Targeted Cancer Therapy Connect
ISSN: 3105-3629
2026, Vol. 2, Cite as: doi:10.x/journal.x.x.x

SCIFINITI PUBLISHING

OPEN ACCESS

Research Article

Association of 12q21.32 cn-LOH Affecting the *KITLG* p53 Response Element with Therapy Resistance in Acute Leukemia

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Abstract

Background: The tumor suppressor p53 is a critical regulator of gene expression in cancer, acting through binding to specific p53 response elements (REs). One of key RE rs4590952 is found in the KITLG gene.

Aims: This study aimed to precisely investigate the allelic variants of the SNP rs4590952 within patient groups with acute leukemia and to analyze their association with the disease and response to therapy. A specific objective was to determine the frequency and nature of regions of homozygosity encompassing the KITLG locus.

Methods: The study cohort included: 37 patients with Ph-negative B-ALL, 38 with T-ALL, and 35 with de novo intermediate-risk AML. A reference group of 200 healthy individuals without oncohematological disorders was used

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for comparison. Chromosomal microarray analysis (CMA) was performed using the CytoScan™ HT-CMA. Statistical analysis was performed using Python 3.12.4 and SAS 9.4.

Results: The allele frequency (AF) of the G allele of rs4590952 was 0.785 in the reference group. Among patients, the AF was 0.833 in T-ALL, 0.757 in B-ALL, and 0.743 in AML. The frequency of copy-neutral loss of heterozygosity (cn-LOH) at 12q21.32, which results in the GG genotype, was significantly higher in the T-ALL group (45%) compared to the reference group (27%) (OR=0.4; 95% CI: 0.2–0.9; p=0.02). A significant association between MRD-positive status and cn-LOH KITLG was found specifically in the T-ALL group (OR=11; 95% CI: 2–62; p=0.005). Cn-LOH KITLG was also significantly associated with poor chemotherapy response in AML (p=0.01).

Summary: The GG genotype of the p53 response element in KITLG (rs4590952) frequently arises from acquired cn-LOH at 12q21.32, observed in 45% of T-ALL and 26-27% of other cases. This treatment-response marker, present irrespective of leukemic status, warrants further validation in expanded cohorts.

Keywords

rs4590952; 12q21.32 cn-LOH (copy-neutral loss of heterozygosity); p53 RE-KITLG; chemotherapy response; MRD (Minimal Residual Disease); T-ALL; B-ALL; AML

Introduction

The tumor suppressor protein p53 is one of the most critical molecules in protecting organisms from cancer, earning it the nickname "the guardian of the genome". Its primary function is to act as a sequence-specific transcription factor [1]. In response to cellular stresses such as DNA damage, oncogene activation, or hypoxia, p53 becomes stabilized and activated. It then binds to specific DNA sequences known as p53 Response Elements (p53 REs) [2]. These response elements have a consensus sequence of RRRCWWGYYY, followed by 0 to 13 random bases, and then another RRRCWWGYYY sequence (where R = A/G, W = A/T, Y = C/T) [3]. These REs are typically located in the regulatory regions (promoters or enhancers) of target genes. Upon binding to its target response elements, p53 functions as a master transcriptional regulator, orchestrating a complex anticancer program by either activating or repressing specific genes.

Due to its powerful anti-proliferative effects, the p53 gene (TP53) is the most frequently mutated gene in human cancers. When p53 is inactivated, these critical protective pathways fail, allowing damaged cells to proliferate uncontrollably. One of the most well-described p53 response elements is located in the *KITLG* gene, where the single nucleotide polymorphism (SNP) rs4590952 (A>G) has been shown to enhance p53 binding, leading to increased KIT ligand expression and potential oncogenic effects. The *KITLG* gene (also known as Stem Cell Factor or Steel Factor), ligand for the KIT receptor tyrosine kinase, is essential for critical physiological processes such as hematopoiesis, melanogenesis, gametogenesis, and mast cell function. However, this vital signaling pathway possesses a dual nature, as its dysregulation through overexpression or constitutive activation can be co-opted in oncogenesis, promoting tumor cell proliferation and survival, angiogenesis, and metastasis [4]. Consequently, the tight regulatory control of *KITLG* expression is paramount, as its loss can lead to significant oncogenic consequences. The role of the *KITLG* polymorphism rs4590952 in cancer risk presents a complex and seemingly contradictory picture. One body of research has identified it as a key functional variant that enhances p53 binding, significantly upregulating *KITLG* expression and conferring one of the largest inherited risks for certain cancers, notably testicular cancer. This view is supported by evolutionary evidence of positive selection, suggesting a past beneficial effect, and the general rarity of such polymorphisms due to negative selection, underscoring their potential detriment [5]. However, this conclusion is not universal. Contrary to the established mechanism, a focused study on breast cancer in a Chinese Han population found no significant association between rs4590952 and disease risk, even when stratified by hormone receptor status [6]. This discrepancy implies that the oncogenic impact of this polymorphism may be highly cancer-type specific, suggesting that heterogeneous mechanisms underlie the etiology of different cancers and cautioning against broad generalizations of its risk profile.

The SNP rs4590952 is located on chromosome 12 (Ch12:88559882 (GRCh38)) within the *KITLG* gene, specifically in an intronic region. This polymorphism has a canonical allelic change of A>G, and its minor allele frequency (MAF) demonstrates significant variation across global populations. For instance, the frequency of the 'A' allele ranges from as low as 14.5% in a Northern Swedish cohort to over 43% in the PAGE_STUDY and nearly 48% in the TOMMO cohort, highlighting substantial inter-population diversity [7]. Despite its intronic location, this variant is of high func-

tional significance as it resides within a critical p53 transcription factor binding site, where the A>G change enhances p53 affinity and alters *KITLG* gene expression.
Given that our primary research focus is the investigation of molecular karyotypes in acute leukemias using chromosomal microarray analysis (CMA) — a method based on the analysis of single nucleotide polymorphism (SNP) arrays — and considering our accumulated data from pilot cohorts of patients with AML, B-ALL, and T-ALL, this study aimed to precisely investigate the allelic variants of rs4590952 (included in the Cytoscan HD CMA panel as marker AX-17068144) within these patient groups. Special attention was paid to chromosomal events involving the *KITLG* locus. Key prognostic covariates (age, initial leukocyte count, cytogenetic/molecular risk, baseline MRD, and ELN risk in AML) were evaluated in our previous studies, with no association found with therapy response in the intermediate-prognosis groups of ALL and AML [8-11]. All clinical patient parameters examined in this study are available in https://doi.org/10.6084/m9.figshare.30739889. To establish the baseline frequency of the *KITLG* RE allelic variants in the Russian population, we analyzed a control cohort of individuals without diagnosed oncopathology, who underwent genetic testing for family planning purposes. Our objectives were to evaluate the association between the rs4590952 allelic variants and the specific type of acute leukemia, as well as to investigate its potential link with therapy response.

Materials and methods

Study Cohort

This study included a total of 110 patients with acute leukemia who were treated at the National Medical Research Center for Hematology. The cohort consisted of:

37 patients with Philadelphia chromosome-negative B-cell Acute Lymphoblastic Leukemia (Ph-negative B-ALL), treated according to the RALL-2016m protocol (2019–2023) [ClinicalTrials.gov NCT06237192]. Male:Female ratio was 16:21. The median age was 36.5 years, ranging from 21 to 55 years. At presentation, the median leukocyte count was 8.23 x 10^9/L (range: 0.86 – 466.53), and the median percentage of blast cells in the bone marrow was 88% (range: 33.8 – 98). According to the EGIL and WHO classifications, the immunophenotypic distribution was as follows: B-I in 5 patients (13.5%), B-II in 30 patients (81.0%), B-III in 1 patient (2.7%), and B-IV in 0 patients (0%).

38 patients with Ph-negative T-cell Acute Lymphoblastic Leukemia (T-ALL), treated according to the RALL-2016m protocol (2017–2023) [ClinicalTrials.gov NCT06237192]. Male:Female ratio was of 28:10 and a median age of 35.5 years (range: 19–53). The median leukocyte count at presentation was 46.18 x 10^9/L, with a wide range from 0.95 to 445. Bone marrow blast cell infiltration was high, with a median of 85.4% (range: 5.2–100). Immunophenotyping according to EGIL and WHO criteria identified the following subtypes: T-I in 5 patients (13.2%), T-II in 16 patients (42.1%), T-III in 14 patients (36.8%), and T-IV in 1 patient (2.6%). Additionally, two cases (5.7%) were classified as mixed-phenotype acute leukemia with T-myeloid features (MPAL T-myelo).

35 patients with de novo Acute Myeloid Leukemia (AML) of intermediate risk according to the ELN-2017 classification (2017–2024) [12]. [ClinicalTrials.gov NCT05339204]. Male:Female ratio was 11:24. The median age was 40 years, ranging from 19 to 62 years. At presentation, the median leukocyte count was 22 x 10^9/L (range: 1 – 254), and the median percentage of blast cells in the bone marrow was 78% (range: 10 – 94.4). For 9 AML patients with identified cn-LOH at 12q21.32, a subsequent analysis of paired DNA samples isolated from non-tumor tissue was performed (sources included buccal epithelium, blood during remission, and mesenchymal stem cells). This analysis was specifically initiated to validate the somatic or germline origin of the cn-LOH after its initial discovery at the *KITLG* locus in tumor DNA.

The reference group included 200 healthy individuals without oncohematological disorders who underwent comparable CMA testing.

Cytogenetic and Molecular Diagnostics at Onset

At diagnosis, all patients underwent comprehensive immunophenotyping, cytogenetic, and molecular analysis of bone marrow samples. Conventional Cytogenetics: Bone marrow cells were analyzed using G-banding for karyotyping and Fluorescence In Situ Hybridization (FISH). All karyotype and FISH results were described according to the International System for Human Cytogenomic Nomenclature (ISCN) 2020 [13].

Minimal Residual Disease (MRD) Assessment

Minimal residual disease (MRD) was assessed in bone marrow samples by multiparameter flow cytometry (MFC), employing a combination of the "different from normal" (DfN) and leukemia-associated immunopheno-

type (LAIP) approaches. In patients with T-ALL, the flow cytometry panel for MRD assessment included CD99, CD7, CD3 (cytoplasmic/surface), CD5, CD45, CD8, CD34, CD56, and CD4 [14]. For B-ALL, the antibody panel included CD19, CD45, CD38, CD10, CD34, CD58, CD20, CD22, and CD24. In AML cases, MRD was assessed using panels of antibodies against the following antigens: CD15, CD38, CD371, CD34, CD117, CD33, CD13, CD99, CD14, CD123, CD11b, CD45RA, CD45, HLA-DR, CD16, and CD10. Additionally, one antibody associated with a patient-specific LAIP was included (e.g., CD2, CD4, CD5, CD7, CD11a, or CD56). Flow cytometry was performed on either a BD FACSCanto II (with 6-color panels before 2020) or a Beckman Coulter CytoFLEX (with 9–10 color panels after 2021). The primary endpoint was the achievement of MRD-negative status at the end of induction therapy.

Chromosomal Microarray Analysis (CMA)

Genomic DNA was isolated from diagnostic bone marrow aspirates. DNA was extracted using a standard phenol-chloroform method [14], quantified on a Qubit 4 fluorometer, and assessed for integrity (fragment length ≥10,000 bp). CMA was performed at the "Genomed" laboratory (Moscow, Russia) using the CytoScan™ HT array (Thermo Fisher Scientific, USA) according to the manufacturer's protocol. Tumor DNA (100–200 ng) was hybridized against reference male DNA. Scanning was performed on a GENOSCAN 3000 or similar platform. Raw data were processed and analyzed using Chromosome Analysis Suite (ChAS v.4.3.0.71) software (Thermo Fisher Scientific). We investigated the allelic variants of rs4590952 and chromosomal events affecting this SNP (Figure 1).

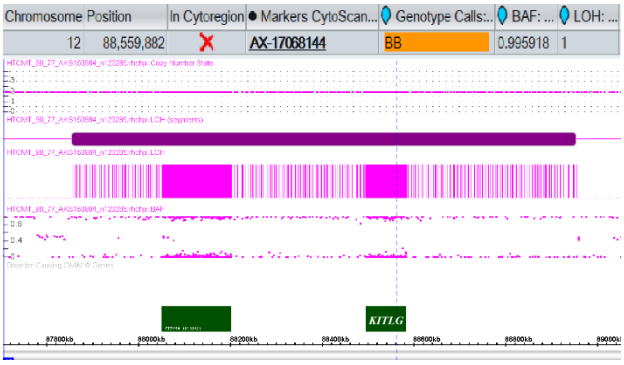

Figure 1: Analysis of the rs4590952 polymorphism in ChAS software (v.4.3.0.71).The region of interest on chromosome 12 is shown. The rs4590952 polymorphism (chr12:88559882 (GRCh38/hg38), CytoScan™ HT-CMA marker AX-17068144) is marked by the blue dashed line and is identified as having the BB (GG) allelic variant (panel above). An expanded view demonstrating that the *KITLG* gene is located within a region of loss of heterozygosity (LOH), approximately 1 megabase in size.

Statistical Analysis

Categorical variables were summarized by frequencies. Hypotheses regarding differences in the distribution of categorical features between comparison groups were tested using Fisher's Exact Test or the Chi-square test, as appropriate. All statistical analyses were performed using Python 3.12.4 and SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Generative AI tools, such as DeepSeek and Perplexity were used for text editing, paraphrasing and grammar checking when preparing the manuscript.

Results

The genotypic distribution within the reference cohort (n=200) is summarized below. The homozygous A/A genotype was observed in 7 subjects (3.5%), one of whom had a recordedcn-LOH. The heterozygous A/G genotype was found in 72 subjects (36%), and the homozygous G/G genotype was the most common, found in 121 subjects (60.5%). Notably, a cn-LOH spanning the *KITLG* gene was identified in a subset of 53 (43.8%) G/G homozygotes (Figure 2). The corresponding allele frequencies, derived from a total of 400 alleles, were 0.215 for allele A and 0.785 for allele G. The association between cn-LOH and demographic parameters such as gender and age was not revealed (Table 1).

Table 1: Association between cn-LOH and demographics of healthy individuals (Gender and Age).

Parameters		Norm	cn-LOH	OR (%95 CI)	p
Gender	Male	37	13	0.85 (0.41-1.74)	0.65
	Female	106	44		
Age	<45 y.o.	129	50	1.29 (0.49-3.38)	0.60
	≥45 y.o.	14	7		

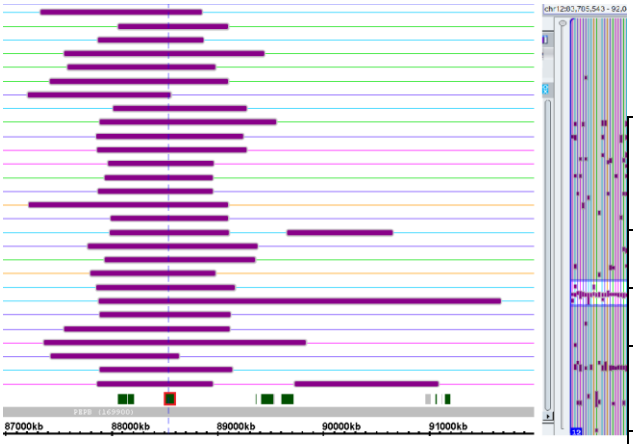

Figure 2: ChAS plot illustrating the sizes and positions of cn-LOH regions (shown in purple) on chromosome 12q21.32 in healthy individuals. The genomic position of the RE *KITLG* is indicated by a blue dashed vertical line.

In the T-ALL cohort (n=38), the genotype distribution was: A/A in 3 patients (7.9%), A/G in 6 (15.7%), and G/G in 27 (71%). Cn-LOH covering the *KITLG* gene was detected in 17 (63%) of the G/G homozygotes. Additionally, two patients carried a duplication containing the *KITLG* gene, with allelic variants G/G/G and A/G/G. The overall allele frequency, including these duplications, was 0.166 for the A allele (13/78) and 0.833 for the G allele (65/78).

Genotype analysis of the B-ALL cohort (n=37) revealed an A/A genotype in 2 patients (5.4%), A/G in 14 (37.8%), and G/G in 21 (56.8%). Furthermore, cn-LOH at the *KITLG* locus was detected in 10 (47.6%) of the G/G homozygotes. The resultant overall allele frequencies were 0.243 for the A allele and 0.757 for the G allele.

In the AML cohort (n=35), the genotype distribution was as follows: A/A in 1 patient (2.9%), A/G in 16 (45.7%), and G/G in 18 (51.4%). Cn-LOH spanning the *KITLG* locus was identified in 9 (50.0%) of the G/G homozygous patients. The overall allele frequency was 0.257 for the A allele (18/70) and 0.743 for the G allele (52/70). Deviation from Hardy-Weinberg equilibrium was tested in each population. The results, including observed allele frequencies, chi-square (χ^2) statistics, and p-values, are presented in Table 2. Notably, significant deviation from HWE was observed only in the T-ALL cohort (p = 0.005), which also demonstrated the highest frequency of cn-LOH events in the 12q21.32 region. This concordance suggests tumor-specific selective pressure favoring homozygosity at this locus in T-cell leukemia.

Table 2: Hardy-Weinberg Equilibrium Analysis results.

Population	N	Allele Frequency (p=A, q=G)	χ^2	p	In HWE? (α=0.05)
T-ALL	38	p = 0.166, q = 0.833	7.698	0.005	No
B-ALL	37	p = 0.243, q = 0.757	0.049	0.825	Yes
AML	35	p = 0.257, q = 0.743	3.117	0.077	Yes (Borderline)
Healthy	200	p = 0.215, q = 0.785	1.625	0.203	Yes

The distribution of allelic variants is shown in Figure 3. Comparison of allele genotypes between the acute leukemia groups and the reference group using the chi-square test revealed no statistically significant differences.

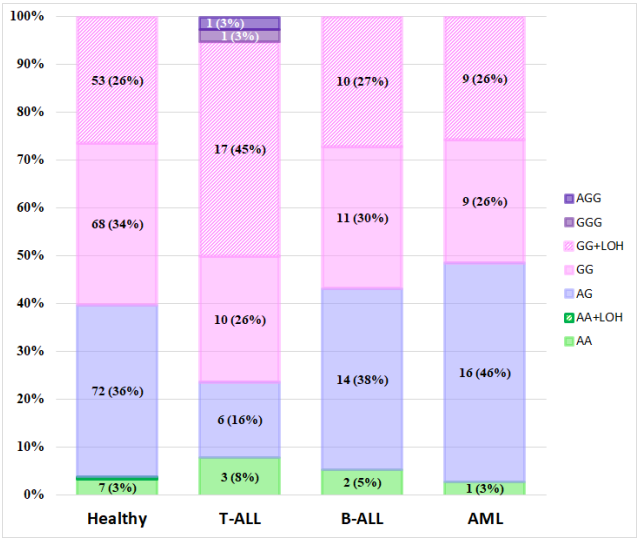

Figure 3: Genotype distribution of the rs4590952 polymorphism across the study cohorts. The figure legend is displayed on the right, and the absolute counts for each genotype group are overlaid on the respective colored bars.

However, evaluation of the cn-LOH 12q21.32 frequency showed a statistically significant increase of this event in the T-ALL group (OR=0.4; 95% CI: 0.2–0.9; p=0.02). Consequently, we chose to use this identified factor, instead of allelic variants, to assess its association with therapy response.

A significant association between MRD+ status and

cn-LOH *KITLG* was found specifically in the T-ALL group (OR=11; 95% CI: 2–62; p=0.005) , unlike in B-ALL (Figure 4) or AML groups (Figure 5).

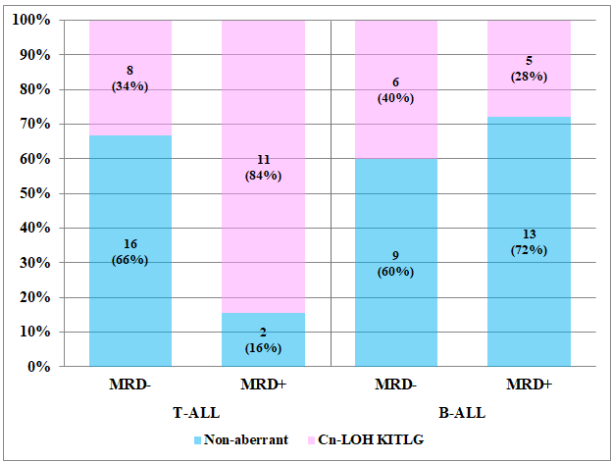

Figure 4: Distribution of *KITLG* cn-LOH in MRD-positive and MRD-negative T-ALL patients (One patient was excluded from the analysis because of early death) and B-ALL patients (MRD status was not assessed in four patients).

A statistically significant association of positive MRD status with cn-LOH *KITLG* was found in patients with T-ALL (OR=11; 95% CI: 2–62; p=0.005).

While no significant impact on outcome was observed in ALL cohorts, likely due to subsequent targeted therapy or HSCT according to RALL-2016m protocol, cn-LOH *KITLG* was significantly associated with poor chemotherapy response in AML (p=0.01) (Figure 5).

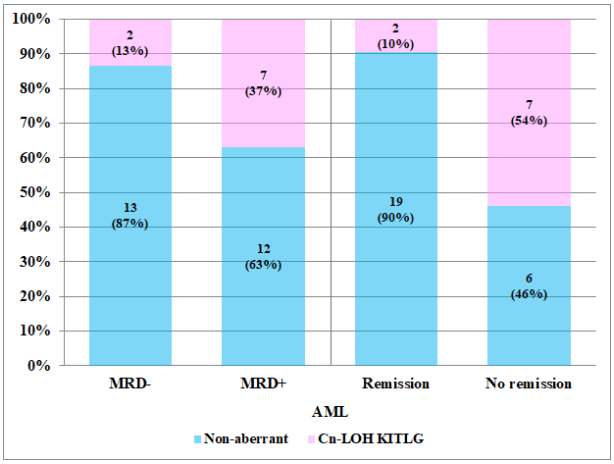

Figure 5: Distribution of *KITLG* cn-LOH in MRD-positive and MRD-negative AML patients (One patient was excluded from the analysis because of early death) and distribution according to chemotherapy response (right)**.**

CMA analysis of matched-pair DNA samples from non-tumor tissue revealed cn-LOH at 12q21.32 in 8 out of 9 AML patients with *KITLG* cn-LOH.

Analysis of 52 healthy individuals (26 with and 26 without cn-LOH *KITLG*) demonstrated a statistically significant increase in allelic imbalance at heterozygous SNP markers within the 2 Mbp region flanking rs4590952 (±1 Mbp) in the cn-LOH group (Mann-Whitney U test, p=0.003) (Figures 6 a,b, and 7) .

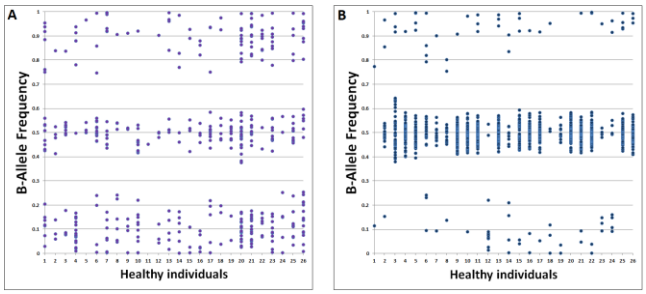

Figure 6: BAF distribution for heterozygous markers within ±1 Mbp of rs4590952 in cn-LOH positive individuals (**a**) and in cn-LOH negative individuals (**b**). Patient identifiers are plotted on the X-axis against B-allele frequency (BAF) values on the Y-axis. Heterozygous SNPs, as determined by CMA, are indicated by purple points.

Figure 6a shows a significant decrease in the number of heterozygous SNP markers with a BAF close to 0.5 and a concurrent significant increase in the number of heterozygous SNP markers with a BAF below 0.3 and above 0.7 compared to the data presented in Figure 6b. This is particularly notable given that we did not perform a precise, patient-specific analysis of the cn-LOH region but instead used a common interval of 2 million base pairs centered on rs4590952 for the entire cohort.

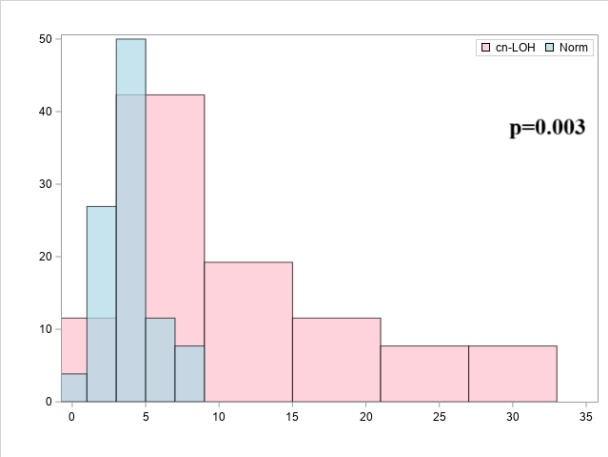

Figure 7: Graphical plot of the Mann-Whitney test. The X-axis shows the possible number of SNPs with allelic imbalance. The Y-axis shows the percentage of individuals with a specific number of SNPs with allelic imbalance. The blue color indicates the distribution of SNPs in the group with the normal variant of 12q21.32 (ranging from 0 to 9 markers per person). The pink color indicates the distribution of SNPs in the group with the homozygosity/cn-LOH region at 12q21.32 (ranging from 0 to 33 markers per person).

This graph visually supports our findings. The pink distribution (cn-LOH group) is shifted sharply to the right compared to the blue distribution (normal group). This means individuals in the cn-LOH group have a significantly higher number of SNPs with allelic imbalance. The difference in the range (0–9 vs. 0–33 markers per person) provides concrete, quantitative evidence for the presence of allelic imbalance in the cn-LOH group. The use of the Mann-Whitney U test confirms that this difference between the two groups is statistically significant, meaning it is very unlikely to have occurred by chance. In summary, this plot is a strong visual and statistical confirmation that the region 12q21.32 in the "pink" group exhibits a genetic profile (high allelic imbalance) consistent with somatic cn-LOH and not a normal inherited homozygosity.

Discussion

The *KITLG* gene encoding stem cell factor (SCF) is an evolutionarily significant locus that has undergone a hard selective sweep in human populations over the past millennia, which is associated with adaptations in skin pigmentation and other features [15]. The *KITLG* locus has not only been subjected to harsh positive selection in the history of mankind, but also demonstrates amazing stability: its adaptive haplotype has maintained a high frequency and signal of selection for thousands of years, experiencing large-scale demographic changes [15]. This evolutionary stability underscores the fundamental importance of this gene and explains why its aberrant regulation is so often observed in pathologies, including malignant neoplasms. The extended homozygosity encompassing the *KITLG* gene, as identified in our analysis, aligns with established signatures of recent positive selection in Eurasian populations, a pattern previously linked to adaptations such as skin pigmentation and winter climate by Yang et al. This provides a crucial evolutionary backdrop, demonstrating that the *KITLG* locus is under strong germline selection [16].

The critical importance of the KITLG signaling pathway is normally emphasized by its key role in regeneration processes. As shown in the study of bone regeneration, *KITLG*, expressed by specialized endothelial cells, is the central organizer of the osteovascular niche, recruiting precursors and directing osteogenic differentiation [17]. This physiological function of the tumor as a niche organizer and a survival factor for stem/progenitor cells directly explains why its aberrant activity is so often observed in the oncological context, where the tumor "captures" these normal support mechanisms.

Seeking to investigate the potential clinical significance of a specific p53 response element in the *KITLG* gene, we were guided by its well-established role as a direct transcriptional target of p53.The genome-wide mapping study by Tebaldi et al. [18] aimed to rank p53 response elements (REs) based on their transactivation potential. Within this research, the gene *KITLG* was robustly validated as a direct p53 transcriptional target. This conclusion was supported by multiple lines of evidence: the p53 retriever algorithm predicted a high-ranking p53 binding site in its promoter, independent ChIP-seq data confirmed direct p53 binding, and microarray analysis showed increased *KITLG* mRNA levels following p53 activation by doxorubicin. Furthermore, subsequent qPCR validation in isogenic cell lines with differing p53 status confirmed that *KITLG* induction was strictly p53-dependent. The study therefore definitively classifies *KITLG* as a direct p53 target gene, linking p53 pathway activation to the regulation of this key player in cell cycle control and tumor progression. Our findings in leukemia are complemented by data from solid tumors, where high *KITLG* expression has been shown to be a hallmark of type A and AB thymomas, driving oncogenesis through MAPK pathway activation [19].

This parallel highlights the broader role of *KITLG* as a potential diagnostic biomarker and therapeutic target in various malignancies. The controversial role of *KITLG* as an oncogene or suppressor is further illustrated by its expression in breast cancer: it is highly expressed and plays an unfavorable role in the HR+ subtype [20],

but is low expressed and associated with a poor outcome in TNBC [21]. In colorectal cancer, for example, increased *KITLG* levels expressed by fibroblasts and tumor endothelium correlate with the activation of infiltrating mast cells and, paradoxically, with improved patient survival, emphasizing its potential protective immunomodulatory role in this context [22]. This contrast illustrates the critical importance of the cellular source of *KITLG* and the type of tumor in determining the final effect of its signal. In addition to the functions of an immunomodulator, KITLG can also act as a classical oncogenic driver. In nasopharyngeal carcinoma (NPC), its overexpression in tumor cells directly correlates with lymph node metastasis and poor prognosis, and *KITLG* suppression inhibits invasion and metastasis, probably through activation of the JAK/STAT pathway [23]. Independent confirmation of the central role of *KITLG* in the pathogenesis of NPC was obtained using co-expression network analysis (WGCNA), where this gene was identified as one of the key hub genes associated with histological grade and tumor stage. Interestingly, this analysis also linked the *KITLG*-containing module to the p53 pathway and cell cycle regulation [24], which is consistent with data on the regulation of its expression through the p53 response element. This demonstrates the ability of tumor cells to autonomously use the KITLG-cKIT pathway to enhance their own aggressiveness.

Stimulation of tumor cell proliferation through KITLG is often mediated by activation of the MAPK/ERK pathway. In multiple myeloma (MM), this activation is achieved through a unique mechanism: oncogenic splicing factor DAZAP1 directly regulates alternative splicing of *KITLG* mRNA, which eventually leads to phosphorylation of ERK and accelerated tumor growth [25]. The role of alternative splicing as a key regulator of the oncogenic function of KITLG has been convincingly demonstrated in lung adenocarcinoma. The tumor suppressor, lncRNA SPAT, by inhibiting the SF1 splicing factor, shifts *KITLG* splicing towards the formation of the less active isoform *KITLG*-201, while suppressing the production of the oncogenic isoform *KITLG*-205. Increased levels of *KITLG*-205 directly correlate with activation of the ERK/MAPK pathway, increased cell migration, and poor patient prognosis [26]. This mechanism highlights that therapeutic strategies targeting the KITLG pathway may include modulating its splicing to suppress specific, most aggressive isoforms. Thus, the KITLG-ERK pathway is a common endpoint for various regulatory violations.

The study of Zhang et al. [27] demonstrates a critical interaction between germline genetic variation in the p53 pathway and somatic TP53 mutations, collectively influencing cancer risk, progression, and therapy response.

The oncogenic role of *KITLG* (SCF) is convincingly confirmed not only in acute leukemias, but also in chronic lymphoproliferative diseases. In chronic lymphocytic leukemia (CLL), leukemic cells overexpress mainly the SCF membrane isoform. This overexpression is an independent unfavorable prognostic factor correlating with a short time to start therapy and overall survival, and also serves as a key regulator of interactions with the microenvironment. It is important that the SCF level decreases under the action of the BTK inhibitor ibutinib, a standard drug for the treatment of CLL, which indicates the involvement of this pathway in the mechanism of action of therapy and makes KITLG itself a promising target for targeted action in this disease [28]. In AML, the scRNA-seq method revealed that a low level of expression of the key stromal factor KITLG in bone marrow aspirates of patients with AML is an independent prognostic marker associated with a significant improvement in overall survival [29, 30]. The role of cn-LOH 12q in the progression of leukemia is confirmed in the work of Sinclair et al. In B-ALL with iAMP21, the cn-LOH 12q event, which leads to homozygous mutations in SH2B3, is an unfavorable prognostic factor [31], which is consistent with the data on the value of cn-LOH 12q21.32 in AML and T-ALL.

Therefore, strategies aimed at suppressing this pathway, whether by direct inhibition or indirect regulation of its expression, are of therapeutic interest. For example, in glioblastoma, one of the mechanisms of the antitumor effect of MSC therapy is precisely the downregulation of the *KITLG* gene [32]. Precision medicine algorithms are starting to consider *KITLG* as a predictor biomarker. For example, the DDPP algorithm for predicting the outcome of therapy identified the *KIT-KITLG* pair as the optimal two-gene signature correlating with the duration of progressive survival (PFS) in patients receiving the antiangiogenic drug axitinib [33]. This indicates that the transcriptomic status of the KITLG pathway can serve as a tool for stratification of patients and selection of optimal targeted therapy. Importantly, chemotherapy itself can enhance the pathogenic effects of KITLG. Sublethal doses of doxorubicin induce the release of extracellular vesicles enriched in KITLG in melanoma cells, which directly inhibit the function of cardiomyocyte mitochondria, revealing a new mechanism of tumor-mediated cardiotoxicity [34].

The universal role of *KITLG* in stromal cell pathology is also confirmed in a non-oncological context. In age-related osteoporosis, it has been identified as one of the key genes whose expression changes in aging BMSCs within the miRNA-mRNA regulatory network affecting the PI3K-Akt pathway [35]. This indicates that abnormalities in the regulation of *KITLG* in the stromal niche can lead not only to malignant transformation (leukemia), but also to degenerative processes associated with aging. Similarly, in renal fibrosis in diabetic nephropa-

thy, where it also acts as a key mediator of tissue damage [36]. The diagnostic potential of disorders at the *KITLG* locus is not limited to genomic variations. Thus, in ovarian seminoma, the analysis of *KITLG* promoter methylation in cfDNA from liquid biopsies (blood plasma) is being investigated as a non-invasive biomarker approach [37], which illustrates the transition from studying the function of the gene to developing applied diagnostic solutions.

The importance of *KITLG* as a gene associated with cancer risk is confirmed even in veterinary medicine: the germinal increase in the number of copies (CNV) of this gene is an established predisposition factor for digital squamous cell carcinoma in Schnauzer dogs [38].

Our study, focused on assessing copy number variations (CNV) and cn-LOH at the *KITLG* locus, employed CMA based on high-resolution SNP microarrays This technology fundamentally relies on the hybridization of fragmented, fluorescently labeled sample DNA to specific oligonucleotide probes immobilized on a chip. The subsequent analysis of signal intensities and genotype calls (B-allele frequency) allows for the simultaneous detection of a wide range of genomic alterations, from large copy number variations (CNVs) to subtle, copy-neutral events [39, 40, 41]. This comprehensive genomic profiling capability was pivotal for our investigation. The SNP array platform provided a dual analytical power: firstly, it allowed for the high-throughput genotyping of the specific rs4590952 SNP across our entire large patient and control cohort. Secondly, and crucially, it enabled a detailed analysis of the molecular genotype across the 12q21.32 locus. It was this specific feature—the ability to detect regions of homozygosity through shifts in B-allele frequency without a corresponding change in copy number—that permitted the unambiguous identification of acquired cn-LOH, a key finding of our study.

To distinguish between evolutionarily selected, germline ROH (regions of homozygosity) and acquired, somatic cn-LOH in our study, a combined analytical approach is essential. Population genetics provides the initial filter: the frequency and genomic architecture of the homozygous segment can be indicative. Long, frequent ROH tracts are often signatures of identity-by-descent due to shared ancestry [42]. However, conclusive evidence for a postzygotic, somatic event comes from the detection of allelic imbalance at heterozygous sites within the region. The presence of heterozygous SNPs with allelic ratios systematically deviating from the expected 0.5, as demonstrated in our data from healthy individuals with cn-LOH, is a hallmark of a somatic genetic alteration [43, 44]. This mosaicism, detectable even in non-malignant cells, confirms the event as acquired rather than inherited. Therefore, integrating population-based allele frequencies with high-resolution analysis of allelic ratios from techniques like microarrays or next-generation sequencing allows for the robust discrimination of cn-LOH from ROH [45]. The study of Kim & Suyama [46] provides critical population-level context, revealing that cn-LOH is a frequent and intrinsic genetic phenomenon in healthy individuals, with an average of 40.7 events per genome. A majority (65%) of these events were classified as gonosomal mosaicism, present in both germline and somatic cells. Importantly, their work suggests that the occurrence of cn-LOH is influenced by genomic architecture, tending to increase in GC-rich regions and on chromosomes with closer spatial proximity between homologs.

In our work we inquired into the nature of the 12q21.32 homozygosity region. Specifically, is it a result of evolutionary selection for a single allele in the population, a classic homozygote inheriting identical alleles from both parents, or is it a somatic event that occurred during early post-zygotic stages? A direct answer to this question would have been provided by genotyping the parents of the individuals included in the study. However, we had neither the opportunity nor the objective to do so.

We hypothesized that in the case of post-zygotic cn-LOH, which implies mosaicism and the parallel existence of a cell population that has not lost the allele, there should be an increase in the number of heterozygous markers exhibiting allelic imbalance. In other words, we would expect to see an increased number of AG markers with a BAF below 0.3 and above 0.7. Conversely, in the case of an inherited homozygosity region, the number of heterozygous markers with allelic imbalance would not exceed this same parameter in the group where no loss of heterozygosity was observed. To minimize technical batch effects when comparing the two groups, we analyzed the BAF of heterozygous SNP markers of panel CytoScan™ HT-CMA specifically for samples processed within a single CMA batch (a run of 96 samples). Consequently, the cohort was structured to include 26 samples with 12q21.32 loss of heterozygosity (27% of 96) and 26 samples without it. Our study, which identified a high frequency of 12q21.32 cn-LOH, aligns with this ACMG technical standard. Our conclusion that this homozygosity is not due to consanguinity but is a recurrent somatic event (postzygotic cn-LOH) is fully consistent with the interpretation principles outlined by the ACMG. The significant allelic imbalance at heterozygous SNP markers within the locus that we detected serves as direct evidence against inherited ROH and confirms the somatic origin of the cn-LOH, precisely as recommended for accurate diagnosis in the ACMG guidelines [47].

In the literature, mentions of 12q21.32 cn-LOH are practically absent because, in CMA diagnostics, loss-of-heterozygosity events smaller than 3 million base pairs are not considered due to their frequent occurrence in the healthy genome. However, Wen et al. identified a recurrent ROH region at 12q21.3 with a frequency greater than

1% in a cohort of 958 cases with normal karyotype and aCGH results, included in the study over the four years from 2014 to 2017; this cohort consisted of 142 parental, 500 postnatal/pediatric, 195 prenatal CVS, and 121 prenatal AF cases [48]. We hypothesize that this genomic feature may not have phenotypic consequences in healthy individuals, but in patients with acute leukemias, it could be indirectly associated with a poorer response to chemotherapy.

In conclusion, our data suggest that acquired 12q21.32 cn-LOH is likely a more critical determinant of chemotherapy response than the germline allelic variants of the p53 response element in *KITLG*. The population frequency of the G allele falls within the range established for other populations and shows no association with leukemia. We can assume that the rs4590952 G allele, especially GG genotype, is not the cause, but merely a marker of some other factor or event in this region of 12q21.32 cn-LOH, and the emergence of the homozygous p53-RE genotype is simply located nearby. However, we are aware of the limitations of our work. Firstly, the small sample size of patients made it difficult to perform statistical analysis and prevented us from conducting a reliable multivariate analysis that included standard prognostic covariates. Secondly, the retrospective nature of the study prevented us from analyzing functional data, such as *KITLG* expression, KIT pathway activation, and downstream signaling pathways, after identifying aberrations affecting *KITLG*.

Our work is a pilot exploratory study aimed at identifying new potential risk factors. Future validation of 12q21.32 homozygosity/cn-LOH phenomenon in larger, prospective acute leukemia cohorts, with mandatory profiling of matched tumor-free samples, could establish it as a novel biomarker to guide the inclusion of targeted agents into first-line therapy for patients carrying this specific genetic marker.

Conclusions

The population frequency of the G allele of the rs4590952 (controls 0.785, T-ALL 0.833, B-ALL 0.757, AML 0.743) falls within the range of frequencies already known for other populations and, in the patient groups we studied, is not associated with acute leukemia ($p>0.05$).The GG genotype frequently arises from acquired cn-LOH at 12q21.32, observed in 45% of T-ALL and 26–27% of other cases ($p=0.02$). This pattern is consistent with a recurrent postzygotic event rather than with evolutionarily selected germline homozygosity, as evidenced by significant allelic imbalance at heterozygous SNPs within this region. Critically, 12q21.32 cn-LOH is associated with MRD positivity in T-ALL and poor chemotherapy response in AML. This treatment-response marker, present irrespective of leukemic status, warrants further validation in expanded cohorts.

List of abbreviations

ACMG	American College of Medical Genetics and Genomics
AF	Allele Frequency
AML	Acute Myeloid Leukemia
BAF	B-Allele Frequency
B-ALL	B-cell Acute Lymphoblastic Leukemia
ChAS	Chromosome Analysis Suite
CMA	Chromosomal Microarray Analysis
cn-LOH	Copy-Neutral Loss of Heterozygosity
CNV	Copy Number Variations
ELN	European Leukemia Net
FISH	Fluorescence In Situ Hybridization
MAF	Minor Allele Frequency
Mbp	Mega Base Pairs
MPAL T-myelo	Mixed-Phenotype Acute Leukemia with T-myeloid Features
MRD	Minimal Residual Disease
mRNA	messenger RNA
qPCR	quantitative PCR
RE	Response Element
ROH	Runs/Regions of Homozygosity
SNP	Single Nucleotide Polymorphism
T-ALL	T-cell Acute Lymphoblastic Leukemia

Author Contributions

Author Contributions: Conceptualization, N.R.; methodology, S.K. (Sergey Kulikov); validation, N.R., S.S., D.B., A.A. and E.K.; formal analysis, S.S., V.S. and Y.C.; investigation, K.N., O.D., A.Y., N.K., A.P., I.K. and S.K.(Sergey Korostelev); resources, E.K., A.A., A.V., Z.F., O.A., A.K., A.V. and I.G.; writing—original draft preparation, N.R. and S.S.; writing—review and editing, S.K. (Sergey Kulikov); visualization, S.S. and Y.C.; supervision, S.K. (Sergey Kulikov); project administration, E.P.; funding acquisition, N.R. and D.B. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The data used in this study is available at:

https://doi.org/10.6084/m9.figshare.30739889

Ethical Commetti Approval and Consent to Participate:

The study was approved by the Ethics Committee of the National Medical Research Center for Hematology (protocol #175/25, 25 October 2023) and the Local Ethical Committee of Genomed Laboratory of Molecular Pathology (protocol #G2024/12, 12 October 2024). Informed consent was taken from all patients and healthy participants.

Human Rights Statement:

The study was conducted in accordance with the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

- The funding for this research was provided by by the Russian Science Foundation (RSF) project No. 23-25-00490 https://www.rscf.ru/en/project/23-25-00490/ (accessed on 25 November 2025)

- CMA for the AML patient cohort was performed with support from the National Hematological Society (NHS), Moscow, Russia

Acknowledgments

The authors acknowledge the use of DeepSeek and Perplexity to improve the English language, including grammar and readability, during manuscript preparation. All scientific content, data analysis, and conclusions were generated and verified by the authors, who take full responsibility for the final text.

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