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LETTER TO THE EDITOR

A novel *KMT2A*::*DCP1B* rearrangement in chronic neutrophilic leukemia

KMT2A (Lysine methyltransferase 2A), also known as MLL (Mixed Lineage Leukemia), is rearranged in 5% of de novo adult acute myeloid leukemia (AML), 24% of pediatric AML, 60%–70% of infant acute lymphocytic leukemia (ALL), and 10% of adult ALL. However, *KMT2A* rearrangement is rare in myelodysplastic syndromes and has never been reported in chronic neutrophilic leukemia (CNL). *KMT2A* is genetically promiscuous and has more than 100 fusion partner genes reported so far. In this study, we identified a novel fusion partner of *KMT2A*, dipeptidyl carboxypeptidase 1B (*DCP1B*), in a patient with classic CNL. To our knowledge, this is the first reported *KMT2A* rearrangement in CNL. Additionally, we have discovered four previously unpublished *DCP1B* rearrangements in cancer through our search of the Cancer Genome Atlas (TCGA) database. We further discussed the crucial role of DCP1B, which is a critical enzyme involved in mRNA turnover, in oncogenesis.

A 69-year-old female patient presented with leukocytosis and no tumor history. A physical examination showed no signs of lymphadenopathy, hepatosplenomegaly, or bruising. Complete blood counts showed a white blood count of 61.17 $\times$ 10^9/L, a hemoglobin level of 116 g/L, a platelet count of 201 $\times$ 10^9/L, and differential counts of 90% neutrophils, 3% myelocytes and metamyelocytes, 5% lymphocytes, 2% monocytes, 0% eosinophils, and 0% basophils (Figure 1A).

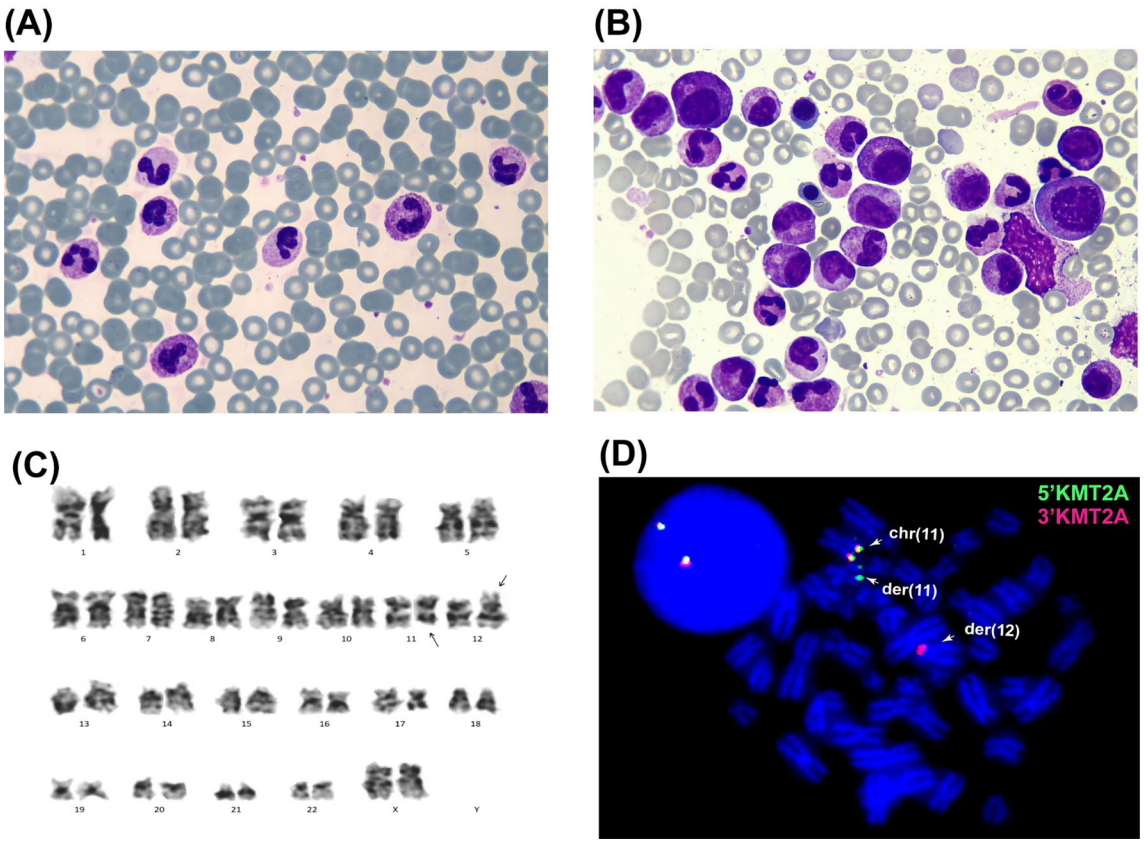

FIGURE 1 (A) Peripheral blood smear showed increased neutrophils with variable degrees of toxic granulation. (B) Bone marrow aspirate smear showed neutrophilic leukocytosis mainly consisting of myelocyte to segmented forms. (C) Karyotype analysis of bone marrow showed a t(11;12) as the sole change. (D) FISH on metaphase using a *KMT2A* split-apart probe revealed *KMT2A* rearrangement, with the *3′ KMT2A* translocated to chromosome 12p.

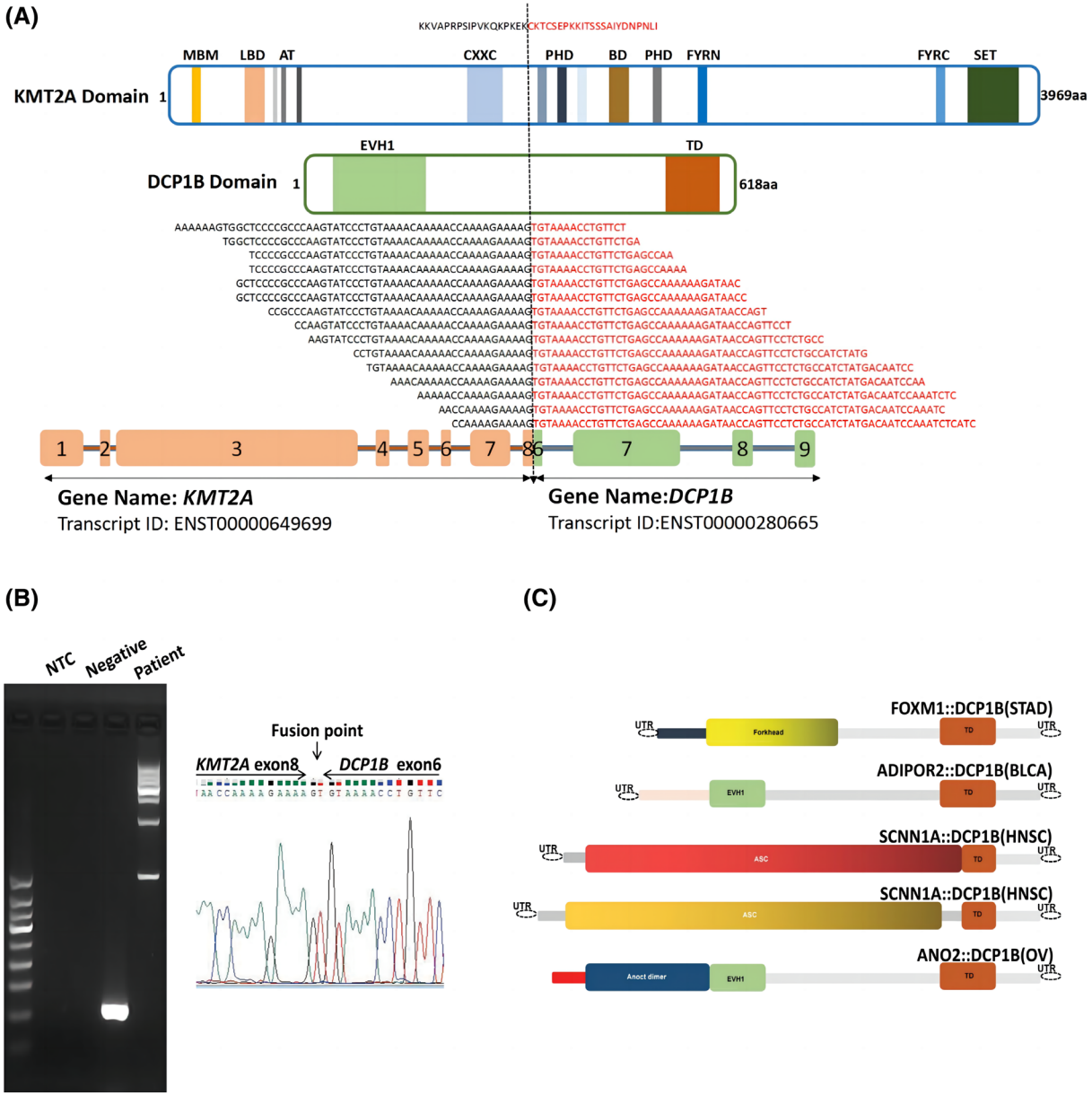

FIGURE 2 (A) The schematic of functional domains of KMT2A and DCP1B and their exon location. The breakpoints were marked by a vertical dotted line. (B) RT-PCR amplified a fusion product of the expected size with primers specific for *KMT2A* and *DCP1B*, while no products were obtained from a AML sample without t(11;12). Sanger sequencing of the PCR product confirmed a fusion between exon 8 of *KMT2A* and exon 6 of *DCP1B*. (C) The schematic of functional domains of 5 DCP1B-rearranged fusion proteins from 4 solid tumors. ADIPOR2, adiponectin receptor 2; ANO2, anoctamin 2; ASC, association with the SNF1 complex; AT, AT hooks; BD, bromo domain; BLCA, bladder urothelial carcinoma; BM, Menin-binding domain; CXXC, zinc finger-CxxC; EVH1, Enabled/VASP Homology-1; FOXM1, forkhead box protein M1; FYRC, FY-rich domain C-terminal; FYRN, FY-rich domain N-terminal; HNSC, head and neck squamous cell carcinoma; LBD, LEGDF binding domain; OV, ovarian serous cystadenocarcinoma; PHD, plant homeodomain; SCNN1A, α subunit of the epithelial sodium channel ENaC; SET, histone methyltransferase domain; STAD, stomach adenocarcinoma; TD, trimerization domain; UTR, untranslated region.

The bone marrow aspirate smear indicated that 85% of cells were myeloid elements, mainly comprising myelocyte to segmented forms. Neutrophils showed varying degrees of toxic granulation, but no signs of neutrophil dysplasia were observed (see Figure 1B). Furthermore, there was no evidence of blasts, erythroid dysplasia, or megakaryocytic dysplasia. A bone marrow biopsy showed a hypercellular marrow (>90% cellularity) with neutrophilic proliferation, normal myeloid maturation, and slightly increased erythroid and megakaryocytic elements with no dysplasia. Mild bone marrow fibrosis was noted in some areas (grade 1 according to European consensus). Flow cytometry of the bone marrow aspirates showed no significant immunophenotypic abnormalities. Cytogenetic analysis showed translocation of chromosomes 11 and 12 as the sole change, 46,XX,t(11;12)(q23; p13)[7]/46,XX [13] (Figure 1C). Fluorescence in situ hybridization (FISH)

using a *KMT2A* split-apart probe showed *KMT2A* rearrangement, with the 3′ *KMT2A* translocated to chromosome 12p (Figure 1D). The FISH assay showed 12.5% of interphase nuclei with the *KMT2A* rearrangement. Targeted DNA next-generation sequencing (NGS) showed *CSF3R c.1853 C>T* p. Thr618Ile (VAF 38.4%) and *SRSF2 c.281_283dupGCC* p. Arg94dup (44.3%). The gene copy number evaluation revealed a balanced genome, consistent with the karyotype results. Based on the defining *CSF3R* mutation and the classic morphologic features, the diagnosis of CNL was made. The patient has been treated with hydroxyurea and remains in stable condition.

To identify the fusion partner of *KMT2A*, we performed targeted RNA NGS, which revealed a fusion transcript of *KMT2A*::*DCP1B*. The first eight exons (exons 1–8) of *KMT2A* were fused to the final three exons (exons 6–9) of *DCP1B* (Figure 2A). An RT-PCR assay was performed with primers specific for *KMT2A* (F_*KMT2A* E8:5′-TCCAGAGCAGAGCAAACAGA) and *DCP1B* (*R_DCP1B* E6: 5′-AGATGGCAGAGGAACTGGTT), which obtained a PCR product at the expected size. Sanger sequencing confirmed the *KMT2A*::*DCP1B* fusion (Figure 2B). The predicted fusion protein comprises the menin-binding domain (MBM), the LEGDF binding domain (LBD), and the zinc finger-CxxC (CXXC) domain of the KMT2A protein, as well as the trimerization domain (TD) of the DCP1B (Figure 2A).

We searched the TCGA database to investigate *DCP1B* rearrangement in other tumors and identified four additional *DCP1B* fusions with intact reading frames that have not been previously reported. These include (1) a *SCNN1A*::*DCP1B* fusion in a 75-year-old male with squamous cell carcinoma of the tongue, which comprises the association with the SNF1 complex (ASC) domain of SCNN1A (α subunit of the epithelial sodium channel ENaC) and partial TD domain of DCP1B. Two fusion transcripts were identified, which are likely products of differential splicing; (2) an *ADIPOR2*::*DCP1B* fusion in a 71-year-old male with transitional cell carcinoma of the bladder, which comprises the Enabled/VASP Homology-1 (EVH1) domain of ADIPOR2 (Adiponectin Receptor 2) and the TD domain of DCP1B; (3) a *FOXM1*::*DCP1B* fusion in a 57-year-old female with gastric adenocarcinoma, which comprises the Forkhead domain of FOXM1 (Forkhead box protein M1) and TD domain of DCP1B; and (4) an *ANO2*::*DCP1B* fusion in a 45-year-old female with serous ovarian cancer, which comprises Anoct dimer domain and EVH1 domain of ANO2 (Anoctamin 2) and TD domain of DCP1B. Figure 2C shows the schematic of the DCP1B fusion proteins.

KMT2A is an essential histone methyltransferase that regulates gene expression, DNA damage response, and hematopoietic stem cell (HSC) differentiation.[1] The SET domain of the KMT2A is responsible for chromatin modifications associated with epigenetic transcriptional activation, including genes critical for normal development, such as Hox genes.[2] KMT2A is involved in recruiting DNA repair factors, including ATM, ATR, and BRAC1, to DNA damage sites, and regulating gene expression in response to DNA damage.[3] Cells with impaired KMT2A function have reduced DNA damage response and increased susceptibility to DNA damage-induced cell death.[4] KMT2A regulates HSC self-renewal and differentiation, and its loss results in reduced production of various blood cell types. Conversely, overexpression of KMT2A can lead to an HSC population expansion.[5] *KMT2A* is frequently rearranged in leukemia, with more than 100 different partner genes identified. The specific partner gene involved in a given *KMT2A* rearrangement can have important implications for the clinical outcome of the associated leukemia, as well as for the underlying molecular mechanisms of the disease.[6,7] *DCP1B* is the latest member of the *KMT2A* fusion partner family. DCP1 is a de-capping enzyme that removes the 5′ m(7)G cap from mRNA and plays a critical role in mRNA decay in eukaryotic cells.[8] DCP1A and DCP1B are two closely related isoforms that likely function redundantly.[8] DCP1A has been observed to be overexpressed in several types of cancer, including colorectal cancer, gastric cancer, melanoma, and hepatocellular carcinoma. In some cases, high levels of DCP1A have been associated with poor prognosis and reduced survival.[9]

KMT2A::DCP1B and other DCP1B fusion proteins as shown in Figure 2C contain the TD of DCP1B, which mediates interactions between three DCP1B molecules and is also responsible for the proper assembly of the proteasome.[8] The oncogenic mechanism of KMT2A::DCP1B is yet to be established, but it may affect mRNA metabolism of critical oncogenes or tumor suppressors by interacting with the wild-type DCP1B via the TD domain.[10] Alternatively, KMT2A::DCP1B could affect KMT2A-related cellular functions by binding to other proteins. Although *ASXL1*, *TET2*, and *DNMT3A*, which are involved in epigenetic regulation, are mutated in CNL, this is the first reported case of *KMT2A* rearrangement in CNL. Because the *KMT2A* rearrangement was detected in only 12.5% of cells, whereas the VAF of *CSF3R c.1853 C>T* p.Thr618Ile was 38.4% in the same specimen, it is likely that the *KMT2A* rearrangement is present in a subclone and represents a later event during disease progression. Consequently, even though the 5th edition of the WHO classification of hematolymphoid tumors suggests diagnosing AML with a *KMT2A* rearrangement without requiring 20% or more blasts, we do not classify this as AML. Instead, it is more appropriately categorized as a CNL with a *KMT2A* rearrangement. The actual effect of *KMT2A*::*DCP1B* on disease progression is currently unknown. The prognosis of *KMT2A*-rearranged leukemia is generally poor, but that target the KMT2A-menin interaction have shown promising effects in treating patients.[11]

In summary, we present the first documented *KMT2A* rearrangement in CNL and first documented *DCP1B* rearrangements in tumor. Recurrent *DCP1B* involvement in a variety of tumors may help understand its role in tumorigenesis and serve as a potential biomarker for future therapeutic targets.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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