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# A novel *UBASH3B::PVT1* fusion in B-cell acute lymphoblastic leukemia with *PAX5-PTD*: a case report and literature review

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## 1. INTRODUCTION

B-cell acute lymphoblastic leukemia (B-ALL) is a genetically heterogeneous malignancy characterized by distinct molecular subtypes resulting from recurrent gene rearrangements, chromosomal abnormalities, or specific mutations. Prognosis depends on factors including age, initial white blood cell (WBC) count, genetic alterations, and treatment response.[1,2] The Paired Box 5 (*PAX5*) gene, located on chromosome 9p13, belongs to the *PAX* family and is essential for B-cell development. *PAX5* alterations (*PAX5*alt) are frequently observed in B-ALL,[3,4] and include rearrangements, sequence mutations, and focal amplifications (*PAX5*amp),[5] all of which contribute to disease pathogenesis. The 2025 National Comprehensive Cancer Network guidelines classify *PAX5*alt as a poor-risk subtype.[6] Recent studies have further identified *PAX5* partial tandem duplications (*PAX5*-PTD) and *PAX5* internal tandem duplications as rare subtypes within the *PAX5*alt category.

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The Pvt1 oncogene (*PVT1*) encodes a long noncoding RNA implicated in oncogenesis. Its amplification and overexpression correlate with multiple malignancies, including breast cancer and acute myeloid leukemia (AML).[7,8] Elevated *PVT1* expression may also promote the proliferation of acute promyelocytic leukemia cell.[9] The Ubiquitin-Associated and SH3 Domain Containing B (*UBASH3B*) protein contains an N-terminal ubiquitin-associated domain, a central SH3 domain, and a C-terminal region homologous to phosphoglycerate mutase.[10] This protein negatively regulates epidermal growth factor receptor endocytosis.[11] The *UBASH3B::PVT1* fusion has not been previously reported.

Our study identified *UBASH3B::PVT1* and *PAX5*-PTD through high-resolution RNA sequencing (RNA-seq), and next-generation sequencing (NGS) revealed mutations in *ETV6*, *EZH2*, and *PTPN11*. These approaches facilitate precise molecular subtyping of B-ALL, thereby improving prognostic accuracy and enabling personalized treatment strategies. However, RNA-seq remains limited by its reliance on targeted RNA detection, which hinders the identification of structural variations such as 3q26 rearrangements that lack fusion protein products and reduces sensitivity for detecting large deletions or inversions. Optical genome mapping (OGM), a genome-wide technique, effectively detects structural variants (SVs) and copy number variants (CNVs), enabling comprehensive characterization of cytogenetic abnormalities.[12] In this study, OGM confirmed both *UBASH3B::PVT1* and *PAX5*-PTD. Continued advancements in genomic and transcriptomic technologies are expected to further refine B-ALL classification, ultimately supporting more targeted therapies and improved clinical outcomes.

## 2. CASE REPORT

A 22-year-old male was admitted to a local hospital with fever (39.1°C), epistaxis, and cough. The fever resolved after treatment with clindamycin. Hematologic tests showed a WBC count of $8.63 \times 10^9$/L, hemoglobin level of 74 g/L, and platelet count of $39 \times 10^9$/L, indicative of anemia and thrombocytopenia. Bone marrow aspiration morphology revealed 92% blasts. Flow cytometry analysis demonstrated positivity for cCD79a, CD10, CD19, HLA-DR, CD22, CD9, cMPO, CD71,

and CD11c; partial positivity for CD34, CD33, and CD15; and negativity for CD117, CD13, CD64, CD14, CD11b, CD5, CD7, CD2, CD56, CD20, and CD36. Therefore, the diagnosis was B-lymphoid leukemia with myeloid lineage expression. Karyotype analysis demonstrated the following abnormalities: 56, XY, +X, ins(1;?)(q21;?), +4, +8, +9, +10, +17×2, +18, +21, +22[4]/46, XY[6] (**Fig. 1A**). Multiplex polymerase chain reaction (PCR) analysis confirmed the absence of all 43 common fusion genes. Fluorescence in situ hybridization detected no *BCR::ABL1* fusion. NGS identified mutations in *ETV6* p.Tyr634Cys (variant allele frequency [VAF]: 63.35%), *EZH2* p.Lys314Asn (VAF: 7.23%), and *PTPN11* p.Ala461Gly (VAF: 83.33%). Based on these findings, the patient was diagnosed with hyperdiploid B-ALL. After 1 week of debulking therapy with vincristine and prednisone, he was referred to our hospital, where RNA-seq and OGM were performed. RNA-seq revealed a *UBASH3B::PVT1* fusion (split reads = 11; discordant mates = 1; junction sequence: TCCTCTCCAT GGGGTTCCCC AGAGCCCGCG CGAAACAGGT TGAGACATCA CACAATAAAT C) and *PAX5*-PTD (split reads = 601; discordant mates = 300; junction sequence: CCAGGCCCGC AGTCCTACCC CATTGTGACA GGACATGGAG GAGTGAATCA GCTTGGGGGG G) (**Fig. 1B–C**). OGM confirmed *UBASH3B::PVT1* (confidence = 1; VAF = 0.27) (**Fig. 1D**) and *PAX5*-PTD (confidence = −1; VAF = 0.42) (**Fig. 1E**) and also detected chromosomal gains, including 1q+, +4, 8q+, +9, +10, +14, +17, +18, +21, and +X (**Fig. 1F**). Because no previous reports have described *UBASH3B::PVT1*, reverse transcription polymerase chain reaction (RT-PCR) was performed using the patient's available complementary DNA (cDNA). The primers were F (5′–3′): GCTGCGAGAGAGGAGCTGTA and R (5′–3′): TGATGTTTAGAACCCAGGCC, with *ABL1* serving as the internal reference. The PCR product was 206 base pairs in length. The results, presented in Figure 1G, confirmed the presence of *UBASH3B::PVT1*. The PCR products were subsequently sequenced using the Sanger method with the same primers. As shown in Figure 1H, the Sanger sequencing results were consistent with those obtained from RNA-seq and OGM. Because *PVT1* is overexpressed in breast cancer and AML, we measured its expression in this patient's cDNA during this period, using 2 ALL and 2 AML patients as controls. The quantitative PCR primers were: F (5′–3′): TTGGCACATACAGCCATCAT and R (5′–3′): GCAGTAAAAGGGGAACACCA. *ABL1* served as the internal reference gene. The results, presented in Figure 1I, demonstrated that *PVT1* expression in this patient was significantly higher than that in the 4 controls, indicating that the *UBASH3B::PVT1* fusion was associated with increased *PVT1* transcription. Based on these findings, the patient was ultimately diagnosed with B-ALL harboring *PAX5*alt. The patient achieved complete hematologic remission after one cycle of IVP (idarubicin, vincristine, prednisone) combined with blinatumomab (a bispecific T-cell engager [BiTE]). Following one cycle of Hyper-CVAD chemotherapy, he attained complete molecular remission (**Fig. 1J**). Treatment continued with alternating Hyper-CVAD chemotherapy and immunotherapy (BiTE and chimeric antigen receptor T-cell [CAR-T] therapy). To date, the patient has maintained event-free survival for more than 1 year.

## 3. DISCUSSION

Familiades et al[13] first reported partial or complete amplification of *PAX5* in 2009, noting that partial amplifications predominantly involved exons 2 to 5 or exon 5 alone. Öfverholm et al[14] later corroborated these findings and introduced the term "intragenic amplifications of *PAX5*." Subsequent studies have shown that such intragenic amplifications frequently span exons 2 to 5 or 2 to 7, although other exons may also be affected.[4,15,16] These regions encode the paired box DNA-binding and octapeptide domains. In 2019, Gu et al[17] described internal tandem duplications in *PAX5*, and Tsai et al[18] first reported partial tandem duplications of the gene in 2023. Here, RNA sequencing identified *PAX5* breakpoints at chr9:36923355 and chr9:37020801, generating a *PAX5::PAX5* fusion transcript joining exons 1 to 7 to exons 2 to 9. This configuration corresponds to a tandem repeat of *PAX5* exons 2 to 7 (**Fig. 1C**). We carefully reanalyzed the *PAX5*-PTD results obtained by OGM, which revealed 2 possible breakpoint combinations: chr9:36969906 and chr9:37031741 or chr9:36920129 and chr9:37031741, producing a tandem repeat of exons 2 to 5 (confidence = −1, VAF = 0.42) or exons 2 to 7 (confidence = −1, VAF = 0.42) (**Fig. 1E**). Based on the operational principle of OGM, only a range interval can be determined for tandem repeats; therefore, this variation manifests as 2 distinct possibilities. The larger interval represents the final result, which was subsequently confirmed by RNA-seq analysis. Following prior nomenclature, we designate tandem repeats of *PAX5* exons 2 to 5 or 2 to 7 as *PAX5*-PTD, with details summarized in Table 1.

The *PVT1* gene resides on chromosome 8q24.21 and is known to form fusion genes with partners such as *MYC* and *CCDC26*.[19] Here, we identified a novel fusion between *UBASH3B*, located at 11q24.1, and *PVT1* (**Fig. 1B and D**). Because RNA-seq and OGM interrogate RNA and DNA, respectively, and reference different transcripts, the exons involved differ between assays. RNA-seq mapped the *PVT1* breakpoint to chromosome 8 position 129032402 and the *UBASH3B* breakpoint to chromosome 11 position 122526918, producing a *UBASH3B::PVT1* fusion transcript joining exon 1 of *UBASH3B* to exons 1 to 3 of *PVT1* (**Fig. 1B**). Because *PVT1* is a long noncoding RNA, the resulting fusion retains only the UBA/TS-N protein domain of UBASH3B (**Fig. 1B**). In contrast, OGM detected the *PVT1* breakpoint at chromosome 8 position 128016168 and the *UBASH3B* breakpoint at chromosome 11 position 122715291, generating a *UBASH3B::PVT1* transcript that covers exon 1 of *UBASH3B* fused to exons 1 to 5 or 1 to 6 of *PVT1* (**Fig. 1K**). Despite differences in the exons involved, the *UBASH3B::PVT1* fusion was unequivocally present (**Fig. 1G–H**). Furthermore, although *PVT1* is a highly unstable long noncoding RNA, its transcription rate substantially outpaces its degradation rate, maintaining a high steady-state expression level (**Fig. 1I**). The *UBASH3B::PVT1* fusion has not been previously reported, and its prognostic significance in B-ALL remains unknown. *PVT1* is established as a key driver of leukemia cell proliferation,[9] and *UBASH3B* represents a potential therapeutic target in this context.[11] Consequently, the *UBASH3B::PVT1* fusion may promote leukemic proliferation; however, this hypothesis requires further experimental validation.

NGS identified mutations in *ETV6*, *EZH2*, and *PTPN11*. *ETV6* mutations result in dysfunctional ETV6 protein, which promotes inflammation and impairs platelet production, thereby contributing to leukemogenesis.[20] Mutations in *EZH2* drive malignant transformation by mediating epigenetic reprogramming in B cells, thereby further promoting leukemia development.[21] In patients with AML without *NPM1* mutations, *PTPN11* mutations are correlated with poor prognosis, although they do not influence outcomes in *NPM1*-mutated cases.[22] Collectively, these genetic alterations are commonly associated with leukemia initiation and adverse prognosis.

The patient was initially diagnosed with B-ALL exhibiting hyperdiploidy at a local hospital and was therefore considered to have a favorable prognosis. Although hyperdiploidy in pediatric B-ALL generally correlates with favorable outcomes,[23] it is associated with poor prognosis in adult cases.[24] Based on established age criteria, this 22-year-old individual was classified within the adult group.[24] Following referral to our center, comprehensive molecular profiling revised the diagnosis to

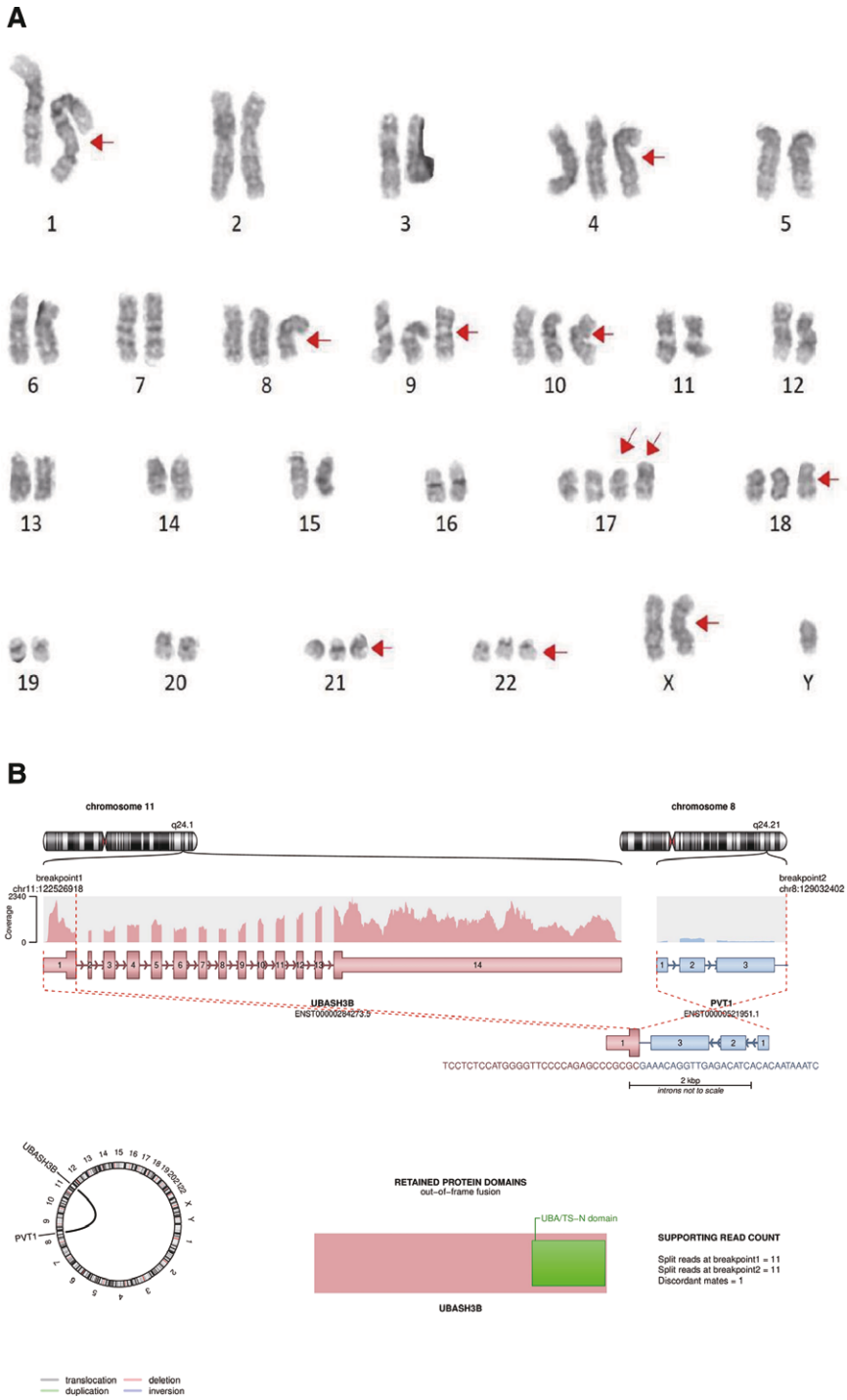


**Figure 1.** Clinical features of a patient with B-cell acute lymphoblastic leukemia with *UBASH3B::PVT1* fusion gene and *PAX5*-PTD. (A) Karyotype analysis of bone marrow revealed a karyotype of 56, XY, +X, ins(1;?)(q21;?), +4, +8, +9, +10, +17×2, +18, +21, +22[4]/46, XY[6]. (B) RNA-seq revealed a rare *UBASH3B::PVT1* fusion. The patient's fusion transcript resulted from a translocation between exon 1 of *UBASH3B* (located on chromosome 11) and exon 1-3 of *PVT1* (chromosome 8). (C) RNA-seq revealed *PAX5*-PTD. The patient's *PAX5*-PTD resulted from a duplication between exons 2 and 7 of *PAX5* (located on chromosome 9). (D) OGM revealed a *UBASH3B::PVT1* fusion. (E) OGM revealed *PAX5*-PTD. (F) OGM revealed a karyotype of 54, XY, +X, 1q+, +4, 8q+, +9, +10, +14, +17, +18, +21. (G) Results of *UBASH3B::PVT1* detected by RT-PCR. The primers were F (5'–3'): GCTGCGAGAGAGGAGCTGTA and R (5'–3'): TGATGTTTAGAACCCAGGCC, with *ABL1* serving as the internal reference. This PCR product is 206 base pairs in length. RT-PCR sequencing results show the fusion between *UBASH3B* exon 1 and *PVT1* exon 1–3. (H) Confirmation of the breakpoint of the *UBASH3B::PVT1* fusion via Sanger sequencing. The *UBASH3B* transcript is ENST00000284273.5, and the *PVT1* transcript is ENST00000521951.1. (I) The expression level of *PVT1* in this patient was confirmed to be higher than that in 2 ALL patients and 2 AML patients by quantitative PCR. The primers were F (5'–3'): TTGGCACATACAGCCATCAT and R (5'–3'): GCAGTAAAAGGGGAACACCA, with *ABL1* serving as the internal reference. The results were statistically significant. $^{**}p < 0.010$, $^{***}p < .001$, $^{****}p < .001$. (J) Previous chemotherapy regimens and treatment response. (K) OGM detected the *UBASH3B::PVT1* fusion at the genomic DNA level. The schematic illustrates this fusion event. According to National Center for Biotechnology Information (NCBI) reference sequences NM_001363365.2 and NC_000008.11, exon 1 of *UBASH3B* is joined to exons 1–5 of PVT1. The University of California Santa Cruz (UCSC) Genome Browser reference sequence ENST00000667305.2, however, indicates a junction between exon 1 of *UBASH3B* and *PVT1* exons 1–6. NCBI = National Center for Biotechnology Information, OGM = Optical genome mapping, RNA-seq = RNA sequencing, RT-PCR = reverse transcription polymerase chain reaction, UCSC = University of California Santa Cruz.

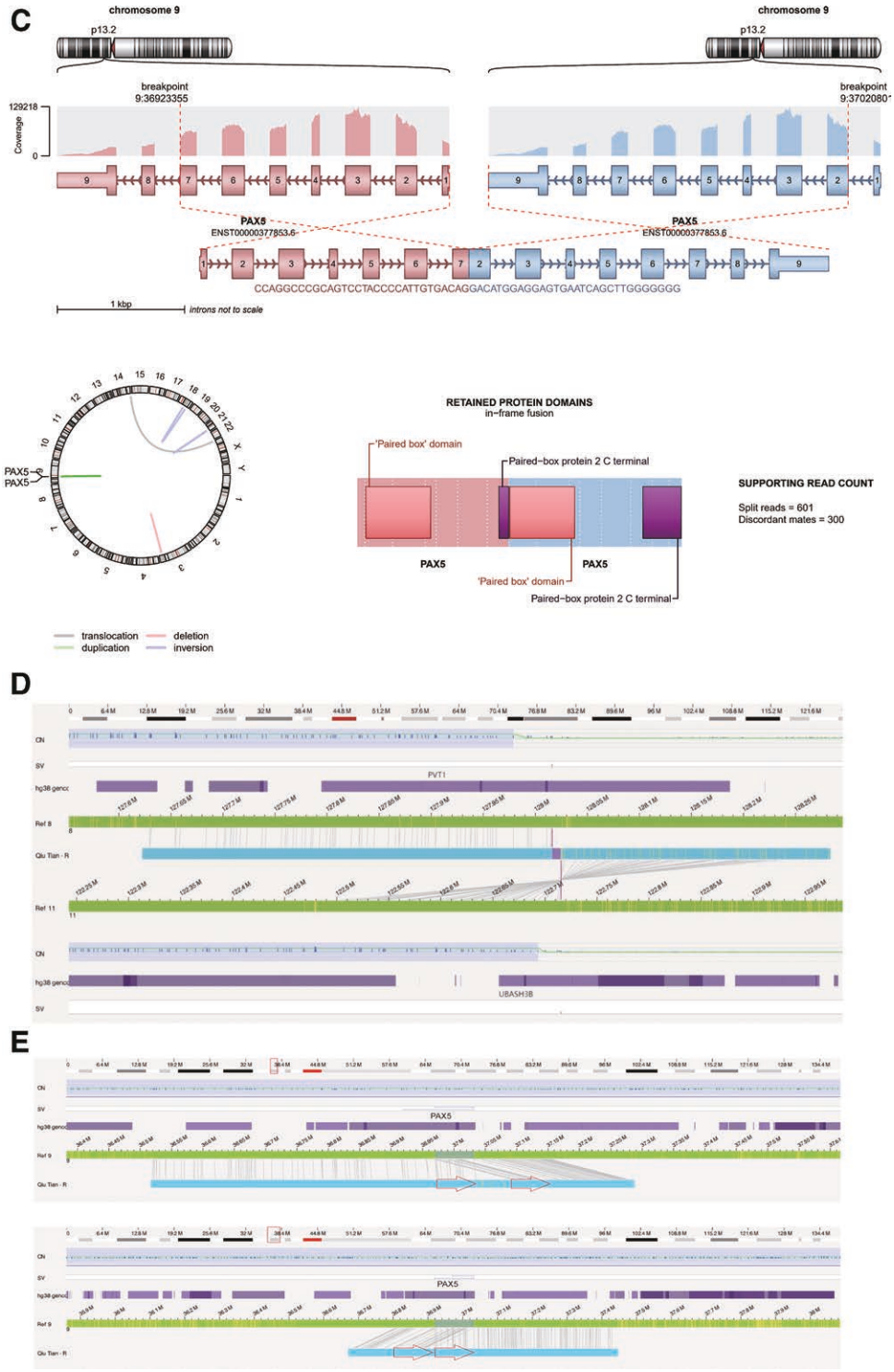


Figure 1. Continued

B-ALL with *PAX5*alt, which is currently recognized as a poor-risk subtype.

Several treatment options warrant further investigation, including intensive chemotherapy and allogeneic hematopoietic stem cell transplantation. The incidence of severe chemotherapy-related complications and transplant-related mortality remains considerable.[25] Over the past decade, immune-targeted and cellular therapies—including BiTEs (eg, blinatumomab), CAR-T therapy, and tyrosine kinase inhibitors—have progressively reshaped the treatment landscape for poor-risk B-ALL. In this study, the patient achieved sustained molecular remission for more than one year following combined treatment with chemotherapy, BiTE, and CAR-T therapy, without experiencing significant chemotherapy-related adverse effects.

Accurate diagnosis and prognostic stratification are essential in the management of leukemia. Conventional chromosome karyotype analysis has limited resolution, detecting only chromosomal abnormalities larger than 5 to 10 Mb and

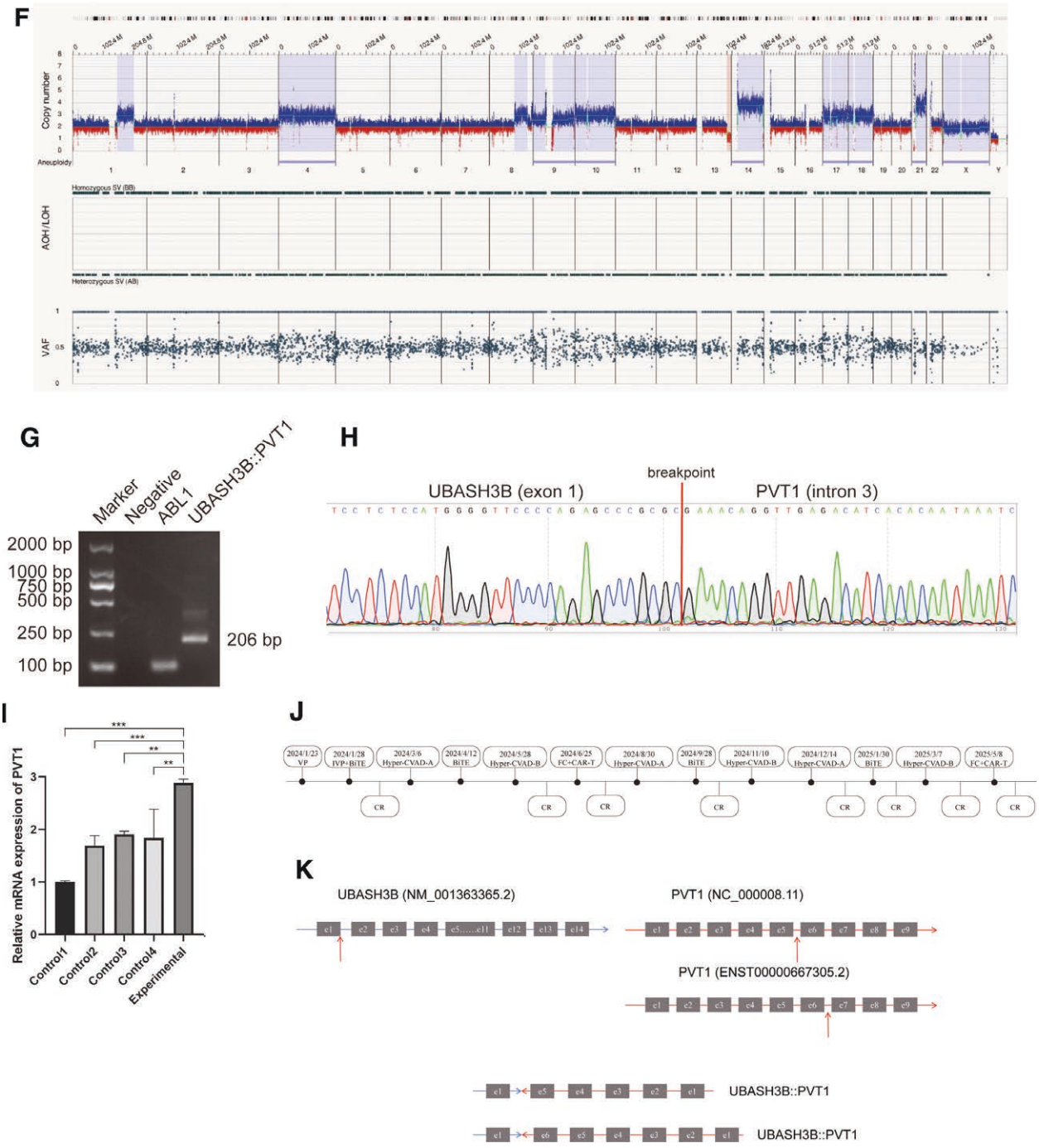


**Figure 1.** Continued

frequently missing smaller SVs, including deletions, duplications, insertions, or translocations. Although RNA-seq reliably identifies SVs that produce fusion proteins, it often fails to detect focal CNVs and SVs located in noncoding regions. OGM can detect SVs smaller than 1 kb and reveal previously unidentified pathogenic variants, enabling more precise molecular diagnosis. Nevertheless, OGM cannot detect chromosomal abnormalities in telomeric and centromeric regions, such as Robertsonian translocations, and must therefore be supplemented with karyotype analysis.[12] Furthermore, OGM cannot identify single-nucleotide variants (SNVs) and must be used in conjunction with NGS.[26] While NGS provides high resolution for detecting SNVs, it has limited ability to detect SVs and CNVs. Owing to the inherent limitations of each individual technology—karyotyping, RNA-seq, OGM, and NGS—our results indicate that combining OGM with NGS provides comprehensive and accurate genome-wide detection of SVs, CNVs, and SNVs.

In summary, RNA-seq and OGM identified both *UBASH3B::PVT1* and *PAX5*-PTD in a patient with B-ALL. These alterations are likely to contribute to B-ALL pathogenesis and disease progression. Further studies involving larger cohorts of patients harboring *UBASH3B::PVT1* and *PAX5*-PTD are required to validate these findings.

**Table 1**

**Several studies of acute lymphoblastic leukemia that exhibit focal amplifications of PAX5.**

| Author | Publication time | Type | Technology | Target | Exons | Domain | Reference |
|---|---|---|---|---|---|---|---|
| Chang et al | 2024 | Focal internal tandem PAX5 amplifications | WGS<br>PCR<br>RNA-Seq<br>Sanger sequencing | DNA/ RNA | 5<br>2–5<br>1–7 | The DNA-binding paired domain | 4 |
| Jean et al | 2022 | PAX5 intragenic tandem multiplication | CMA<br>OGM | DNA | 2–5<br>1–5 | The paired box/DNA-binding domain | 16 |
| Tsai et al | 2023 | Partial tandem duplications of PAX5 | RNA-Seq<br>MLPA | DNA/ RNA | 2–5<br>2–7 | | 18 |
| Schwab et al | 2017 | Intragenic amplification of PAX5 | MLPA<br>FISH | DNA | 1<br>2<br>5<br>6<br>8<br>10 | The DNA-binding and octapeptide domains | 15 |
| Gu et al | 2019 | In-frame internal tandem duplication of PAX5 | WGS<br>RT-PCR<br>Sanger sequencing<br>FISH | DNA | 2–5 | The DNA-binding domain | 17 |
| Öfverholm et al | 2013 | Intragenic amplifications of PAX5 | MLPA | DNA | 5<br>2<br>2–5 | | 14 |
| Familiades et al | 2009 | Partial amplification of PAX5<br>Complete amplification of PAX5 | qPCR<br>FISH<br>RT-PCR | DNA | 2–5<br>5<br>1–10 | | 13 |
| Present case | | Partial tandem duplications of PAX5 | RNA-Seq<br>OGM | RNA<br>DNA | 2–7<br>2–5 | | Our case |

CMA = chromosomal micro array, FISH = Fluorescent in situ hybridization, MLPA = multiplex ligation-dependent probe amplification, OGM = optical genome mapping, PCR = polymerase chain reaction, qPCR = quantitative PCR, RNA-Seq = RNA sequencing, RT-PCR = PCR with reverse transcription, WGS = whole genome sequencing.

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## ETHICS APPROVAL

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. This study was conducted with the patients' consent.

## AUTHOR CONTRIBUTIONS

All authors contributed to the work and approved the manuscript for publication. X.Z. and Y.W. analyzed data and wrote the manuscript. X.Z., Q.Y., H.S., and M.W. performed most of the experiments. M.G., B.X., T.L., J.Z., T.Y., Q.W., Y.K., and X.X. helped edit the paper. M.C. and Y.Z. analyzed data. H.H., S.C., and Q.W. analyzed data and helped edit the paper.

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