

RESEARCH ARTICLE

Genomic Disruption of CAMKMT by t(2;11)(p21;q23) Reveals a Glycolytic Reprogramming Mechanism in Acute Myeloid Leukemia

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Abstract: Introduction: The t(2;11)(p21;q23) translocation without *KMT2A* rearrangement has been reported in ~16 hematologic neoplasms, but its molecular target(s) remain unknown. We aimed to identify the genes disrupted by this translocation and to clarify its contribution to Acute Myeloid Leukemia (AML) pathogenesis.

Methods: We performed Whole-Genome Sequencing (WGS), targeted RNA next-generation sequencing (86-gene panel), and transcriptome profiling on diagnostic bone-marrow samples from a 64-year-old male with AML. Karyotype analysis and Sanger sequencing confirmed chromosomal breakpoints and fusion junctions. CAMKMT expression and correlations with glycolysis-related genes were validated in TCGA (n = 173) and GTEx (n = 70) datasets.

Results: Karyotyping revealed a main clone with sole t(2;11)(p21;q23) and a subclone with an additional del(5q). WGS uncovered an inverted, tail-to-tail fusion between *CAMKMT* (2p21) and *GRIA4* (11q22.3) that truncates both genes. RNA-seq showed marked CAMKMT down-regulation ($p < 0.01$) and up-regulation of ENO1, PGK1, GPI, TPI1, and CXCL2 (all $p < 0.05$). Public datasets confirmed that low CAMKMT expression inversely correlates with these glycolytic genes ($r = -0.18$ to -0.31 ; $p < 0.05$). No functional chimeric protein is predicted.

Discussion: CAMKMT truncation, rather than a gain-of-function fusion, appears to drive leukemogenesis by reprogramming energy metabolism. This mechanism aligns with CAMKMT's role as a negative regulator of glycolysis and calmodulin signaling. However, a major limitation of the present study is the lack of protein-level evidence, which precludes definitive confirmation that functional loss of CAMKMT occurs at the cellular level.

Conclusion: We demonstrate that the t(2;11)(p21;q23) translocation is associated with disruption of *CAMKMT* at the genetic level and may promote leukemogenesis through metabolic reprogramming. These findings broaden the molecular spectrum of AML and suggest CAMKMT loss as a potential therapeutic vulnerability. However, our conclusions are based on transcriptomic evidence, and protein-level validation will be required in future studies to confirm the functional consequences of CAMKMT disruption.

Keywords: CAMKMT disruption, t(2;11)(p21;q23), metabolic reprogramming, glycolysis, acute myeloid leukemia, therapeutic target.

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1. INTRODUCTION

Acute Myeloid Leukemia (AML) is a highly heterogeneous hematologic malignancy, characterized by recurrent cytogenetic abnormalities, such as *RUNX1::RUNX1T1* and *CBFB::MYH11* fusions, as well as diverse somatic mutations and epigenetic alterations. This genetic and epigenetic heterogeneity influences disease classification, prognosis, and response to therapy, highlighting the need for integrated molecular profiling [1-3]. Among recurrent but rare chromosomal abnormalities, the translocation t(2;11)(p21;q23) has been documented in over 100 cases [4, 5]. While some of these cases involve a *KMT2A* rearrangement at 11q23, a subset is negative for *KMT2A* involvement. A cumulative total of 16 instances exhibiting the t(2;11) chromosomal translocation without the presence of *KMT2A* rearrangement have been recorded [4] (Table 1). This cohort comprises 5 instances of Myelodysplastic Syndrome (MDS) [5, 6], 4 instances of Acute Myeloid Leukemia (AML) [7, 8], 1 instance of Poly-

cythemia Vera (PV) [9], 1 instance of Chronic Myeloid Leukemia (CML) [10], 1 instance of Plasma Cell Neoplasms (PCN) [10], and 4 instances characterized by both MDS and AML. This cohort exhibits the following clinicopathological features: (1) Deletion of 5q was observed in 9 of the 16 cases (56.25%). (2) All cases with available data (10/10, 100%) exhibited significant megakaryocytic dysplasia. The genes targeted by this translocation have not yet been identified. Although the previous studies mapped breakpoints using a set of genomic clones, they failed to identify any specific target genes [11]. Furthermore, initial gene expression screening of loci near the breakpoints revealed no significant changes in expression levels [12]. Independent high-resolution cytogenetic studies have further characterized the biological behavior and molecular consequences of 5q deletions in myeloid neoplasms, providing additional context for understanding the cytogenetic landscape associated with cases harboring both t(2;11) and 5q loss.

Table 1. Clinical, histological, and genomic features of 16 cases of neoplasms with chromosomal translocation t(2;11).

Case No.	Sex/Age (Year)	Karyotype	WBC (10e9/L)	CR/Duration (mo)	Diagnosis	MKC	Survival Status	Author (Year)
1	M/64	46, XY, t(2;11)(p21;q23)[4]/46, idem, del(5)(q31g35)[10]/46, XY[6]	9.6	YES/4	AML	YES	Alive	this study
2	M/59	46, XY, t(2;11)(p21;q23)[8]/46, XY[12]	N/A	NO/13	MDS	YES	Deceased	Dvorak P <i>et al.</i> (2014)
3	M/71	46, XY, t(2;11)(p21;q23), del(5)(q12q33)[10]/46, XY[7]	N/A	NO/33	MDS	YES	Deceased	Dvorak P <i>et al.</i> (2014)
4	M/37	46, XY, t(2;11)(p21;q23)[20]	N/A	NO/127	MDS/AML	YES	Deceased	Dvorak P <i>et al.</i> (2014)
5	M/50	46, XY, t(2;11)(p21;q23)[8]/46, idem, del(5)(q13q33)[7]	N/A	YES/130	MDS	YES	Alive	Dvorak P <i>et al.</i> (2014)
6	M/52	46, XY, t(2;11)(p21;q23), del(5)(q14q33)[34]	N/A	NO/72	MDS/AML	YES	Deceased	Dvorak P <i>et al.</i> (2014)
7	M/54	46, XY, t(2;11)(p21;q23), del(5)(q13q33)[13]/46, XY[7]	N/A	YES/144	MDS	YES	Alive	Dvorak P <i>et al.</i> (2014)
8	M/47	46, XY, t(2;11)(p21;q23), del(5)(q13q33)[20]	N/A	NO/22	MDS/AML	YES	Deceased	Dvorak P <i>et al.</i> (2014)
9	M/65	46, XY, t(2;11)(p22;q2324), del(5)(q13q33)[cp6]/46, XY[1]	2.5	YES/6	MDS	YES	Alive	Thorsen J <i>et al.</i> (2012)
10	M/66	46, XY, t(2;11)(p21;q23)[14]	53	NO/12	AML	N/A	Deceased	Gozzetti A <i>et al.</i> (2003)
11	F/11 mo	46, XX, t(2;11;9)(q31;p15;q22), t(6;11;15)(q21;q23;q22), t(8;10)(q13;q22)	24.4	YES/30	AML	N/A	Alive	Hidaka E <i>et al.</i> (2007)
12	M/61	46, XY, t(2;11)(p21;q23), del(5)(q13q33)	N/A	N/A	AML	N/A	Deceased	Finke J <i>et al.</i> (1994)
13	M/52	46, XY, t(2;11)(p21;q2324)[4]/46, idem, del(5)(q15q31)[4]/46, XY, del(5)(q13q31)[2]/46, XY[10]	12.5	YES/70	PV	YES	Alive	McCormick SR <i>et al.</i> (2015)
14	M/63	46, XY, t(2;11)(p21;q23), t(9;22)(q34;q11)[20]	N/A	YES/22	CML	N/A	Alive	Royer-Pokora B <i>et al.</i> (2003)
15	F/51	46, XY, t(2;11)	10.2	YES/1	PCN	N/A	Alive	Peterson JF <i>et al.</i> (2019)
16	F/1	46, XY, t(2;11)(q31;p15)[2]/44, XX, idem, -21x2[4]	151.8	YES/7	MDS/AML	N/A	Alive	Hou X <i>et al.</i> (2021)

Abbreviations: AML, Acute Myeloid Leukemia; CML, Chronic Myeloid Leukemia; MDS, Myelodysplastic Syndrome; PCN, plasma cell neoplasms; PV, Polycythemia Vera.

One of the hallmark features of cancer is metabolic reprogramming, typically manifested as the Warburg Effect, in which cancer cells preferentially convert glucose into lactate *via* highly efficient glucose metabolism even under oxygen-rich conditions to support the biosynthesis required for their rapid proliferation [13]. AML cells, particularly the disease-driving leukemic stem cells, exhibit high metabolic dependency, with enhanced glycolysis recognized as a key feature across many AML subtypes [14-16]. Recent studies have highlighted that AML is not only genetically heterogeneous but also metabolically diverse, with leukemic stem cells displaying unique energetic dependencies that differ from bulk blasts [17-21]. Such metabolic heterogeneity may influence response to chemotherapy and survival outcomes. To support rapid proliferation and therapy resistance [22, 23]. Given the critical importance of metabolic pathways for AML cell survival, identifying and targeting metabolic vulnerabilities driven by specific genetic mutations or chromosomal abnormalities has emerged as a key direction for developing novel and personalized AML therapeutic strategies [24, 25]. However, for certain rare leukemic cytogenetic abnormalities, such as *t(2;11)(p21;q23)*, the potential molecular targets and their underlying mechanisms of action within cellular metabolic networks remain unexplored. Integrative multi-omics approaches have demonstrated that combining genomic, transcriptomic, and metabolomic data can identify novel therapeutic targets and biomarkers in genetically complex leukemias [23, 26-28].

In this study, we report a case of AML with *t(2;11)(p21;q23)* as the sole chromosomal aberration in the main clone, and an additional 5q deletion in a subclone harboring the same translocation. Whole-genome sequencing revealed that the breakpoints at 2p21 and 11q23 are located within the *CAMKMT* and *GRIA4* genes, respectively. The resulting *GRIA4::CAMKMT* fusion is in an inverted orientation, which precludes the formation of a chimeric protein. Gene expression analysis demonstrated marked downregulation of *CAMKMT*, while *GRIA4* was not expressed. These findings suggest that the *t(2;11)* translocation primarily targets *CAMKMT*, which encodes a lysine methyltransferase that methylates calmodulin.

2. MATERIALS AND METHODS

2.1. Cytochemistry

Bone marrow aspirates were collected, and smears were prepared, air-dried, and stained with Wright-Giemsa for morphological analysis. Biopsy samples were preserved using 10% neutral-buffered formalin,

subjected to decalcification, embedded in paraffin wax, sliced into sections, and subsequently stained with Hematoxylin and Eosin (H&E). Cellular morphology and marrow architecture were evaluated under light microscopy.

2.2. R-Banding and Karyotype Analysis

Bone marrow aspirates were cultured overnight, and mitotic cells were harvested for karyotype analysis. Metaphase spreads were prepared on pre-cleaned slides and stained using a standard R-banding technique involving heat denaturation and Giemsa staining [29]. A minimum of 20 metaphases were examined for each sample, and the karyotypes were evaluated and characterized in accordance with the International System for Human Cytogenomic Nomenclature (ISCN 2020).

2.3. DNA Next-Generation Sequencing (NGS)

Genomic DNA was isolated from bone marrow samples utilizing the QIAamp DNA Blood Mini Kit (Qiagen). DNA was fragmented to 300-500 bp using a Bioruptor Pico (Diagenode), followed by end repair, phosphorylation, and dA-tailing. Adaptors with Unique Molecular Identifiers (UMIs) were ligated, and the library was amplified using seven cycles of PCR. The products were hybridized with biotin-labeled probes targeting 86 AML-related genes and enriched using streptavidin beads. The QIAseq FX DNA Library Kit (Qiagen, Hilden/Germany) was utilized for the preparation of libraries for whole-genome DNA sequencing [30, 31]. The sequencing process was conducted using the Illumina NovaSeq platform. Variants, including SNVs, indels, CNVs, and structural variants, were analyzed using SeqNext (JSI) and in-house bioinformatics pipelines.

2.4. Transcriptome Sequencing

In the context of transcriptomic investigations, total RNA was isolated from diagnostic bone marrow specimens utilizing the RNeasy Mini Kit (Qiagen, Hilden, Germany), followed by a thorough quality assessment. RNA sequencing libraries were generated employing the TruSeq Stranded mRNA Panel and subsequently sequenced on an Illumina platform (San Diego, CA, USA), achieving an approximate depth of 50 million paired-end reads for each sample. The sequencing reads were aligned to the human reference genome (GRCh38) through the application of the STAR aligner, while transcript quantification was carried out using featureCounts [32, 33]. Furthermore, differential expression analysis and the identification of fusion genes were performed utilizing DESeq2 [34] and Fusion-Catcher [35], respectively.

2.5. Statistical Analysis

Statistical evaluations were conducted utilizing GraphPad Prism version 8.4.2 (GraphPad Software, San Diego, CA, USA). The data are expressed as mean $\pm$ Standard Deviation (SD), except where indicated otherwise. The assessment of differences among groups was carried out employing suitable statistical tests, with p -values below 0.05 deemed statistically significant. The criteria for statistical significance are denoted as follows: $p < 0.05$ (*), $p < 0.01$ (**), and $p < 0.001$ (***)

3. RESULTS

3.1. Clinical Findings

A 64-year-old male patient, who has a medical history that includes hypertension, type 2 diabetes, and a prior gastric polypectomy, reported experiencing chest tightness and fatigue over the past two months. He had a 40-year history of smoking and alcohol consumption, with no significant lymphadenopathy, sternal tenderness, or hepatosplenomegaly on physical examination. Complete Blood Count (CBC) showed the following results: white blood cells, $9.6 \times 10^9/L$; basophils, $0.8 \times 10^9/L$; monocytes, $1.8 \times 10^9/L$; red blood cells, $2.13 \times 10^{12}/L$; hemoglobin, 75 g/L; platelets, $76 \times 10^9/L$; and Mean Corpuscular Volume (MCV), 109.4 fL.

3.2. Histopathological Findings

The analysis of the bone marrow through aspiration and biopsy revealed a hypercellular composition, characterized by a granulocytic lineage constituting 86.0% of the total cellularity, an erythroid lineage accounting for 4.5%, and a myeloid-to-erythroid ratio of 19.11:1, as illustrated in Fig. (1A). Megakaryocytes were scattered and predominantly exhibited multilobulated nuclei, with occasional forms showing reduced nuclear lobulation (Fig. 1B). Blasts constituted 26.5% of nucleated cells, with increased promyelocytes and myelocytes, and dysplastic granulopoiesis with basophilia. Erythropoiesis was decreased with megaloblastic changes in erythroid precursors. Bone marrow histopathology revealed hypercellular marrow (70-80%) with immature precursor cells, granulocytic hyperplasia, and scattered early myeloid cells (Fig. 1B). The bone marrow flow cytometry showed 24.7% of CD34+ cells with CD10 bright+, CD38+, CD117+, CD33dim+, CD13+, HLA-DR+, CD15+, CD3-, CD19- and CD79a-. A diagnosis of AML was made.

3.3. Cytogenetics

Karyotype analysis revealed two clonal cell populations. In the study, four cells demonstrated a translocation t(2;11)(p21;q23) as the only chromosomal alteration (Fig. 1C). In contrast, ten cells exhibited the same t(2;11) translocation in conjunction with an interstitial deletion on the long arm of chromosome 5, specifically del(5)(q31q35) (Fig. 1D). The remaining six cells maintained a standard karyotype, characterized by 46,XY,t(2;11)(p21;q23)[4]/46,idem,del(5)(q31q35)[10]/46,XY[6].

3.4. Molecular Analysis

RNA NGS analysis of 53 leukemia-associated genes, including the *KMT2A* gene, did not detect any relevant fusion gene expression. Whole-genome sequencing identified a *GRIA4::CAMKMT* fusion event involving exon 4 of *CAMKMT* and exon 15 of *GRIA4* (Fig. 2A). This fusion is in a tail-to-tail orientation; therefore, no chimeric mRNA or protein is expected. The breakpoints were further validated at the genomic DNA level using PCR amplification with gene-specific primers (F_ *GRIA4*: 5'- TCCTTTGCCTCTAAGAATGCC -3'; R_ *CAMKMT*: 5' - AAATTAGCTGGGTGTGGTGG -3') and nested primers (F_ *GRIA4* nest: 5'- ATGTGGGTTTAGTGTGCTCG -3'; R_ *CAMKMT* nest: 5' - TGGAGAATCGTGTGAACCTG -3'). A DNA fragment of the expected size was successfully amplified, and subsequent Sanger sequencing confirmed the genomic breakpoint (Fig. 2B and 2C). In addition to the *GRIA4::CAMKMT* rearrangement, additional gene mutations were identified, including *U2AF1* (p.Ser34Ty; VAF 46.23%) and *BCOR* (p.Arg1375Trp; VAF 88.73%).

3.5. CAMKMT Alterations in AML

Because the *GRIA4::CAMKMT* rearrangement results in the truncation of both *CAMKMT* and *GRIA4*, we evaluated its impact on their RNA expression levels. The patient with the *GRIA4::CAMKMT* fusion showed markedly decreased *CAMKMT* expression compared to four normal bone marrow samples (Fig. 3A). In contrast, *GRIA4* expression was absent or at very low levels in both the patient and all control samples (Fig. 3A). To investigate potential downstream effects, gene expression profiling of the patient versus the four normal bone marrow samples revealed significant upregulation of several genes, including *ENO1*, *PGK1*, *GPI*, *TPIL*, and *CXCL2* (Fig. 3A), all key enzymes involved in glycolysis and energy metabolism. Overexpression of these genes has been associated with enhanced tumor growth and prolifera-

tion. In order to assess the potential regulatory role of CAMKMT on specific genes, we conducted an analysis utilizing the expression dataset from The Cancer Genome Atlas (TCGA) for AML with a sample size of 173. The results of our analysis indicated a noteworthy

inverse relationship between the expression levels of CAMKMT and the genes *ENO1*, *PGK1*, *GPI*, *TPI1*, and *CXCL2*, with statistical significance ($p < 0.05$) (Fig. 3B). These results imply that CAMKMT may function as a negative regulator for genes that are associated with glycolysis and the progression of tumors.

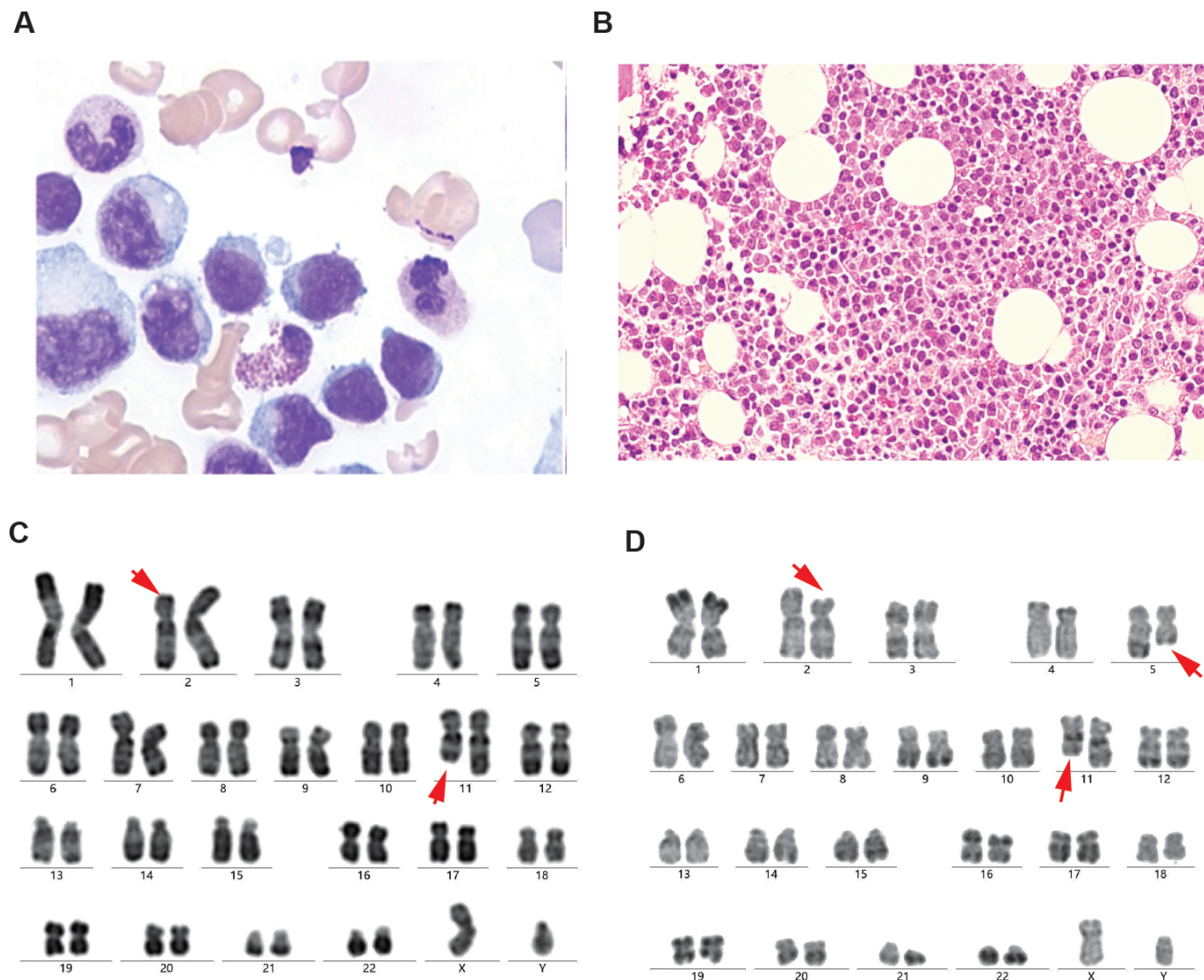
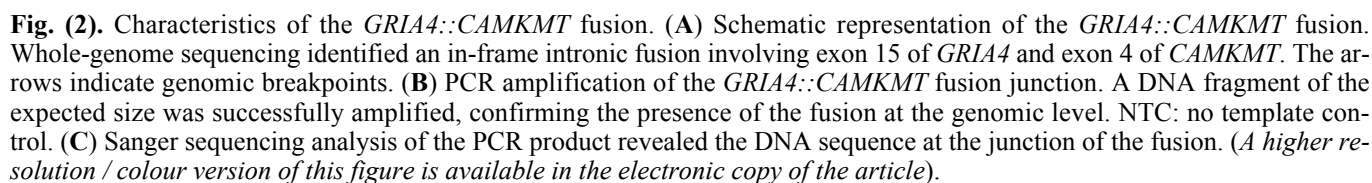


Fig. (1). Morphological and cytogenetic characteristics of a patient diagnosed with Acute Myeloid Leukemia (AML) exhibiting a t(2;11) translocation. (A) Examination of the bone marrow aspirate revealed the presence of medium to large-sized blasts, characterized by round to slightly irregular nuclei, fine and delicate chromatin structure, along with prominent nucleoli. The cytoplasmic component was observed to be scant to moderate, showing deep basophilia and occasional azurophilic granules. (B) Analysis of a bone marrow biopsy stained with H&E demonstrated significant hypercellularity, characterized by a diffuse infiltration of medium to large-sized blasts that presented a markedly elevated nuclear-to-cytoplasmic (N:C) ratio. (C, D) Cytogenetic evaluation through karyotype analysis (R-banding) of unstimulated bone marrow cells identified a singular abnormality, specifically the t(2;11)(p21;q23) in the primary clone (C), alongside an additional deletion at 5q within a subclone (D). (A higher resolution / colour version of this figure is available in the electronic copy of the article).



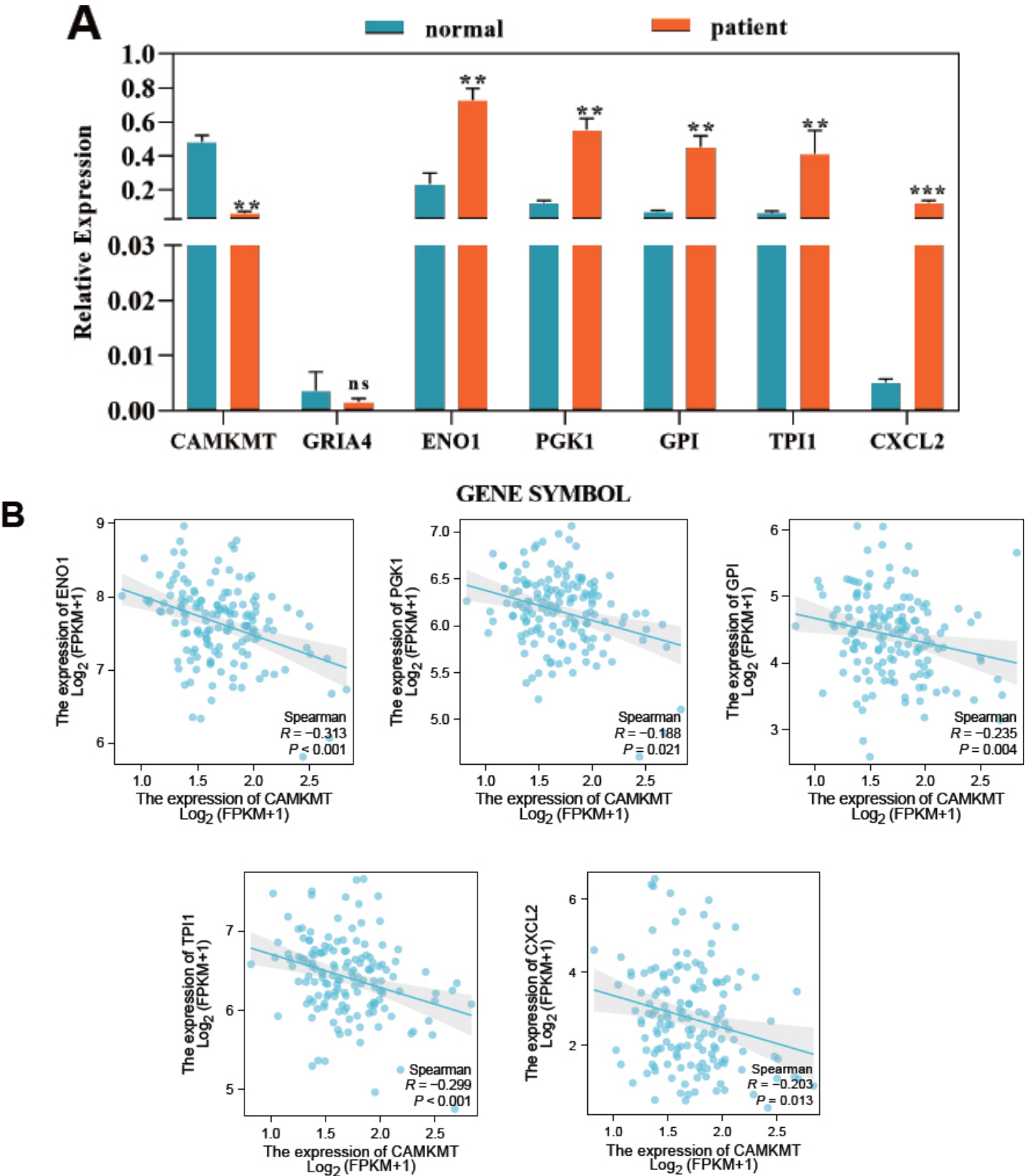


Fig. (3). Contd....

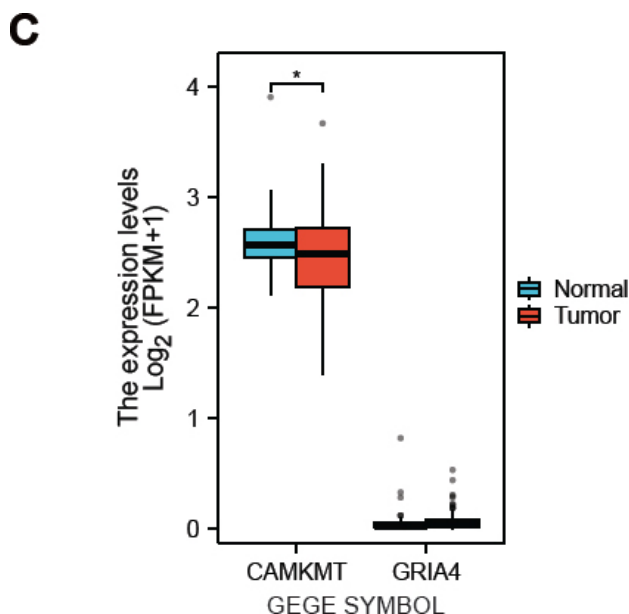


Fig. (3). Expression analysis of *CAMKMT* and its correlation with glycolysis pathway genes in AML. (A) Transcriptome analysis of the patient's bone marrow sample showed reduced *CAMKMT* expression and increased expression of several glycolysis-related genes, including *ENO1*, *GPI*, *TP11*, *PGK1*, and *CXCL2* ($p < 0.05$), compared to normal bone marrow specimens. (Student's t-test). (B) Correlation assessment utilizing data from TCGA specific to AML ($n = 173$) demonstrated a notable inverse correlation between *CAMKMT* expression and the expression levels of *ENO1*, *GPI*, *TP11*, *PGK1*, and *CXCL2* ($p < 0.05$). The correlation coefficients (r) and corresponding p -values for each gene pair are provided. (C) Expression analysis derived from the Genotype-Tissue Expression (GTEx) project (normal, $n = 70$) and TCGA (AML, $n = 173$) datasets indicated that *GRIA4* expression did not exhibit significant variation between normal and AML samples ($p > 0.05$). In contrast, *CAMKMT* expression levels were considerably lower in AML samples in comparison to normal controls ($p < 0.01$, as per Student's t-test). *Error bars denote mean $\pm$ SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

In order to evaluate the potential downregulation of *CAMKMT* in additional cases of AML, we conducted a comparative analysis of its expression levels between a cohort of healthy individuals ($n = 70$) sourced from the GTEx database and AML patients ($n = 173$) from the TCGA database. The findings revealed a significant decrease in *CAMKMT* expression in the AML samples when juxtaposed with the healthy control group (Fig. 3C; $p < 0.01$, Student's t-test). In contrast, *GRIA4* expression remained low in both cohorts, with no statistically significant difference observed.

4. DISCUSSION

CAMKMT is classified within the protein lysine methyltransferase family and exhibits significant conservation across a wide range of organisms, spanning from plants to animals [33]. This gene encodes a class I protein methyltransferase responsible for the trimethylation of lysine 115 on Calmodulin (CaM) [36, 37]. *CAMKMT* is expressed in numerous human tissues, and abnormalities in its transcription are strongly linked to the 2p21 deletion syndrome [36, 38]. The

CAMKMT protein is primarily localized in the nucleoplasm and nucleoli, suggesting a potential role in nuclear transcriptional regulation. Studies have shown that *CAMKMT* deficiency leads to reduced methylation of calmodulin, thereby affecting calcium signaling pathways. Furthermore, *CAMKMT* is considered the principal—and possibly the sole—calmodulin methyltransferase in human cells. It has also been identified as a client protein of heat shock protein 90 (Hsp90), implying a possible role in protein folding and stability [38, 39]. Emerging evidence also suggests a role for *CAMKMT* in inflammation and disease. It has been observed that elevated levels of *CAMKMT* facilitate the activation of the non-canonical inflammasome via caspase-11, consequently augmenting anti-inflammatory responses *in vivo* [36]. More broadly, dysregulation of lysine methyltransferases has been increasingly recognized as a critical mechanism in cancer biology, affecting chromatin organization, transcriptional control, and cellular metabolism [40–43]. Alterations in methyltransferase activity can lead to profound epigenetic remodeling, thereby promoting oncogenic transformation and

disease progression in hematologic malignancies [44-46].

To date, only one case of *CAMKMT* fusion has been reported. The patient was a 67-year-old female diagnosed with Primary Pulmonary Mucinous Adenocarcinoma (PPMA), in whom FISH analysis revealed a *CAMKMT::ALK* fusion. The identified breakpoint occurred within intron 3 of *CAMKMT* and intron 19 of *ALK*, leading to the formation of a fusion gene comprising *CAMKMT* exons 1 through 3 and *ALK* exons 20 to 29. This rearrangement retained the full kinase domain of *ALK*, representing a functionally active oncogenic fusion [47]. In contrast, the *GRIA4::CAMKMT* fusion identified in our study involves exons 15-17 of *GRIA4* and exons 4-11 of *CAMKMT*, resulting in a loss-of-function of both genes. Analysis of data from GTEx and TCGA revealed that *GRIA4* expression is low and not significantly different between normal and tumor samples. In contrast, *CAMKMT* expression is significantly higher in normal tissues than in tumors. This trend was also validated in our patients' transcriptomic data. Therefore, we speculate that the pathogenic mechanism of the *GRIA4::CAMKMT* fusion is primarily driven by the inactivation of *CAMKMT*. To date, the *GRIA4::CAMKMT* fusion has not been previously reported in AML, and its functional impact and oncogenic mechanisms remain largely unknown. To explore the potential molecular consequences of this fusion event, we performed transcriptomic analysis and identified significantly upregulated expression of several glycolysis and energy metabolism-related genes, including *ENO1*, *PGK1*, *GPI*, and *TP11*, in the bone marrow sample of our patient (Fig. 3A). Glycolysis serves as a fundamental metabolic pathway that is vital for all forms of life, significantly influencing stem cell differentiation and cancer biology [48, 49]. Tumor cell proliferation and growth rely heavily on the energy provided by glycolysis [50]. Alpha-enolase (*ENO1*), which is alternatively referred to as 2-phospho-D-glycerate hydrolase, facilitates the transformation of 2-phosphoglycerate into phosphoenolpyruvate as part of the glycolytic pathway [50-54]. *ENO1* is frequently overexpressed in various cancers and acts as a multifunctional oncoprotein. It facilitates the advancement of tumors by increasing glycolytic activity, promoting cellular proliferation, enhancing migration and invasion, fostering drug resistance, and activating oncogenic signaling pathways. Consequently, this process leads to an energy imbalance and heightened resistance to programmed cell death [50, 55]. Phosphoglycerate Kinase 1 (*PGK1*) serves as a pivotal enzyme in the glycolytic pathway, facilitating the initial ATP-producing reaction during glycolysis [56, 57]. In addition to its

metabolic function, *PGK1* acts as a protein kinase, phosphorylating various substrates that play essential roles in processes such as tumor proliferation, migration, and invasion. Elevated levels of *PGK1* expression have been linked to resistance against chemoradiotherapy and unfavorable outcomes in cancer patients [58-60]. Similarly, Glucose-6-Phosphate Isomerase (*GPI*) is responsible for catalyzing the second reaction in glycolysis, wherein glucose-6-phosphate is converted into fructose-6-phosphate within the cytoplasm [61, 62]. Triosephosphate Isomerase 1 (*TP11*), another critical glycolytic enzyme, is frequently upregulated in various cancers [62, 63]. *TP11* promotes tumor progression and glycolysis by stabilizing *CDCA5* and activating the *PI3K/AKT/mTOR* signaling pathway [64]. C-X-C motif chemokine ligand 2 (*CXCL2*) plays a crucial role in promoting leukocyte recruitment and inflammatory responses and has been implicated in tumor progression through the activation of multiple oncogenic signaling pathways [65]. Studies have demonstrated that *CXCL2* enhances the survival, migration, and drug resistance of AML cells under hypoxic conditions, and elevated *CXCL2* expression is associated with poor prognosis and reduced disease-free survival in AML patients [66]. Importantly, targeting key enzymes involved in glycolysis has emerged as a promising therapeutic strategy, with several small-molecule inhibitors currently under preclinical and clinical investigation [67-70]. These metabolic interventions aim to disrupt the energy supply and biosynthetic capacity of leukemic cells, thereby enhancing treatment efficacy and overcoming drug resistance [71, 72].

To further investigate the relationship between *CAMKMT* downregulation and these glycolysis pathway genes, we analyzed public datasets and confirmed that *CAMKMT* expression negatively correlates with the expression levels of *ENO1*, *PGK1*, *GPI*, *TP11*, and *CXCL2* (Fig. 3B). Collectively, these findings suggest that the *GRIA4::CAMKMT* fusion may contribute to AML pathogenesis by truncating *CAMKMT*, thereby resulting in the overexpression of key glycolytic genes and promoting tumor progression through metabolic reprogramming. Alternatively, *CAMKMT* may also contribute to oncogenesis by modulating the function of CaM (calmodulin-dependent kinase). Calmodulin is a well-conserved protein that binds calcium and serves as a key messenger in the regulation of numerous cellular functions. It is integral to various processes, including the progression of the cell cycle, programmed cell death, the formation of new blood vessels, cellular migration, and invasion [73, 74]. These processes represent vital pathways involved in the progression of cancer. CaM directly interacts with several kinases in-

volved in key signaling cascades, such as the CaMK pathway, the PI3K/AKT/mTOR pathway, and the MAPK/ERK signaling pathway. In AML, CaM acts as an essential regulator of signaling networks that drive leukemic cell proliferation, inhibit apoptosis, and sustain the differentiation block [75, 76].

Although *CAMKMT* mRNA is significantly down-regulated in the patient with the t(2;11) translocation, presumably as a consequence of *CAMKMT* gene truncation at the chromosomal breakpoint, a major limitation of this study is the lack of protein-level validation. Diagnostic specimens were exhausted during MICM evaluation, precluding further protein analyses. In addition, the patient was lost to follow-up because of disease progression and treatment-related financial burden, and declined subsequent clinical visits. As a result, the conclusions regarding glycolytic pathway regulation in this study are based primarily on transcriptomic data. Accordingly, the proposed effects at the protein level are indirect and hypothesis-generating, rather than supported by direct experimental evidence. Moreover, the current evidence is based on a single case. Although the t(2;11) translocation has been reported in more than 16 cases, the true prevalence and specificity of *CAMKMT* truncation in such leukemias remain unclear. Functional assays directly linking *CAMKMT* loss to glycolytic reprogramming or leukemic transformation were not performed, and the transcriptomic correlations, derived from bulk RNA-seq, may not fully capture leukemia stem cell-specific effects. The absence of *in vitro* or *in vivo* rescue experiments further limits causal interpretation.

As a next step, we plan to generate hematopoietic stem cell-based models to recapitulate the molecular features of the patient's leukemia.

CONCLUSION

This study characterizes a rare t(2;11)(p21;q23) rearrangement involving disruption of *CAMKMT* in a single AML patient. Our data indicate an association between reduced *CAMKMT* transcript levels and the up-regulation of glycolysis-related genes, suggesting a possible link between *CAMKMT* loss and metabolic alterations. While these findings raise the possibility that *CAMKMT* disruption may contribute to leukemogenesis, this hypothesis requires further validation in additional cases and functional studies.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: Study conception and design: SX and YC; Data collection: SL, PF; Analysis and interpretation of re-

sults: SL, PF; Experiment validation: XL, HC; Draft manuscript: XY, DL. All authors reviewed the results and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The studies involving human participants were reviewed and approved by Xiangya Hospital of Central South University.

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Written informed consent for participation in this study was obtained directly from the patient after a full explanation of the study objectives and procedures.

AVAILABILITY OF DATA AND MATERIALS

The data and materials of this study will be available from the corresponding author [Yan Chen] upon reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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