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Clinical and Genomic Profiles of Korean Patients with *MECOM* Rearrangement and the t(3;21)(q26.2;q22.1) Translocation

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The translocation (3;21)(q26.2;q22.1) is a unique cytogenetic aberration that characterizes acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) in patients with AML and myelodysplastic syndrome (MDS) or a therapy-related myeloid neoplasm. Using multigene target sequencing and FISH, we investigated the clinical and genomic profiles of patients with t(3;21) over the past 10 years. The frequency of t(3;21) among myeloid malignancies was very low (0.2%). Half of the patients had a history of cancer treatment and the remaining patients had *de novo* MDS. Twenty-one somatic variants were detected in patients with t(3;21), including in *CBL, GATA2,* and *SF3B1*. Recurrent variants in *RUNX1* (c.1184A>C, p.Glu395Ala) at the same site were detected in two patients. None of the patients with t(3;21) harbored germline predisposition mutations for myeloid neoplasms. *MECOM* rearrangement was detected at a higher rate using FISH than using G-banding, suggesting that FISH is preferable for monitoring. Although survival of patients with t(3;21) is reportedly poor, the survival of patients with t(3;21) in this study was not poor when compared with that of other AML patients in Korea.

Key Words: Gene rearrangement, Chromosomal translocation, Myelodysplastic syndrome, Acute myeloid leukemia

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Acute myeloid leukemia (AML) with inv(3)(q21.3q26.2) or t(3;3)(q21.3q26.2) was added to the 2016 WHO classification as a distinct entity categorized within AML with recurrent genetic abnormalities [1]. The translocation t(3;21) is regarded as an myelodysplastic syndrome (MDS)-related cytogenetic abnormality occurring after chemotherapy or radiation therapy that suggests a poor prognosis and rapid disease progression [2]. Detection of t(3;21) is clinically important because of the grave prognostic implications [3]. The WHO distinguishes AML with t(3;21)(q26.2;q22.1) from AML with inv(3) or t(3;3), which is typical of therapy-related neoplasms (t-MN) [1]. Without a history of cytotoxic or radiation treatment, t(3;21)(q26.2;q22.1) is included in the cytogenetic abnormalities within the diagnostic criteria for AML with myelodysplasia-related changes (AML-MRC) [1]. The t(3;21)(q26.2;q22.1) translocation involves gene rearrangement in the *MDS1-EVI1* complex (*MECOM*) locus on chromosome 3q26 [4]. Although inv(3)(q21.3q26.2), t(3;3)(q21.3q26.2), and t(3;21)(q26.2;q22.1) commonly involve 3q26.2, hematologic neoplasms with t(3;21)(q26.2;q22.1) are classified as AML-MRC or t-MN. We attempted to determine the clinical signatures of patients with t(3;21)(q26.2;q22.1) using multigene target sequencing.

Based on a retrospective review of 1,945 patients diagnosed as having a myeloid neoplasm (928 patients with AML, 811 patients with MDS, 127 patients with AML-MRC, and 79 patients

with t-MN) over the past 10 years (January 2010 to December 2019), four patients had the chromosome aberration t(3;21)(q26.2;q22.1) based on G-banding analysis. To detect hidden t(3;21), which was not detected using G-banding in follow-up samples, we performed FISH for *MECOM* rearrangement using XL *MECOM* (3q26) Dual Color Break Apart Rearrangement Probe (MetaSystems, Altlussheim, Germany). To find unique gene variants associated with t(3;21), we sequenced a 506- or 650-gene panel for hematologic malignancies using the Illumina NextSeq550 platform (Illumina, San Diego, CA, USA). The institutional review boards of Seoul National University Hospital and Seoul National University Boramae Medical Center in Korea approved this study (Nos. 2008-068-1147 and 20-2020-149, respectively).

Case 1 (23-year-old male) was diagnosed as having hypoplastic MDS at the age of two years (Table 1, Fig. 1). Prednisolone and oxymetholone were administered without chemotherapy. At 23 years of age, the patient developed pancytopenia (Hb, 45 g/L; white blood cell [WBC] count, $1,290\times10^6$/L; platelet [PLT] count, 10×10^9/L), and he was diagnosed as having MDS with excess blasts 1 (MDS-EB1). The bone marrow (BM) was markedly hypocellular (cellularity, 1%–10%) with blasts (7.5%). A peripheral blood smear showed a dysgranulopoietic feature in the neutrophils. G-banding revealed the cytogenetic aberration 46,XY,t(3;21)(q26;q22)[8]/46,XY[15]. *MECOM* rearrangement was detected in 49% of the BM nucleated cells (Supplemental Data Figure S1). Multigene sequencing revealed eight somatic variants in *RUNX1* (c.1184A>C, p.Glu395Ala), *BCOR* (c.4071+1G>A, p?), *MXRA5* (c.6508G>T, p.Ala2170Ser), *RAF1* (c.353A>G, p.Tyr118Cys), *TERF1* (c.186_188del, p.Glu62del), *RELN* (c.3513G>C,

Table 1. Clinical characteristics of patients with a hematologic diagnosis with t(3;21)

Characteristics	Case 1	Case 2	Case 3	Case 4
Diagnosis*	MDS-EB1	t-MDS	t-MDS	MDS-U
Age† (yr)/sex	23/male	17/male	66/male	72/female
Underlying disease (age, yr)	MDS (2)	Osteosarcoma (16)	Rectal cancer (59)	Bladder cancer (67)
Chemotherapy or RT	None	Methotrexate, ifosfamide, etoposide, carboplatin, busulfan, melphalan	Oxaliplatin, folinic acid, fluorouracil	None
Survival‡	78 months (alive)	31 months	37 months (alive)	36 months
CBC (Hb, WBC, PLT)	60 g/L, $1,800\times10^6$/L, 60×10^9/L	119 g/L, $2,980\times10^6$/L, 73×10^9/L	117 g/L, $2,130\times10^6$/L, 47×10^9/L	74 g/L, 900×10^6/L, 48×10^9/L
Blast count in BM§	9.0%	<5%	<5%	<5%
Dysplasia	Dysgranulopoiesis	Dyserythropoiesis, dysmegakaryopoiesis	Dysmegakaryopoiesis	N/A
Chromosome (G-banding)‖	46,XY,t(3;21)(q26.2;q22)	45,XY,t(3;21)(q26.2;q22),–7	46,XY,t(3;21)(q26.2;q22)	46,XX,t(3;21)(q26.2;q22)
MECOM FISH positivity‖	Positive (52.7%)	Positive (46%)	Positive (50%)	N/A
Somatic variant genes (VAF, %)	*RUNX1* (16.1)	*RUNX1* (43.6)		*SF3B1* (23.9)
	BCOR (62.1)	*DHX58* (13.0)	*TERF1* (17.3)	*GATA2* (27.9)
	MXRA5 (48.9)	*RTEL1* (44.1)		*GNAS* (22.6)
	RAF1 (38.8)	*DDX54* (57.3)		
	TERF1 (12.3)	*CBL* (57.7)		
	RELN (22.5)	*PASD1* (14.5)		
	STRIP2 (49.5)	*STAT5B* (73.5)		
	CACNA1E (39.4)	*FAH* (50.0)		
		TNFAIP3 (46.4)		

*Initial hematologic diagnosis in the presence of a *MECOM* rearrangement; †Age at initial hematologic diagnosis with *MECOM* rearrangement; ‡Survival time from initial hematologic diagnosis to April 2021 for patients who are still alive; §Blast count observed on BM aspiration or BM section at initial diagnosis; ‖Chromosome and *MECOM* FISH results at AML transformation.
Abbreviations: MDS, myelodysplastic syndrome; MDS-EB1, myelodysplastic syndrome with excess blasts 1; t-MDS, treatment-related myelodysplastic syndrome; MDS-U, myelodysplastic syndrome, unclassifiable; RT, radiotherapy; CBC, complete blood count; BM, bone marrow; N/A, not available due to poor quality; VAF, variant allele frequency; WBC, white blood cell; PLT, platelet.

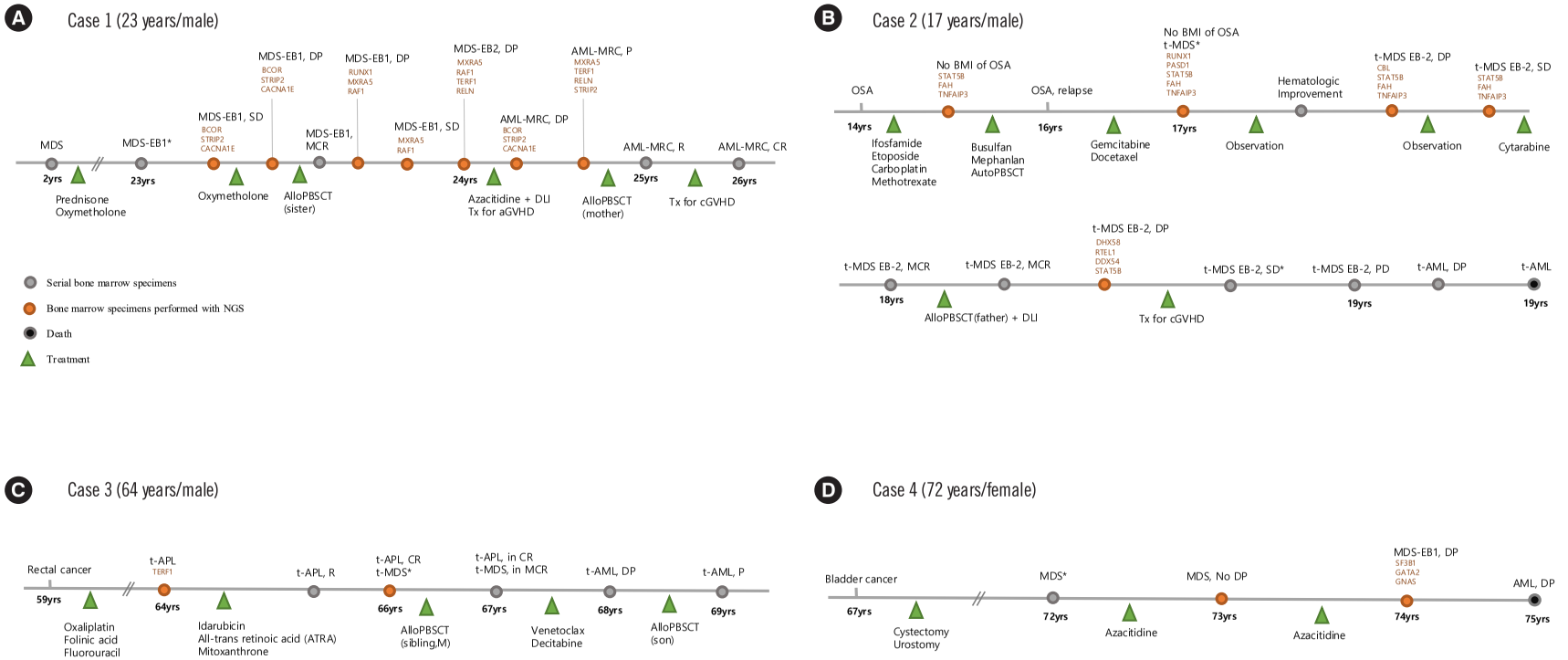

Fig. 1. Detailed flow charts of clinical and genomic events in four patients with t(3;21). Serial BM analyses of cases 1 (A) to 4 (D) are indicated as round circles in the charts. Orange and gray circles represent BM samples analyzed and not analyzed using multigene target sequencing, respectively. All detected somatic variants are indicated in brown letters. Black circles indicate the death of a patient. Diagnosis is indicated above the timeline and treatments are indicated below the timeline as green triangles. *BM with initial detection of *MECOM* rearrangement.

Abbreviations: M, male; F, female; OSA, osteosarcoma; MDS-EB, myelodysplastic syndrome with excess blasts; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; t-MDS, therapy-related myelodysplastic syndrome; t-AML, therapy-related acute myeloid leukemia; APL, acute promyelocytic leukemia; MDS-U, myelodysplastic syndrome, unclassifiable; AlloPBSCT, allogenic peripheral blood stem cell transplantation; MCR, marrow complete remission; DLI, donor leukocyte infusion; GVHD, graft-versus-host disease; d/t, due to; SD, stable disease; R, remission; CR, continuous remission; DP, disease progression; P, persistent; Tx, treatment; BMI, bone marrow involvement.

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p.Met1171Ile), *STRIP2* (c.560G>A, p.Arg187Gln), and *CACNA1E* (c.598C>G, p.Leu200Val). The patient underwent two peripheral blood stem cell transplantations (PBSCTs) from his sister and from his mother, respectively. The disease subsequently progressed to AML-MRC and remission was achieved after chemotherapy. He is currently planning to undergo lung transplantation for chronic graft-versus-host disease (GVHD).

Case 2 (17-year-old male) was previously diagnosed as having osteosarcoma (OSA). Nine months after chemotherapy with alkylating agents (methotrexate, busulfan, and melphalan), the patient developed pancytopenia (Hb, 119 g/L; WBC, $2,980\times10^6$/L; PLT, 73×10^9/L), and he was diagnosed as having t-MDS. G-banding revealed the cytogenetic aberration 45,XY,t(3;21)(q26;q11.2),–7[1]/51,idem,+8,+9,+13,+14,+20,+mar[4]/46,XY[17]. *MECOM* rearrangement was present in 7% of the BM nucleated cells. Nine somatic variants were detected in *RUNX1* (c.1184A>C, p.Glu395Ala), *DHX58* (c.1613C>T, p.Ala538Val), *RTEL1* (c.2395C>G, p.Leu799Val), *DDX54* (c.1529G>A, p.Arg510His), *CBL* (c.122_127dup, p.His41_His42dup), *PASD1* (c.706_708del, p.Ala236del), *STAT5B* (c.881G>A, p.Arg294His), *FAH* (c.391C>T, p.Arg131Trp), and *TNFAIP3* (c.991G>C, p.Asp331His). He died 31 months after PBSCT from his father.

Case 3 (66-year-old male) was diagnosed as having rectal cancer at 59 years of age and was administered chemotherapy (oxaliplatin, folinic acid, and fluorouracil). He was diagnosed as having t-AML 5 years later. The BM was hypercellular (cellularity 81%–90%), with 32.2% blasts. G-banding revealed the cytogenetic aberration 46,XY,t(15;17)(q24;q21)[12]/46,XY[8] and FISH revealed 99% *PML/RARA* rearrangement. Two years after the patient achieved remission, he was diagnosed as having t-MDS, and FISH revealed 9% *MECOM* rearrangement, without *PML/RARA* rearrangement. A somatic variant in *TERF1* (c.186_188del, p.Glu62del) was detected.

Case 4 (72-year-old female) was diagnosed as having bladder cancer 5 years earlier. She was diagnosed as having MDS, unclassifiable (Hb, 74 g/L; WBC, 900×10^6/L; PLT, 48×10^9/L). G-banding revealed the cytogenetic aberration 46,XX,t(3;21)(q26.2;q22), and FISH was not performed because of poor sample quality. Three somatic variants were detected in *SF3B1* (c.2098A>G, p.Lys700Glu), *GATA2* (c.99C>G, p.Tyr33*), and *GNAS* (c.107C>G, p.Ala36Gly). The disease progressed to AML after 36 months and the patient died of AML.

The frequency of the t(3;21)(q26.2;q22.1) *MECOM* rearrangement was 0.2% among AML and MDS patients (4/1,945). Two patients with *de novo* MDS had no history of chemotherapy or radiotherapy (cases 1 and 4). The other two patients, with t-MN, had a history of OSA as the primary cancer (case 2) and a history of chemotherapy due to rectal cancer and subsequent therapy-related acute promyelocytic leukemia (APL) (case 3), respectively.

Ninety consecutive FISH analyses for *MECOM* rearrangement were performed in cases 1, 2, and 3. The G-banding and FISH results were 100% concordant at initial diagnosis, whereas the concordance was 83.3% at follow-up when 16.7% of the samples were analyzed only using the FISH probe for *MECOM*, which was not detected using G-banding. Dysmegakaryopoietic features were observed in all four patients, with a percentage of dyspoietic megakaryocytes ranging from 10% to 75.0% (mean, 52.3%). Dysmegakaryopoietic features were determined using Wright–Giemsa staining of BM aspirates and immunohistochemical staining for CD61 (CD61 Mouse Monoclonal Antibody, Roche, Indianapolis, IN, USA) in BM sections, based on WHO criteria [5].

The overall survival (OS) was 78 months (case 1), 31 months (case 2), 37 months (case 3), and 36 months (case 4) (mean OS, 45.5 months). Two-year survival was 100% and 3-year survival was 75%, whereas 5-year survival was 25%. Case 4 was the oldest patient, who died 36 months after the initial diagnosis. Case 2 showed the shortest OS; this patient harbored monosomy 7 in the context of t(3;21) at initial karyotyping, whereas the other patients had t(3;21) only. Summerer, *et al.* [6] reported poor outcomes in patients with *MECOM* rearrangement and multiple cytogenetic alterations, especially in chromosome 7, compared to those of patients with a single aberration. Case 2 showed a poor prognostic implication of monosomy 7 in a patient with t(3;21). In case 1, the patient was still alive after 78 months. The survival of these patients was not as poor as expected for patients with t(3;21), with a reported median OS for AML and MDS in Korea of 15.7 and 17.7 months, respectively [7, 8].

Targeted multigene sequencing was performed using a 356- or 507-gene panel including known leukemia-related genes and WHO 2016 genetic predisposition genes. The variant-calling strategy is described in Supplemental Data Figure S2, and pathogenicity was assessed according to the 2015 American College of Medical Genetics (ACMG) guidelines [9]. Variant calling revealed 21 somatic variants that were sorted into tier groups (Table 2) [10]. Somatic variants in *RUNX1* and *CBL* are strongly associated with a short OS in MDS patients [11]. *RUNX1* (c.1184A>C, p.Glu395Ala) was detected at the same site in two patients (cases 1 and 2) and *CBL* (c.122_127dup, p.His41_His42dup) was detected in one patient (case 2). None of the patients with t(3;21) harbored germline predisposition mutations to myeloid neoplasms. Ripperger, *et al.* [12] suggested the *MECOM* locus as a novel

Table 2. Somatic variants in four patients with *MECOM* rearrangement with t(3;21)

Case	No.	Chr	Start	End	Ref	Variant	Gene	Type	Accession No.	Base change	AA change	SIFT†	Polyphen2†	CADD‡	Tier [10]
1	1	21	36,164,610	36,164,610	T	G	*RUNX1**	Substitution	NM_001001890	c.1184A>C	p.Glu395Ala	D	B	23.5	2
	2	X	39,921,998	39,921,998	C	T	*BCOR*	Substitution	NM_001123383	c.4071+1G>A	p?	.	.	25.2	2
	3	X	3,235,214	3,235,214	C	A	*MXRA5*	Substitution	NM_015419	c.6508G>T	p.Ala2170Ser	D	D	25.8	3
	4	3	12,645,774	12,645,774	T	C	*RAF1*	Substitution	NM_001354695	c.353A>G	p.Tyr118Cys	T	P	14.16	3
	5	8	73,921,284	73,921,286	GAG	-	*TERF1*	Deletion	NM_003218	c.186_188del	p.Glu62del	.	.	.	3
	6	7	103,236,929	103,236,929	C	G	*RELN*	Substitution	NM_005045	c.3513G>C	p.Met1171Ile	T	P	25.4	3
	7	7	129,094,012	129,094,012	G	A	*STRIP2*	Substitution	NM_001134336	c.560G>A	p.Arg187Gln	D	D	35	3
	8	1	181,546,987	181,546,987	C	G	*CACNA1E*	Substitution	NM_000721	c.598C>G	p.Leu200Val	D	D	28.3	3
2	9	21	36,164,610	36,164,610	T	G	*RUNX1**	Substitution	NM_001001890	c.1184A>C	p.Glu395Ala	D	B	23.5	2
	10	17	40,255,767	40,255,767	G	A	*DHX58*	Substitution	NM_024119	c.1613C>T	p.Ala538Val	T	P	11.83	3
	11	20	62,325,796	62,325,796	C	G	*RTEL1*	Substitution	NM_001283010	c.2395C>G	p.Leu799Val	D	D	26.1	3
	12	12	113,603,723	113,603,723	C	T	*DDX54*	Substitution	NM_001111322	c.1529G>A	p.Arg510His	T	P	16.74	3
	13	11	119,077,232	119,077,232	-	CACCAC	*CBL*	Duplication	NM_005188	c.122_127dup	p.His41_His42dup	.	.	.	3
	14	X	150,817,142	150,817,144	GCT	-	*PASD1*	Deletion	NM_173493	c.706_708del	p.Ala236del	.	.	.	3
	15	17	40,370,849	40,370,849	C	T	*STAT5B*	Substitution	NM_012448	c.881G>A	p.Arg294His	D	D	34	3
	16	15	80,454,614	80,454,614	C	T	*FAH*	Substitution	NM_000137	c.391C>T	p.Arg131Trp	D	P	24.2	3
	17	6	138,199,573	138,199,573	G	C	*TNFAIP3*	Substitution	NM_001270507	c.991G>C	p.Asp331His	D	D	24.7	3
3	18	8	73,921,284	73,921,286	GAG	-	*TERF1*	Deletion	NM_003218	c.186_188del	p.Glu62del	.	.	.	3
4	19	2	198,266,834	198,266,834	T	C	*SF3B1*	Substitution	NM_012433	c.2098A>G	p.Lys700Glu	D	D	28	1
	20	3	128,205,776	128,205,776	G	C	*GATA2*	Substitution	NM_001145661	c.99C>G	p.Tyr33*	.	.	37	1
	21	20	57,428,427	57,428,427	C	G	*GNAS*	Substitution	NM_080425	c.107C>G	p.Ala36Gly	D	B	23.5	3

**RUNX1* (c.1184A>C, p.Glu395Ala) was detected in cases 1 and 2; †Protein-level prediction algorithms (SIFT, Polyphen2) are presented for the nonsynonymous variants. Tolerated and deleterious variants found in the SIFT prediction algorithm are annotated as T and D, respectively, and benign, possibly damaging, and probably damaging variants identified from Polyphen2 prediction are annotated as B, P, and D, respectively; ‡The prediction algorithm CADD can score human single nucleotide variants and short insertion/deletions. Variants with score above 10 to 20 indicate potential deleteriousness in CADD prediction.

Abbreviations: Chr, chromosome; Ref, reference sequence; AA, amino acid; SIFT, sorting intolerant from tolerant; Polyphen2, polymorphism phenotyping version 2; T, tolerated; D, deleterious; B, benign; P, possibly damaging; CADD, combined annotation-dependent depletion.

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candidate gene for hereditary hematological malignancies, and their literature review revealed that constitutional *MECOM* variants include mutations and microdeletions. Reported variants in *MECOM* are p.His751Arg (missense), p.Arg750Trp (missense), and p.Cys766Gly (missense), with the latter as the most frequently reported *MECOM* variant [12]. Inherited predisposition genes related to myeloid neoplasms and *MECOM* variants were not detected in patients with t(3;21)(q26.2;q22.1) in this study.

The limitation of this study is that the germline analysis results could not be confirmed using saliva samples. Alternatively, the detected variants from serial BM samples in the same patients were reviewed based on clinical associations and correlated with the patient's clinical course. As a small number of patients were enrolled because t(3;21)(q26.2;q22.1) is rare, we compared the survival length of MDS and AML patients who received intensive treatment in Korea. To consider the Korean ethnicity, we filtered out the variants observed in healthy Korean controls [13].

In conclusion, the frequency of t(3;21) is very low (0.2%), and the association between t(3;21) and t-MN is 50%. Targeted multigene sequencing revealed 21 somatic variants in patients with *MECOM* rearrangement with t(3;21), including in *CBL, GATA2,* and *SF3B1. RUNX1* (c.1184A>C, p.Glu395Ala) was detected in half of the patients. The detection rate of t(3;21) by FISH was higher than that by G-banding at follow-up; thus, FISH is recommended for monitoring and should be considered a routine evaluation for patients with *MECOM* rearrangements.

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AUTHOR CONTRIBUTIONS

Lee DS and Lee J designed the study and wrote the manuscript. Lee DS and Roh EY collected the samples. Lee DS, Lee J, and Yun J reviewed the medical records of the patients. Kim S performed the cytogenetic analyses. Kim SM processed the data. Yun J, Jeong D, and Lee Y interpreted the data. Lee DS contributed to the revision of the manuscript. All authors approved the final manuscript to be published.

CONFLICTS OF INTEREST

None.

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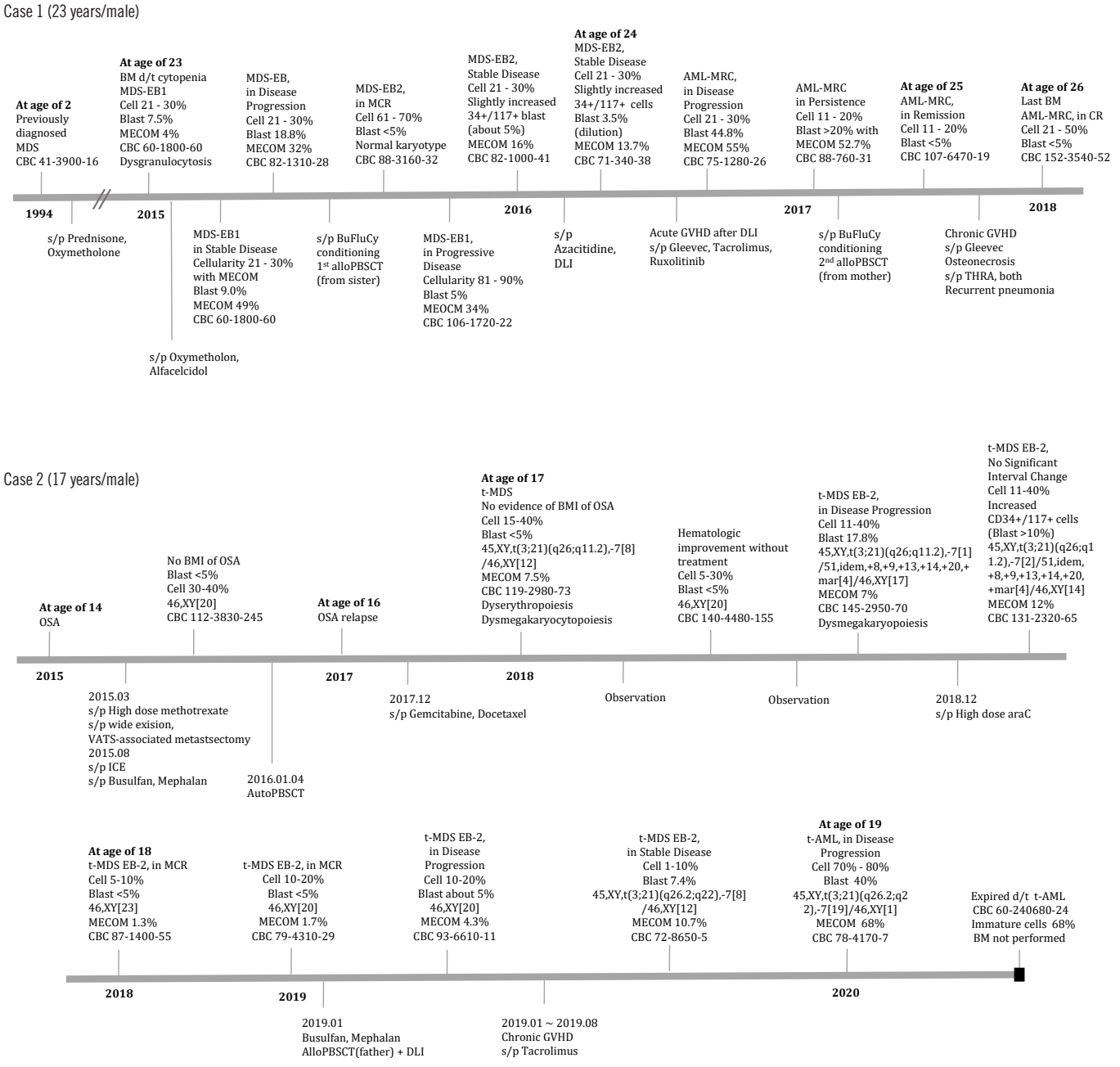

Supplemental Data Figure S1. Progression timelines with patient information from BM, CBC, and cytogenetic analyses. Disease progression and treatments are presented in the timeline by year. CBC, hematologic diagnosis, and bone marrow blast counts are shown. The chromosome and FISH results are described. The black rectangle indicates a patient's death.

Abbreviations: M, male; F, female; BM, bone marrow; Cell, cellularity; CBC, complete blood count; APL, acute promyelocytic leukemia; AlloPBSCT, allogeneic peripheral blood stem cell transplantation; MCR, marrow complete remission; DLI, donor leukocyte infusion; GVHD, graft-versus-host disease; d/t, due to; CR, continuous remission; THRA, total hip replacement arthroplasty; VATS, video-assisted thoracic surgery; LAR, low anterior resection; Bu, busulfan; Flu, fludarabine; Cy, cyclophosphamide; ATG, antithymocyteglobulin; PTCy, transplantation cyclophosphamide; ICE, ifosfamide, carboplatin, and etoposide; High-dose araC, high-dose cytarabine; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ATRA, all-trans-retinoic acid.

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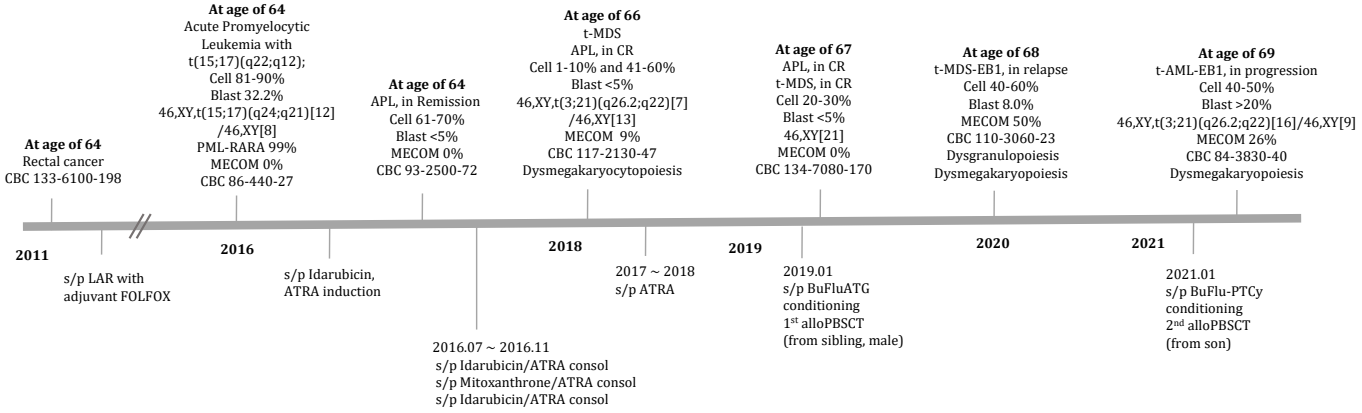
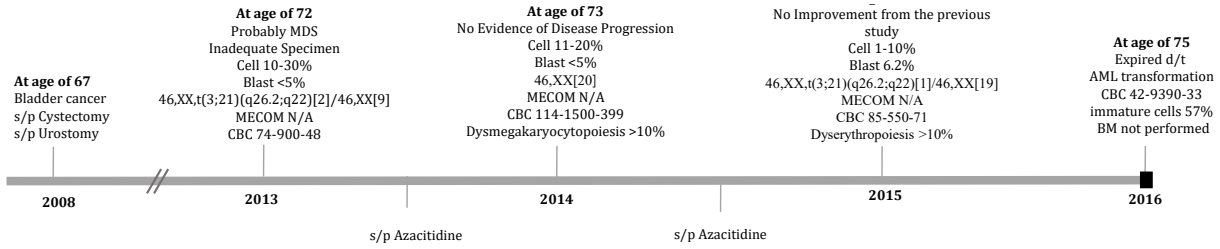
Case 3 (64 years/male)

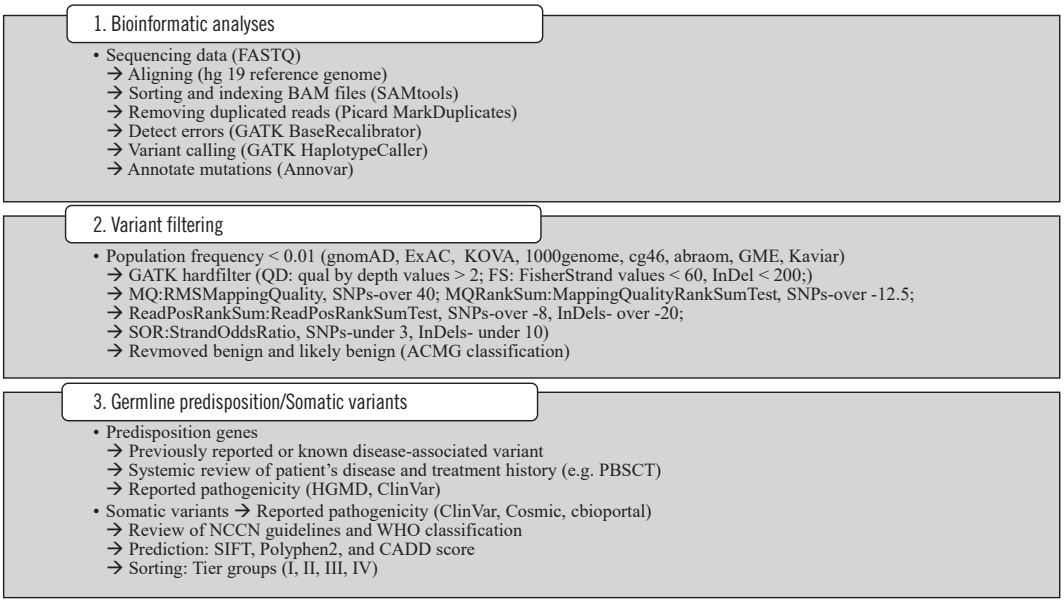


Case 4 (72 years/male)



Supplemental Data Figure S1. Continued.

https://doi.org/10.3343/alm.2022.42.5.590



Supplemental Data Figure S2. Variant-calling strategy for somatic and germline variants. Evaluation of the multigene target sequencing results for somatic and germline variants from bioinformatics analyses to the interpretation of the variants.
Abbreviations: PBSCT, peripheral blood stem cell transplantation; ACMG, American College of Medical Genetics; HGMD, Human Gene Mutation Database; NCCN, National Comprehensive Cancer Network; SIFT, sorting intolerant from tolerant; CADD, combined annotation-dependent depletion.