Received: 22 November 2021 | Revised: 27 April 2022 | Accepted: 28 April 2022

DOI: 10.1002/gcc.23051

BRIEF REPORT

WILEY

A novel *HNRNPH1::ERG* rearrangement in aggressive acute myeloid leukemia

Feiling Jiang[1] | Xingping Lang[2] | Nan Chen[2] | Liqin Jin[2] | Lingfeng Liu[2] | Xiaobin Wei[1] | Jianhua Pan[1] | Feng Yu[3] | Angella Blake[4] | Sheng Xiao[4]

[1]Clinical Laboratory of Medicine, Affiliated Haikou Hospital of Xiangya Medical College, Central South University, Haikou, Hainan, China

[2]Suzhou Sano Precision Medicine Ltd, Suzhou, China

[3]Department of Hematology, Affiliated Haikou Hospital of Xiangya Medical College, Central South University, Haikou, China

[4]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence
Sheng Xiao, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.
Email: sxiao@partners.org

Abstract

FUS::ERG rearrangement is a recurrent abnormality seen in a subgroup of acute myeloid leukemia (AML) with a poor prognosis. We described here a novel *HNRNPH1::ERG* rearrangement in a de novo AML. The patient was unresponsive to routine chemotherapy and succumbed to the disease just 3 months after diagnosis. Two additional cases of AML with *HNRNPH1::ERG* rearrangement were discovered by searching a publicly available sequencing database. The three patients share several clinical phenotypes with the *FUS::ERG* rearranged AML, including high blast count at diagnosis, pediatric or young adult-onset, and poor overall survival. In addition, hnRNPH1 and FUS are both hnRNP family members, a group of RNA-binding proteins functioning in RNA metabolism and transport. Therefore, we suggest that patients with *HNRNPH1::ERG* or *FUS::ERG* rearrangement belong to the same distinct clinicopathologic subtype of AML, that is, AML with *ERG* rearrangement. Based on a previous study showing that *FUS::ERG* binds to the retinoic acid-responsive elements and that all-*trans* retinoic acid-induced cell differentiation of AML cells, we support the clinical evaluation of an APL-like therapeutic regimen for AML with *ERG* rearrangement.

KEYWORDS
AML, *ERG*, *HNRNPH1*

1 | INTRODUCTION

Acute myeloid leukemia (AML) represents a group of heterogeneous diseases that currently consist of 11 unique subtypes based on their mutation profiles.[1] Because genomic profiles determine clinical management, both cytogenetic and molecular testing is required for a newly diagnosed AML. AML subtypes known to poorly respond to the routine 7 + 3 chemotherapy regimen are recommended for upfront clinical trials. A subgroup of AML is defined by gene rearrangement between ERG (ETS-related gene) and FUS (fused in sarcoma). ERG belongs to the E26 transformation-specific (ETS) transcription factors, a large family characterized by a unique DNA binding domain (the ETS domain) that specifically binds to a ~10 bp long DNA sequence containing GGAAG core motif.[2] ERG plays a major role in the embryonic development of the vascular system, urogenital tract, and bones, along with involvement in hematopoiesis. In murine models, loss of ERG led to decreased megakaryocytic progenitors and hematopoietic stem and progenitor cells.[3] ERG is rearranged in several types of tumors, including prostate cancer, Ewing sarcoma, acute lymphoblastic leukemia (ALL), and AML. Approximately 80 cases of AML with FUS::ERG rearrangement have been described.[4] The FUS::ERG oncoprotein retained the ETS domain of ERG and, not surprisingly, bound to DNA fragments containing GGAAG in a genome-wide evaluation by CHIP-seq.[5] The occupancy of FUS::ERG in ETS-binding sites prevents the access of the wild-type ETS transcription factors, some of which are major regulators in cell differentiation, cell proliferation, angiogenesis, and apoptosis, thus leading to the deregulation of a wide range of cellular processes.[5]

Feiling Jiang and Xingping Lang contributed equally to this study.

We describe here three cases of AML with HNRNPH1::ERG rearrangement, including our patient and two additional cases from a publicly available sequencing database from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative AML study (TARGET-AML; https://target-data.nci.nih.gov/Public/AML).[6,7] The hnRNPH1::ERG protein shares the same ETS DNA binding domain as the FUS::ERG and therefore likely functions similarly, that is, as a transcriptional repressor by competing for GGAAG binding.

2 | MATERIALS AND METHODS

2.1 | Cytochemistry

Bone marrow aspirate was smeared, air-dried, and then treated to cytochemical staining. For the POX stain, slides were covered with eosin before adding azure stain (eosin stain: azure stain = 1; 1) for 30 s and then rinsed and blot dried before adding a mixture of potassium iodide dye solution with 400 μl Rigi's solution for 60 s. For the alpha-naphthyl acetate esterase (ANAE) stain, slides were fixed in formaldehyde for 3 min, stained in α-naphthol acetate solution at 37°C for 60 min, and restained with hematoxylin dye solution for 3 min. For the CE stain, slides were fixed in formaldehyde for 3 min, rinsed and blot dried, and stained with chloroacetic acid AS-D naphthol esterase staining solution for 20 min.

2.2 | Targeted DNA next-generation sequencing

Bone marrow was used for DNA isolation with QIAamp DNA Blood Mini Kits (Qiagen). DNA was fragmented with a Bioruptor Pico (Diagenode) to 300–500 bp, subjected to end-polishing, phosphorylation, and dA extension by incubating with the end-repair mix, Klenow exo- and Taq polymerase (Enzymatics) for 15 min at 12°C, 15 min at 37°C, and 15 min at 72°C, and ligated to a UMI containing adaptor. Seven cycles of PCR were performed with adaptor-specific primers and the PCR products were incubated with a pool of biotin-labeled bait oligos that targeted 129 genes commonly involved in leukemia for 16 h. Targeted regions were enriched by pull-down with streptavidin beads, amplified by PCR, and sequenced in an Illumina NovaSeq sequencer. Sequencing results for single-nucleotide variations, insertion/deletion, copy number variations (CNVs), and structure variations were analyzed with SeqNext software (JSI) and laboratory-developed pipelines (Sano Medical Laboratories). The list of targeted genes included *ABL1*, *ANKRD26*, *ASXL1*, *ATM*, *ATRX*, *B2M*, *BCL11B*, *BCL9*, *BCOR*, *BCORL1*, *BIRC3*, *BRAF*, *BTK*, *CALR*, *CARD11*, *CBL*, *CBLB*, *CCND1*, *CCND3*, *CD33*, *CD79B*, *CDKN1B*, *CDKN2A*, *CDKN2B*, *CEBPA*, *CKS1B*, *CNOT3*, *CREBBP*, *CRLF2*, *CSF1R*, *CSF3R*, *CUX1*, *CXCR4*, *DDX41*, *DHX15*, *DIS3*, *DLEU2*, *DNMT3A*, *DNMT3B*, *EGFR*, *EGR1*, *EP300*, *ERG*, *ETV6*, *EZH2*, *FAM46C*, *TENT5C*, *FANCA*, *FBXW7*, *FLT3*, *GATA1*, *GATA2*, *GNAS*, *GNB1*, *HLA-A*, *HRAS*, *ID3*, *IDH1*, *IDH2*, *IKZF1*, *IL7R*, *IRF4*, *JAK1*, *JAK2*, *JAK3*, *KDM6A*, *KIT*, *KLF2*, *KRAS*, *MAP2K1*, *MAX*, *MEF2B*, *KMT2A(MLL)*, *MPL*, *MYC*, *MYD88*, *NCAM2*, *NOTCH1*, *NOTCH2*, *NOTCH3*, *NPM1*, *NRAS*, *NT5C2*, *PAX5*, *PDGFRA*, *PHF6*, *PIK3CA*, *PIM1*, *PLCG2*, *PPM1D*, *PRPF40B*, *PTEN*, *PTPN11*, *RAD21*, *RBPJ*, *RET*, *RHOA*, *RPL10*, *RPS14*, *RUNX1*, *SETBP1*, *SETD2*, *SF1*, *SF3B1*, *SH2B3*, *SMC1A*, *SMC3*, *SRP72*, *SRSF2*, *SRSF6*, *STAG2*, *STAT3*, *STAT5B*, *TERC*, *TERT*, *TET2*, *TLE1*, *TLR2*, *TMEM14B*, *TNFAIP3*, *TP53*, *TRAF3*, *U2AF1*, *USP25*, *UTRN*, *WHSC1*, *WT1*, *XPO1*, *ZFHX4*, *ZRSR2*.

2.3 | Targeted RNA next-generation sequencing

Total RNA from bone marrow aspirate was isolated with the TRIZOL reagent according to the manufacturer's instructions (Thermo Fisher Scientific). The reverse transcription, end repairing, dA-tailing, and adaptor ligation were performed according to standard next-generation sequencing (NGS) protocols (NEB, Cat #E7771 and E6111). PCR enrichment was performed using primers specific to a group of 81 genes commonly involved in hematological malignancies, and the PCR products were sequenced in an Illumina NovaSeq sequencer. Sequencing results were analyzed with SeqNext software (JSI). The list of targeted genes included *ABL1*, *ABL2*, *ACTB*, *ALK*, *BCL11B*, *BCL2*, *BCL6*, *BCR*, *CBFB*, *CHD1*, *CIITA*, *CREBBP*, *CRLF2*, *CSF1R*, *CTLA4*, *DDX3Y*, *DUSP22*, *EBF1*, *EPOR*, *ERBB4*, *ERG*, *ETV6*, *FGFR1*, *FLT3*, *GLIS2*, *HLF*, *HOXA9*, *IKZF1*, *IKZF2*, *IKZF3*, *IL2RB*, *ITK*, *JAK2*, *KMT2A*, *LYN*, *MALT1*, *MECOM*, *MEF2D*, *MLK1*, *MLLT10*, *MLLT4*, *MYC*, *MYH11*, *MYST3*, *NOTCH1*, *NPM1*, *NTRK1*, *NTRK2*, *NTRK3*, *NUP214*, *NUP98*, *NUTM1*, *P2RY8*, *PAG1*, *PAX5*, *PBX1*, *PDCD1LG2*, *PDGFRA*, *PDGFRB*, *PICALM*, *PML*, *PTK2B*, *RARA*, *RARB*, *RARG*, *RET*, *RUNX1*, *RUNXT1*, *SPI1*, *STIL*, *SYK*, *TAL1*, *TBL1XR1*, *TCF3*, *TLX3*, *TP63*, *TSLP*, *TYK2*, *VAV1*, *ZCCHC7*, *ZNF384*.

2.4 | RT-PCR

Total RNA was isolated with the TRIZOL reagent according to the manufacturer's instructions. The RNA integrity was evaluated in agarose gel electrophoresis. cDNA was synthesized with random priming and SuperScript III RT reverse transcriptase (Thermo Fisher Scientific). PCR was performed with primers specific for *HNRNPH1* and *ERG* (F_HnRNPH1 E2: 5′-GCTCAAGGTATTCGTTTCATCTACACCAG; R_ERG E11: 5′-TCCCAGGTGATGCAGCTGGAG). The PCR condition was 94°C 2 min for 1 cycle followed by 30 cycles of 94°C 30 s, 68°C 30 s, and 72°C 30s, 1 cycle of 72°C 1 min, and holding at 4°C.

This study is approved by the institutional review boards at the respective institutions.

3 | RESULTS

3.1 | Clinical information of AML with *HNRNPH1::ERG* rearrangement

3.1.1 | Case 1

A 42-year-old female presented with decreased white blood cell (WBC) during a routine pregnancy examination. Physical examination

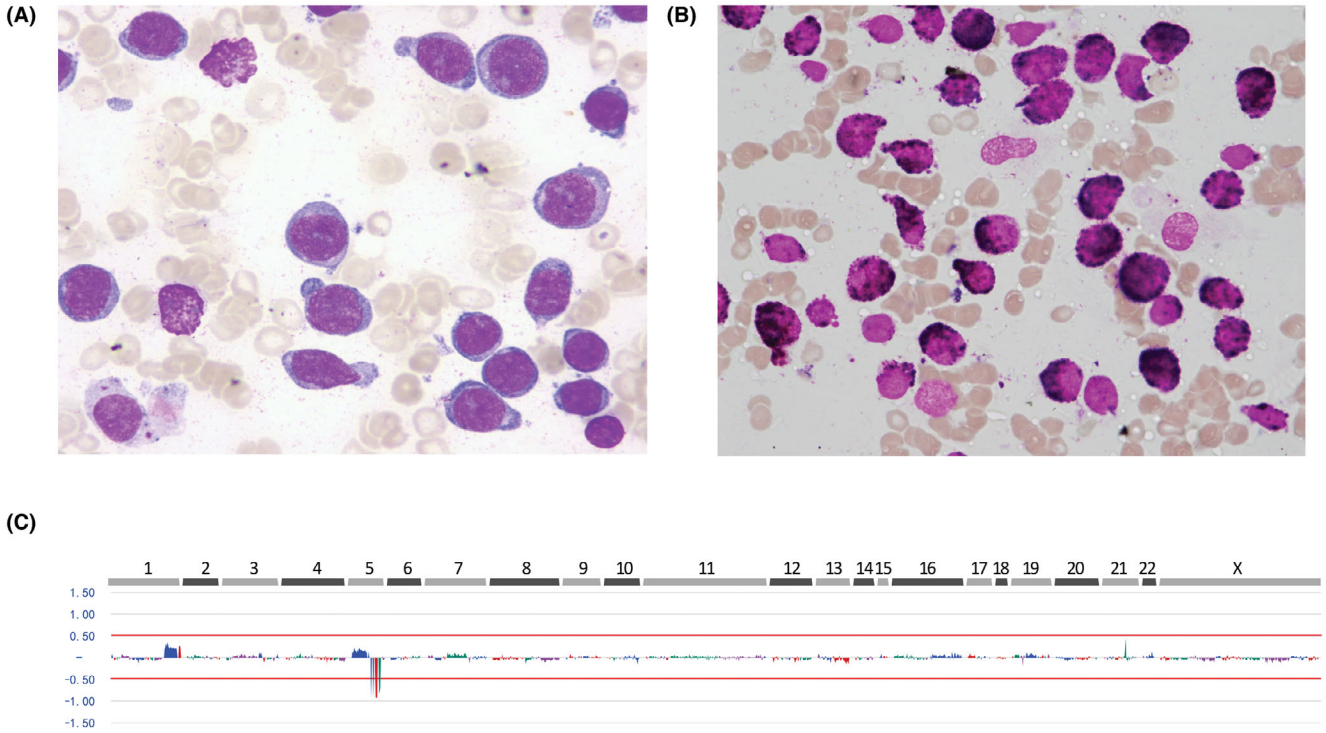

FIGURE 1 (A) Wright stain of bone marrow aspirate smears showed small blasts with immature chromatin, 1–2 nucleoli, and bluish cytoplasm without granules. (B) Blasts were stained positive for POX. (C) CNV analysis of bone marrow DNA by NGS showed 1q gain, 5p gain, and an interstitial loss of 5q. CNV, copy number variation; NGS, next-generation sequencing.

was unremarkable with no bruising or organomegaly. Complete blood counts showed WBC 1.52×10^9/L, Hb 81 g/L, PLT 213×10^9/L, 16.4% neutrophils, 77% lymphocytes, 5.3% monocytes, 0% eosinophils, and 0% basophils. The bone marrow smear showed 82% of small blasts with immature chromatin, 1–2 nucleoli, and bluish cytoplasm without cytoplasmic granules (Figure 1A). Cytochemistry was positive for myeloperoxidase (70%) and ANAE (100%) and negative for chloroacetate esterase (Figure 1B). The bone marrow biopsy showed increased cellularity with approximately 40% of diffuse blasts. Erythroid and lymphoid elements were markedly decreased with no significant dysplasia. Megakaryocytes were occasionally seen with no dysplasia. Local mild bone marrow fibrosis was noted. The bone marrow flow cytometry showed 80.7% of CD34+ cells with CD117+, CD33+, CD13 dim, HLA-DR−, CD4−, CD64−, CD36−, CD56−, CD19−, CD7−, CD5−, CD61−, and CD71−. A diagnosis of AML was made. Cytogenetic analysis of bone marrow was unsuccessful due to a lack of mitosis in vitro. A targeted DNA-NGS assay of 129 leukemia-related genes found no point mutation; however, CNV analysis revealed 1q gain, 5p gain, and 5q interstitial loss (Figure 1C). The 5q interstitial loss started at 5q32 (*CSF1R*) and stopped at 5q35.3 (*DDX41*). The *HNRNPH1*, which is not included in this DNA-NGS panel, is located on the telomeric side of *DDX41* and is presumably spared from the deletion. A targeted RNA NGS analysis with bait probes covering 81 leukemia-related genes, including the *ERG*, discovered the *HNRNPH1*::*ERG* fusion transcript, which presumably resulted from a chromosome translocation between 5q35.3 (*HNRNPH1* locus) and 21q22.2 (*ERG* locus).

The patient was treated with standard 7 + 3 chemotherapy, with cytarabine 120 mg/m^2 on Days 1–7 and daunorubicin 60 mg/m^2 on Days 1–3. The bone marrow aspirate on Day 14 found 89% of blasts, indicating no response. The patient was then treated with homoharringtonine 2 mg/m^2 on Days 1–7 and cytarabine 2 g/m^2 bid on Days 1–3. Still, 73% of blasts in peripheral blood were scored at the end of the chemotherapy. The disease progressively deteriorated, and patient died 3 months after diagnosis due to a severe lung infection.

3.1.2 | Case 2

TARGET-AML; patient ID PARUBT is a 7-year-old female with WBC 7.7×10^9/L in peripheral blood. The bone marrow aspirate showed 96% of blasts and AML was diagnosed. Karyotype analysis was normal (46,XX[20]). Whole-genome sequencing (WGS) found an *HNRNPH1*::*ERG* rearrangement, with additional genomic aberrations involving *CCND3* and *ETS2*. The patient was classified as standard risk and treated with the AAML0531 protocol (standard chemotherapy with the addition of gemtuzumab ozogamicin). The disease relapsed 10 months later and the patient died 18 months after diagnosis (https://target-data.nci.nih.gov/Public/AML).[6]

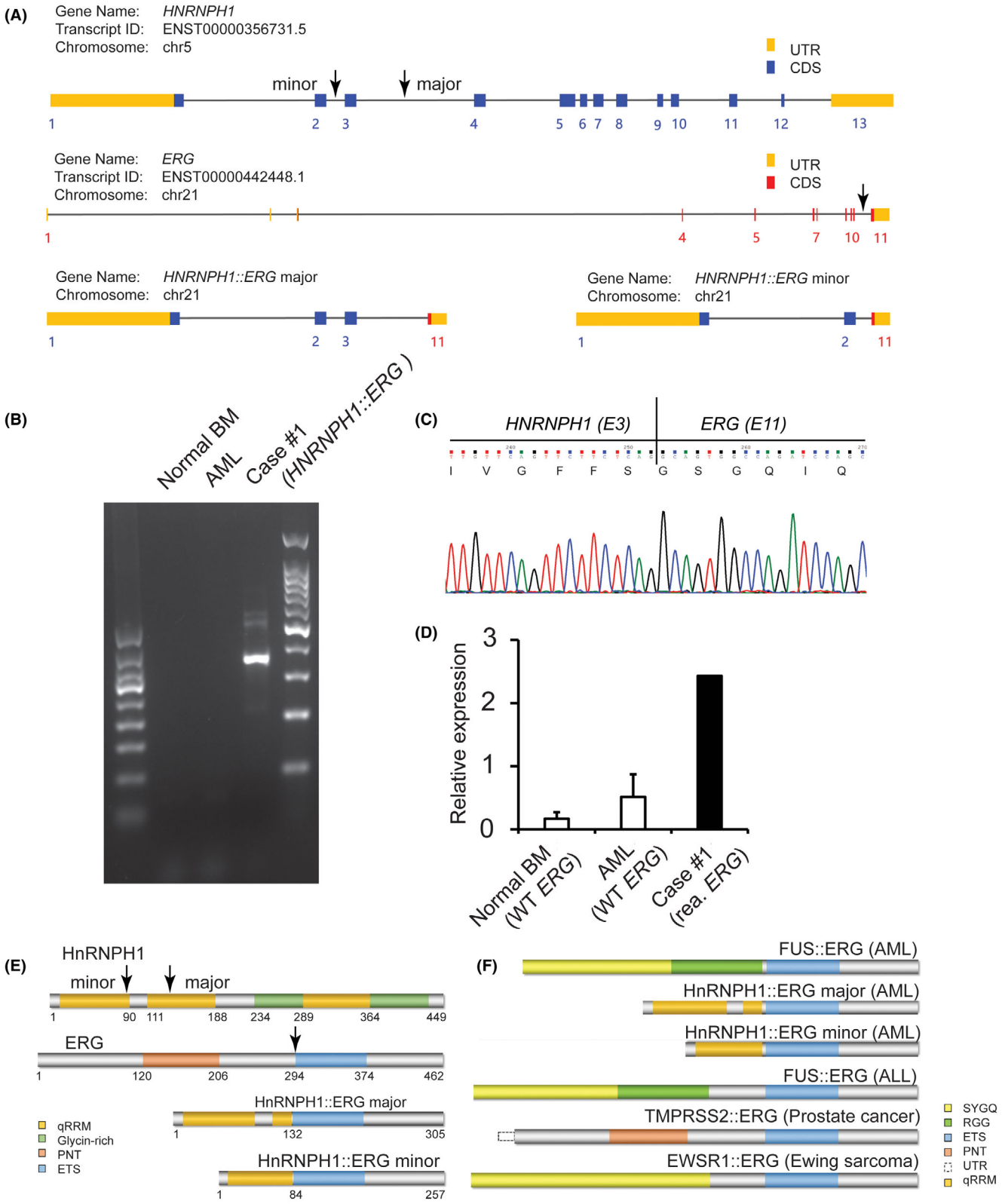

FIGURE 2 (A) RNA NGS of bone marrow aspirate showed major and minor *HNRNPH1*::*ERG* transcript. The breakpoints of *HNRNPH1* and *ERG* are marked with arrows. (B) RT-PCR with primers specific to *HNRNPH1* and *ERG* detected an *HNRNPH1*::*ERG* transcript at the expected size in Case 1 but not in negative controls. (C) Sanger sequencing of the RT-PCR products confirmed a fusion between exon 3 of *HNRNPH1* and exon 11 of *ERG*. (D) The relative expression level of *HNRNPH1*::*ERG* transcript in Case 1 was compared to that of wild-type *ERG* from non-neoplastic bone marrow and other AML without the t(5;21) after being normalized to *ACTB*. (E) Functional motifs of hnRNPH1, ERG, and hnRNPH1::ERG. Breakpoints are marked by arrows. (F) Functional motifs of other ERG chimeric oncoproteins from AML, ALL, Ewing sarcoma, or prostate cancer. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ETS, E26 transformation-specific (ETS) domain; NGS, next-generation sequencing; PNT, pointed domain; qRRM, quasi-RNA recognition motif; RGG, RGG/RG domain; SYGQ, SYGQ-rich domain; UTR, untranslated region.

3.1.3 | Case 3

TARGET-AML; patient ID PATIHH was an 8.9-year-old female with WBC 16.2 × 10^9/L in peripheral blood. The bone marrow aspirate showed 78% of blasts and AML was diagnosed. Karyotype analysis of bone marrow was normal (46,XX[20]). WGS revealed an *HNRNPH1::ERG* rearrangement. She was classified as standard risk and was treated with the AAML0531 protocol. The disease relapsed 14 months later; however, complete remission was achieved after additional therapy and the patient survived with the last follow-up recorded 5 years after the initial diagnosis (https://target-data.nci.nih.gov/Public/AML).[6]

3.2 | Characterization of *HNRNPH1::ERG* rearrangement

RNA NGS from Case 1 detected two *HNRNPH1::ERG* transcripts. The main fusion transcript contained the first three exons of *HNRNPH1* and the last exon of the *ERG*. A minor transcript, constituting only 5% of the total *HNRNPH1::ERG* rearrangement based on read counts, contained the first two exons of *HNRNPH1* and the last exon of the *ERG*, presumably originating from alternatively splicing (Figure 2A). Both transcripts were in-frame fusions between *HNRNPH1* and *ERG*. The *HNRNPH1::ERG* rearrangement was further confirmed by an RT-PCR assay followed by Sanger sequence, using a forward primer from *HNRNPH1* and a reverse primer from *ERG* (Figure 2B,C). The reciprocal *ERG::HNRNPH1* transcript was not detected in an RT-PCR assay. The expression level of *HNRNPH1::ERG* was compared to that of wild-type *ERG* from six cases of non-neoplastic bone marrow and four other AML cases (without *ERG* rearrangement), which showed approximately 5× and 14× higher *HNRNPH1::ERG* expression as compared to the wild-type *ERG* in AML and normal bone marrow, respectively. These results are consistent with a more potent *HNRNPH1* promoter as compared to the *ERG* promoter in bone marrow cells, which, when fused to *ERG*, led to a high level of *HNRNPH1::ERG* expression (Figure 2D). The predicted fusion protein consists of the N-terminal quasi-RNA recognition motifs of the hnRNPH1 and the ETS domain of ERG (Figure 2E). While hnRNPH1::ERG and FUS::ERG share the same ERG breakpoints in AML, the ERG breakpoints differ in other tumors, including ALL, Ewing sarcoma, and prostate cancer (Figure 2F), leading to chimeric proteins containing variously sized C-terminal ERG.

4 | DISCUSSION

FUS::ERG is a rare but recurrent rearrangement in AML. We describe here three cases of AML with a novel *HNRNPH1::ERG* rearrangement. Both hnRNPH1 and FUS (also known as hnRNPP2) belong to the same hnRNP family and both function in splicing.[8] Several clinical phenotypes are shared between patients with *FUS::ERG* or *HNRNPH1::ERG* rearrangement: (1) both are typically young adults or pediatric patients; (2) the blast counts are high at diagnosis, with an average of 77% in 49 cases of *FUS::ERG* and 85% in three cases of *HNRNPH1::ERG*,[4] and (3) both carry poor prognosis with a mean survival time of 13 months in 52 cases of *FUS::ERG* and two out of three *HNRNPH1::ERG* rearranged AML died within 16 months.[4] Due to overlapping clinical features, identical *ERG* breakpoints, and functional similarity between hnRNPH1 and ERG (both hnRNP proteins), we suspect that patients with *HNRNPH1::ERG* or *FUS::ERG* belong to the same distinct clinicopathologic subtype of AML, that is, AML with *ERG* rearrangement; however, additional cases of *HNRNPH1::ERG* are needed to confirm this observation.

In addition to AML, *ERG* is rearranged in several other tumors, including *TMPRSS2::ERG* in prostate cancer,[9] *EWS::ERG* and *FUS::ERG* in Ewing sarcoma,[10] and *FUS::ERG* in B-ALL.[11] Interestingly, the *ERG* breakpoints are tumor type-specific (Figure 2E), which may contribute to their different oncogenic mechanisms. In prostate cancer, the *TMPRSS2-ERG* encodes almost the entire ERG, with no amino acid residues contribution from *TMPRSS2*. The *TMPRSS2* provides a potent promoter, leading to the overexpression of *ERG*, similar to other oncogenes driven by the promoter switching mechanism. Therefore, the expression/activation of genes downstream of ERG, such as FZD4 and MMP1, are likely the major drivers for prostate cancer development.[12,13] For other ERG-rearranged tumors, the chimeric proteins contain only partial ERG, although all had the intact ETS domain (Figure 2E). These oncoproteins likely compete with wild-type ETS proteins for DNA binding and function as transcription repressors. The actual binding affinity to a particular DNA region may vary among different chimeric proteins due to their differently sized ERG fragment, which could contribute to the development of different tumors. The N-terminals of chimeric oncoproteins are from EWSR1, hnRNPH1, or FUS, all RNA-binding proteins. Therefore, interference of RNA metabolism could be another important oncogenic mechanism for these tumors.

In addition to the ETS-binding motif, FUS::ERG is also bound to the same genomic regions as the retinoic acid receptor α/retinoid X receptor complex. The addition of all-*trans* retinoic acid (ATRA) led to decreased FUS-ERG binding and increased regional histone H3 acetylation. More importantly, the ATRA treatment resulted in cell differentiation and decreased proliferation of AML cells with *FUS-ERG* rearrangement.[5] Because AML patients with *ERG* rearrangement respond poorly to chemotherapy, ATRA, a drug well-known in the hematology and oncology community, is undoubtedly worth further evaluation in a clinical setting. In addition, the FUS-ERG expression led to decreased expression of apoptotic genes such as *CASP10*, *ATM*, *SAMD3*, *BMF*, and *FAF1*, and increased expression of antiapoptotic genes such as *BCL-2*, *GADD45B*, *IL1B*, and *IL2RA*.[5] The deficient apoptosis in patients with *ERG* rearrangement could explain the lack of response to chemotherapy, which kills dividing cells by largely inducing apoptosis. Therefore, induction of cell differentiation with an APL-like therapeutic regimen, rather than killing tumor cells, might be a more effective approach for this type of AML.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
2. Reddy ES, Rao VN. erg, an ets-related gene, codes for sequence-specific transcriptional activators. *Oncogene*. 1991;6(12):2285-2289.
3. Xie Y, Koch ML, Zhang X, et al. Reduced *Erg* dosage impairs survival of hematopoietic stem and progenitor cells. *Stem Cells*. 2017;35(7):1773-1785.
4. Buchanan J, Tirado CA. A t(16;21)(p11;q22) in acute myeloid leukemia (AML) resulting in fusion of the FUS/TLS and ERG genes: a review of the literature. *J Assoc Genet Technol*. 2016;42(1):24-33.
5. Sotoca AM, Prange KHM, Reijnders B, et al. The oncofusion protein FUS-ERG targets key hematopoietic regulators and modulates the all-*trans* retinoic acid signaling pathway in t(16;21) acute myeloid leukemia. *Oncogene*. 2016;35(15):1965-1976.
6. Bolouri H, Farrar JE, Triche TJ Jr, et al. The molecular landscape of pediatric acute myeloid leukemia reveals recurrent structural alterations and age-specific mutational interactions. *Nat Med*. 2018;24(1):103-112.
7. Herlin MK, Yones SA, Kjeldsen E, Holmfeldt L, Hasle H. What is abnormal in normal karyotype acute myeloid leukemia in children? Analysis of the mutational landscape and prognosis of the TARGET-AML cohort. *Genes*. 2021;12(6):792.
8. Geuens T, Bouhy D, Timmerman V. The hnRNP family: insights into their role in health and disease. *Hum Genet*. 2016;135(8):851-867.
9. Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of *TMPRSS2* and ETS transcription factor genes in prostate cancer. *Science*. 2005;310:644-648.
10. Chen S, Deniz K, Sung YS, et al. Ewing sarcoma with *ERG* gene rearrangements: a molecular study focusing on the prevalence of *FUS-ERG* and common pitfalls in detecting *EWSR1-ERG* fusions by FISH. *Genes Chromosomes Cancer*. 2016;55:340-349.
11. Kanazawa T, Ogawa C, Taketani T, Taki T, Hayashi Y, Morikawa A. *TLS/FUS-ERG* fusion gene in acute lymphoblastic leukemia with t(16;21)(p11;q22) and monitoring of minimal residual disease. *Leuk Lymphoma*. 2005;46(12):1833-1835.
12. Gupta S, Iljin K, Sara H, et al. *FZD4* as a mediator of *ERG* oncogene-induced WNT signaling and epithelial-to-mesenchymal transition in human prostate cancer cells. *Cancer Res*. 2010;70(17):6735-6745.
13. Wu L, Zhao JC, Kim J, Jin HJ, Wang CY, Yu J. ERG is a critical regulator of Wnt/LEF1 signaling in prostate cancer. *Cancer Res*. 2013;73(19):6068-6079.

How to cite this article: Jiang F, Lang X, Chen N, et al. A novel *HNRNPH1::ERG* rearrangement in aggressive acute myeloid leukemia. *Genes Chromosomes Cancer*. 2022;1-6. doi:10.1002/gcc.23051