

Mutational Spectrum of T-Cell Large Granular Lymphocytic Leukemia: Insights From the AACR Project GENIE Consortium

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Abstract

Background/Aim: T-cell large granular lymphocyte leukemia (T-LGLL) is a rare, indolent lymphoproliferative disorder of cytotoxic T cells in the peripheral blood, bone marrow, and spleen. This analysis was conducted to characterize genomic alterations and highlight potential therapeutic targets, with the goal of refining the molecular landscape of T-LGLL by emphasizing population-specific biomarkers.

Materials and Methods: This study utilized the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database to identify common gene mutations. Using the AACR GENIE database, a retrospective analysis of T-cell large granular lymphocyte leukemia (T-LGLL) samples was performed. The data was evaluated by extracting patient demographics and excluding synonymous mutations from consideration. Statistical significance was assessed using chi-squared tests and computational analyses in RStudio (R Foundation for Statistical Computing, Boston, MA, USA). Somatic mutations and chromosomal copy number variations were evaluated, with statistical significance defined as $p=0.001$.

Results: Frequently observed somatic mutations included *STAT3* (41.7%), *STAT2* (20.9%), *KMT2D* (11.3%), *SETD1B* (8.7%), *TP53* (7.0%), *TNFAIP3* (6.1%), *DNMT3A* (5.2%), *FAS* (4.3%), *SMARCA4* (3.5%), *EPHB1* (2.6%), *KSR2* (2.6%), *ALOX12B* (2.6%), *EGFR* (2.6%), *DDX3X* (7.0%), and *IKZF3* (1.7%). When stratified by demographic variables, males and White patients demonstrated a higher frequency of mutations.

Conclusion: This study provides a comprehensive genomic profile of T-LGLL, identifying recurrent somatic mutations and commonly affected pathways. Notably, frequent alterations were observed in the *FAS-FASL* signaling pathway, underscoring its potential as a target for therapeutic development.

Keywords: T-cell large granular lymphocyte leukemia (T-LGLL), American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE), *STAT2*, *KMT2S*, *FAS*, somatic mutations.



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Introduction

T-cell large granular lymphocyte leukemia (T-LGLL) is a rare, indolent lymphoproliferative disorder characterized by the proliferation of cytotoxic T cells, affecting the peripheral blood, bone marrow, and spleen. In the fifth edition of the World Health Organization (WHO) classification, T-LGLL is categorized under “Mature T-cell and NK-cell leukemias” (1). Peripheral blood smears typically reveal intermediate-sized lymphocytes with round to slightly irregular nuclei, reticulated chromatin, and abundant pale cytoplasm containing azurophilic granules (2). Most patients are asymptomatic at diagnosis and are later identified after developing recurrent or severe infection (2). T-LGLL carries a mean overall survival of approximately 10 years, with the majority of deaths attributed to severe infection (3).

Risk factors for T-LGLL include cytopenias, particularly anemia and neutropenia, as well as splenomegaly and rheumatoid arthritis. Recurrent mutations in *STAT3* and *STAT5* are frequently observed, with *STAT5* mutations associated with more severe clinical outcomes (1, 2, 4). Although the true prevalence of T-LGLL is not well established, large granular lymphocyte leukemia (LGLL) overall has an estimated incidence of 200,000 to 720,000 cases annually, with T-LGLL comprising approximately 85% of cases (3). Prevalence also varies geographically: LGLL accounts for 5% to 6% of chronic lymphoproliferative disorders in Asia compared with 2% to 5% in North America and Europe (1, 3). Asian patients also demonstrate higher rates of anemia and neutropenia but fewer symptoms at diagnosis (5).

Diagnosis is confirmed using molecular assays and flow cytometry immunophenotyping, with bone marrow biopsies performed in cases of concomitant infection (2). Although no standard therapy exists, immunosuppressive monotherapy remains the predominant approach. First-line regimens include methotrexate (MTX), cyclophosphamide (Cy), and cyclosporine A (CsA) (6). Cy and CsA are generally preferred in patients with anemia, whereas MTX is recommended for those with concomitant

rheumatoid arthritis (6). Reported overall response rates (ORRs) are 38% to 55% for MTX, 60% to 70% for Cy, and 50% to 56% for CsA (6). Patients harboring *STAT3* mutations demonstrate higher response rates to MTX (5).

Preliminary research has highlighted the potential role of *STAT3*, *STAT3B*, and, in more severe cases, *STAT5* variants as diagnostic biomarkers, in part due to their association with downregulation of the MAPK–RAS–ERK and IL-15 pathways, both frequently dysregulated in LGLL (7-9). The STAT pathways are involved in various malignancies and are often a therapeutic target (10). These variants have also been linked to tumor suppression via null mutations in *TNFAIP3.42* and *TNFAIP3.43*, as well as mutations in epigenetic regulators including *KMT2D*, *SETD1B*, and *TET2* (8). However, *STAT3* and *STAT5* variants alone are insufficient for diagnosis, as they are not present across all T-LGLL subtypes.

By leveraging data from the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) consortium, this study aims to define the mutational landscape of T-LGLL with particular attention to population-specific biomarkers, including those relevant to Asian patients, to better inform precision diagnostics and therapeutic strategies.

Materials and Methods

Study population and data collection. The institutional review board at Creighton University (Phoenix, AZ, USA) waived institutional review board (IRB) approval for this study, as we utilized publicly available, deidentified data from the AACR Project GENIE® database. Records were obtained through the cBioPortal (v18.0-public) web platform, spanning 2017 to the present, with data collection initiated on July 29, 2025.

The AACR GENIE consortium comprises data from 19 leading cancer centers and features clinical-grade genomic sequencing from multiple platforms, including whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted panels that range from

50 to 555 genes. Coverage depth varies across modalities, ranging from >500× for targeted panels to approximately 150× for WES and 30× for WGS. For the T-cell large granular lymphocyte leukemia (T-LGLL) cohort, all cases were sequenced using targeted panels. No normalization beyond GENIE harmonization protocols was applied. Samples from the GENIE database were filtered by tissue type to determine sorting and mutation prevalence and further analyzed by patient demographic and molecular profiles.

Cohort categorization. Although member institutions use independent computational workflows for variant identification and annotation, all centers adhere to harmonization protocols outlined by Genome NEXUS. Frequently used tools include GATK for variant calling and ANNOVAR for annotation, though software versions may vary between institutions. We acknowledge that computational workflow variability may exist both between and within institutions, which may affect reproducibility. While the repository encompasses clinical information and treatment outcome data for select malignancies, this data is not available for T-LGLL. Selection criteria identified T-LGLL patients from a wider cohort of mature T and NK neoplasms. Tissue categorization was based on neoplastic origin, separating primary (the initial tumor) from metastatic (tumors arising from the spread of the primary tumor) sites (1, 11). Statistical assessment of primary vs. metastatic mutation patterns utilized chi-squared testing based on mutation prevalence within each category.

To comprehensively characterize the genomic landscape of T-LGLL, patient demographics (age, sex, race, and ethnicity), molecular profiles [*e.g.*, copy number alterations (CNAs) and somatic mutations], and pathologic classifications (*e.g.*, sample type) were extracted. A total of 93 patients with T-LGLL and 15 tumor samples met inclusion criteria. Despite institutional variability in targeted panel designs, the database maintained consistent coverage of principal cancer-linked genes such as *STAT3*, *TET2*, and *KMT2D*. Non-actionable genes, structural

variants, and cases with missing data were excluded. CNA analysis focused on homozygous deletions and amplifications to determine recurrent event frequencies.

Statistical analysis. Statistical analyses were performed using R/RStudio (R Foundation for Statistical Computing, Boston, MA, USA). A value $p=0.001$ was considered statistically significant. Continuous variables were summarized as means with standard deviations (SDs) and tested for normality. Depending on distribution, comparisons were made with either two-sided Student's *t* tests or Mann-Whitney *U*-tests. Categorical variables were reported as frequencies and percentages, with associations tested using chi-square analysis. To adjust for multiple comparisons and reduce type I error, the Benjamini-Hochberg false discovery rate (FDR) correction was applied.

Somatic mutation calls were obtained from AACR GENIE mutation annotation format (MAF) files, which provide harmonized annotation of gene- and protein-level alterations across contributing institutions. Filtering criteria included retention of functionally relevant alterations, including missense, in-frame, splice-site, and truncating variants, as well as deep deletions. Synonymous variants and variants of unknown significance were excluded. Mutations required a minimum variant allele frequency (VAF) of ≥5% and a sequencing coverage threshold of ≥100× for inclusion.

Results

T-cell large granular lymphocytic leukemia patient demographics. The patient demographics of the T-LGLL cohort are summarized in Table I. A total of 93 patients and 115 tumor samples were analyzed. Among patients, 59 (63.4%) were males and 32 (34.4%) were females. By ethnicity, 62 (66.7%) were non-Hispanic, 6 (6.5%) were Hispanic, and 25 (26.9%) were categorized as Unknown/Not Collected. By race, 60 (64.5%) identified as White, 6 (6.5%) as Black, 5 (5.4%) as Asian, 11 (11.8%) as Other, and 11 (11.8%) as Unknown. The cohort was almost entirely adult, with 92 (98.9%) adult patients and 1

Table I. Patient demographics in T-cell large granular lymphocyte leukemia (T-LGLL).

Demographics	Category	n (%)
Sex	Male	59 (63.4)
	Female	32 (34.4)
Age category	Adult	92 (98.9)
	Pediatric	1 (1.1)
Ethnicity	Non-Hispanic	62 (66.7)
	Unknown/Not collected	25 (26.9)
Race	Hispanic	6 (6.5)
	Asian	5 (5.4)
	White	60 (64.5)
	Black	6 (6.5)
	Other	11 (11.8)
Sample type	Unknown	11 (11.8)
	Primary	29 (25.2)
	Metastasis	14 (12.2)
	Not specified/Not applicable	72 (62.6)

(1.1%) pediatric case. Of the 115 tumor samples, 29 (25.2%) were derived from primary tumors, 14 (12.2%) from metastatic sites, and 72 (62.6%) were not specified. The results categorizing patient demographics can be visualized in Table I.

Copy number alterations and somatic mutations. The most prevalent somatic mutation was *STAT3* (n=48; 41.7%), followed by *TET2* (n=24; 20.9%), *KMT2D* (n=13; 11.3%), *SETD1B* (n=10; 8.7%), *TP53* (n=8; 7.0%), *TNFAIP3* (n=7; 6.1%), *DNMT3A* (n=6; 5.2%), *FAS* (n=5; 4.3%), *SMARCA4* (n=4; 3.5%), *EPHB1* (n=3; 2.6%), *KSR2* (n=3; 2.6%), *ALOX12B* (n=3; 2.6%), *EGFR* (n=3; 2.6%), *DDX3X* (n=2; 1.7%), and *IKZF3* (n=2; 1.7%) (Figure 1).

Recurrent copy number alterations (CNAs) were identified in 92 profiled samples. Loss-of-heterozygosity (LOH) events predominated, with 8 of the 9 CNAs affecting tumor suppressor genes. *TNFAIP3* was the most frequently altered gene (n=2; 2.2%), while *CD58*, *SGK1*, *ROS1*, *SETD1B*, *POT1*, *PRDM1*, and *FYN* were each affected in 1 sample (1.1% each). The sole amplification event involved *MYC* (n=1; 1.1%).

Sex and race differences. Sex-stratified analysis (Table II) identified mutations enriched exclusively in female

Table II. Sex-enriched alterations.

Gene (Chi-squared)	Male, n (%)	Female, n (%)	p-Value
<i>MCM8</i>	0 (0.0)	1 (100.0)	0.0167
<i>NIPBL</i>	0 (0.0)	1 (100.0)	0.0167
<i>DDX3X</i>	0 (0.0)	3 (11.1)	0.0451

patients, including *MCM8* (n=1; $p=0.0167$), *NIPBL* (n=1; $p=0.0167$), and *DDX3X* (n=3; $p=0.0451$). In this study, sex categorization was based on biological attributes recorded in the American Association for Cancer Research (AACR) Genomics Evidence Neoplasia Information Exchange (GENIE) database.

Race-stratified analysis (Table III) revealed *RET*, *PAX5*, *IKZF3*, *NSD1*, *FOXP1*, *STAT5B*, and *UBR5* mutations (n=1 each; $p<0.01$) exclusively in Asian patients. Among Black patients, recurrent alterations were observed in *LRP1B*, *SMARCA1*, *PIK3CA*, *CD274*, *NTRK3*, and *JAK1* (n=1 each; $p<0.01$). In White patients, *MCM8* was altered (n=1; $p<0.01$).

Mutual exclusivity and co-occurrence patterns. Analysis of mutational relationships revealed notable co-occurrence and exclusivity patterns. *KMT2D* mutations co-occurred with *STAT3* (n=9/47; $p=0.003$), *EPHB1* (n=3/9; $p<0.001$), *KSR2* (n=3/9; $p<0.001$), *FAS* (n=3/11; $p=0.006$), and *IKZF3* (n=2/9; $p=0.009$). *STAT3* co-occurred with *KMT2D* (n=9/47; $p=0.003$), *TNFAIP3* (n=8/47; $p=0.006$), and *SETD1B* (n=8/48; $p=0.031$). *FAS* co-occurred with *KMT2D* (n=3/11; $p=0.006$), *EPHB1* (n=3/5; $p<0.001$), and *KSR2* (n=3/5; $p<0.001$). Additionally, *EPHB1* and *KSR2* co-occurred (n=3/3; $p<0.001$), as did *TET2* and *SETD1B* (n=4/17; $p=0.017$). Mutual exclusivity was identified between *STAT3* and *DNMT3A* (n=0/52; $p=0.025$).

Primary and metastatic comparisons. The T-LGLL cohort included 29 primary and 14 metastatic cases. For tumor sample type analyses, 26 primary and 12 metastatic tumor samples were assessed. Only one alteration reached statistical significance: *SETD1B*, with enrichment in metastatic tumors (n=4 vs. n=1; $p=0.0387$).

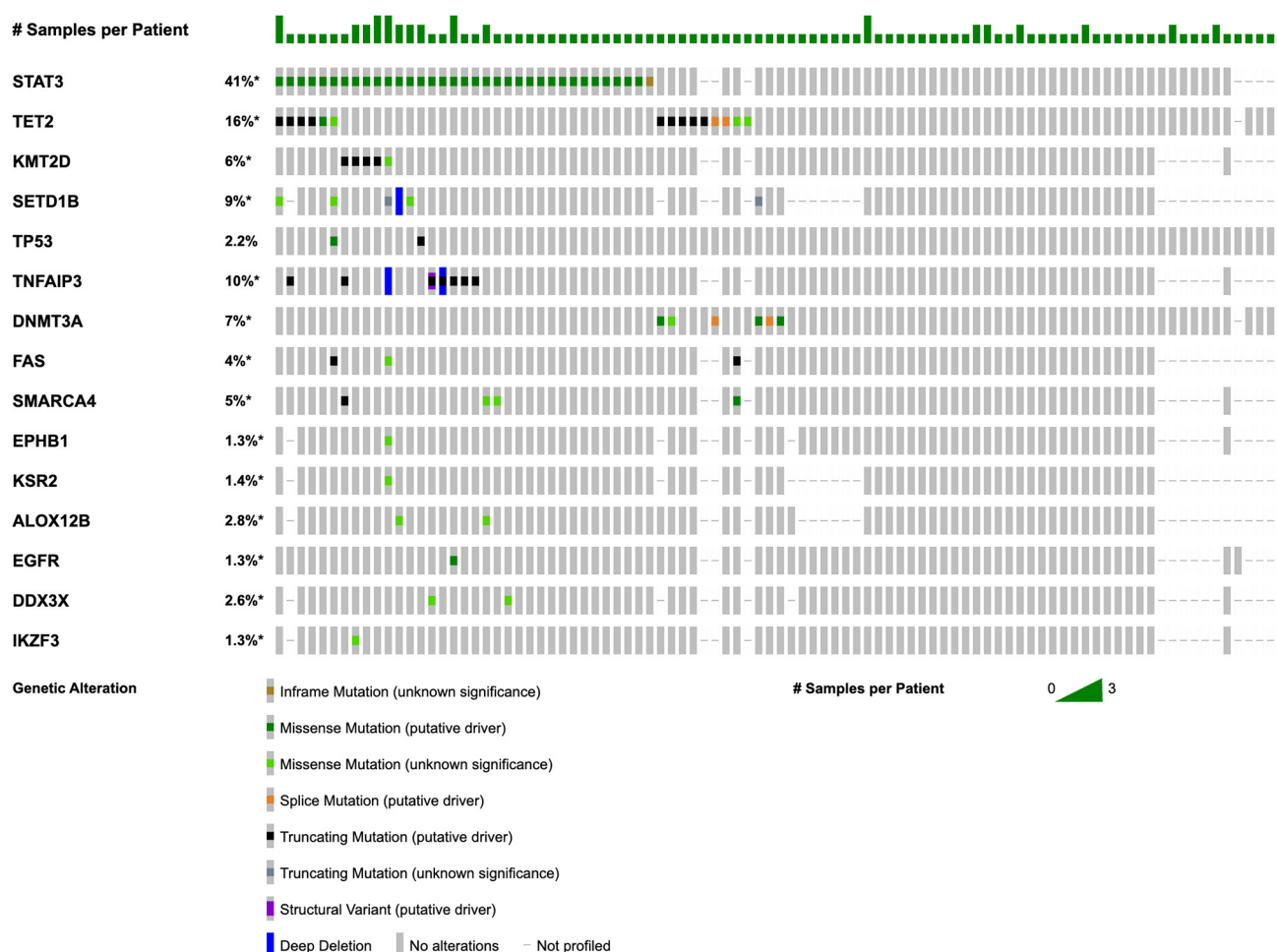


Figure 1. OncoPrint of recurrently mutated mutations in T-cell large granular lymphocyte leukemia (T-LGLL) (for genes with $n \geq 5$, coverage $\geq 100\times$, VAF $\geq 5\%$). Asterisks (*) indicate samples with incomplete genomic profiling.

Discussion

Subgroups and mutational landscape. This study aimed to characterize the genomic landscape of T-LGLL using the AACR Project GENIE repository to identify mutational patterns across demographic subgroups. Distinct mutational profiles were observed, including recurrent alterations in key oncogenic pathways such as *STAT3*, *TET2*, and *KMT2D*. The largest racial group in the cohort was White ($n=60$), while Asian patients ($n=5$) demonstrated exclusive mutations in *RET*, *PAX5*, *IKZF3*, *NSD1*, *FOXP1*, *STAT5B*, and *UBR5* ($n=1$ each; $p < 0.001$). These findings align with prior

reports linking T-LGLL in Asian populations to unique molecular pathways and an association with pure red cell aplasia responsive to fludarabine-based regimens (12, 13). In Black patients, *LRP1B*, *SMARCA1*, *PIK3CA*, *CD274*, *NTRK3*, and *JAK1* mutations ($n=1$ each; $p < 0.001$) were observed, with *JAK1* variants potentially enhancing JAK/STAT signaling and promoting tumor growth (14). In White patients, *MCM8* mutations ($n=1$; $p < 0.001$) were identified.

Sex-based analysis revealed the cohort was predominantly male ($n=59$; 63.4%), with females representing 32 (34.4%) cases. Genes *MCM8* ($n=1$; $p=0.0167$), *NIPBL* ($n=1$; $p=0.0167$), and *DDX3X* ($n=3$;

Table III. Race-enriched alterations.

Gene (Chi-squared)	Asian, n (%)	Black, n (%)	White, n (%)	p-Value
<i>RET</i>	1 (20.0)	0 (0.0)	0 (0.0)	0.01
<i>PAX5</i>	1 (20.0)	0 (0.0)	0 (0.0)	0.01
<i>IKZF3</i>	1 (20.0)	0 (0.0)	0 (0.0)	0.01
<i>NSD1</i>	1 (20.0)	0 (0.0)	0 (0.0)	0.01
<i>FOXP1</i>	1 (20.0)	0 (0.0)	0 (0.0)	0.01
<i>STAT5B</i>	1 (20.0)	0 (0.0)	0 (0.0)	0.01
<i>UBR5</i>	1 (20.0)	0 (0.0)	0 (0.0)	0.01
<i>MCM8</i>	0 (0.0)	0 (0.0)	1 (100.0)	0.01
<i>LRP1B</i>	0 (0.0)	1 (50.0)	0 (0.0)	0.01
<i>SMARCA1</i>	0 (0.0)	1 (50.0)	0 (0.0)	0.01
<i>PIK3CA</i>	0 (0.0)	1 (16.7)	0 (0.0)	0.01
<i>CD274</i>	0 (0.0)	1 (16.7)	0 (0.0)	0.01
<i>NTRK3</i>	0 (0.0)	1 (16.7)	0 (0.0)	0.01
<i>JAK1</i>	0 (0.0)	1 (16.7)	0 (0.0)	0.01

$p=0.0451$) were uniquely enriched among female patients. Comparison of tumor types revealed *ASNS*, *CD40*, *CHD7*, and *ITPKB* mutations exclusive to primary tumors ($p=0.0147$), whereas *NFKB1* and *RNF213* mutations were observed only in metastatic tumors.

Commonly mutated genes and known pathways. Consistent with prior literature, this cohort demonstrated substantial genetic heterogeneity in T-LGLL. The most frequent mutations were *STAT3* (n=48; 41.7%), followed by *TET2* (n=24; 20.9%), *KMT2D* (n=13; 11.3%), *SETD1B* (n=10; 8.7%), and *TP53* (n=8; 7.0%). Previous studies have similarly identified *STAT3*, *KMT2D*, and *TET2* as common alterations in T-LGLL (7, 8). Notably, *SETD1B* and *TP53* have been reported less frequently in the literature, yet their recurrence here suggests they may contribute to disease biology and warrant further exploration as potential drivers or modifiers of pathogenesis.

The most recurrently mutated genes identified in this dataset function across diverse biological processes. *STAT3* is a central mediator of JAK/STAT signaling, regulating transcriptional programs that influence T-cell proliferation, survival, and immune evasion (14). *TP53* serves as a key tumor suppressor, orchestrating DNA damage response and apoptosis (15). *TET2* and *KMT2D* act as epigenetic regulators, while *SETD1B* is involved in

histone methylation and transcriptional control (16). Collectively, these alterations implicate dysregulated cytokine signaling, impaired apoptosis, and disrupted epigenetic regulation as major contributors to T-LGLL pathogenesis.

***STAT3* mutations.** In this cohort, *STAT3* mutations were the most frequent, occurring in 41.7% of patients. *STAT3* is a transcription factor that regulates cell growth, division, migration, and apoptosis, and plays critical roles in normal development, immune function, and inflammation. *STAT3* when dysregulated can influence the expression of genes leading to oncogenesis and prevent apoptosis (10). Its activity is essential for the maturation of immune cells such as T cells and B cells, as well as for transmitting signals that drive cell survival, proliferation, and differentiation (14). In T-LGLL, gain-of-function *STAT3* mutations are found in approximately 30-40% of patients (7, 17). These variants result in constitutive activation of *STAT3*, driving malignant clonal expansion of cytotoxic T cells. Mutant *STAT3* has been shown to upregulate genes such as *CD38*, contributing to disease progression and more severe clinical features (9, 10, 17).

Clinically, patients harboring *STAT3* mutations often respond favorably to methotrexate (MTX), particularly in cases with the *STAT3* Y640F mutation (6, 18, 19).

Additionally, high *CD38* expression in T-LGLL has been linked to responsiveness to anti-CD38 antibody therapies (9). Targeted *STAT3* inhibitors, which block activation, DNA binding, or upstream signaling, have also been proposed as therapeutic strategies (20).

FAS-FASL ligand signaling. *FAS* is a crucial cell surface receptor that plays a role in the regulation of programmed cell death, or apoptosis. In T-LGLL, somatic *FAS* mutations enable leukemic T cells to evade apoptosis, allowing them to accumulate in tissues and proliferate uncontrollably (8). Furthermore, the interplay between *STAT3* and *FAS*/FAS ligand (*FASL*) production has been documented in prior studies, linking these pathways functionally in T-LGLL pathogenesis. *STAT3* activation can regulate *FASL* expression and modulate downstream apoptotic signaling, a relationship that has also been associated with neutrophil apoptosis (17).

Clinically, *FAS* mutations are associated with unfavorable outcomes in T-LGLL. Affected patients often have persistent disease, higher lymphocyte counts, and greater risk of autoimmune symptoms due to the survival of autoreactive lymphocyte clones (8). Resistance to *FAS*-mediated apoptosis also reduces the effectiveness of standard immunosuppressive therapies, which depend on intact apoptotic pathways (21). Identifying *FAS* mutations in T-LGLL may aid in patient stratification and support the development of novel therapies that restore apoptosis or bypass defective *FAS* signaling.

Co-occurrence patterns and functional implications. Significant co-occurrence was observed between *KMT2D* and *STAT3* ($n=9/47$; $p=0.003$) and between *KMT2D* and *FAS* ($n=3/11$; $p=0.006$), suggesting cooperative effects. This association between *KMT2D* and *STAT3* has also been described previously, reinforcing the hypothesis that *STAT3* activation may synergize with epigenetic alterations (7). In contrast, mutual exclusivity between *STAT3* and *DNMT3A* ($n=0/52$; $p=0.025$) suggests distinct pathogenic mechanisms, supporting the existence of molecularly defined subgroups within T-LGLL.

Study limitations. This study leveraged the AACR Project GENIE database to investigate the genomic landscape of T-LGLL; however, several limitations must be acknowledged. The first limitation is the lack of transcriptomic data, which is important for identifying information about gene expression, pathway activity, and tumor suppressor miRNA, particularly in relation to the over- and under-expression of genes. The second limitation concerns treatment response, as the database did not collect data on genomic changes in relation to novel therapies, preventing direct comparison. The third limitation arises from the fact that the AACR GENIE database gathers data from multiple centers, each of which may use different sequencing protocols. The fourth limitation relates to the biological understanding that can be achieved with this study, as the influence of DNA methylation on tumor behavior or treatment response could not be analyzed. The fifth limitation is the relatively small cohort size from which the data were collected. The sixth limitation stems from the study design, as tumor evolution could not be assessed from the available samples. The seventh limitation involves confounding variables that may arise due to sample similarity within the GENIE database. The eighth limitation is the restricted availability of clinical outcome data in the GENIE repository, which was gathered using NPC analysis, limiting the ability to detect mutation patterns. The ninth limitation results from the structure of the database, in which various histological subtypes are aggregated into a single group. This constrains the analysis of distinct mutational profiles and limits the ability to observe recurrent mutations in future research. A final constraint is the inability to connect genetic alterations with protein expression patterns of immune-related markers through immunohistochemistry.

Conclusion

The AACR Project GENIE analysis provides important insights into the genomic alterations underlying T-LGLL and highlights pathways that may inform novel therapeutic strategies. These findings contribute to the growing

understanding of recurrent mutations in T-LGLL and underscore the need for validation in larger, clinically annotated cohorts. Future studies should integrate genomic, transcriptomic, and proteomic data with clinical outcomes to establish prognostic biomarkers and actionable therapeutic targets. Focused investigation of *STAT3* mutations and related signaling pathways is particularly important for clarifying their predictive and therapeutic value. Expanding cohorts, especially among underrepresented populations, will be essential for defining population-specific mutational patterns and advancing precision medicine in T-LGLL.

Supplementary Material

Supplementary data associated with this article can be found online at the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database: <https://www.cbiportal.org/genie>

Conflicts of Interest

The Authors declare no competing interests.

Authors' Contributions

Conceptualization, A.S., B.H. and A.T.; methodology, A.S. and B.H.; validation, G.S.S., T.M., A.S., and B.H.; formal analysis, G.S.S., T.M., A.S., and B.H.; data curation, B.S.U., G.S.S., E.G., and A.G.; writing—original draft preparation, B.S.U., G.S.S., E.G., and A.G.; writing—review and editing, B.S.U., G.S.S., E.G., A.G., T.M., A.S., B.H., and A.T.; visualization, G.S.S., T.M., A.S., and B.H.; supervision, A.T.; project administration, A.T. All Authors have read and agreed to the published version of the manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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