


# SET-CAN Fusion Gene in Acute Leukemia and Myeloid Neoplasms: Report of Three Cases and a Literature Review

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**Objective:** To investigate the characteristics of hematological malignancies in patients with the *SET-CAN* fusion gene and provide a literature review.

**Methods:** We retrospectively analyzed the clinical data of three cases of acute leukemia and myeloid neoplasms harboring the *SET-CAN* fusion gene who were treated at our hospital. Their clinical manifestations, pathological results and treatment strategies were investigated.

**Results:** The three cases were diagnosed with T-cell acute lymphoblastic leukemia (T-ALL), acute myeloid leukemia (AML) and myeloid sarcoma (MS), respectively. Karyotype analyses identified a normal result in all three patients. Subsequently, we confirmed del(9q34) utilizing FISH analysis. Mutation of the *BRAF* gene was detected in case 1, while mutations in *PHF6* and *BCOR* were detected in case 2, which have not been officially reported in patients with *SET-CAN* fusions. Finally, relevant literature focusing on adult patients with hematological malignancies harboring the *SET-CAN* fusion gene were summarized.

**Conclusion:** Adult patients with the *SET-CAN* fusion gene were rare among cases of hematological malignancies. There was a large degree of heterogeneity between different patients. Notably, some patients remained sensitive to chemotherapy. Overall prognosis may be related to the type of disease and other cytogenetic abnormalities. Systemic cytogenetic and molecular studies are needed to make accurate diagnoses. Additional cases need to be accumulated and summarized to better understand these diseases.

**Keywords:** T-lymphoblastic lymphoma/leukemia, acute myeloid leukemia, myeloid sarcoma, *SET-CAN*, ASCT, prognosis

## Introduction

Recurrent genetic abnormalities are considered to be diagnostic and prognostic markers in patients with hematological malignancies.<sup>1,2</sup> Although intensive chemotherapy and allogeneic stem cell transplantation have greatly contributed to therapeutic strategies, it is still difficult to guarantee long survival and predict clinical outcomes for many individuals. More studies focusing on cytogenetic aberrations and molecular abnormalities are required for further exploration.<sup>3</sup> The *SET-CAN/NUP214* fusion gene is a relatively rare genetic event in leukemia. It was first detected in a patient with acute undifferentiated leukemia (AUL)<sup>4</sup> and was later detected in a patient with acute myeloid leukemia (AML).<sup>5</sup> Subsequently, additional T-ALL patients with this fusion gene have been identified. Until now, fewer than 60 adult cases have been reported, among which over 40 cases have been diagnosed with T-ALL. The estimated incidence of the *SET-CAN* fusion gene in adult patients with T-ALL has been reported

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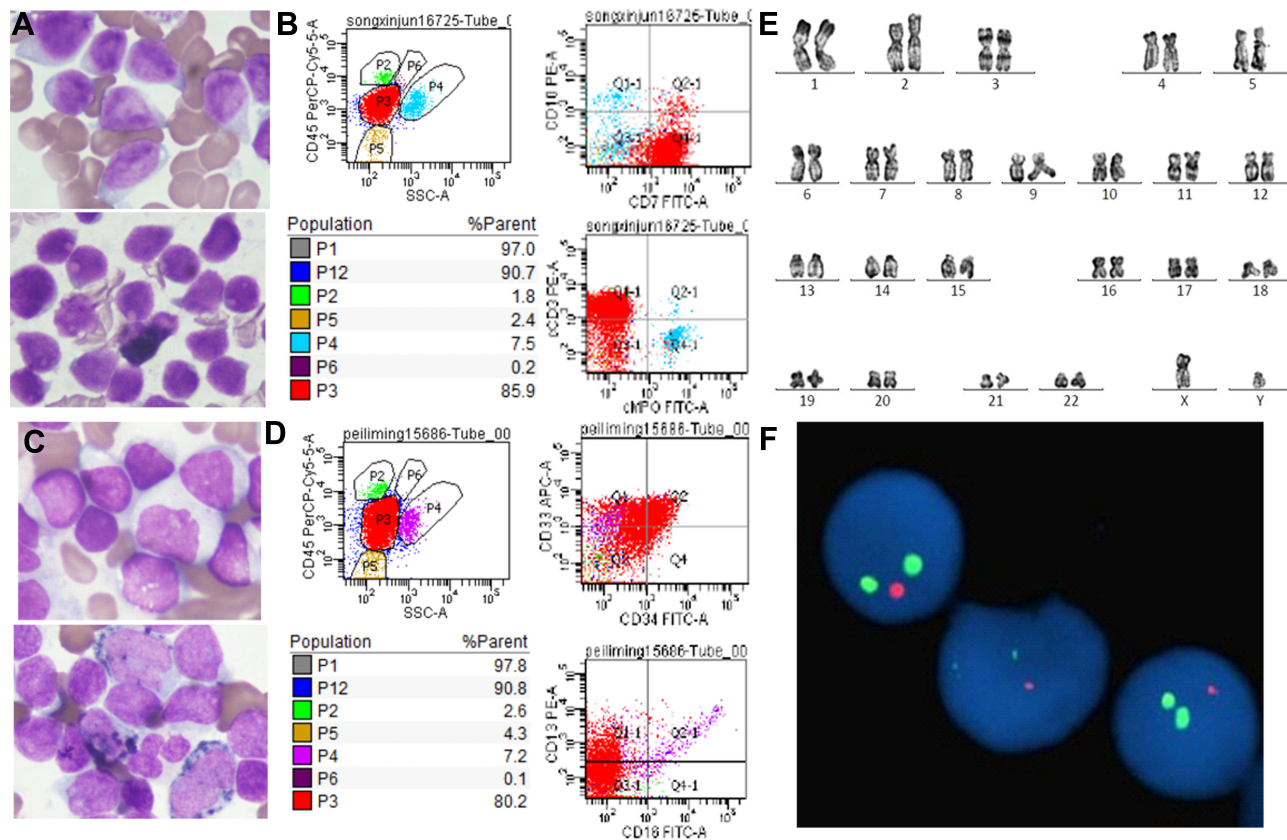
to be ~5%.<sup>6</sup> On the cytogenetic level, it is unclear if the *SET-CAN* fusion is generated by a t(9;9)(q34;q34) or an interstitial deletion at 9q34. The precise role of the *SET-CAN* fusion in hematopoietic cells and its contribution to leukemogenesis remains unknown.<sup>7</sup> It is generally believed that the prognosis of such patients is poor and that these patients are insensitive to traditional chemotherapy and corticosteroids, so hematopoietic stem cell transplantation (HSCT) may improve the prognosis of such patients.<sup>8,9</sup>

Here, we report three patients carrying the *SET-CAN* fusion gene who were diagnosed with T-ALL, AML and myeloid sarcoma (MS), respectively. Furthermore, to the best of our knowledge, no cases of myeloid sarcoma carrying the *SET-CAN* fusion gene have been reported thus far. In the present study, the relevant literature regarding adult patients with the *SET-CAN* fusion gene was reviewed in order to provide a comprehensive profile of this rearrangement. This study was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University. Written informed consent was obtained from all the three patients.

## Case Presentation

### Case 1

A 21-year-old male patient was admitted to our center in December 2019 due to lymphadenopathy with fever and fatigue. Ultrasonographic findings suggested splenomegaly and generalized lymphadenopathy on both sides of the diaphragm. Immunohistochemical staining for cervical lymph node biopsy displayed as diffused abnormal proliferative lymphoblastic cells with CD3(+) TdT(+) CD99(+) CD4(+) Ki67(70%), while a few scattered cells were positive for MPO, CD117 and CD8. The patient was diagnosed with T-lymphoblastic lymphoma (LBL). The complete blood cell (CBC) of the patient showed a white blood cell (WBC) count of  $37.16 \times 10^9/L$ , a hemoglobin (HGB) level of 150 g/L and a platelet level of  $244 \times 10^9/L$ . Intriguingly, a bone marrow aspirate revealed hypercellularity with predominant blasts (Figure 1A), and flow cytometry showed the T-lymphoblasts (P3 group, 85.9%) mainly expressed CD7, cCD3 and CD38; partially expressed CD5 and HLA-DR; and did not express CD33, CD117, CD34, CD19,



**Figure 1** (A) Morphology of leukemic cells at diagnosis (original magnification,  $\times 1000$ ) for case 1. (B) Flow cytometry result for case 1. (C) Morphology of leukemic cells at diagnosis (original magnification,  $\times 1000$ ) for case 2. (D) Flow cytometry result for case 2. (E) Karyotype analysis showed normal result of case 1. (F) Dual-color FISH analysis of case 1 with LSI BCR-ABL1 dual-color, dual-fusion translocation probe showing a monoallelic loss of the ABL gene. The ABL gene (9q34) was labeled as orange, and the BCR gene (22q11.2) was labeled as green.



CD10, MPO, cCD79a, CD2, CD1a, CD15, CD13, CD56, TdT, CD123, CD25, CD99, CD4, CD8, CD3, TCRa/b, TCRg/d and CD45RO, which indicated Pro-T-ALL (Figure 1B). Karyotyping analysis of a bone marrow (BM) sample illustrated that the patient had a 46,XY karyotype[20] (Figure 1E). In total, reverse transcriptase (RT)-PCR covering 56 commonly detected fusion genes in leukemia (listed in Supplementary Table 1) was performed on the bone marrow sample. The *SET-CAN* fusion gene was detected. To determine whether the *SET-CAN* fusion identified in this case was derived from deletion of 9q34, fluorescence in situ hybridization (FISH) analysis using the *BCR/ABL* fusion probe covering this region was applied to the cultured bone marrow cells. The *ABL* gene (9q34) was labeled as orange, and the *BCR* gene (22q11.2) was labeled as green (Figure 1F). A total of 200 cells were analyzed, and ~83% of the cells showed deletion of *ABL* and two copies of *BCR*. The remaining cells showed a normal hybridization pattern. The FISH result was nuc ish(BCR×2),(ABL×1) [166/200]. Then, next generation sequencing (NGS) was performed on 39 commonly mutated genes in ALL (listed in Supplementary Table 2), and we identified a missense mutation c.1803A>T (p.Lys601Asn) in *BRAF* (NM\_004333). Based on the clinical course and laboratory findings, the patient was finally diagnosed with T-LBL/ALL and subsequently received an induction chemotherapy VICP (vinorelbine 4 mg/d, d1, 8, 15, 22; idarubicin 8 mg/d, d8-10; cyclophosphamide 1.2 g/d, d8; dexamethasone 15 mg/d, d1-5, 11-14). Complete remission (CR) was achieved after the first cycle of chemotherapy. The patient will continue consolidation therapy and wait for allogeneic HSCT.

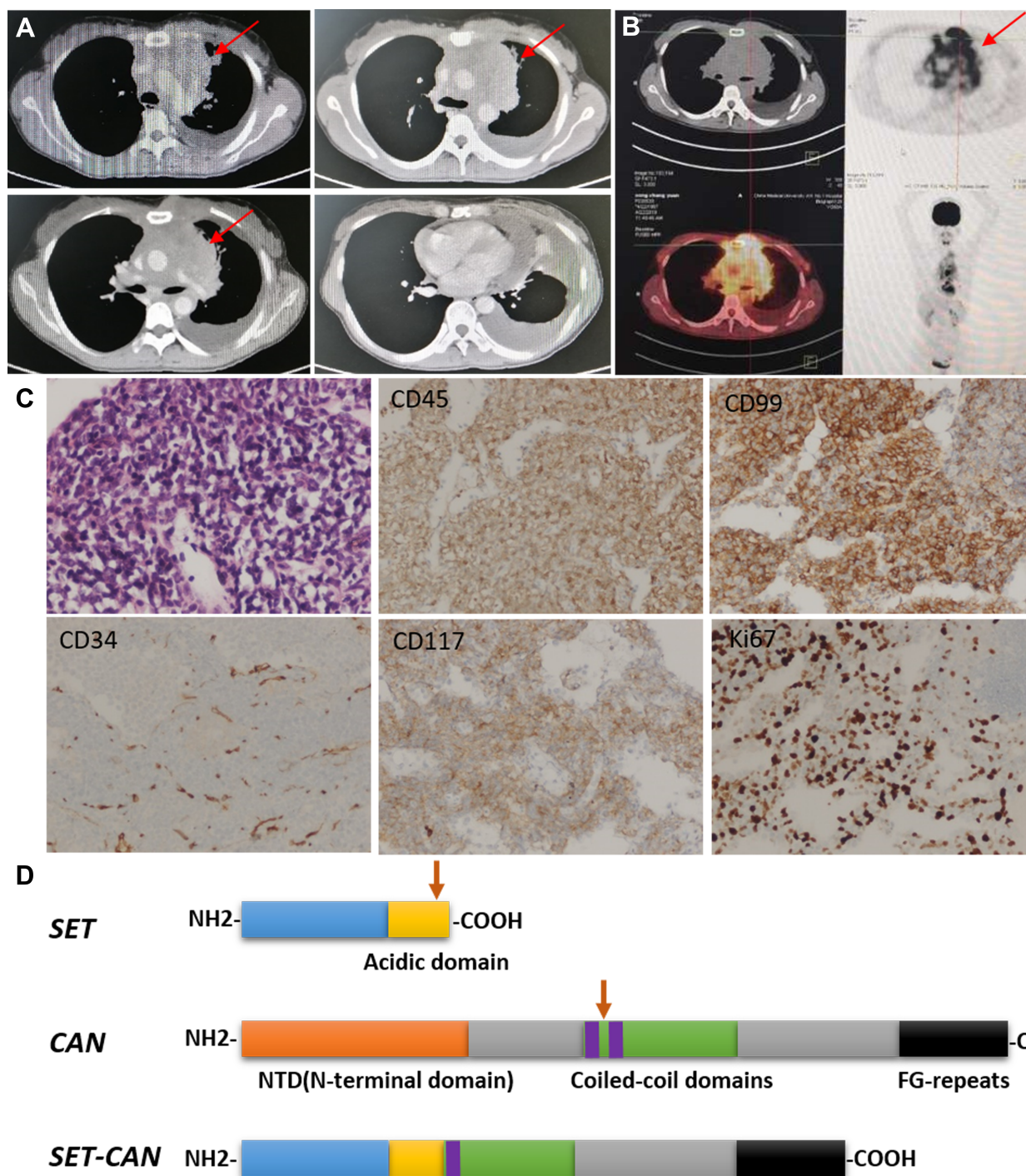
### Case 2

A 24-year-old male presented with lymphadenopathy for half a month without fever and was admitted to our center in August 2019. The routine blood test showed a WBC count of  $11.41 \times 10^9/L$ , a HGB level of 126 g/L and a platelet level of  $211 \times 10^9/L$ . CT findings suggested mediastinal and bilateral axillary lymphadenopathy as well as splenomegaly. The proportion of blasts in bone marrow was 81.2% (Figure 1C), and flow cytometry (Figure 1D) showed the blasts (P3 group, 80.2%) mainly expressed CD7, CD33 and CD34; partially expressed CD11b, HLA-DR, CD123, CD64 and CD13; and did not express CD10, CD117, CD16, CD19, CD10, MPO, cCD3, cCD79a, CD14, CD3, CD15, CD4, CD8, CD2, CD25, CD9 and CD11c, which indicated AML. The karyotype result was normal. The *SET-CAN* fusion gene was detected in

the bone marrow sample by RT-PCR. Then, NGS identified insertion mutation c.4834dupC (p.Leu1612fs) in the *BCOR* gene (NM\_01123383) (38.51%); a *PHF6* (NM\_001015877) mutation (85.21%): c.746C>T (p. Thr249Ile); and a *CEBPA* (NM\_004364) mutation (6.1%): c.857G>A (p.Arg286Gln). The patient was diagnosed with AML-M5. A standard DA (Daunorubicin 120 mg×3 days, Cytarabine 200 mg×7 days) was given for two cycles; then, Cytarabine 3.5g Q12h×3 days was given for five cycles. CR was achieved. The patient declined HSCT and has been alive for 8 months.

### Case 3

A 32-year-old female presented with a mediastinal mass for 2 months with no fever and was admitted to our center in October 2018. The CBC of the patient showed a WBC count of  $4.15 \times 10^9/L$ , an HGB level of 111 g/L and a platelet level of  $128 \times 10^9/L$ . Ultrasonographic findings suggested generalized lymphadenopathy. The result of Lung CT+ enhancement showed left hilar and mediastinal space occupying lesions,  $5.6 \times 4.0$  cm in diameter, with left upper lobe obstructive changes, pericardial effusion and left pleural effusion (Figure 2A). The PET-CT showed soft tissue shadow in the mediastinum and chest wall, wrapping mediastinal vessels, with SUVmax=10.1, which were considered to be malignant lesions. The left pleura was thickened with increased metabolism, and the metabolism of the left neck and upper and lower clavicle lymph nodes was also increased (Figure 2B). Immunohistochemical staining of the mediastinal mass biopsy (Figure 2C) displayed diffused abnormal proliferative cells with CD7(+), Pax8(+), CD33(+), CD43(+), CD99(+), CD4(+), LMO-2(+), Ki67 (85%), while a few scattered cells were positive for CD117, Pax5 and CD8. Other staining results showed CD1a(-), CD5(-), CD20(-), CD3(-), CK(-), CD19(-), CD21(-), CD163(-), EMA(-), P63(-), CD68(-), MPO (-), CD34(-), TdT(-), CAM5.2(-), TTF1(-), ALK(-), CD30(-), CD10(-), CD56(-), CgA(-), GB(-), SYN(-), TIA1(-) and EBER(-). The patient was diagnosed with myeloid sarcoma (MS). The results of bone puncture, bone marrow biopsy and bone marrow flow cytometry were all negative. The karyotype result was normal. The *SET-CAN* fusion gene was detected. Pericardial effusion was exudate. The Rivalta test was positive, and the cell count was  $4481 \times 10^6/L$ . After the initial chemotherapy with an HIA regimen (Idarubicin 20 mg×2 days, cytarabine 100 mg m<sup>2</sup>×7 days, homoharringtonine 2 mg×4 days), the mediastinal mass was significantly reduced. However, the follow-up treatment did



**Figure 2** (A) The result of Lung CT+ enhancement for case 3. The tumor is marked by arrow. (B) The result of PET-CT for case 3. The tumor is marked by arrow. (C) Immunohistochemical staining of the mediastinal mass biopsy for case 3. (D) Schematic representation of SET, CAN, and SET-CAN proteins. Fusion breakpoints are indicated with vertical arrowhead.

not further alleviate the disease, and the negative effect of myelosuppression was particularly prominent, with a rapidly increased pericardial effusion. At last, the patient discontinued treatment due to intestinal infection.

## Discussion

Both the *SET* and *CAN* genes are located at chromosome 9q34. The SET protein is a potent endogenous inhibitor of protein phosphatase 2A (PP2A). It is overexpressed in

numerous cancer types.<sup>10,11</sup> The SET protein has multiple functions, being involved in, for example, apoptosis, the cell cycle and nucleosome assembly.<sup>12</sup> CAN/NUP214 is a type of nucleoporin, which is the main component of the nuclear pore complex and plays a role in nuclear protein import, mRNA export and cell cycle progression.<sup>13</sup> The SET-NUP214 fusion protein consists of almost the whole SET protein fused to the C-terminus of NUP214 (Figure 2D).

LBL/ALL is an aggressive malignant proliferative disease of the hematopoietic system. It is characterized by uncontrolled proliferation of T-lineage progenitor cells with a 5-year-overall survival of ~48%.<sup>14</sup> The clinical features include presentation with hyperleukocytosis and extramedullary infiltration of the lymph nodes and other organs. This form accounts for 25% of total adult ALL cases.<sup>15</sup> Most patients with T-ALL have a high tumor load, with rapid disease progression and a high risk of disease recurrence. Until now, just over 40 adult T-ALL patients with the *SET-CAN* fusion gene have been reported. Relevant articles with detailed information on patients have been collected in Table 1. Here, we collected eight studies, including 35 adult T-ALL patients with the *SET-CAN* fusion.<sup>6,9,16-21</sup> Another two studies also mentioned patients with the *SET-CAN* fusion gene but were not included because they lacked the detailed information.<sup>22,23</sup> Most of the reported T-ALL cases with the *SET-CAN* fusion gene occurred in young and middle-aged men. Flow cytometry analysis showed that patients not only had the differentiation antigen of T lymphocytes, but also expressed many myeloid antigens, suggesting that the tumor cells of these patients may be in the early stage of T lymphocyte development. The deletion or translocation of the small segment on chromosome 9 is difficult to detect using conventional cytogenetic methods, and the aberration needs to be further confirmed by FISH or array. More than one-third of the patients described in the literature had normal karyotype results. Complex karyotypes and other abnormal karyotypes have also been reported. However, del(9q34) can be detected in all patients who received FISH or array tests. Most of the patients presented with the SET exon7-NUP214 exon18 (S7N18 type) fusion transcript (13/14). Only one patient presented with the SET exon7-NUP214 exon17 (S7N17 type) fusion transcript (1/14). Mutation of the *NOTCH1* gene as well as the *PHF6* gene has also been identified in several patients.

It is reported that patients with a *SET-CAN* fusion have poor prognosis and are not sensitive to chemotherapy,

especially to high dose glucocorticoids. It is suggested that HSCT should be carried out as early as possible after remission. Yang, et al<sup>9</sup> reported three patients with T-ALL harboring the *SET-CAN* fusion gene, all of whom were refractory to high dose glucocorticoid-based chemotherapy. The authors sorted CD34<sup>+</sup>Lin<sup>-</sup> cells from one patient as primary T-ALL cells and found that these cells were insensitive to dexamethasone. Additionally, *SET-CAN* mediated the loss of regulation of histone H3 acetylation, which might be a potential mechanism of glucocorticoid resistance. Furthermore, CLAG chemotherapy in combination with asparaginase might be a potential treatment option for adult SET-CAN<sup>+</sup>T-ALL patients. The *SET-CAN* fusion gene is also considered to be a contributor to the poor responsiveness of SET-CAN-harboring leukemic cells to glucocorticoids. In one study, the *SET-CAN* fusion protein did not interact with the glucocorticoid receptor, was constitutively coprecipitated with glucocorticoid response elements and suppressed glucocorticoid receptor transcriptional activity and histone acetylation.<sup>24</sup> In our case report, patient 1 showed a normal karyotype result accompanied with del(9q34) confirmed by FISH. A missense mutation of *BRAF*, which has not been previously reported in patients harboring the *SET-CAN* fusion gene, was identified by NGS. The mutant BRAF protein continuously activates the Ras/BRAF signaling pathway, which is essential for tumor growth, proliferation, invasion and metastasis.<sup>25</sup>

While the majority of the adult patients experienced T-ALL, other subtypes of acute leukemia with the *SET-CAN* fusion gene are summarized in Table 2. Here, we collected seven studies<sup>4,5,7,8,26-28</sup> including nine adult patients with the *SET-CAN* fusion gene. Three patients were diagnosed with AUL, four patients were diagnosed with AML and the other two were diagnosed with B-ALL. Another study conducted by Choi et al<sup>23</sup> also mentioned two cases of AML, but was not included in our table because it lacked detailed information. According to the literature, only one B-ALL patient was female, while all the patients with AML and AUL were male. The median age was 36.5 years (19–46 years). In our report, case 2 was diagnosed with AML-M5. A mutation in *PHF6* was identified in this patient, which has also been mentioned in other patients with the *SET-CAN* fusion gene.<sup>18</sup> *PHF6*, located in the nucleolus, is an X-linked tumor suppressor gene which functions in transcriptional regulation. *PHF6* mutations can be found in 15% of AML patients and is associated with poor prognosis.<sup>29</sup> Additionally, *BCOR* gene mutations have been found in 8–10% of AML

Table 1 Characteristics of Adult SET-CAN<sup>+</sup> T-ALL Cases Reported in the Literature

	Sex	Age (y)	Country	WBC (*10 <sup>9</sup> /L)	Blast (%)	Karyotype	Array	FISH	Immunophenotype	Gene Mutation	Fusion Position	Treatment	Follow-Up
Dai 2012 <sup>18</sup>	Male	20	China	34.1	NR	46,XY [20]	NR	del(9q34)/ ABLI	Positive for CD7, cCD3,CD13,CD33, CD34	PHF6, NOTCH1	5'SET exon7- NUP214 exon18 3'	NR	Relapse and death, 9 months
	Female	56	China	6.81	NR	92-93,XXXX, +1, +3,+4,-5,-6,-7, +10,-18, + dmin * 3-4[CP10]	NR	del(9q34)/ ABLI	Positive for CD7, cCD3,CD33,CD34	NA	5'SET exon7- NUP214 exon18 3'	NR	NR
	Male	23	China	2.65	NR	46,XY [19]	del(9)(q34, 11q34.13),del (12) (p13.2p11.23)	del(9q34)/ ABLI	Positive for CD7, cCD3,CD33,CD34	PHF6, NOTCH1	5'SET exon7- NUP214 exon18 3'	NR	Relapse and survive in CR2, 17. 8 months
	Male	27	China	NA	NR	46,XY [20]	del(1)(p36.33, p36.12),del(2) (q37.1), del(9) (q34.11q34.13)	NR	Positive for CD7, cCD3,CD13,CD33, CD34	NOTCH	5'SET exon7- NUP214 exon18 3'	NR	Relapse and death, 15 months
	Male	45	China	33.3	NR	46,XY [20]	NR	NR	Positive for CD7, cCD3,CD34	PHF6, NOTCH1	5'SET exon7- NUP214 exon18 3'	NR	Relapse and death, 30 months
	Male	23	China	15.1	NR	46,XY [20]	del(9)(q34, 11q34.13),del (11)(p13),del (12) (p13.2p11.21), del(17)(q11.2)	del(9q34)/ ABLI	Positive for CD7, cCD3,CD10,CD33, CD34	PHF6, NOTCH1	5'SET exon7- NUP214 exon17 3'	NR	NR



Chae 2011 <sup>17</sup>	Female	55	Korea	24.43	87	47,XX,del(11)(q22q23), del(12)(p13),+14	del(9)(q34.11-34.13)	del(9q34)/ ABLI	CD33, CD34, CD13, CD7, cy-CD3	NIR	5'SET exon7- NIUP214 exon18 3'	NIR	Relapse 31 months
	Male	32	Korea	18.04	95	46,XY,del(13)(q12q14)	NR	del(9)(q34)/ ABLI	CD33, CD34, CD13, CD7, CD5, cy-CD3	NIR	5'SET exon7- NIUP214 exon18 3'	NIR	Relapse and death, 42 months
	Male	32	Korea	39.06	97	46,XY,del(6)(q21q23),del(12)(p11.2)	NR	del(9)(q34)/ ABLI	CD33, CD34, HLA-DR, CD7, cy-CD3	NIR	5'SET exon7- NIUP214 exon18 3'	NIR	Relapse and death, 21 months
	Female	20	Korea	5.07	83	46,XX,+del(3)(q11.2),del(12)(p13),-13,add(17)(p.11.2)	NR	del(9)(q34)/ ABLI	CD33, CD34, CD7, CD5, CD8, Cy-CD3	NIR	5'SET exon7- NIUP214 exon18 3'	NIR	33 months
Ben Abdelali 2014 <sup>16</sup>	Male	34	France	30.4	NIR	46,XY,t(3;10)(q1;q?) [20]	NR	NIR	CD34, CD33, CD7, cCD3 (ETP-ALL)	NIR	NIR	GRAALL trail	CR, relapse, SCT, died 49 months
	Female	37	France	8.6	NIR	46,XX,t(4;16)(q21;q23) [30]	del(9)(q34.11q34.13)	NIR	CD34, CD7, cCD3 (ETP-ALL)	NIR	NIR	GRAALL trail	CR, SCT, alive 64 months
	Male	29	France	10.1	NIR	46,XY,del(6)(q14q24),del(11)(q21),del(12)(p12)[9]/46,XY[3]### del(9)(q34.11q34.13)### NR	del(9)(q34.11q34.13)	NIR	CD34, CD13, CD33, CD7, cCD3 (ETP-ALL)	NIR	NIR	GRAALL trail	CR, relapse, SCT, alive 44 months
	Male	41	France	18.4	NIR	47,XY,+4[15]	NR	NIR	CD34, CD33, CD7, cCD3 (ETP-ALL)	NIR	NIR	GRAALL trail	CR, SCT, alive 46 months

(Continued)

Table 1 (Continued).

Sex	Age (y)	Country	WBC (*10 <sup>9</sup> /L)	Blast (%)	Karyotype	Array	FISH	Immunophenotype	Gene Mutation	Fusion Position	Treatment	Follow-Up
Male	23	France	604.4	NR	46,XY[3,1]	NR	NR	CD7, cCD3	NR	NR	GRAALL trail	Died 5 months
Male	30	France	24.9	NR	46,XY[2,1]	NR	NR	CD7, cCD3	NR	NR	GRAALL trail	CR, SCT, relapse, CR, alive 66 months
Male	36	France	181.8	NR	46,XY,add(5)(q22), del(12)(p11p13)[2]/46,XY,der(5)t(5;12)(q11.2;p13), del(12)(p11p13), der(12)t(5;12)(q11.2;p13)add(5)(q22)[2]/46,XY[16]	NR	NR	CD34, CD33, CD7, cCD3	NR	NR	GRAALL trail	CR, SCT, alive 24 months
Male	45	France	50.8	NR	46,XY,del(5)(q?)[7]/46,XY,del(13)(q12q14),inv(14)(q11q32),del(16)(p12p13.3)[5]/46,XY[5]	NR	NR	CD7, cCD3	NR	NR	GRAALL trail	CR, alive 33 months
Male	38	France	2.8	NR	88,XX,-Y,-[4n], add(2)(q24),+4,-5,-5,add(5)(q35),-7,-9,add(9)(p21),del(9)(q11q12),+10, del(12)(p13)x2,-17x2,+2mar[cp7]/77-89,sl,+Y,+Y,-add(9),-del(9),+9,+9,+1-2mar[cp3]/78-88,sd11,-9,add(15)(p11)[cp6]/46,XY[1]	NR	NR	CD34, CD33, CD7, cCD3 (ETP-ALL)	NR	NR	GRAALL trail	CR, SCT, died 9 months

	Male	28	France	41.8	NR	46,XY,del(5)(q31q35),del(6)(q12q216),del(7)(q34),del(12)(p12),del(16)(q22)[29]/47,idem,del(11q),+mar[6]/46,XY[3]	NR	NR	NR	CD34, CD33, CD7, cCD3	NR	NR	NR	GRAALL trail	CR, SCT, alive 30 months
	Male	20	France	30.9	NR	48,XY,+21,+21[5]/46,XY [25]	NR	NR	NR	CD7, cCD3	NR	NR	NR	GRAALL trail	CR, SCT, alive 28 months
Prokopiou C 2015 <sup>19</sup>	Female	48	Cyprus	NR	59	NR	del(17)(q11.2), del(6)(q16.1-q21) and del(12)(p12.1-13.1)	NR	NR	CD7+, CD5 dim, sCD3+, cCD3+, CD4-, CD8-, CD34+, HLA-DR+, CD117+, MPO+	NR	NR	NR	combination chemotherapy	ASCT from her fully matched sibling, relapsed one year after ASCT, died during induction therapy
	Male	45	Cyprus	NR	NR	NR ### del(17)(q11.2), del(6)(q16.1-q21) and del(12)(p12.1-13.1) ### NR	del(17)(q11.2), del(6)(q16.1-q21) and del(12)(p12.1-13.1)	NR	NR	CD7+, CD38+, CD34+, CD3+, CD4-, CD8-, CD33+, CD1a-	NR	NR	NR	combination chemotherapy	ASCT from a fully matched unrelated donor, died six months after ASCT
Lee 2011 <sup>20</sup>	Male	28	Korea	37.2	62.5	47,XY,del(1)(p13p22),del(6)(q13q21),del(9)(q12),del(11)(q13),-12,add(15)(p11.2),del(16)(q22),+19,+mar[3]/46,XY [17]	NR	NR	NR	positive expression of CD5 (67%), CD7 (95%), CD33 (79%), and CD34 (53%), negative for CD3, CD10, CD19, and CD20.	NR	NR	NR	prednisolone, vincristine, L-asparaginase, daunomycin, cytarabine, and methotrexate,	CR, SET-NUP214 fusion transcript+. The patient is scheduled to receive HSCT from an unrelated donor.

(Continued)

Table 1 (Continued).

	Sex	Age (y)	Country	WBC (*10 <sup>9</sup> /L)	Blast (%)	Karyotype	Array	FISH	Immunophenotype	Gene Mutation	Fusion Position	Treatment	Follow-Up
Yang 2020 <sup>9</sup>	Male	26	China	12.3	97	46, XY, del(11)(q13), del(13)(q14), inv(16)(p13.3q23)	NR	NR	Positive for CD7, CD99; partial expressed cCD3, CD33, CD34, CD10; weak expressed CD2; negative for Surface CD3, cCD79a, CD117, CD13, CD19, HLA-DR, cTDT, CD56, CD4, CD5, CD1a, CD8, cMPO, CD15, CD64	NR	NR	VICP with cytarabine 2 g/dl-3.	Candida tropicalis epicemicia, died +15 days
	Male	51	China	109.1	89.7	Normal	NR	NR	Positive for CD7, CD33, CD99, CD10; partial expressed CD34, cCD3, CD5; weak expressed cTDT; negative for surface CD3, CD1a, CD4, CD2, CD3, CD8, CD117, CD13, CD19, HLA-DR	NR	NR	VICP; mitoxantrone; etoposide and cytarabine	Infected with Pseudomonas aeruginosa and Stenotrophomonas maltophilia, died +37 days





Table 1 (Continued).

Sex	Age (y)	Country	WBC (*10 <sup>9</sup> /L)	Blast (%)	Karyotype	Array	FISH	Immunophenotype	Gene Mutation	Fusion Position	Treatment	Follow-Up
Female	27	Italy	NR	NR	Failed	NR	del(9)(p21)/CDKN2A-B del(9)(q34)/ABL1 del(11)(p13)/LMO2 del(11)(q14)/CALM	Pre-T	NOTCH1	NR	NR	Resistant died +12 months
Male	19	Italy	NR	NR	Failed	NR	del(9)(q34)/ABL1 del(11)(p13)/LMO2 del(11)(q14)/CALM del(12)(p13)/ETV6	Pro-T	NR	NR	NR	CR, alive +3 months
Male	18	Italy	NR	NR	Failed	NR	del(9)(q34)/ABL1 del(5)(q35)/TLX3	Pre-T	NR	NR	NR	CR, relapse, died +24 months
Male	23	Italy	NR	NR	46,XY[12]	NR	del(9)(q34)/ABL1	Pre-T	NR	NR	NR	CR, relapse, ASCT, died +17months

**Abbreviations:** SCT, stem-cell transplantation; ASCT, allogeneic stem cell transplantation; CR, complete remission; NR, not report; VICEP, vindesine, idarubicin, cyclophosphamide, dexamethasone; CALGB9111, cyclophosphamide, doxorubicin, vincristine, prednisone, L-asparaginase; CLAG, cladribine, cytarabine, granulocyte colony-stimulating factor (G-CSF).

**Table 2** Characteristics of Other Subtypes of Adult SET-CAN<sup>+</sup> Leukemia Cases Reported in the Literature

	Sex	Age (y)	Country	Diagnosis	Blast (%)	WBC (#10 <sup>9</sup> /L)	Karyotype	Array	FISH	Immunophenotype	Gene Mutation	Fusion Position	Treatment	Follow-Up
Vonlindern 1992 <sup>4</sup>	Male	19	Netherlands	AUL	NR	NR	46,XY	t(9;9)(q34;q34) and no del(9)(q34.11q34.13)	NR	NR	NR	5'SET exon7-NUP214 exon18 3'	NR	NR
Kim 2010 <sup>27</sup>	Male	40	Korea	AUL	84	53	46,XY[20]	del(9)(q34.11q34.13) del(9)(q22)	del(9)(q34)/ABL1	CD7 (95.6%), CD33 (51.7%), CD117 (73.8%), and CD38 (94.8%), cCD3 (1.3%), MPO(-),cCD22 (0.1%), cCD79a (2.6%), CD19 (0%)	NR	5'SET exon7-NUP214 exon18 3'	Cytosine arabinoside and idarubicin	CR, alive 7 months, lost to follow-up
Dong 2017 <sup>26</sup>	Male	31	China	AUL	56.8	3.6	46,XY[2]	NR	NR	Positive for CD34, CD117, CD7, CD71, CD38, CD33, CD123, HLA-DR	NR	5'SET exon7-NUP214 exon18 3'	mitoxantrone, cytarabine (MA)	CR was achieved after 2 cycles of MA regimen, but in the fourth course of consolidation chemotherapy, central nervous system leukemia was suspected, and the patient refused further treatment
	Male	35	China	M1	91.2	8.0	46-49,XY, del(1)(p13p31), t(3;6)(q27;q21), del(2)(p11)inc [cp13] / 46,XY[7]	NR	NR	Positive for CD34, CD117, CD38, HLA-DR, CD33, CD11b, CD7, CD71, CD123, CD4	NR	5'SET exon7-NUP214 exon18 3'	Mitoxantrone, etoposide, cytarabine (MEA)	CR, relapse 14 months after diagnosis
	Male	38	China	M2	56	1.6	46,XY [20]	NR	NR	positive for CD34, CD38, HLA-DR, CD33, CD13, CD123, CD19, CD7, CD71, MPO	NR	5'SET exon7-NUP214 exon18 3'	daunorubicin, cytarabine (DA)	CR, die of septic shock during the second treatment course

(Continued)

Table 2 (Continued).

	Sex	Age (y)	Country	Diagnosis	Blast (%)	WBC (*10 <sup>9</sup> /L)	Karyotype	Array	FISH	Immunophenotype	Gene Mutation	Fusion Position	Treatment	Follow-Up
Jeong 2019 <sup>8</sup>	Male	46	Korea	M1	89	17.1	59-90, XXXY,-1,-2,-5,-7,-7,-10,-13,-13,-16,-17,-18,-21[cp23]	NR	del(9)(q34)/ABL1	positive for MPO, CD33, CD7, CD34, and CD71 antigens	NR	5'SET exon8-NUP214 exon18 3'	idarubicin and cytosine arabinoside	CR and MR, the patient received allogeneic peripheral blood stem cell transplantation from a full-matched sibling donor. still alive for 8 months
Rosati 2007 <sup>5</sup>	Male	35	Italy	M4	90	40	Normal	del(9)(q34.1)	del(9)(q34)/ABL1	positive for myeloperoxidase, CD34, CD33, CD13, CD45, CD66b, CD15 and CD11b antigens	none	5'SET exon7-NUP214 exon18 3'	daunorubicin and cytosine arabinoside	CR, HSCT from his HLA-identical brother four months after diagnosis
Zhu 2016 <sup>7</sup>	Male	19	China	B-ALL (pro-B)	92.5	217	56,XY,+6,+8,+12,+13,+15,+19,+20,+21,+21,+mar(1)/45-49 and 48,XY,+12,+15,+16,(17)(q10),+21,+22,+mar2(cp5)/46,XY(4).	NR	NR	HLA-DR+, CD34+, CD38+, CD58+, cytoplasmic (c) CD79a+, CD19+ (dim), CD22+ (dim), CD33+, CD13+, CD7+, CD11b+, CD10-, CD117-, cCD3-, CD3-, CD4-, CD8-, CD20-, CD25-, CD103-, CD14-, CD64+, CD11c-, FMC7-, c myeloperoxidase (MPO)-, c immunoglobulin (Ig)M-, IgG- and IgA-	NR	5'SET exon7-NUP214 exon18 3'	cyclophosphamide, vindesine, daunorubicin and prednisone	Not remission. waiting for allo-HSCT
Nowak 2010 <sup>28</sup>	Female	42	The USA	B-ALL	NR	NR	Normal	del(9)(q34)	del(9)(q34)	NR	NR	5'SET exon8-NUP214 exon17/18 3'	NR	NR

**Abbreviations:** AUL, acute undifferentiated leukemia; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; ASCT, allogeneic stem cell transplantation; CR, complete remission; NR, not report; MR, molecular remissions.



cases and is usually associated with poor prognosis and secondary AML.<sup>30</sup> The detected mutations in the present case have not been reported in the related literature.

Case 3 in our report was diagnosed with MS. This is a manifestation of extramedullary soft tissue masses which may develop as part of AML, myeloproliferative neoplasm, myelodysplastic syndrome or at relapse, especially in patients following allogeneic HSCT.<sup>31</sup> Additionally, most of the literature about MS consists of case reports and small retrospective studies, and thus there is limited clinical knowledge of the cases and their presentation and management plans.<sup>32</sup> Remarkably, this present case did not show any blast infiltration into the bone marrow, which is termed isolated or primary MS. Because high proportions of isolated MS patients may progress to AML, the recommended treatment regimen is conventional AML protocols.<sup>33</sup>

At present, research on the *SET-CAN* fusion gene mainly focuses on T-ALL. Although many studies have been performed on the *SET-CAN* fusion gene, the related clinical biological characteristics and the pathogenesis of leukemia are still unclear. Van Vlierberghe et al<sup>34</sup> analyzed 92 patients with T-ALL. The *SET-CAN* fusion gene was identified in three patients and in the T-ALL cell line LOUCY. Further study revealed that the *SET-CAN* fusion gene inhibited the differentiation of T-cells by increasing the expression level of *HOXA*, thus promoting the occurrence of T-ALL. Similarly, another study conducted by Gorello et al<sup>6</sup> showed that the *SET-CAN* fusion gene was identified in seven out of 152 patients with T-ALL. Subsequently, gene expression profiling identified a signature characterized by *HOXA* and *NUP214* upregulation and *SET* downregulation. Quentmeier et al<sup>11</sup> performed RT-PCR-based screening of 141 leukemia/lymphoma cell lines of T-, B- and myeloid cell origin to detect the *SET-NUP214* fusion gene. That study only demonstrated the presence of the *SET-NUP214* gene in the T-ALL cell line LOUCY and in the AML cell line MEGAL. Moreover, quantitative RT-PCR confirmed a positive correlation between *SET-NUP214* and *HOX* gene expression in the cell line LOUCY when compared to six other T-ALL cell lines. Meanwhile, genomic sequencing localized the breakpoints of the *SET* gene to regions downstream of the stop codon and to *NUP214* intron 17/18 in both the LOUCY and MEGAL cell lines.

As for the study of the *SET-CAN* fusion in the pathogenesis of leukemia, it has been reported that it may be related to aberrant intracellular localization of hCRM1, a nuclear export factor. Current research results indicated that SET

and CAN were found in the nucleus and the nuclear envelope, respectively, whereas SET-CAN was primarily localized in the nucleus and interacts with hCRM1. Thus, the export of SET-CAN could be affected by hCRM1, which may lead to oncogenesis.<sup>35</sup> Kandilci, et al<sup>36</sup> verified that the *SET-CAN* fusion gene not only inhibits the differentiation of primitive progenitors but also committed myeloid cells (U937T) and therefore contribute to leukemogenesis. Subsequently, that same research group presented a transgenic mouse model that expresses the *SET-CAN* fusion gene in hematopoietic progenitor cells to further explore the role of *SET-CAN* in leukemogenesis.<sup>37</sup> However, *SET-CAN* mice were not leukemia-prone and did not show shortening of disease latency after retroviral tagging. Surprisingly, *SET-CAN* mice developed spontaneous hyperplasia of the stomach mucosa, which indicated a role of *SET-CAN* in the proliferation of certain epithelial cells. A study conducted by Saito et al<sup>38</sup> revealed that the *SET-CAN* fusion gene affected hematopoietic cell differentiation in a mouse model. Erythroid and megakaryocytic differentiation was impaired in SET-CAN transgenic mice.

## Conclusion

In conclusion, the *SET-CAN* fusion gene was very rare in patients with leukemia, but was more prevalent in young men, most of whom are diagnosed with T-ALL. Conventional karyotype analysis was unable to detect this chromosomal abnormality, and the overall prognosis may be relatively poor. Allogeneic HSCT may improve the prognosis. However, there was a great heterogeneity between different patients. The clinical characteristics of *SET-CAN* positive patients and the pathogenesis of leukemia are not clear at present. The treatment efficacy and prognosis of patients may be also correlated with other genetic changes. More cases should be accumulated and summarized to better understand diseases related to this translocation.

## Ethical Statement

Written informed consent to have the case details published was obtained from all the three patients, and the study was approved by Ethics Committee of the First Affiliated Hospital of China Medical University.

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## Disclosure

The authors report no conflicts of interest for this work.

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