Novel tripartite *CPSF7*::*RARG*::*CPSF7* fusion confers primary ATRA resistance in atypical acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia characterized by pathognomonic morphological features and a rapidly progressive, fatal natural course. In classical APL, defined by the *PML*::*RARA* fusion gene, excellent outcomes have been achieved with all-*trans* retinoic acid (ATRA) and arsenic trioxide treatment. In contrast, a small subset of patients present with an APL phenotype driven by individually rare and diverse retinoic acid receptor (*RAR*) rearrangements involving *RARA, RARB*, and *RARG*.[1-7] These cases have been previously described as "APL-like acute myeloid leukemia with non-*PML*::*RARA* (atypical) translocations"; we will refer to this entity as "atypical APL (aAPL)" given their shared *RAR*-related biology. To date, eight 5′ fusion partners for *RARG* have been identified, with *CPSF6* being the most frequent (16 reported cases).[5,6,8-13] Notably, recent evidence suggests that all *RARG* fusions may exist as previously overlooked tripartite fusions (*X*::*RARG*::*X/Y*) rather than conventional bipartite fusions (*X*::*RARG*).[5,13] In these cases, *RARG* 3′ splicing-mediated truncation of the ligand-binding domain (LBD) confers complete resistance to ATRA. Here, we report the first case of a novel tripartite *CPSF7*::*RARG*::*CPSF7* fusion, expanding the known spectrum of *RAR* fusion partners and reinforcing the paradigm of tripartite structures in *RARG* fusion-positive aAPL (*RARG*-aAPL). This study was approved by the Ethics Committee of Hebei Yanda Lu Daopei Hospital.

A 42-year-old male was admitted with a 1-month history of gingival bleeding, cutaneous hemorrhage, and significant weight loss. Initial laboratory evaluation revealed leukocytosis (white blood cell count, 45.7×10^9/L), anemia (hemoglobin, 65.0 g/L), and thrombocytopenia (platelet count, 91.0×10^9/L). Coagulation profiles showed a prolonged prothrombin time of 15.0 s (reference, 9.4-12.5 s), a normal activated partial thromboplastin time of 29.4 s (25.1-36.5 s), a decreased fibrinogen level of 1.6 g/L (2.0-4.0 g/L), and a markedly elevated D-dimer level of 16.2 mg/L (0-0.2 mg/L), consistent with coagulopathy and disseminated intravascular coagulation. Peripheral blood and bone marrow smears showed hypercellularity with abnormal promyelocytes (72% and 91.5%, respectively) characterized by coarse granules (Figure 1A) and intense myeloperoxidase positivity (Figure 1B), morphologically suggestive of classical APL. Flow cytometric analysis identified an abnormal promyelocytic population (90.3% of nucleated cells) that was positive for CD13, CD33, CD64, CD123, and myeloperoxidase, with partial expression of CD56 and CD117, but negative for CD3, CD7, CD11b, CD14, CD34, CD38, and HLA-DR. Cytogenetic analysis showed a normal karyotype, and screening for *PML*::*RARA* (via fluorescence *in situ* hybridization and reverse transcription polymerase chain reaction) and 35 other common leukemia fusion genes (full panel in *Online Supplementary Table S1*) was negative.

Initial treatment with ATRA and hydroxyurea was promptly initiated but failed to achieve cytoreduction (Figure 1C). Upon transfer to our center, the patient exhibited worsening hematologic parameters and progressive coagulopathy, with a prothrombin time of 15.4 s, an activated partial thromboplastin time of 29.5 s, a further decrease in fibrinogen of 1.2 g/L, and a further elevation of D-dimer level to 37.8 mg/L. Subsequent regimens, including an idarubicin and cytarabine-based 3+7 regimen combined with venetoclax, as well as azacitidine/lisaftoclax/ATRA, failed to control the disease (Figure 1C). Bone marrow morphology and immunophenotyping confirmed persistent disease, with abnormal promyelocytes accounting for 78.0% and 82.1% of nucleated cells, respectively.

Whole-transcriptome sequencing of the diagnostic bone marrow sample demonstrated a gene-expression profile that clustered closely with a consecutive cohort of canonical *PML*::*RARA*-APL cases,[14] while remaining significantly distinct from other subtypes of acute myeloid leukemia and healthy controls (Figure 2A). Mutational analysis identified a somatic *ARID2* c.3563G>A/p.S1188N mutation with a variant allele frequency of 72.4 % (Figure 2B). Fusion gene analysis identified a tripartite *CPSF7* (exon 1_7)::*RARG* (exon 4_9)::*CPSF7* (exon 10@c.*1143) fusion (Figure 2C, *Online Supplementary Figure S1A, B*). Whole-genome sequencing confirmed the genomic breakpoints between *CPSF7* intron 7 and *RARG* intron 3 (*Online Supplementary Figure S1C*), and between *RARG* intron 9 and *CPSF7* exon 10 (*Online Supplementary Figure S1D*).

The treatment was modified to a combination of homoharringtonine, chidamide, selinexor, and gemtuzumab ozogamicin. Following 10 days of therapy, bone marrow promyelocytes decreased to 2.5%, and the patient achieved complete remission by day 24. He subsequently underwent haploidentical allogeneic hematopoietic stem cell transplantation with his daughter as the donor and remains in complete remission at the 3-month follow-up (Figure 1C).

Unlike previously reported tripartite *RARG* fusions that splice in-frame with 3′ coding sequences or transposons,[5,13] this case involves the 3′ untranslated region of *CPSF7*. Genomic rearrangement generated a *de novo* branch site (A) and splice acceptor (AG) within *CPSF7* exon 10, utilizing

its polyadenylation signal (Figure 3A). This fusion truncates the *RARG*-LBD helices 11_12 (H11_12), a region essential for ligand-induced activation (Figure 3B), and introduces a novel C-terminal tail derived from the 3′ untranslated region. These findings define a previously uncharacterized mechanism of *RARG* 3′ fusion.

Cellular reporter assays confirmed that while a simulated bipartite CPSF7::RARG retained dose-dependent ATRA responsiveness (consistent with the wild-type RARG baseline), the patient-specific tripartite CPSF7::RARG::CPSF7 and the CPSF7::RARG-H11_12del mutant were entirely unresponsive to ATRA (Figure 3C). Notably, although the histone deacetylase 3 inhibitor chidamide markedly enhanced ATRA sensitivity in the bipartite CPSF7::RARG model – mirroring its effect on wild-type RARG – it completely failed to rescue transcriptional activity in the tripartite fusion and the H11_12del mutant models.

CPSF6 and its paralog CPSF7 are core subunits of the cleavage factor Im (CFIm) complex, which is essential for mRNA 3′ end processing.[15] They contribute to CFIm complex assembly by forming CPSF6 homodimers, CPSF7 homodimers, or CPSF6/CPSF7 heterodimers. Although *CPSF6* is established as the most frequent fusion partner for *RARG*, no rearrangements involving *CPSF6* with *RARA* or *RARB* have been reported to date. This patient represents the first reported case of a fusion between the *CPSF7* and *RAR* genes.

The CPSF7 moiety within the fusion protein mirrors CPSF6 by retaining the N-terminal RNA recognition motif (RRM) while lacking the C-terminal arginine/serine-like domain (RSLD). The RRM module is required for RNA binding, CFIm complex assembly, and mRNA looping, whereas the RSLD of CPSF6 is essential for alternative polyadenylation and assembly of the mRNA 3′ end processing machinery.[15] Structurally, the tripartite fusion protein might be erroneously recruited to RNA processing hubs via the truncated CPSF7 component or, conversely, mislocalize CFIm factors to DNA promoter regions through the RARG DNA-binding domain. This resulting “transcriptional and processing traffic jam” could interfere with regulation of the length of the 3′ untranslated region of target genes, potentially driving aAPL

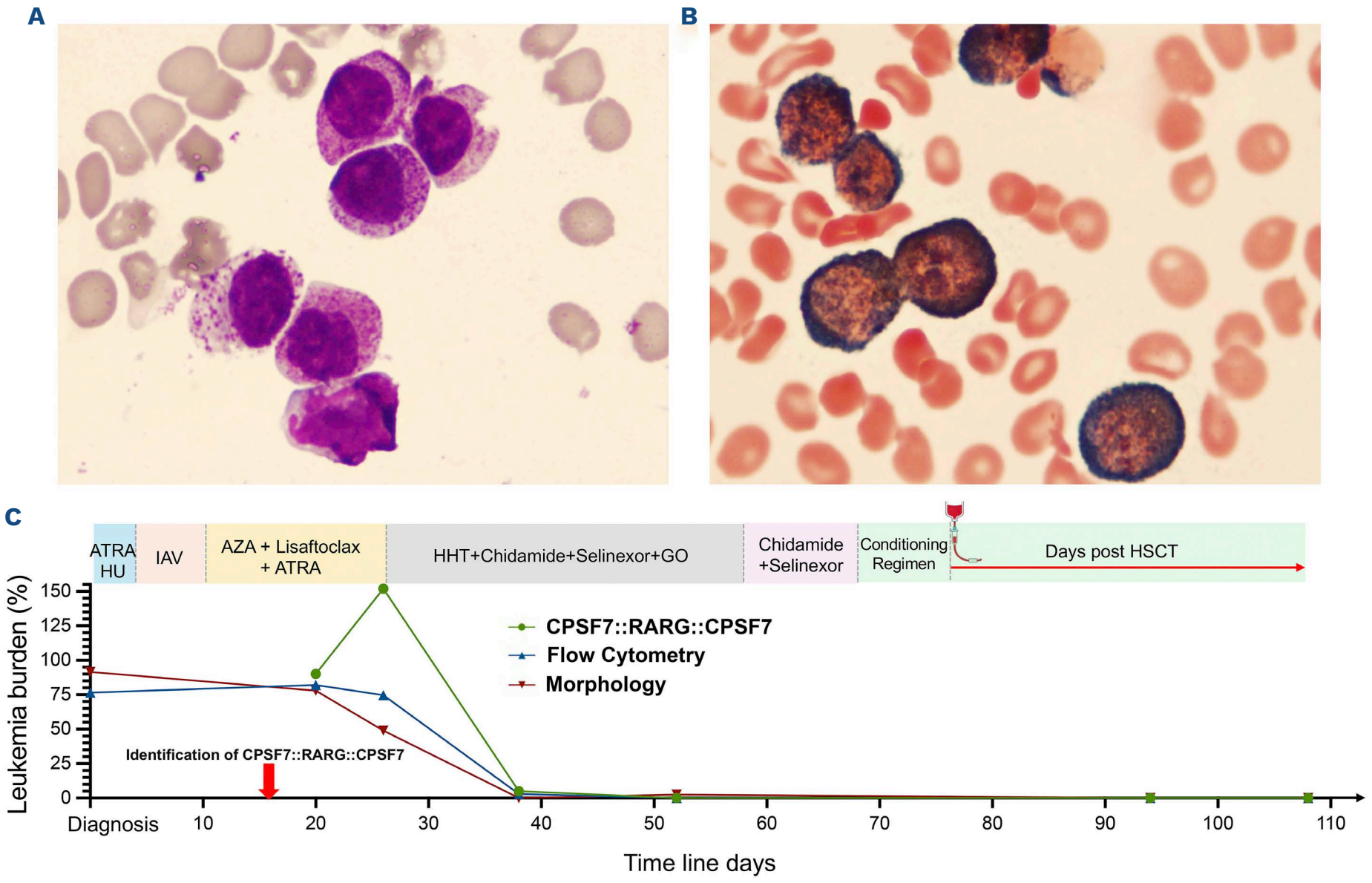


Figure 1. Morphological findings of the patient. (A) Wright staining of the peripheral blood smear at diagnosis showing aberrant promyelocytes with coarse azurophilic granules (original magnification, ×1,000). (B) Myeloperoxidase staining of the peripheral blood smear demonstrating strong positivity in abnormal promyelocytes (original magnification, ×1,000). (C) Timeline of the clinical course and treatment response of the patient. ATRA: all-*trans* retinoic acid; AZA: azacitidine; GO: gemtuzumab ozogamicin; HHT: homoharringtonine; HSCT: hematopoietic stem cell transplantation; HU: hydroxyurea; IAV: idarubicin, cytarabine, and venetoclax; VEN: venetoclax.

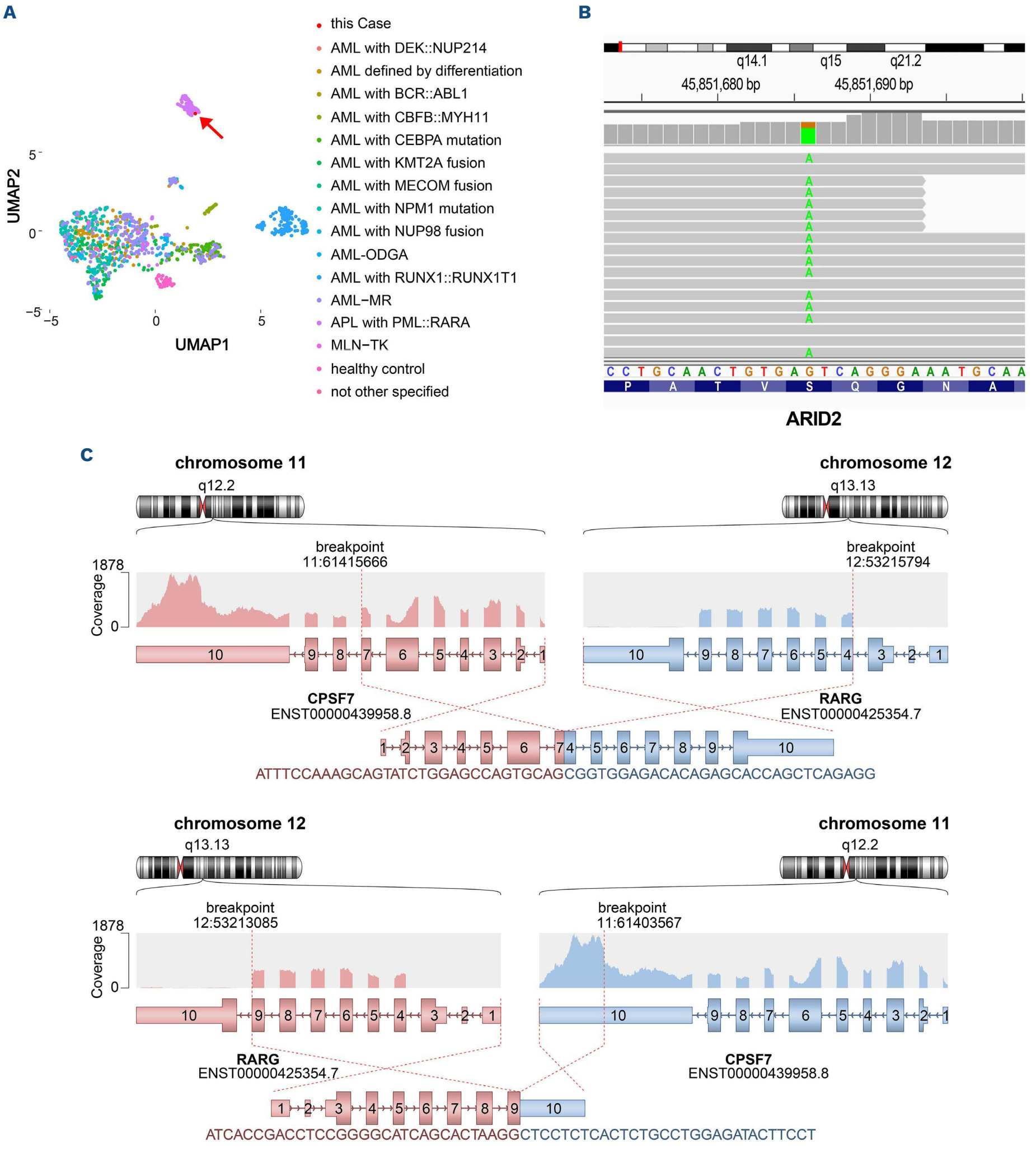


Figure 2. Molecular identification of the patient. (A) Uniform manifold approximation and projection clustering of gene expression profiles. The patient's transcriptomic profile clustered closely with canonical *PML*::*RARA* fusion-positive acute promyelocytic leukemia, while it was significantly distinct from that of other subtypes of acute myeloid leukemia and healthy controls. (B) Integrated Genomic Viewer view of the *ARID2* NM_152641.4:c.3563G>A/p.S1188N mutation detected in whole-transcriptome sequencing. (C) Structural schematic of *CPSF7* exon 7::*RARG* exon 4 (top panel) and *RARG* exon 9::*CPSF7* exon 10@c.*1143 splicing (bottom panel) as analyzed by Arriba v2.5.1 software. AML: acute myeloid leukemia; AML-ODGA: acute myeloid leukemia with other defined genetic alterations; AML-MR: acute myeloid leukemia with myelodysplasia-related changes; APL: acute promyelocytic leukemia; MLN-TK: myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; UMAP: uniform manifold approximation and projection.

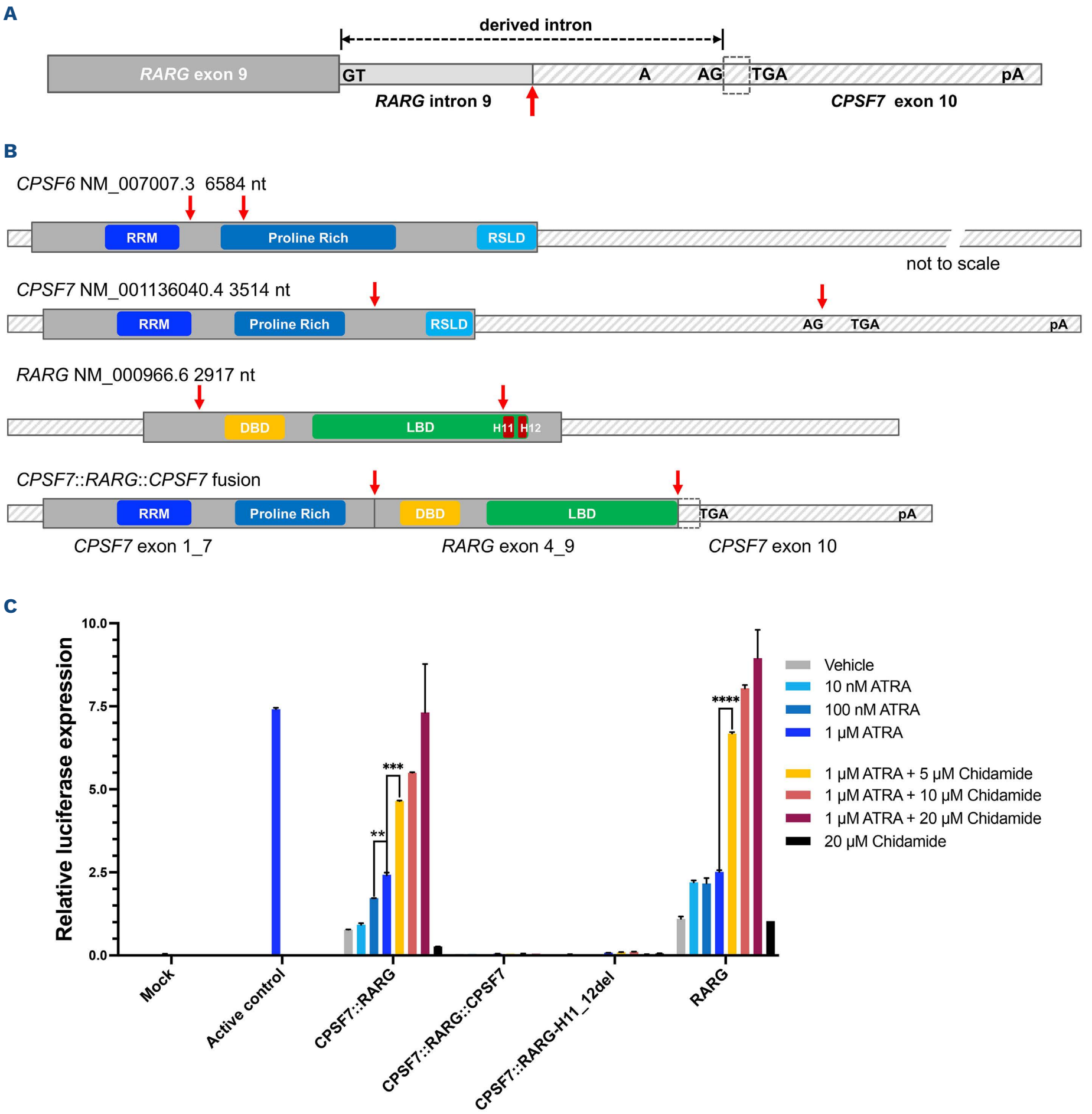


Figure 3. Fusion protein and cellular assay analysis. (A) Analysis of derived mRNA splice sites and fusion transcripts formed between *RARG* and the 3′ untranslated region of *CPSF7*. (B) Schematic diagram of *CPSF6, CPSF7, RARG*, and fusion transcripts. Red arrows indicate the breakpoints and splicing junctions at the genomic level during fusion transcript formation. (C) Responsiveness to all-*trans* retinoic acid (ATRA) was assessed using a modified GAL4-UAS luciferase reporter assay in 293T cells. Constructs encoding the bipartite CPSF7::RARG (with intact ligand-binding domain), the tripartite CPSF7::RARG::CPSF7, and the CPSF7::RARG-H11_12del mutant were cloned into the pBIND vector containing *Renilla* luciferase. CPSF7::RARG exhibited dose-dependent responsiveness to ATRA, similar to wild-type RARG (positive control). In contrast, the tripartite fusion and the H11_12del mutant showed no response. Chidamide significantly enhanced ATRA sensitivity in the bipartite CPSF7::RARG model (similar to its synergistic effect on wild-type RARG) but failed to rescue transcriptional activity in the tripartite fusion and the H11_12del mutant. Data are mean ± standard deviation of three biological replicates. The Welch *t* test was used for pairwise comparisons between groups (**P<0.01, ***P<0.001, ****P<0.0001). A representative experiment out of three with similar results is displayed. ATRA: all-*trans* retinoic acid; DBD: DNA-binding domain; LBD: ligand-binding domain; RRM: RNA recognition motif; RSLD: arginine/serine-like domain; UTR: untranslated region.

pathogenesis, a hypothesis warranting further investigation.

Consistent with all previously identified tripartite *RARG* fusions, the 3′ splicing of *RARG* led to the loss of exon 10 and the encoded LBD-H11_12, providing the molecular basis for ATRA resistance. Consequently, all patients carrying *RARG* fusions exhibit primary resistance to ATRA therapy, as exemplified by the case reported in this study. Our dual-luciferase reporter assays confirmed that, while a simulated bipartite *CPSF7*::*RARG* fusion retained ATRA sensitivity, the patient-specific tripartite *CPSF7*::*RARG*::*CPSF7* fusion was almost entirely non-responsive.

The leukemic cells in this case exhibited morphology and immunophenotype largely consistent with classical APL, except for CD38 negativity. This finding further supports that CD38 is consistently absent in cases with *RARG* rearrangement, distinguishing this ATRA-resistant subtype from classical APL.[6]

Our patient harbored a somatic *ARID2* mutation. Given that *ARID2* is a fundamental component of the SWI/SNF complex required for nuclear receptor-mediated transcriptional activation, its disruption, alongside the loss-of-function *ARID1A/B* mutations previously reported by our group,[3,7] underscores that chromatin-remodeling dysregulation is likely a recurrently involved pathway in the pathogenesis of aAPL.

Clinical management was challenging due to the patient's primary resistance to ATRA and multiple chemotherapeutic agents. Complete remission was ultimately achieved through a combination of homoharringtonine, chidamide, selinexor, and an anti-CD33 monoclonal antibody. Selinexor was administered off-label under compassionate use, while chidamide was included based on prior *in vitro* evidence suggesting that histone deacetylase 3 inhibitors could rescue dysregulated hematopoiesis in bipartite *CPSF6*::*RARG* fusions,[8] despite its unclear efficacy in tripartite configurations.

Our functional analyses demonstrated that chidamide failed to restore transcriptional activity of the tripartite *CPSF7*::*RARG*::*CPSF7* fusion, while enhancing ATRA responsiveness in the bipartite *CPSF7*::*RARG* fusion (Figure 3C). Consequently, patients harboring tripartite *RARG* fusions, characterized by LBD-H11_12 deletion, are unlikely to benefit from therapy based on histone deacetylase 3 inhibition.

In a collaborative study of *RARG*-aAPL clinical management, seven of eight patients achieved complete remission using homoharringtonine-based regimens, underscoring the therapeutic potential of homoharringtonine.[6] Consistently, recent *in vitro* studies have demonstrated the efficacy of homoharringtonine in mitigating *CPSF6*::*RARG*-driven dysregulated hematopoiesis.[9] While gemtuzumab ozogamicin, an anti-CD33 antibody-drug conjugate, is increasingly utilized in high-risk *PML*::*RARA*-APL as a substitute for conventional chemotherapy,[2] its application in aAPL has not been reported. In the present case, complete remission was achieved with a quadruple regimen comprising homoharringtonine, gemtuzumab ozogamicin, chidamide, and selinexor after failure of multiple prior therapies. Given the complexity of this regimen, the individual contributions of each agent cannot be delineated, and further investigation is warranted.

In summary, we characterized the first case of aAPL harboring a tripartite *CPSF7*::*RARG*::*CPSF7* fusion. This case expands the repertoire of *RAR* fusion partners and reinforces the recurrence and structural consistency of tripartite *RARG* fusions via a novel 3′ splicing mode. Despite multidrug resistance, the patient achieved complete remission through combined targeted and salvage therapy, followed by successful allogeneic hematopoietic stem cell transplantation. The rapid diagnosis and effective management of *RARG*-aAPL remain formidable challenges that necessitate continued exploration of its unique molecular landscape.

Authors

Xiaosu Zhou,[1*] Zhanglin Zhang,[2*] Fang Xu,[3*] Mei Jiang,[4] Yang Zhang,[1,5] Panxiang Cao,[5] Jiancheng Fang,[5] Xiaoli Ma,[5] Fang Wang,[5] Jiaqi Chen,[1,5] Xue Chen,[1,5] Ping Wu,[5] Tong Wang,[5] Yue Lu[3#] and Hongxing Liu[1,5,6#]

[1]Precision Medicine Center, Beijing Lu Daopei Institute of Hematology, Beijing; [2]Department of Blood Transfusion, The First Affiliated Hospital of Nanchang University, Nanchang; [3]Department of Transplantation, Hebei Yanda Lu Daopei Hospital, Langfang; [4]Department of Clinical Laboratory, the First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang; [5]Division of Pathology & Laboratory Medicine, Hebei Yanda Lu Daopei Hospital, Langfang and [6]Division of Pathology & Laboratory Medicine, Beijing Lu Daopei Hospital, Beijing, China

*XZ, ZZ, and FX contributed equally as first authors.

Correspondence:
H. LIU - starliu@pku.edu.cn
Y. LU - dpluyue@sina.com

https://doi.org/10.3324/haematol.2026.300904

Received: March 15, 2026.
Accepted: May 18, 2026.
Early view: May 28, 2026.

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

Disclosures

No conflicts of interest to disclose.

Contributions

HL, ZZ and XZ designed the experiments, supervised the study and analysis, and wrote the manuscript. FX and YL collected

clinical data. MJ, YZ, XM, FW, JC, XC, PW, and TW performed and analyzed the experiments. PC and JF analyzed the bioinformatics data. All authors discussed the results and implications of the manuscript.

Acknowledgments

The authors thank Siyuan Liu for his help in bioinformatic analysis and valuable discussions.

Funding

This work was supported by the Natural Science Foundation of China (82570228) and the Hebei Provincial Medical Science Research Project (20261157).

Data-sharing statement

Original data can be made available on reasonable request by contacting starliu@pku.edu.cn.

References

1. Rérolle D, Wu HC, de Thé H. Acute promyelocytic leukemia, retinoic acid, and arsenic: a tale of dualities. Cold Spring Harb Perspect Med. 2024;14(9):a041582.
2. Benitez LL, Marx KR, Rausch CR, et al. Multicenter retrospective evaluation of treatment for high-risk acute promyelocytic leukemia: real-world outcomes from the HERO Consortium. Am J Hematol. 2025;100(6):1094-1097.
3. Zhou X, Chen J, Tang YL, et al. Epidemiology, clinical features, and molecular basis of TTMV::RARA-driven acute promyelocytic leukemia. Blood. 2025;146(18):2229-2243.
4. Chen X, Wang F, Zhou X, et al. Torque teno mini virus driven childhood acute promyelocytic leukemia: the third case report and sequence analysis. Front Oncol. 2022;12:1074913.
5. Zhou X, Chen X, Chen J, et al. Critical role of tripartite fusion and LBD truncation in certain RARA- and all RARG-related atypical APL. Blood. 2024;114(14):1471-1485.
6. Zhu HH, Qin YZ, Zhang ZL, et al. A global study for acute myeloid leukemia with RARG rearrangement. Blood Adv. 2023;7(13):2972-2982.
7. Zhou X, Mu Q, Chen H, et al. Torque teno virus drives atypical acute promyelocytic leukemia as a novel molecular subtype. Am J Hematol. 2026;101(5):1084-1090.
8. Liu T, Wang T, Qi L, et al. CPSF6-RARγ interacts with histone deacetylase 3 to promote myeloid transformation in RARG-fusion acute myeloid leukemia. Nat Commun. 2025;16(1):616.
9. Wang F, Zhao L, Tan Y, et al. Oncogenic role of RARG rearrangements in acute myeloid leukemia resembling acute promyelocytic leukemia. Nat Commun. 2025;16(1):617.
10. Liu T, Wen L, Yuan H, et al. Identification of novel recurrent CPSF6-RARG fusions in acute myeloid leukemia resembling acute promyelocytic leukemia. Blood. 2018;131(16):1870-1873.
11. Han X, Jin C, Zheng G, et al. Acute myeloid leukemia with CPSF6-RARG fusion resembling acute promyelocytic leukemia with extramedullary infiltration. Ther Adv Hematol. 2021;12:2040620720976984.
12. Zhang Z, Jiang M, Borthakur G, et al. Acute myeloid leukemia with a novel CPSF6-RARG variant is sensitive to homoharringtonine and cytarabine chemotherapy. Am J Hematol. 2020;95(2):E48-E51.
13. Wu S, Yu Y, Lin X, et al. Atypical acute promyelocytic leukemia with tripartite fusion gene PML::RARG::LINE-L2a is resistant to ATRA but sensitive to arsenic-based therapy. Haematologica. 2025;110(12):3083-3087.
14. Chen X, Yuan L, Zhang Y, et al. Advances towards genome-based acute myeloid leukemia classification: a comparative analysis of WHO-HAEM4R, WHO-HAEM5, and International Consensus Classification. Am J Hematol. 2024;99(5):824-835.
15. Liu S, Wu R, Chen L, et al. CPSF6 regulates alternative polyadenylation and proliferation of cancer cells through phase separation. Cell Rep. 2023;42(10):113197.