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**[Case Report]**

# Successful cord blood transplantation for a unique case of bone marrow failure presenting t(2 ; 19)(p23 ; q13.3) translocation suggesting disruption of *DPY30*

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**Abstract**

H3K4 methylation, primarily mediated by MLL family proteins, plays a pivotal role in the epigenetic regulation of gene transcription. Among the MLL family, *KMT2A* is known for its critical role in hematopoiesis. MLL family proteins feature C-terminal SET catalytic domains, requiring the formation of MLL complexes with proteins like DPY30 to maximize their enzymatic activity. Deletion of DPY30 results in a significant reduction in H3K4me1, H3K4me2, and H3K4me3 levels in bone marrow (BM) cells, underscoring the essential role of DPY30 in facilitating optimal catalytic activity within MLL family complexes. Here, we present a unique case of myelodysplastic neoplasms (MDS) associated with a novel t(2 ; 19)(p23 ; q13.3) translocation. A 22-year-old pregnant woman initially sought consultation due to thrombocytopenia, which temporarily improved following a miscarriage. However, she later presented with progressive pancytopenia. RNA sequencing analysis of BM mononuclear cells using STAR-Fusion revealed the translocation breakpoint on chromosomes, resulting in the disruption of the *DPY30* and *CEACAM6* genes. BM failure showed marked improvement following cord blood transplantation. This case represents a novel form of MDS associated with the disruption of the *DPY30* gene. Our findings underscore the importance of considering early hematopoietic stem cell transplantation for MDS cases attributed to DPY30 dysfunction.

**Key words** : DPY30, MLL complex, KMT2A, CEACAM6, myelodysplastic neoplasms

## Introduction

H3K4 methylation, which is primarily mediated by MLL family proteins, plays a pivotal role in epigenetic gene transcription regulation[1)]. Aberrations in H3K4 methylation have been strongly associated with a broad spectrum of hematologic and solid malignancies[2)]. Among the MLL family members, *KMT2A* is known for its critical function in hematopoiesis[3)]. MLL family proteins contain C-terminal SET catalytic domains, necessitating the formation of MLL complexes that include WD repeat-containing protein (WDR5) ; retinoblastoma-binding protein (RBBP5) ; absent, small, or homeotic 2-like (ASH2L) ; and dumpy-30 (DPY30) to maximize their enzymatic activity[4)]. The precise role of DPY30 in the enzymatic activity of the MLL complex remains less understood than that of other constituent factors. Although DPY30 is a compact protein composed of 99 amino acids, it is indispensable for the MLL complex to exert its enzymatic activity[5)]. Deletion of DPY30 results in a significant reduction in H3K4me1/H3K4me2/H3K4me3 levels in bone marrow (BM) cells[6)], highlighting the essential role of DPY30 in facilitating optimal catalytic activity within MLL family complexes.

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Herein, we present a unique case of BM failure (BMF) associated with a novel t(2 ; 19)(p23 ; q13.3) translocation that disrupts the *DPY30* and *CEACAM6* genes. A 22-year-old pregnant woman initially presented with thrombocytopenia, which is temporarily improved following a miscarriage. However, she later developed progressive pancytopenia. RNA sequencing (RNA-seq) analysis of BM mononuclear cells using STAR-Fusion (v1.11.0) revealed translocation breakpoints on the chromosomes, resulting in disruption of the *DPY30* and *CEACAM6* genes. Remarkably, BMF markedly improved following cord blood transplantation (CBT). This case represents a novel form of myelodysplastic neoplasms (MDS) that has not been previously reported. Our findings underscore the importance of considering early hematopoietic stem cell transplantation (HSCT) in patients with MDS attributed to DPY30 dysfunction.

## Case report

A 22-year-old pregnant woman sought consultation from our obstetrics department due to thrombocytopenia. Notably, her grandmother had a history of acute myeloid leukemia (AML) at a similar age. Physical examination revealed no deficiencies or limb/finger malformations, and her skin exhibited no abnormalities. Her platelet count was $5.6\times10^4/\mu$L, accompanied by a slightly elevated immature platelet fraction (IPF) of 9.6%. Her white blood cell count was $4.9\times10^3/\mu$L, comprising 68% neutrophils, 21% lymphocytes, 8% eosinophils, 1% basophils, and 2% monocytes, with no observable blast cells. Her hemoglobin (Hb) level was 12.1 g/dL, indicating a slight decrease (Table 1). The patient demonstrated a normal prothrombin time with a slight increase in activated partial thromboplastin time. Notably, lupus anticoagulants were detected in her plasma, and no anticardiolipin antibody or anti-cardiolipin-$\beta$2-glycoprotein I complex antibody was detected. The patient experienced a miscarriage due to placental insufficiency at 26 weeks of gestation. Pathological analysis attributed the miscarriage to placental infarction. Consequently, she was suspected to have antiphospholipid syndrome. Following the miscarriage, her platelet count improved to $14.0\times10^4/\mu$L. However, when she returned three months later, her Hb concentration had decreased to 7.2 g/dL, and the platelet count was $12.9\times10^4/\mu$L. Vitamin B12, folate, and iron deficiency were not detected, and there were no findings suggestive of hemolysis. Consequently, BM aspiration was performed to investigate the underlying cause. BM aspiration and biopsy revealed several noteworthy features : (1) erythroblasts with karyorrhexis and multinuclearity (Fig. 1A-C), (2) hyposegmented mature neutrophils and degranulated neutrophils (Fig. 1A), and (3) micromegakaryocytes and megakaryocytes with widely separated nuclei (Fig. 1D), accompanied by a low blast count (1.6% blasts). Chromosome analysis revealed a novel chromosomal translocation (46, XX, t(2 ; 19)(p23 ; q13.3)) in 20 of 20 examined BM cells. The same chromosomal abnormality was also detected in 20 out of 20 peripheral lymphocytes using a commercially available laboratory test for chromosome analysis. Notably, the results of the chromosomal fragility test with mitomycin C treatment were negative. The patient's platelet count decreased to less than $2\times10^4/\mu$L. Her refractory anemia also progressed, with Hb levels decreasing below 5.0 g/dL. Based on these findings, the patient was diagnosed with intermediate-risk MDS (revised international prognostic scoring system score of 4.5). She required weekly red blood cell transfusions. Two months later, she developed further pancytopenia, and a subsequent BM examination revealed progressive marrow fibrosis (Fig. 1E). Additionally, splenomegaly was detected on the computed tomography scan obtained at that time. No erythroblasts, megakaryocytes, or myeloblasts were observed in the peripheral blood. Due to the patient's young age and the idiopathic nature of the BMF, HSCT was deemed necessary for a potential cure. However, donor matching took considerable time because the patient had a broad range and high levels of donor-specific anti-human leukocyte antigen (HLA) antibodies. One year and six months later, she underwent CBT from an HLA-DR 1 allele mismatched unrelated male donor. The conditioning regimens included fludarabine (180 mg/m$^2$), melphalan (80 mg/m$^2$), and total body irradiation (3.3 Gy). Prophylaxis for graft versus host disease (GVHD) included tacrolimus and mycophenolate mofetil. The graft was infused on Day 0, containing $2.27\times10^7$ cells/kg (CD34+ cells ; $0.56\times10^5$/kg). Neutrophil engraftment was confirmed on Day 36. Chimerism analysis revealed 99.8% of cells with the donor's normal male karyotype. However, thrombocytopenia with elevated IPF persisted. The patient was administered prednisolone (0.5 mg/kg/day) starting on Day 45, followed by eltrombopag olamine (EPAG) (12.5 mg/day) beginning on Day 62, in response to a diagnosis of immune thrombocytopenia. The patient's platelet count recovered to $20\times10^4/\mu$L by

Day 76. She did not develop ≥Grade 2 GVHD (Fig. 2A). Currently, more than a year has passed since transplantation, and her blood count has normalized with EPAG treatment.

To identify the breakpoint of this rare translocation, we conducted RNA-seq analysis on BM mononuclear cells before CBT. Total RNA was extracted from BM mononuclear cells using a NucleoSpin RNA Plus kit (TaKaRa, Shiga, Japan). Library preparation was performed using the library using a TruSeq stranded mRNA Library kit (Illumina, San Diego, USA). RNA-seq was performed using the Illumina NovaSeq 6000 platform with paired-end 100 bp reads. A total of 5,276,743,182 reads were generated, with 95% passing the quality filter. The mean Q30 score was 93.2%, indicating high read quality. The total read count for raw data was 52.24. The obtained FASTQ files were trimmed using Trimmomatic (v0.39). Mapping to the reference genome and fusion gene detection were subsequently conducted using STAR-Fusion (v1.11.0). These results revealed the translocation breakpoints

Table 1. Laboratory findings at initial presentation

| | At initial presentation |
|---|---|
| Hematology | |
| White blood cell count (/μL) | 4900 |
| Differential count (%) | |
| Neutrophils | 68 |
| Lymphocytes | 21 |
| Monocytes | 2 |
| Eosinophils | 8 |
| Basophils | 1 |
| Red blood cell count ($\times10^4$/μL) | 377 |
| Hemoglobin (g/dL) | 12.1 |
| Hematocrit (%) | 35.8 |
| Mean corpuscular volume (fL) | 96.8 |
| Reticulocytes ($\times10^4$/μL) | 6.18 |
| Platelet count ($\times10^4$/μL) | 5.6 |
| Immature platelet fraction (%) | 9.6 |
| Chemistry | |
| Sodium (mmol/L) | 137 |
| Potassium (mmol/L) | 4.0 |
| Chloride (mmol/L) | 102 |
| Urea nitrogen (mg/dL) | 11 |
| Creatinine (mg/dL) | 0.52 |
| Aspartate aminotransferase (U/L) | 27 |
| Alanine aminotransferase (U/L) | 49 |
| Total bilirubin (mg/dL) | 0.4 |
| Lactate dehydrogenase (U/L) | 185 |
| Coagulation | |
| Prothrombin time (%) | 118 |
| Activated partial thromboplastin time (second) | 38.5 |
| Fibrinogen (mg/dL) | 374 |
| Fibrinogen/fibrin degradation products (μg/dL) | <2.5 |
| D-dimer (μg/dL) | 0.6 |
| Immunology | |
| Antinuclear antibody (fold) | <160 |
| Anti-double stranded DNA immunoglobulin G (U/mL) | <0.5 |
| Anti-cardiolipin immunoglobulin G (U/mL) | 3 |
| Anti-cardiolipin-beta2 glycoprotein 1 complex antibody (U/mL) | <1.3 |
| Lupus anticoagulant | 1.36 |
| Platelet-associated immunoglobulin G | <12.5 |

on the chromosomes, resulting in the disruption of the *DPY30* (Ensembl gene ID ENSG00000162961) and *CEACAM6* (Ensembl gene ID ENSG00000086548) genes (Fig. 2B). The junction read count for the *DPY30-CEACAM6* was 12. We visualized the waveform data using Unipro UGENE[7], confirming the cleavage points of the *DPY30* and *CEACAM6* genes detected by Sanger sequencing (Fig. 2C). This fusion gene is unable to code for a protein due to the presence of a stop codon in the middle (Fig. 2D).

## Discussion

We encountered a patient with MDS resulting from an unidentified chromosomal translocation, t(2 ; 19)(p23 ; q13.3), which disrupted the *DPY30* and *CEACAM6* genes. Despite suspicion of congenital BMF, the criteria for diagnosing Fanconi anemia or congenital dyserythropoietic anemia were not met. This case appears to be unique, as no similar instances have been reported. The associations between mutations or functional abnormalities in CEACAM6 and MDS remain unclear. Conversely, DPY30, the smallest subunit of the MLL complex, significantly impacts its histone methyltransferase activity. We speculate that DPY30 disruption contributes to the clinical manifestations of MDS, subsequent marrow fibrosis progression, and BMF advancement. Additionally, MLL translocation leukemia is characterized by very few additional genetic abnormalities, suggesting that a single-hit gene mutation is primarily responsible for the disease[8,9]. These facts support the onset of MDS solely due to the disruption of DPY30, as seen in this case.

Furthermore, the patient's maternal grandmother had early-onset leukemia, but the mother had not developed any hematological disorders, precluding chromosomal testing due to a lack of consent. The patient had not exhibited cytopenia before the first pregnancy. Additionally, no findings indicated other congenital BMF manifestations, such as short stature, developmental delay, limb deficiencies, or skin pigmentation. This case suggests that functional abnormalities in DPY30 or CEACAM6 may contribute to early-onset MDS and demonstrates that HSCT, such as CBT, can be an effective treatment. The MLL complex, including DPY30, accelerates the self-renewal of hematopoietic stem cells (HSCs). A previous study indicated that DPY30 disruption inhibited HSC differentiation, particularly affecting myelomonocytic cells, while concurrently promoting erythroid maturation in HPCs

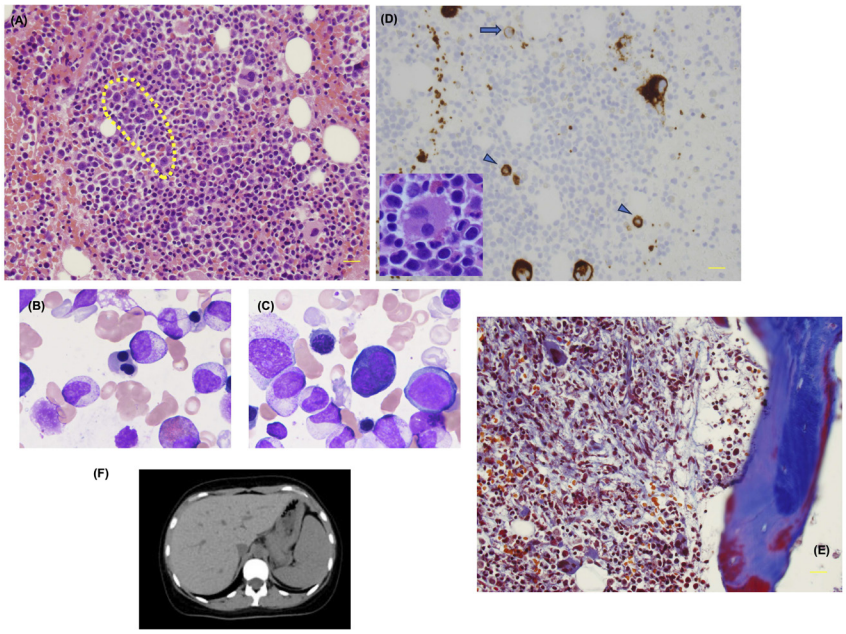


Fig. 1. Pathological and morphological analysis of a bone marrow (BM) biopsy specimen from the patient.
(A) Under a 40x objective, the hematoxylin and eosin (HE)-stained specimen exhibits erythroblasts with megaloblastic changes (indicated by the yellow dotted line). Hyposegmented mature neutrophils are also prominent. The BM smear shows multinucleated polychromatic erythroblasts (B) and basophilic erythroblasts (C). (D) CD42b staining reveals micromegakaryocytes (arrowheads) and megakaryoblasts (arrows). The enlarged inset shows a megakaryocyte with multiple widely separated nuclei. (E) Masson's trichrome staining demonstrates the progression of BM fibrosis, with a significant increase in collagen fibers compared to those at the initial examination. (F) Computed tomography image shows mild hepatosplenomegaly during the disease course.

and erythroleukemia cells through stable lentiviral *DPY30* knockdown in HSCs/hematopoietic progenitor cells (HPCs)[1]. Microarray analysis of *DPY30*-knockdown HPCs revealed that DPY30 directly promotes the expression of genes critically involved in DNA replication and cell cycle progression in human HPCs[1]. One or more of the SET1/MLL family members may be responsible for the H3K4 methylation activity involved in hematopoiesis. Previous studies revealed that DPY30 may regulate hematopoiesis through functions other than facilitating H3K4 methylation[10,11]. Based on these findings, MDS and BMF in this patient may be attributed to DPY30 disruption. Further studies are needed to identify the underlying mechanisms involved.

In conclusion, this case exemplifies the essential role of DPY30 in maintaining normal hematopoietic stem cell function. This finding highlights the function of the MLL complex in HSCs/HPCs and underscores the importance of DPY30 within the MLL complex.

## Conflicts of interest

The authors have no conflicts of interest to declare.

## Patient consent

We obtained informed consent from the patient for the publication of this work.

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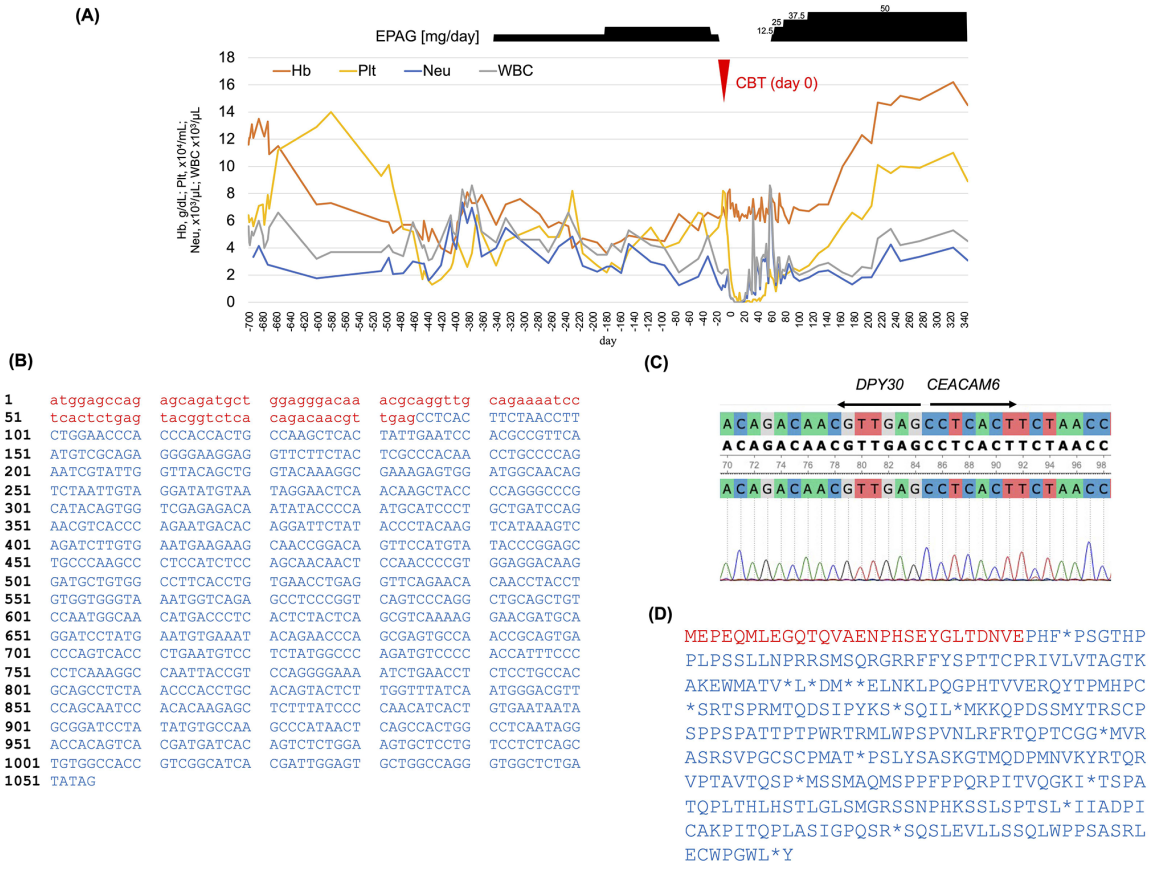


Fig. 2. Destruction of the *DPY30* and *CEACAM6* genes by t(2 ; 19)(p23 ; q13.3) translocation.
(A) Day 0 of the clinical course is set as the day of umbilical cord blood transplantation. (B) Predictions of chromosomal translocations detected by STAR-Fusion (v1.11.0) reveal coding effects. Red lowercase letters represent DNA sequences from the *DPY30* gene, while blue uppercase letters correspond to sequences from the *CEACAM6* gene. (C) Waveform data visualized using Unipro UGENE confirm the cleavage points of the *DPY30* and *CEACAM6* genes detected by Sanger sequencing. (D) Predicted amino acid sequences are shown by STAR-Fusion (v1.11.0).

## Data Availability Statement

RNA sequencing data were deposited in the JGA database (accession number JGAS000666).

## References

1. Yang Z, Augustin J, Chang C, Hu J, Shah K, Chang CW, *et al.* The DPY30 subunit in SET1/MLL complexes regulates the proliferation and differentiation of hematopoietic progenitor cells. Blood, **124** : 2025–2033, 2014.
2. Zhao A, Zhou H, Yang J, Li M, Niu T. Epigenetic regulation in hematopoiesis and its implications in the targeted therapy of hematologic malignancies. Signal Transduct Target Ther, **8** : 71, 2023.
3. Khan I, Amin MA, Eklund EA, Gartel AL. Regulation of HOX gene expression in AML. Blood Cancer J, **14** : 42, 2024.
4. Zhao L, Huang N, Mencius J, Li Y, Xu Y, Zheng Y, *et al.* DPY30 acts as an ASH2L–specific stabilizer to stimulate the enzyme activity of MLL family methyltransferases on different substrates. iScience, **25** : 104948, 2022.
5. Haddad JF, Yang Y, Takahashi YH, Joshi M, Chaudhary N, Woodfin AR, *et al.* Structural Analysis of the Ash2L/Dpy–30 Complex Reveals a Heterogeneity in H3K4 Methylation. Structure, **26** : 1594–603 e4, 2018.
6. Yang Z, Shah K, Khodadadi–Jamayran A, Jiang H. Dpy30 is critical for maintaining the identity and function of adult hematopoietic stem cells. J Exp Med, **213** : 2349–2364, 2016.
7. Rose R, Golosova O, Sukhomlinov D, Tiunov A, Prosperi M. Flexible design of multiple metagenomics classification pipelines with UGENE. Bioinformatics, **35** : 1963–1965, 2019.
8. Lavallee VP, Baccelli I, Krosl J, Wilhelm B, Barabe F, Gendron P, *et al.* The transcriptomic landscape and directed chemical interrogation of MLL–rearranged acute myeloid leukemias. Nat Genet, **47** : 1030–1037, 2015.
9. Andersson AK, Ma J, Wang J, Chen X, Gedman AL, Dang J, *et al.* The landscape of somatic mutations in infant MLL–rearranged acute lymphoblastic leukemias. Nat Genet, **47** : 330–337, 2015.
10. Kouzarides T. Chromatin modifications and their function. Cell, **128** : 693–705, 2007.
11. Jiang H, Shukla A, Wang X, Chen WY, Bernstein BE, Roeder RG. Role for Dpy–30 in ES cell–fate specification by regulation of H3K4 methylation within bivalent domains. Cell, **144** : 513–525, 2011.