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Identification of a novel *MYO1F*::*MLLT10* fusion in adult acute monocytic leukemia

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Authorship:

The original concept was developed by B.S. and J.P. Diagnostic workup was performed by B.S., N.M., and R.N. The literature review was conducted by B.S. and J.P. Data collection and analysis were carried out by J.P., J.T., R.N., R.F., and B.S. Data interpretation was performed by J.P., J.T., and B.S. B.S. wrote the original draft of the manuscript. Critical review and editing were undertaken by B.S., J.P., J.T., N.M., R.F., and R.N. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Data availability

De-identified raw RNA-sequencing data supporting the identification of the *MYO1F::MLLT10* and *MLLT10::MYO1F* fusions, together with a tab-separated values (TSV) file containing fusion gene details, breakpoints, read support, and transcript annotations generated using FusionCatcher, STAR-Fusion, and Arriba, are available upon reasonable request. These data can be obtained by contacting the corresponding author, Reza Nejati (Reza.Nejati@fccc.edu), subject to compliance with the Institutional Review Board (IRB) policies of Fox Chase Cancer Center to ensure patient confidentiality and ethical standards.

TO THE EDITOR

Acute myeloid leukemia (AML) is a heterogeneous malignancy characterized by clonal proliferation of myeloid precursors, often driven by recurrent cytogenetic and molecular abnormalities. Translocations involving the *KMT2A* (*MLL*) gene at 11q23.3 occur in AML, particularly in infant and pediatric cases, and are associated with monocytic differentiation and poor prognosis [1-3]. The *MLLT10* gene at 10p12.31, a frequent *KMT2A* fusion partner, is implicated in AML and T-cell acute lymphoblastic leukemia (T-ALL) with monocytic features [3, 4]. *MYO1F* at 19p13.2, encoding an unconventional myosin protein, is a rare *KMT2A* fusion partner reported in a few infant and pediatric AML cases (two infants with *KMT2A*::*MYO1F*, one with a complex rearrangement and one pediatric case with a complex translocation involving chromosomes 7, 11, 19, and 22) [1, 2, 5, 6]. To our knowledge, *MYO1F*::*MLLT10* fusion has not previously been described in AML. We report the first adult case of acute monocytic leukemia (WHO/ICC 2022) with reciprocal in-frame *MYO1F*::*MLLT10* and *MLLT10*::*MYO1F* fusions, identified by RNA sequencing and supported by interphase FISH.

A 58-year-old man with diabetes mellitus, chronic kidney disease, hypertension, and renal stones presented with right lower quadrant abdominal pain, nausea, vomiting, and fatigue. Imaging revealed left staghorn calculus, atrophic right kidney, splenic infarct, hepatosplenomegaly, and non-bulky multi-station lymphadenopathy. Laboratory findings revealed rapidly progressive leukocytosis (WBC 33.7 K/mm³ initially, rising to 104 K/mm³ pre-percutaneous nephrostomy [PCN]), anemia (Hb 8 g/dL), thrombocytopenia (platelets 128 K/mm³), and acute kidney injury. Bone marrow aspiration and biopsy demonstrated a markedly hypercellular marrow (>95%) with >80% blasts/blast equivalents. Flow cytometry confirmed 73% blasts, positive for CD117, HLA-DR, CD11b, CD11c, CD13, CD15, CD33, CD38, partial CD14 and CD64, and negative for CD34, CD19, TdT, MPO. Abnormal monocytes (11%) expressed CD56 with decreased CD14. Peripheral smear revealed predominantly monoblasts and promonocytes with characteristic cytomorphology**.**

Bone marrow cells cultured for 24 hours revealed a karyotype of 45,X,-Y/46,XY (75% of cells with -Y), confirmed by chromosomal microarray analysis (CMA) (-Y in ~70% of cells). Standard FISH was negative for common AML rearrangements (*MECOM*, *DEK*::*NUP214*, *RUNX1T1*::*RUNX1*, *BCR/ABL1*, *KMT2A*, *PML/RARA*, and *CBFB*) and *TP53* deletion. NGS-based targeted DNA sequencing (275-gene panel) revealed no pathogenic mutations, including *FLT3-ITD/TKD* or *NPM1*, with a low tumor mutation burden (2.4 muts/Mb). RNA fusion panel (TruSight 507-gene panel) detected two novel in-frame chimeric fusion transcripts:

MYO1F::*MLLT10 and MLLT10*::*MYO1F* (Figures 1 and 2). Metaphase spreads lacked a discernible t(10;19)(p12.31; p13.2). Therefore, an *MLLT10/KMT2A* dual fusion probe on destained G-banded metaphase spreads (Figure 3A, B), showed *MLLT10* signals only on chromosome 10 short arms; no signals on either chromosome 19. However, 49% of interphase nuclei (98/200) displayed three MLLT10 signals—one large, two smaller—often close together (82/98 nuclei, 83.7%; Figure 3C) **—**indicating a split *MLLT10* allele, potentially involving an insertion of *MYO1F* sequences from 19p13.2 into the *MLLT10* gene region at 10p12.31, suggesting *MLLT10* rearrangement. Initial management included leukapheresis (WBC reduced to 39.3 K/mm³) and hydroxyurea (1 g BID for 4 days), followed by azacitidine/venetoclax induction (7+21 days, VIALE-A protocol). The patient had a partial response, but persistent disease (20% blasts) on bone marrow biopsy two weeks later. He later received FLAG-IDA-Ven salvage therapy and achieved short-lived complete remission. He relapsed (43% blasts, WBC 183.6 K/mm³) three weeks after first consolidative HiDAC (~four months from the diagnosis) and was treated with leukapheresis (×2) and hydroxyurea. At the latest follow-up, two weeks post-relapse, he was on supportive care only, without AML-directed therapy, amid multiorgan failure (renal, ocular), awaiting hospice care.

The biospecimens and clinical data used in this study were collected previously as part of the patient's routine diagnostic work up and clinical care. No separate specimens were collected for the study. The Institutional Review Board of Fox Chase Cancer Center provided ethical approval for this work.

This case represents the first report of *MYO1F::MLLT10* and reciprocal *MLLT10::MYO1F* fusions in AML (Supplemental Table 1), identified by RNA sequencing, confirmed by multiple fusion-calling algorithms (using FusionCatcher, STAR-Fusion, and Arriba; Supplemental Table 2), and supported by orthogonal testing using FISH (Figure 3A–C). *MLLT10* (also known as *AF10*), a known fusion partner in AML and T-ALL (e.g., *KMT2A::MLLT10, PICALM::MLLT10*), drives leukemogenesis via its 3' domains (PHD-finger, leucine zipper), promoting monocytic differentiation through chromatin remodeling and transcriptional dysregulation (e.g., DOT1L recruitment, H3K79 methylation) [3, 4]. In *MYO1F*::*MLLT10* fusion protein (443 amino acids), *5' MYO1F* exon 1 (start codon, promoter/enhancer elements) fuses to the C-terminal exons 15–23 (442 amino acids) of the *3' MLLT10* partner, potentially upregulating *MLLT10*'s oncogenic domains. In the reciprocal *MLLT10*::*MYO1F* fusion protein (839 aa), 5' *MLLT10* exons 1–18 (816 aa; N-terminal domains including PHD-finger, zf-HC5HC2H) fuses to *3' MYO1F* exons 25-28 (23 aa, partial myosin tail). The *MYO1F::MLLT10* fusion transcript (breakpoints: *5′ MYO1F*,

chr19:8,642,191 [− strand]; *3′ MLLT10*, chr10:22,015,173 [+ strand]) showed high expression levels and strong read support: STAR-Fusion (62 fragments: 39 junction, 23 spanning; FFPM = 13.4276), FusionCatcher (61 fragments: 19 unique, 42 spanning), and Arriba (42 fragments: 6/27 split reads, 9 discordant mates). The fusion maintains the reading frame and encodes a chimeric protein (MANTLSGSS…, 443 amino acids; Supplemental Table 1). The reciprocal *MLLT10::MYO1F* fusion (breakpoints: *5′ MLLT10*, chr10:22,022,016 [+ strand]; *3′ MYO1F*, chr19:8,590,446 [− strand]) was detected by STAR-Fusion (43 fragments: 40 junction reads, 3 spanning; FFPM = 9.3126), FusionCatcher (54 fragments: 12 unique reads, 42 spanning pairs), and Arriba (24 fragments: 14/8 split reads, 2 discordant mates; coverage 309/85). This chimeric transcript was predicted to be in-frame according to STAR-Fusion and FusionCatcher, but out-of-frame according to Arriba due to selection of a shorter *MYO1F* isoform (507 bp in ENST00000596245.1 versus 4,303 bp in ENST00000338257.8). It encodes a chimeric fusion protein (MVSSDR…, 839 amino acids; Supplemental Table 1). STAR-Fusion and FusionCatcher confirm canonical GT/AG splice sites for both fusions with Arriba's CDS/splice site annotations reflecting minor junction mapping differences. High expression levels (FFPM 13.4276 for *MYO1F*::*MLLT10* versus 9.3126 for *MLLT10*::*MYO1F*) and Arriba's coverage support *MYO1F*::*MLLT10* as the driver (Supplemental Table 2), with C-terminal domains of 3' *MLLT10* driving leukemogenesis, akin to *KMT2A*::*MLLT10* fusions. In the reciprocal *MLLT10*::*MYO1F* fusion, the retained N-terminal PHD-finger and SH3 domains from 5′ *MLLT10* suggest potential functionality with a secondary regulatory role, possibly contributing to stabilization of the rearrangement/translocation; however, it may be less oncogenic due to the lack of C-terminal oncogenic leucine zipper. Only 23 amino acids (part of the myosin tail) from *3'* exons 25-28 of *MYO1F* are included, indicating truncation of the fusion protein by a stop codon (EPTRKGMAKGKPRRSSQAPTRAA*) and translation of only part of *MYO1F* exon 25 sequence (chr19:8590446 to 8590363 [− strand], 84bp, 28 aa). This region lacks significant functional domains (e.g., the motor domain encoded by earlier exons), suggesting a primarily structural rather than functional role in the fusion protein. The asymmetric breakpoints in *MLLT10* and *MYO1F* in both fusion products likely indicate an unbalanced reciprocal translocation. However, the presence of *MLLT10* exons 15–18 in both derivative chromosomes raises the possibility of a duplicated segment and thus cannot entirely exclude a complex rearrangement from additional events. FISH with an *MLLT10/KMT2A* probe showed no detectable *MLLT10* signal splitting in metaphase spreads (limited by suboptimal banding quality and insufficient metaphase spreads), but 49% of interphase nuclei displayed three *MLLT10* signals (one large, two smaller), indicating a split *MLLT10* allele, likely due to a cryptic insertion of *MYO1F* sequences from 19p13.2 into

the *MLLT10* gene at 10p12.31. Interphase FISH confirmed the *MLLT10* rearrangement, while the absence of visible chromosomal alterations suggests a submicroscopic cryptic insertion or underrepresentation of the malignant clone in metaphase spreads. The cryptic nature of the 10p;19p rearrangement, without other AML-defining cytogenetic changes, highlights the value of RNA fusion analysis for identifying rare gene fusions.

MYO1F, a rare *KMT2A* partner in infant AML, may contribute to cytoskeletal or signaling abnormalities, a novel role when fused with *MLLT10* [5,6]. The *MYO1F::MLLT10* fusion in this case is likely driving the monocytic phenotype (>80% blasts, CD117+, CD34-, CD56+, partial CD14+), consistent with *MLLT10*-rearranged AML [3, 4]. Although the absence of *FLT3/NPM1* mutations was favorable, the relapse after first consolidative HiDAC indicates poor prognosis [7]. The patient's complex clinical course, including retinal hemorrhages and renal failure, underscores the systemic impact of AML.

This case expands the spectrum of *MLLT10* rearrangements in AML and contributes to the evolving understanding of rare AML-associated fusions. Its identification by targeted RNA sequencing—with robust read support, high expression, and in-frame predictions across multiple fusion calling algorithms—underscores the importance of integrated molecular and cytogenetic profiling in AML. Because *MYO1F*::*MLLT10* was identified only through RNA sequencing, similar cryptic events may currently be under-recognized. Broader screening of AML cohorts using targeted RNA-seq or PCR analysis of cDNA from diagnostic bone marrow aspirates will be essential to ascertain its prevalence. The *MYO1F*::*MLLT10* fusion is the probable leukemogenic driver, analogous to *KMT2A*::*MLLT10* or cytoskeletal perturbations from *MYO1F*'s functional domains. In line with the approaches for novel fusion genes such as *NUP98-NSD1,* the transforming activity of *MYO1F*::*MLLT10* can be assessed using in vitro assays—including foci formation or anchorage-independent growth by transfection of a plasmid expressing *MYO1F*::*MLLT10* into NIH-3T3 fibroblasts. Additional insights could be obtained by evaluating proliferation rates and/or altered differentiation in normal or immortalized myeloid cell lines [8]. Furthermore, assessing therapeutic vulnerabilities—such as to *DOT1L* inhibitors that target chromatin-remodeling pathways implicated in *MLLT10*-driven malignancies—could reveal actionable targets for this rare AML subtype.

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Figure 1. Schematic of *MYO1F*::*MLLT10* fusion in acute monocytic leukemia.

This diagram illustrates the *MYO1F::MLLT10* fusion generated by a chromosomal rearrangement between 10p12.31 and 19p13.2. The breakpoint in the *MYO1F* occurs at chr19:8642191 (exon 1, start codon, negative strand) from chromosome 19, which fuses to the *MLLT10* gene at chr10:22015173–22015284 (exon 15/16, positive strand). The resulting in-frame chimeric transcript, confirmed by RNA sequencing, encodes a protein that combines promoter/enhancer elements and the start codon of *MYO1F* with the transcriptional regulatory domains of *MLLT10*, driving acute monocytic leukemia (AML).

Exons are represented as boxes, introns as lines, and the fusion junction is indicated by a dashed line. Chromosomal orientations and breakpoints are annotated for clarity.

Abbreviations: AML, acute myeloid leukemia.

Figure 2. Schematic of *MLLT10::MYO1F* fusion in acute monocytic leukemia.

This diagram shows *MLLT10::MYO1F* reciprocal fusion from the same chromosomal translocation. The breakpoint in the *MLLT10* is at chr10:22022016 (exon 18/19, positive strand), retaining regulatory domains including the PHD-finger, zf-HC5HC2H, and Jnk-SapK_ap motifs, which fuses to the *MYO1F* at chr19:8590363–8590446 (exon 25, negative strand). RNA sequencing confirmed the fusion transcript, which combines the N-terminal region of *MLLT10* with the C-terminal exons of *MYO1F*, encoding an in-frame chimeric protein according to STAR-Fusion and FusionCatcher and an out-of-frame protein according to Arriba. While *MLLT10's* retained regulatory domains may contribute to fusion stability or minor functions, the fusion likely has reduced oncogenic potential.

Exons are represented as boxes, introns as lines, and the fusion junction is indicated by a dashed line. Chromosomal orientations and breakpoints are annotated for clarity.

Abbreviations: PHD, plant homeodomain; zf-HC5HC2H, zinc finger; AML, acute myeloid leukemia.

Figure 3. Hybridization of MLLT10 probe in patient bone marrow cells.

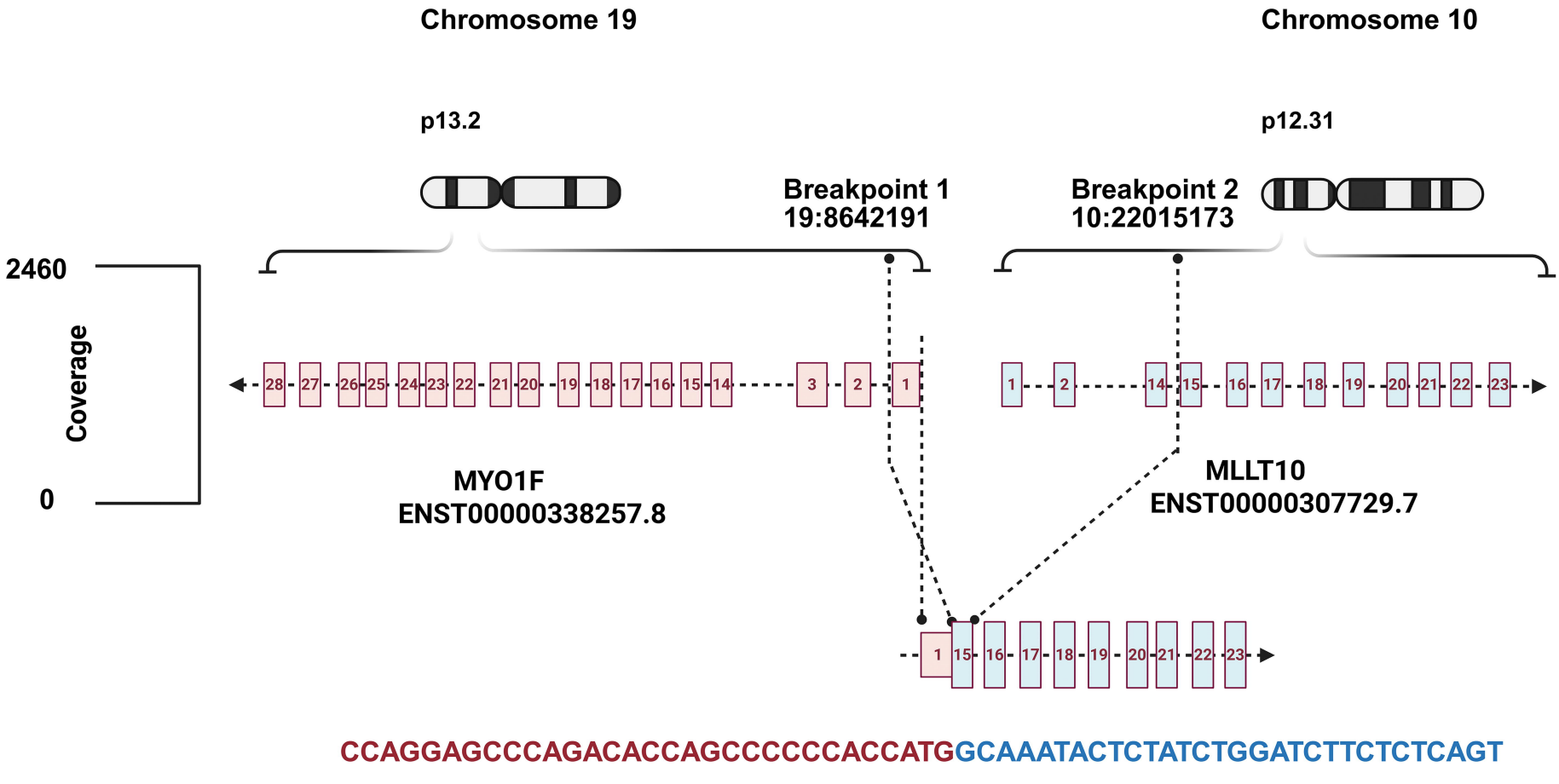
(A) Schematic of orange-labeled MLLT10 probe hybridizing to the entire *MLLT10* locus and flanking sequences at sub-band 10p12.3 (adapted from the MetaSystems XL t(10;11) MLLT10/KMT2A Dual Fusion Probe [MetaSystems, Medford, MA]), which comprises an orange-

labeled probe targeting the *MLLT10* gene region at 10p12.31 and a green-labeled probe targeting the *KMT2A* gene region at 11q23.3; the latter probe is not shown).

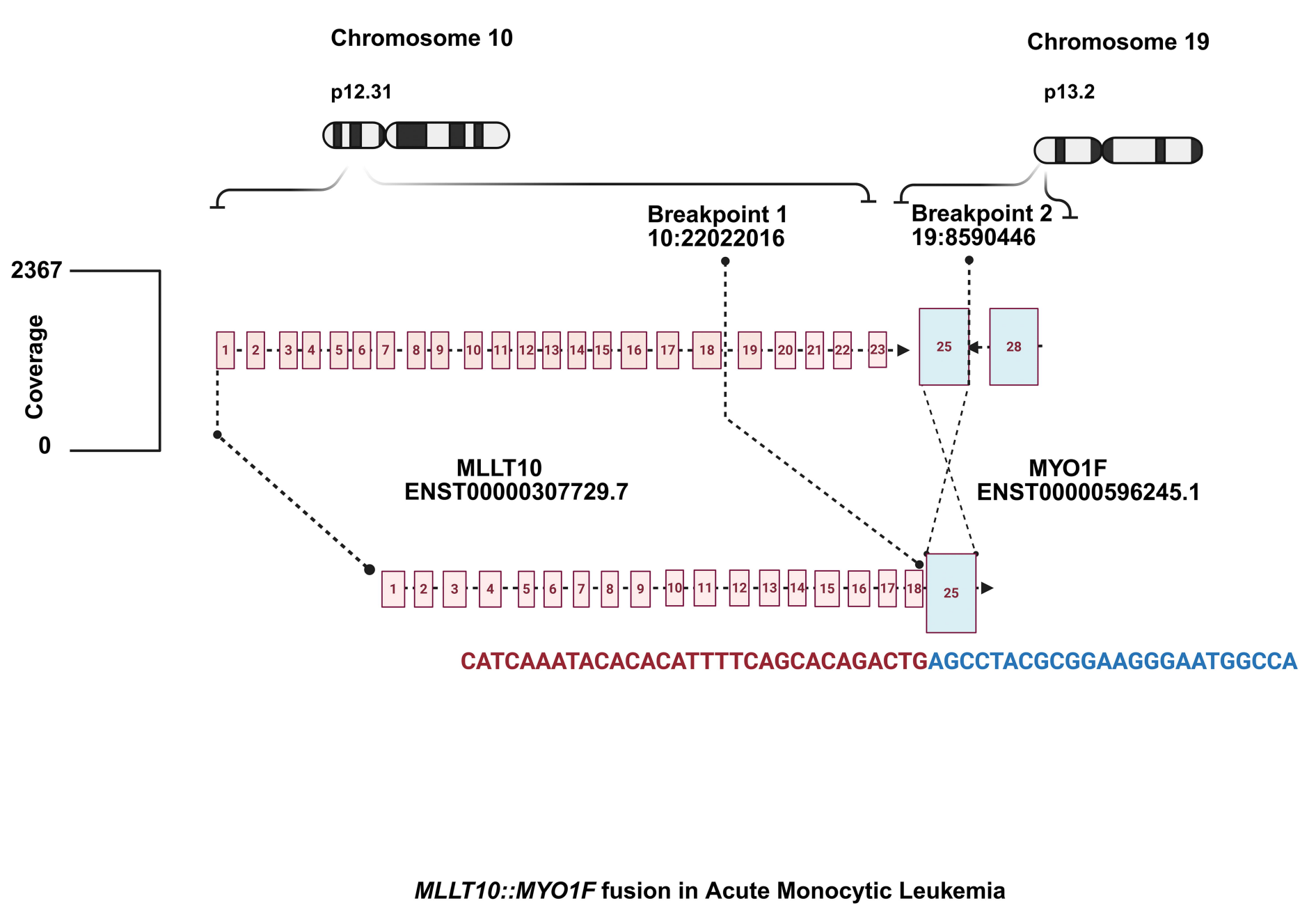
(B) G-banding (left) and hybridization of MLLT10/KMT2A probe (right) to a representative 4′,6-diamidino-2-phenylindole (DAPI)-stained metaphase spread from the patient's bone marrow. The MLLT10 probe hybridizes to the short arm of chromosome 10 only (red arrows), with no hybridization to chromosome arm 19p.

(C) Representative FISH images showing nuclei with: (top panel) normal two MLLT10 signal pattern; (bottom panel) abnormal pattern, exhibiting one larger *MLLT10* signal (thick vertical arrow on far right) and two smaller *MLLT10* signals (thin red arrows in same nucleus). Images of interphase nuclei were captured using a MetaSystems Metafer microscope workstation, and the raw images were extracted and processed to depict *MLLT10* signals in magenta and DAPI-stained nuclei in blue, with blue outlines marking nuclear boundaries.

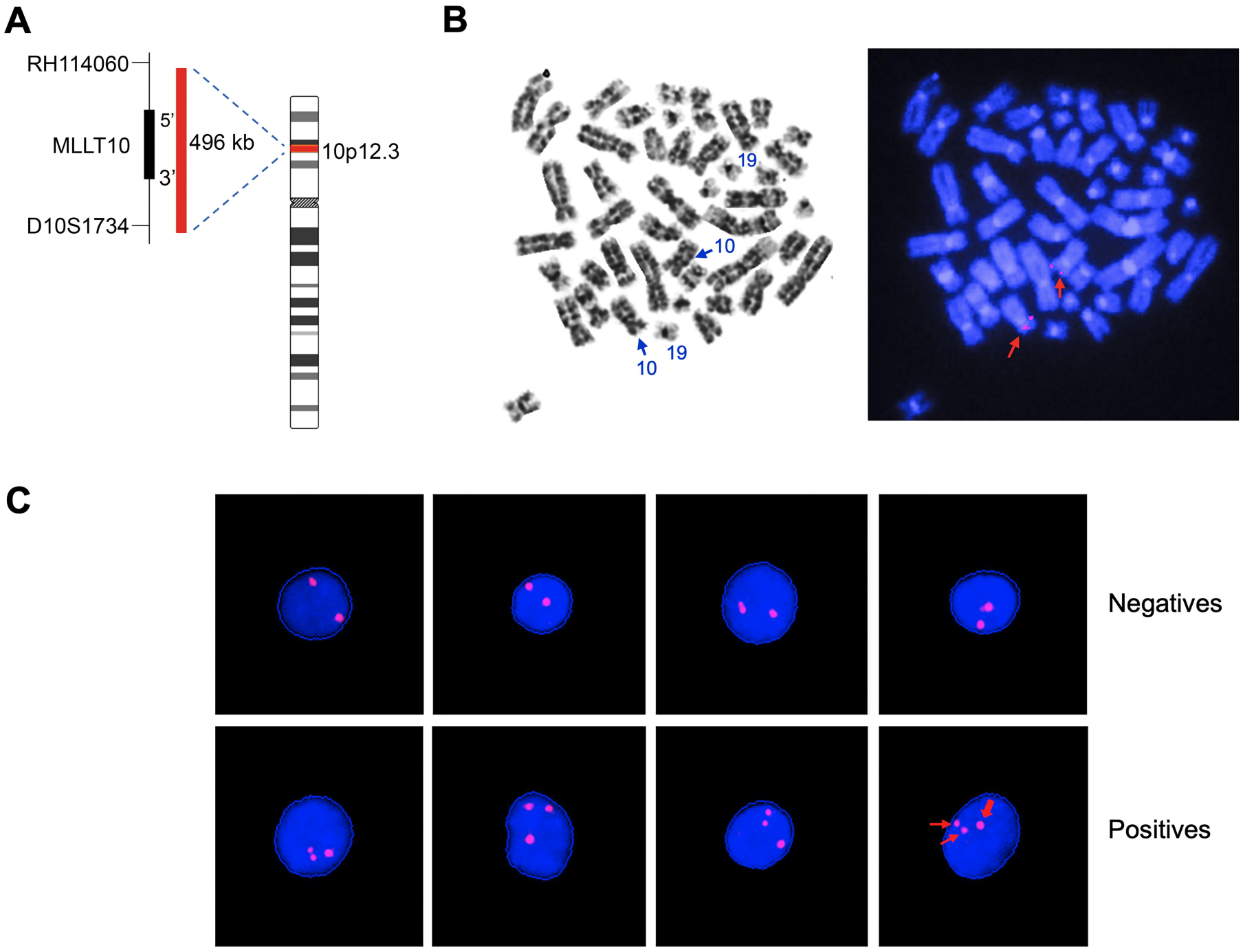
Abbreviations: FISH, fluorescence in situ hybridization; DAPI, 4′,6-diamidino-2-phenylindole.



***MYO1F::MLLT10* fusion in Acute Monocytic Leukemia**



***MLLT10::MYO1F* fusion in Acute Monocytic Leukemia**


A
RH114060
MLLT10
5'
3'
496 kb
10p12.3
D10S1734
B
19
10
10
19
C
Negatives
Positives

Supplemental Table 1. Comparison of *MYO1F*::*MLLT10* and *MLLT10*::*MYO1F* reciprocal fusions (in-frame)

Parameter	**MYO1F::MLLT10**	**MLLT10::MYO1F**
Breakpoint Coordinates (hg19)	5′ (MYO1F): chr19:8642191 (-) 3′ (MLLT10): chr10:22015173 (+)	5′ (MLLT10): chr10:22022016 (+) 3′ (MYO1F): chr19:8590446 (-)
Transcript IDs (GENCODE v19)	MYO1F: ENST00000338257.8 MLLT10: ENST00000307729.7	MLLT10: ENST00000377072.3 MYO1F: ENST00000338257.8
Base Pairs at Breakpoints	MYO1F: 8642191 (3′ splice-site) MLLT10: 22015173 (5′ splice-site)	MLLT10: 22022016 (3′ splice-site) MYO1F: 8590446 (5′ splice-site)
Transcript Length (bp, aa, exons)	MYO1F-001: 4303 bp, 1098 aa, 28 exons MLLT10-002: 5032 bp, 1068 aa, 23 exons	MLLT10-001: 5126 bp, 1027 aa, 24 exons MYO1F-001: 4303 bp, 1098 aa, 28 exons
Exons Involved	MYO1F: Exon 1 (chr19:8642191–8642357, –) MLLT10: Exon 15/16 (chr10:22015173–22015284, +)	MLLT10: Exon 18/19 (chr10:22021828–22022016, +) MYO1F: Exon 25 (chr19:8590363–8590446, –)
Domains Retained (PFAM)	MYO1F: 5′ UTR and ATG start codon MLLT10: PHD-finger, leucine zipper	MLLT10: PHD-finger, zf-HC5HC2H, Jnk-SapK_ap_N MYO1F: C-terminal exon 25 (part of Myosin tail)

Parameter	MYO1F::MLLT10	MLLT10::MYO1F
Length of Fusion Protein	443 amino acids (including stop codon) 1 amino acid (0.2%) from 5′MYO1F; 442 from 3′MLLT10	839 amino acids (including stop codon) 816 (97%) from 5′ MLLT10; 23 from 3′ MYO1F
Amino Acid Sequence	See sequence block below Table 1	See sequence block below Table 1
Fusion Structure & Mechanism	MYO1F exon 1 (5′ UTR, start codon) fuses to MLLT10 exon 15/16, resulting in a chimeric transcript with minimal MYO1F coding sequence and MLLT10 C-terminal region. Promoter/enhancer elements from MYO1F5′ UTR drive MLLT10 expression, enhancing oncogenic activity.	MLLT10 exon 18/19 fuses to MYO1Fexon 25, resulting in a chimeric transcript with MLLT10 N-terminal region and MYO1FC-terminal exons. MLLT10 regulatory domains may confer fusion stability or minor functions but lack key oncogenic domains.
Functional & Expression	In-frame, 443 amino acids; 1 aa from MYO1F (start codon), 442 aa from MLLT10's C-terminal oncogenic domains (PHD-finger, leucine zipper)	In-frame (STAR-Fusion, FusionCatcher), 839 amino acids; N-terminal MLLT10domains (PHD-finger, zf-HC5HC2H) with regulatory potential; lacks oncogenic leucine zipper
FFPM & Coverage	FFPM: 13.4276 (STAR-Fusion); Arriba: high coverage (284/220), strong expression	FFPM: 9.3126 (STAR-Fusion), Arriba: moderate coverage (309/85), intermediate expression

Parameter	MYO1F::MLLT10	MLLT10::MYO1F
Oncogenicity	Primary driver: MLLT103′ domains drive leukemogenesis, akin to KMT2A::MLLT10	Secondary: MLLT105′ domains less critical for leukemogenesis
Biological/Clinical Significance	Likely novel driver in AML/ALL.MLLT103′ domains promote transformation via transcriptional dysregulation. High expression suggests major oncogenic event, validating experimental targeting.	Reciprocal product; potentially functional but less oncogenic due toMLLT105′ domains. Moderate expression fits secondary role; may stabilize translocation or confer regulatory effects.

*** Amino acid sequence of chimeric *MYO1F::MLLT10* Fusion protein**

MANTLSGSSLSQAPSHMYGNRSNSSMAALIAQSENNQTDQDLGDNSRNLVGRGSSPRGSLS
PRSPVSSLQIRYDQPGNSSLENLPPVAASIEQLLERQWSEGQQFLLEQGTPSDILGMLKSLHQL
QVENRRLEEQIKNLTAKKERLQLLNAQLSVPFPTITANPSPSHQIHTFSAQTAPTTDSLNSSKSP
HIGNSFLPDNSLPVLNQDLTSSGQSTSSSSALSTPPPAGQSPAQQGSGVSGVQQVNGVTVGA
LASGMQPVTSTIPAVSAVGGIIGALPGNQLAINGIVGALNGVMQTPVTMSQNPTPLTHTTVPPN
ATHPMPATLTNSASGLGLLSDQQRQILIHQQQFQQLLNSQQLTPEQHQAFLYQLMQHHHQQH
HQPELQQLQIPGPTQIPINNLLAGTQAPPLHTATTNPFLTIHGDNASQKVARLSDKTGPVAQEKS
*

**** Amino acid sequence of chimeric *MLLT10::MYO1F* Fusion protein**

MVSSDRPVSLEDEVSHSMKEMIGGCCVCSDERGWAENPLVYCDGHGCSVAVHQACYGIVQV
PTGPWFCRKCESQERAARVRCELCPHKDGALKRTDNGGWAHVVCALYIPEVQFANVSTMEPI
VLQSVPHDRYNKTCYICDEQGRESKAATGACMTCNKHGCRQAFHVTCAQFAGLLCEEEGNG
ADNVQYCGYCKYHFSKLKKSKRGSNRSYDQSLSDSSSHSQDKHHEKEKKKYKEKDKHKQKH
KKQPEPSPALVPSLTVTTEKTYTSTSNNSISGSLKRLEDTTARFTNANFQEVSAHTSSGKDVSE
TRGSEGKGKKSSAHSSGQRGRKPGGGRNPGTTVSAASPFPQGSFSGTPGSVKSSSGSSVQS
PQDFLSFTDSDLRNDSYSHSQQSSATKDVHKGESGSQEGGVNSFSTLIGLPSTSAVTSQPKSF
ENSPGDLGNSSLPTAGYKRAQTSGIEEETVKEKKRKGNKQSKHGPGRPKGNKNQENVSHLSV
SSASPTSSVASAAGSITSSSLQKSPTLLRNGSLQSLSVGSSPVGSEISMQYRHDGACPTTTFSE
LLNAIHNDRGDSSTLTKQELKFIGIYNSNDVAVSFPNVVSGSGSSTPVSSSHLPQQSSGHLQQV
GALSPSAVSSAAPAVATTQANTLSGSSLSQAPSHMYGNRSNSSMAALIAQSENNQTDQDLGD
NSRNLVGRGSSPRGSLSPRSPVSSLQIRYDQPGNSSLENLPPVAASIEQLLERQWSEGQQFLL
EQGTPSDILGMLKSLHQLQVENRRLEEQIKNLTAKKERLQLLNAQLSVPFPTITANPSPSHQIHT

FSAQTEPTRKGMAKGKPRRSSQAPTRAAPAPPRGMDRNGVPPSARGGPLPLEIMSGGGTHR
PPRGPPSTSLGASRRPRARPPSEHNTEFLNVPDQGMAGMQRKRSVGQRPVPGVGRPKPQP
RTHGPRCRALYQYVGQDVDELSFNVNEVIEILMEDPSGWWKGRLHGQEGLFPGNYVEKI*

Abbreviations:
UTR, untranslated region; PFAM, protein family database; PHD, plant homeodomain; zf-HC5HC2H, zinc finger domain; FFPM, fragments per million; bp, base pairs; aa, amino acids; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia.

Supplemental Table 2: Parameters supporting detection of *MYO1F*::*MLLT10* and *MLLT10*::*MYO1F* fusions across multiple fusion-calling algorithms.

Parameter	*MYO1F::MLLT10*	*MLLT10::MYO1F*
Breakpoints (hg19)	FusionCatcher: chr19:8642191 (-), chr10:22015173 (+) STAR-Fusion: chr19:8642191 (-), chr10:22015173 (+) Arriba: chr19:8642191 (-), chr10:22015173 (+)	FusionCatcher: chr10:22022016 (+), chr19:8590446 (-) STAR-Fusion: chr10:22022016 (+), chr19:8590446 (-) Arriba: chr10:22022016 (+), chr19:8590446 (-)
Junction Type	FusionCatcher: Exon-exon STAR-Fusion: ONLY_REF_SPLICE (GT/AG) Arriba: CDS/splice-site	FusionCatcher: Exon-exon STAR-Fusion: ONLY_REF_SPLICE (GT/AG) Arriba: CDS/splice-site
Read Support	STAR-Fusion: 39 junction reads, 23 spanning fragments Arriba: 6/27 split reads, 9 discordant mates FusionCatcher: 19 unique reads, 42 spanning pairs	STAR-Fusion: 40 junction reads, 3 spanning fragments Arriba: 14/8 split reads, 2 discordant mates FusionCatcher: 12 unique reads, 42 spanning pairs
Total Supporting Fragments	FusionCatcher: 61 STAR-Fusion: 62 (FFPM 13.4276) Arriba: 42 (coverage 284/220)	FusionCatcher: 54 STAR-Fusion: 43 (FFPM 9.3126) Arriba: 24 (coverage 309/85)
Confidence	FusionCatcher: High (multiple aligners) STAR-Fusion: High (Presence of Long Double Anchor Support) Arriba: High	FusionCatcher: High (multiple aligners) STAR-Fusion: High (Presence of Long Double Anchor Support) Arriba: High
Filters	FusionCatcher: None STAR-Fusion: None Arriba: duplicates (19), inconsistently clipped (1), mismatches (14)	FusionCatcher: None STAR-Fusion: None Arriba: duplicates (25), mismatches (1)

Functional Effect	FusionCatcher: In-frame STAR-Fusion: In-frame Arriba: In-frame	FusionCatcher: In-frame STAR-Fusion: In-frame Arriba: Out-of-frame* Due to transcript selection ending at exon 25 (short isoform)
Retained Protein Domains	FusionCatcher: Not provided STAR-Fusion: None Arriba: None	FusionCatcher: Not provided STAR-Fusion: PHD-finger, zf-HC5HC2H (MLLT10) Arriba: PHD-finger, SH3 (MLLT10)
Annotations	FusionCatcher: cancer, tumor, t17, exon-exon, reciprocal STAR-Fusion: ["MLLT10: Oncogene"], INTERCHROMOSOMAL [chr19--chr10] Arriba: None	FusionCatcher: cancer, tumor, t17, exon-exon, reciprocal STAR-Fusion: ["MLLT10: Oncogene"], INTERCHROMOSOMAL [chr10--chr19] Arriba: None
Transcript	FusionCatcher: ENSE00003459507 (MYO1F), ENSE00001612483 (MLLT10) STAR-Fusion: ENST00000338257.8 (MYO1F), ENST00000307729.7 (MLLT10) Arriba: ENST00000338257.8 (MYO1F), ENST00000377072.3 (MLLT10)	FusionCatcher: ENSE00001750689 (MLLT10), ENSE00003182580 (MYO1F) STAR-Fusion: ENST00000377072.3 (MLLT10), ENST00000338257.8 (MYO1F) Arriba: ENST00000377072.3 (MLLT10), ENST00000596245.1 (MYO1F)

Abbreviations:
UTR, untranslated region; PHD, plant homeodomain; zf-HC5HC2H, zinc finger domain; SH3, Src homology 3 domain; FFPM, fragments per million; CDS, coding sequence; bp, base pairs; aa, amino acids.