in CML, T-ALL, and MDS, and narrower clustering in AML t(15;17), AML t(8;21), and B-ALL t(8;14) (Figure 4). TET2 expression spanned log2 6.0–9.2, with wider variability in CML, T-ALL, and AML complex karyotype compared to more compact ranges in healthy bone marrow and selected AML/ALL subtypes (Figure 5).

CC: BY-ND-NC

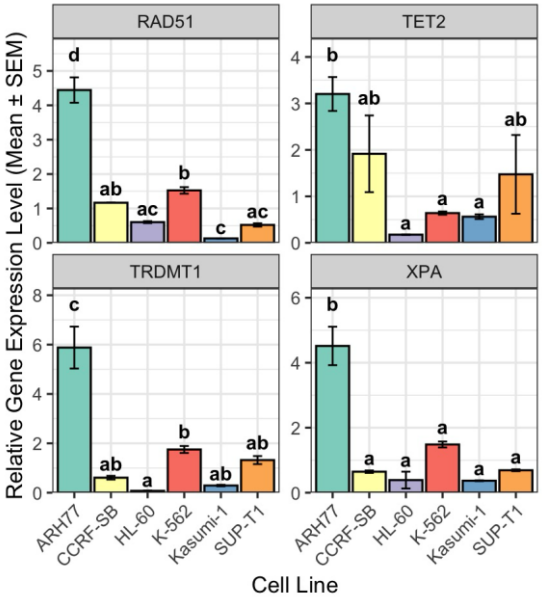


Figure 2: Baseline mRNA expression of TRDMT1, RAD51, TET2, and XPA in leukemia cell lines. Relative mRNA levels were measured by qPCR in ARH-77, CCRF-SB, HL-60, K-562, Kasumi-1, and SUP-T1 cell lines under untreated conditions. Data are presented as mean ± standard error of mean (SEM) (n = 3). Different letters above the bars indicate statistical groupings; bars sharing at least one common letter are not significantly different, whereas bars with no letters in common represent statistically distinct groups (one-way ANOVA with Tukey's post-hoc test; $p < 0.05$) (Supplementary Table 2).

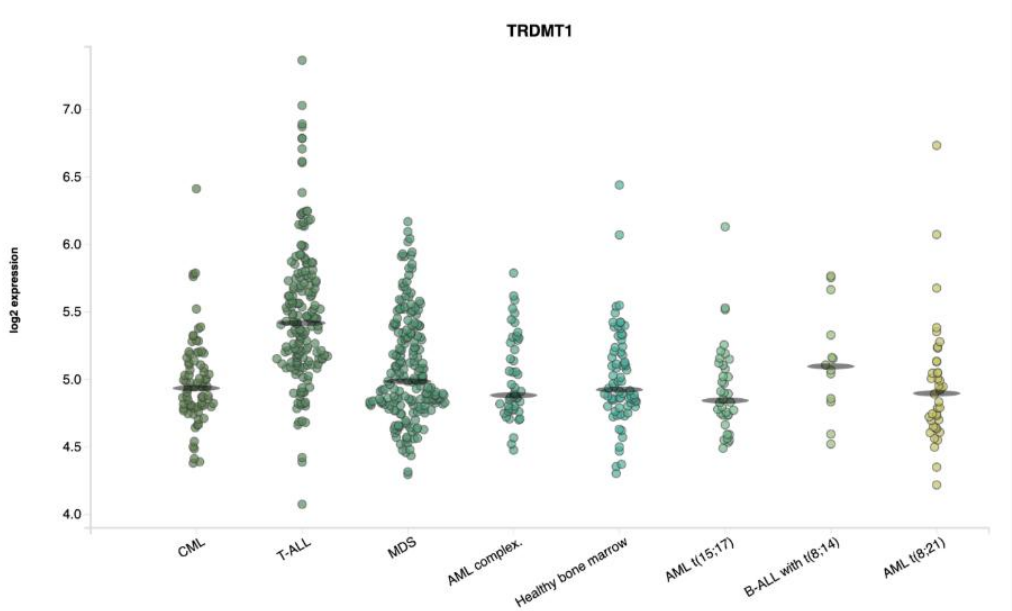


Figure 3: Expression of TRDMT1 (DNMT2) across hematologic malignancies visualized using BloodSpot (https://bloodspot.eu; dataset GSE13159). Corresponding subtypes for the cell lines analyzed: ARH-77 (AML–MDS), CCRF-SB (B-ALL t(8;14)), HL-60 (AML t(15;17)-like), K562 (CML), Kasumi-1 (AML t(8;21)), and SUP-T1 (T-ALL).

XPA expression ranged roughly from log2 5.0 to 10.0, with wider scatter in CML, T-ALL, and AML complex and narrower distributions in AML t(15;17), B-ALL t(8;14), and AML t(8;21) (Figure 6). Examination of both datasets demonstrated that TRDMT1, RAD51, TET2, and XPA display non-uniform baseline expression across leukemia models at both the experimental and patient-derived transcriptomic levels. Importantly, the relative expression patterns observed in leukemia cell lines

were concordant with the subtype-dependent heterogeneity captured in the BloodSpot dataset, supporting pattern-level alignment between in vitro models and clinical samples.

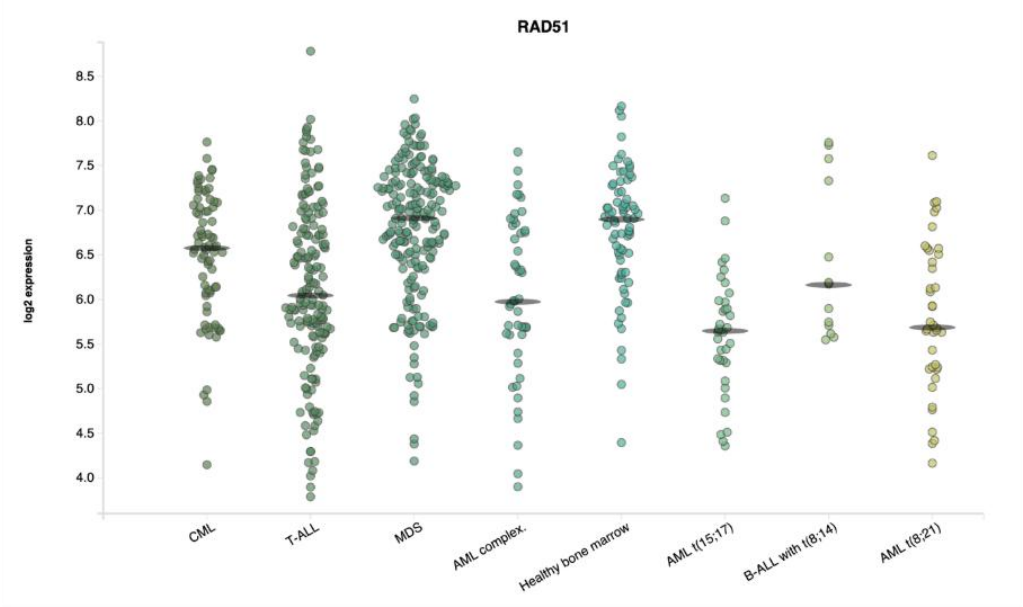


Figure 4: Expression of RAD51 across hematologic malignancies visualized using BloodSpot (https://bloodspot.eu; dataset GSE13159). Corresponding subtypes for the cell lines analyzed: ARH-77 (AML–MDS), CCRF-SB (B-ALL t(8;14)), HL-60 (AML t(15;17)-like), K562 (CML), Kasumi-1 (AML t(8;21)), and SUP-T1 (T-ALL).

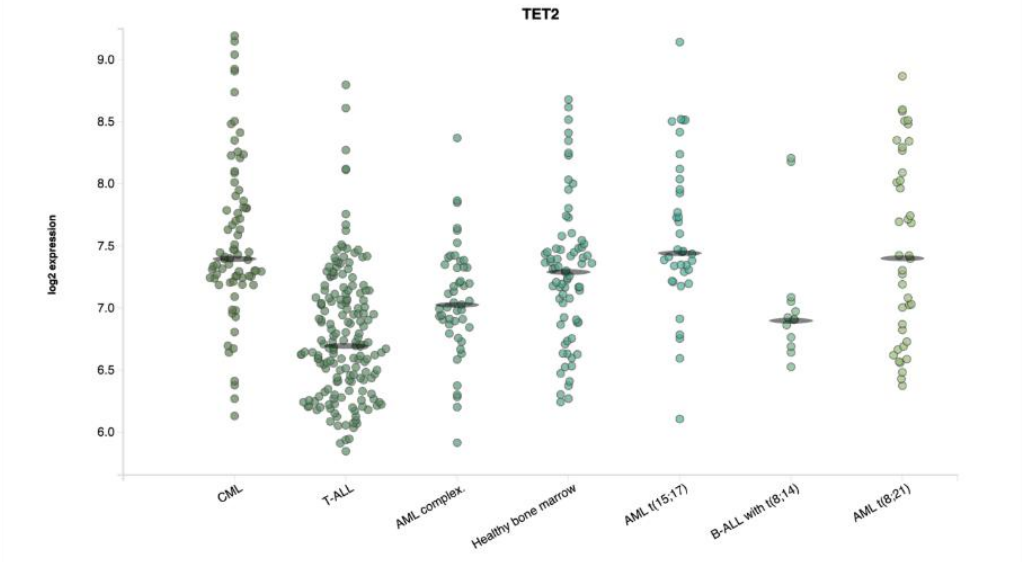


Figure 5: Expression of TET2 across hematologic malignancies visualized using BloodSpot (https://bloodspot.eu; dataset GSE13159). Corresponding subtypes for the cell lines analyzed: ARH-77 (AML–MDS), CCRF-SB (B-ALL t(8;14)), HL-60 (AML t(15;17)-like), K562 (CML), Kasumi-1 (AML t(8;21)), and SUP-T1 (T-ALL).

CC: BY-ND-NC

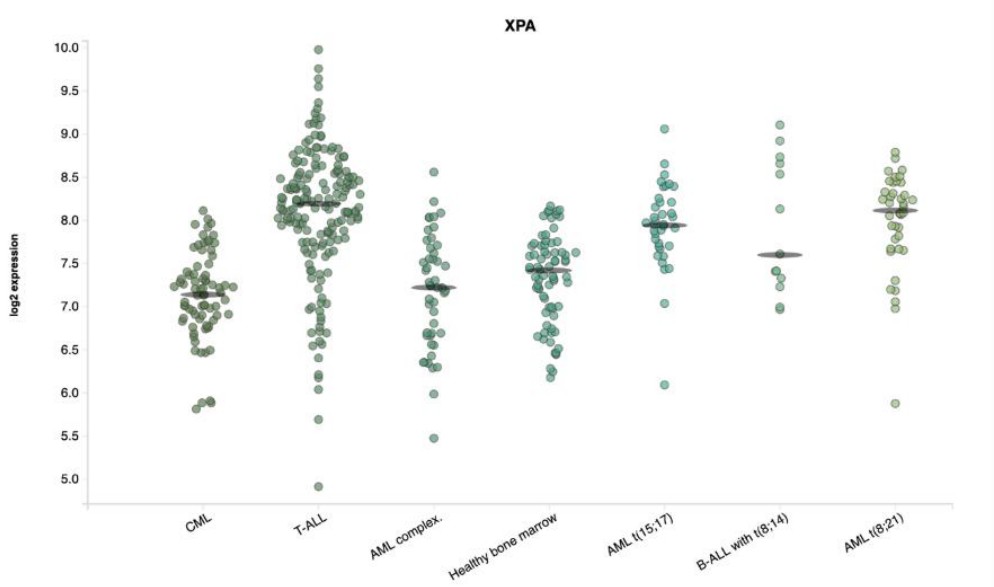


Figure 6: Expression of XPA across hematologic malignancies visualized using BloodSpot (https://bloodspot.eu; dataset GSE13159). Corresponding subtypes for the cell lines analyzed: ARH-77 (AML–MDS), CCRF-SB (B-ALL t(8;14)), HL-60 (AML t(15;17)-like), K562 (CML), Kasumi-1 (AML t(8;21)), and SUP-T1 (T-ALL).

DISCUSSION

In this study, we examined baseline expression of TRDMT1 (DNMT2), RAD51, TET2, and XPA across six leukemia cell lines representing distinct hematopoietic malignancies and evaluated their proliferation profiles. These genes participate in key RNA-modification and DNA-repair pathways that contribute to leukemic cell survival and genomic maintenance. Our findings demonstrate subtype-specific transcriptional diversity and growth characteristics, establishing a molecular baseline for subsequent functional analyses.

TRDMT1 (DNMT2) encodes a cytosine-5 RNA methyltransferase responsible primarily for tRNA methylation (m^5C modification), which supports RNA stability, translational accuracy, and stress-response signaling (Goll et al., 2006; Tuorto & Lyko, 2016). Emerging evidence suggests that TRDMT1 contributes to cellular survival under oxidative and DNA-damage stress by modulating mRNA and tRNA metabolism (Belew et al., 2021). Elevated TRDMT1 expression has been linked to malignant cell growth and chemoresistance in hematologic and solid cancers (Lewinska et al., 2023). RAD51 is a central mediator of homologous recombination (HR) DNA repair, facilitating DNA strand invasion and repair of double-strand breaks (DSBs) (Lord & Ashworth, 2016). High RAD51 expression has been associated with genomic stability, aggressive proliferation, and resistance to DNA-damaging agents in leukemia and other cancers (Liao et al., 2022; Xu et al., 2021). Conversely, reduced RAD51 function sensitizes hematologic malignancies to PARP inhibitors and replication-stress–inducing therapies (Malka et al., 2021). TET2 catalyzes oxidation of 5-methylcytosine to 5-hydroxymethylcytosine, initiating DNA demethylation and regulating hematopoietic stem cell differentiation (Ko et al., 2010; Cimmino et al., 2017). TET2 loss-of-function mutations are common in myeloid neoplasms and influence transcriptional programs, clonal evolution, and treatment response (Morinishi et al., 2021; Mehmetbeyoglu Duman, 2023). Although none of the tested cell lines harbored engineered TET2 mutations, baseline expression patterns varied by lineage, which may contribute to epigenetic regulation differences among leukemia subtypes.

XPA is an essential factor in the nucleotide-excision repair (NER) pathway, recognizing DNA helix-distorting lesions and coordinating repair complex assembly (Sugitani & Chazin, 2015). XPA expression influences the cellular response to genotoxic stress—including alkylating agents—and has

CC: BY-ND-NC

been associated with chemotherapy sensitivity in hematologic malignancies (Cierna et al., 2020). Across our panel, ARH-77 cells demonstrated the highest basal expression of all genes examined, whereas HL-60 and K-562 showed comparatively lower expression. In parallel, proliferation rates varied, with SUP-T1 and CCRF-SB showing the most rapid growth kinetics. These findings reinforce the concept that leukemia subtype, lineage origin, and differentiation status are associated with unique molecular profiles and proliferative behavior (Cancer Genome Atlas Research Network, 2013; Martincorena & Campbell, 2015). Establishing such baseline signatures is essential when interpreting drug-response data and designing targeted therapeutic approaches, particularly those involving DNA-repair vulnerability or epigenetic modulation.

The integration of public transcriptomic data from the BloodSpot GSE13159 cohort provided an external validation framework for the baseline expression patterns observed in our leukemia cell line panel. Across TRDMT1, RAD51, TET2, and XPA, patient-derived samples demonstrated subtype-dependent variability that paralleled the heterogeneity detected experimentally in vitro. The broad expression ranges observed in CML, T-ALL, and MDS, as well as the narrower distributions in defined AML subtypes (t(15;17), t(8;21)) and healthy bone marrow, support the notion that these genes exhibit intrinsic transcriptional diversity across hematologic malignancies. Such concordance between clinical and experimental datasets strengthens the reproducibility of our findings and indicates that the expression differences identified in cell lines reflect broader patterns present in primary leukemia samples. This alignment provides confidence that the cell line models used in this study capture relevant aspects of disease-associated transcriptional variation and offers a useful molecular reference for subsequent functional analyses.

Together, these results provide a transcriptional and phenotypic reference framework for our subsequent functional studies, including assessments of PARP-inhibitor response, hypomethylating therapy, and DNA-damage assays, enabling alignment of experimental outcomes with intrinsic molecular states.

Peer-review: External, Independent.

Acknowledgements: None

Conflict of Interest: The authors declare no competing interests.

Ethical Approval: This study does not require ethics committee approval.

Author Contributions: Conceptualization, : E.M.D. and S.T..;S.T.; formal analysis, : E.M.D, A.U., A.S.S,A.S.S., V.C., and M.R.S.A.; investigation, : E.M.D,E.M.D., A.U., A.S.S, V.C., and M.R.S.A; resources, : S.T.; data curation, : E.M.D., A.U., and A.S.S. ; writing-original draft preparation, : E.M.D,E.M.D., A.U., and A.S.S. ; editing, : E.M.D;E.M.D.; visualization, : A.U., and A.S.S,; supervision, : S.T.; project administration: S.T.; funding acquisition, : S.T., and E.M.D. All authors have read and agreed to the published version of the manuscript.

Financial Support: This project is funded by Health the Health Institutes of Türkiye (TUSEB) with the project code 2025-A4-01-43829.

Sustainable Development Goals:

☐ ☐ ☒ ☒ ☐ ☐ ☐ ☐

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

☐ ☐ ☐



REFERENCES

Belew, M. D., Chien, E., Wong, M., & Michael, W. M. (2021). A global chromatin compaction pathway that represses germline gene expression during starvation. The Journal of Cell Biology, 220(9), e202009197. https://doi.org/10.1083/jcb.202009197

Böhme, M., & Kayser, S. (2021). Immune-based therapeutic strategies for acute myeloid leukemia. Cancers, 14(1), 105. https://doi.org/10.3390/cancers14010105

Chen, J., Pang, W., Deng, M., Zheng, R., Chen, Y., Zhang, Z., Tan, Z., & Bai, Z. (2025). Global, regional, and national burden of leukemia, 1990–2021: a systematic analysis of the global burden of disease in 2021. Frontiers in Medicine, 12. https://doi.org/10.3389/fmed.2025.1542317

Cierna, Z., Miskovska, V., Roska, J., Kalavska, A., Babal, P., & Mego, M. (2020). Increased levels of XPA might be the basis of cisplatin resistance in germ cell tumours. BMC Cancer, 20(1), 17. https://doi.org/10.1186/s12885-019-6496-1

Cimmino, L., Dolgalev, I., Wang, Y., Yoshimi, A., Martin, G. H., Wang, J., Ng, V., Xia, B., Witkowski, M. T., Mitchell-Flack, M., Grillo, I., Bakogianni, S., Ndiaye-Lobry, D., Martín, M. T., Guillamot, M., Banh, R. S., Xu, M., Figueroa, M. E., Dickins, R. A., & Aifantis, I. (2017). Restoration of TET2 function blocks aberrant Self-Renewal and leukemia progression. Cell, 170(6), 1079–1095.e20. https://doi.org/10.1016/j.cell.2017.07.032

Dombret, H., & Gardin, C. (2016). An update of current treatments for adult acute myeloid leukemia. Blood, 127(1), 53–61. https://doi.org/10.1182/blood-2015-08-604520

Du, M., Chen, W., Liu, K., Wang, L., Hu, Y., Mao, Y., Sun, X., Luo, Y., Shi, J., Shao, K., Huang, H., & Ye, D. (2022). The global burden of leukemia and ıts attributable factors in 204 countries and territories: findings from the global burden of disease 2019 study and projections to 2030. Journal of Oncology, 2022. https://doi.org/10.1155/2022/1612702

Gbenjo, J., McCrary, G., & Wilson, S. (2023). Leukemia: what primary care physicians need to know. American Family Physician, 107(4), 397–405.

Ghosh, I., & Mukherjee, S. (2023). Acute lymphocytic leukemia incidence and survivability trends in the United States over the last two decades: SEER data set from 2000-2019. Journal of Clinical Oncology, 41(16_suppl), e19050. https://doi.org/10.1200/jco.2023.41.16_suppl.e19050

Goll, M. G., Kirpekar, F., Maggert, K. A., Yoder, J. A., Hsieh, C. L., Zhang, X., Golic, K. G., Jacobsen, S. E., & Bestor, T. H. (2006). Methylation of tRNAAsp by the DNA methyltransferase homolog Dnmt2. Science (New York, N.Y.), 311(5759), 395–398. https://doi.org/10.1126/science.1120976

Heidari, A. (2021). Common types of Leukemia and its Symptoms. Arch Can Res, 9(S1), e002.

Hochhaus, A., Baccarani, M., Silver, R., Schiffer, C., Apperley, J., Cervantes, F., Clark, R., Cortes, J., Deininger, M., Guilhot, F., Hjorth-Hansen, H., Hughes, T., Janssen, J., Kantarjian, H., Kim, D., Larson, R., Lipton, J., Mahon, F., Mayer, J., Nicolini, F., Niederwieser, D., Pane, F., Radich, J., Réa, D., Richter, J., Rosti, G., Rousselot, P., Saglio, G., Saussele, S., Soverini, S., Steegmann, J., Turkina, A., Zaritskey, A., & Hehlmann, R. (2020). European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia, 34(4), 966–984. https://doi.org/10.1038/s41375-020-0776-2

Huerga-Domínguez, S., Villar, S., Prósper, F., & Alfonso-Piérola, A. (2022). Updates on the management of acute myeloid leukemia. Cancers, 14(19), 4756. https://doi.org/10.3390/cancers14194756

Ilyas, M., Ramzan, M., Deriche, M., Mahmood, K., & Naz, A. (2025). An efficient leukemia prediction method using machine learning and deep learning with selected features. PLOS One, 20(4), e0320669. https://doi.org/10.1371/journal.pone.0320669

Karrar, H., Nouh, M., Juman, A., Almutiri, M., Alqudairy, L., Aljameeli, A., Aljameeli, A., Alabdullatif, A.,

Alsuqayh, K., Alhuthayli, A., Alkredees, M., Alriyaee, A., Alaithan, M., & Alshmrany, B. (2022). Leukemia perspective in current practice. World Family Medicine Journal/Middle East Journal of Family Medicine, 95(251581). https://doi.org/10.5742/mewfm.2023.95251581

Ko, M., Huang, Y., Jankowska, A. M., Pape, U. J., Tahiliani, M., Bandukwala, H. S., An, J., Lamperti, E. D., Koh, K. P., Ganetzky, R., Liu, X. S., Aravind, L., Agarwal, S., Maciejewski, J. P., & Rao, A. (2010). Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. Nature, 468(7325), 839–843. https://doi.org/10.1038/nature09586

Lewinska, A., Adamczyk-Grochala, J., & Wnuk, M. (2023). TRDMT1-mediated RNA C-5 methylation as a novel target in anticancer therapy. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 1878(6), 188964. https://doi.org/10.1016/j.bbcan.2023.188964

Liao, C., Talluri, S., Zhao, J., Mu, S., Kumar, S., Shi, J., Buon, L., Munshi, N. C., & Shammas, M. A. (2022). RAD51 Is Implicated in DNA damage, chemoresistance and ımmune dysregulation in solid tumors. Cancers, 14(22), 5697. https://doi.org/10.3390/cancers14225697

Liu, J., Jiang, P., Lu, Z., Yu, Z., & Qian, P. (2024). Decoding leukemia at the single-cell level: clonal architecture, classification, microenvironment, and drug resistance. Experimental Hematology & Oncology, 13(1), 10. https://doi.org/10.1186/s40164-024-00479-6

Livak, K. J., & Schmittgen, T. D. (2001). Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods (San Diego, Calif.), 25(4), 402–408. https://doi.org/10.1006/meth.2001.1262

Lord, C., & Ashworth, A. (2016). BRCAness revisited. Nature Reviews Cancer, 16(2), 110–120. https://doi.org/10.1038/nrc.2015.21

Malka, M. M., Eberle, J., Niedermayer, K., Zlotos, D. P., & Wiesmüller, L. (2021). Dual PARP and RAD51 Inhibitory drug conjugates show synergistic and selective effects on breast cancer cells. Biomolecules, 11(7), 981. https://doi.org/10.3390/biom11070981

Martincorena, I., & Campbell, P. J. (2015). Somatic mutation in cancer and normal cells. Science (New York, N.Y.), 349(6255), 1483–1489. https://doi.org/10.1126/science.aab4082

Mehmetbeyoglu Duman, S. (2023). Imbalance of DNA methylation and demethylation as pathogenic mechanism of acute leukaemia [Unpublished doctoral dissertation, Cardiff University].

Morinishi, L., Kochanowski, K., Levine, R. L., Wu, L. F., & Altschuler, S. J. (2020). Loss of TET2 affects proliferation and drug sensitivity through altered dynamics of cell-state transitions. Cell Systems, 11(1), 86–94.e5. https://doi.org/10.1016/j.cels.2020.06.003

Mukhtiar, V., Gandhi, O., Bhanushali, C., Mehta, M., Parikh, K., Shah, R., Namjoshi, D., Shubhangi, F., & Seetharaman, K. (2024). Chronic myeloid leukemia: ımpact of social and demographic disparities on survival outcomes. Blood, 144(Supplement 1), 210751. https://doi.org/10.1182/blood-2024-210751

Shimony, S., Stahl, M., & Stone, R. (2023). Acute myeloid leukemia: 2023 update on diagnosis, risk-stratification, and management. American Journal of Hematology, 98(3), 502–526. https://doi.org/10.1002/ajh.26822

Sugitani, N., & Chazin, W. J. (2015). Characteristics and concepts of dynamic hub proteins in DNA processing machinery from studies of RPA. Progress in Biophysics and Molecular Biology, 117(2–3), 206–211. https://doi.org/10.1016/j.pbiomolbio.2014.12.001

Taheri, S., Karaca, Z., Rassoulzadegan, M., Mehmetbeyoglu, E., Zararsiz, G., Sener, E. F., Bayram, K. K., Tufan, E., Sahin, M. C., Marasli, M. K., Memis, M., Canatan, H., Ozturk, F., Tanriverdi, F., Unluhizarci, K., & Kelestimur, F. (2022). The characterization of sex differences in hypoglycemia-ınduced

CC: BY-ND-NC

activation of HPA axis on the transcriptomic level. Cellular and Molecular Neurobiology, 42(5), 1523–1542. https://doi.org/10.1007/s10571-021-01043-0

Tebbi, C. (2021). Etiology of acute leukemia: A Review. Cancers, 13(9), 2256. https://doi.org/10.3390/cancers13092256

The Cancer Genome Atlas Research Network, Weinstein, J., Collisson, E., Mills, G., Shaw, K., Ozenberger, B., Getz, G., Ellrott, K., Santra, S., Newton, Y., Heiman, D., & Sander, C. (2013). The Cancer Genome Atlas Pan-Cancer analysis project. Nature Genetics, 45(10), 1113–1120. https://doi.org/10.1038/ng.2764

Tuorto, F., & Lyko, F. (2016). Genome recoding by tRNA modifications. Open Biology, 6(12), 160287. https://doi.org/10.1098/rsob.160287

Xu, J., Zhao, L., Peng, S., Chu, H., Liang, R., Tian, M., Connell, P. P., Li, G., Chen, C., & Wang, H. W. (2021). Mechanisms of distinctive mismatch tolerance between Rad51 and Dmc1 in homologous recombination. Nucleic Acids Research, 49(22), 13135–13149. https://doi.org/10.1093/nar/gkab1141

Zhao, Y., Wang, Y., & Li, S. (2018). Racial differences in four leukemia subtypes: comprehensive descriptive epidemiology. Scientific Reports, 8(1), 1835. https://doi.org/10.1038/s41598-017-19081-4

CC: BY-ND-NC