Recurrent Novel P2RY8/IGH Translocations in B-Lymphoblastic Leukemia/Lymphoma

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Translocations involving the immunoglobulin heavy chain (IGH) locus are common abnormalities in B-lymphoblastic leukemia/lymphoma (B-ALL) and multiple myeloma. These rearrangements result in a juxtaposition of IGH enhancers to the vicinity of oncogenes, such as MYC and CRLF2, leading to the upregulation of oncogenes. Here, we identified recurrent novel P2RY8/IGH translocations in three B-ALL patients by transcriptome sequencing. Noncoding exon 1 of P2RY8 was translocated to different sites of the IGH gene, resulting in transcripts of P2RY8/IGHM, P2RY8/IGHV, and P2RY8/IGHD. However, a high expression level of truncated P2RY8 was observed in the patients compared with healthy donors, which might be related to the aggressive clinical course and inferior outcome. In summary, we described recurrent novel P2RY8/IGH translocations with high expression levels of P2RY8, which may contribute to the guidelines for clinical diagnosis and treatment.

Keywords: translocation, fusion gene, B-lymphoblastic leukemia/lymphoma, P2RY8, IGH

INTRODUCTION

B-lymphoblastic leukemia/lymphoma (B-ALL) is a malignant disorder that originates from precursor B cells. The genetic basis of B-ALL is characterized by chromosomal rearrangement, structural variations, and sequence mutations that perturb lymphocyte development, growth, and epigenetic regulation. The genetic abnormalities that drive disease progression impact prognosis and treatment stratification (1, 2).

Immunoglobulin heavy chain (IGH) translocations are common and early oncogenic events in B cells and plasma cell malignancies (3). It has been reported that the recurrent translocation partner genes of IGH in B-ALL include five members of the CCAAT/enhancer binding protein (CEBP) family of transcription factors (4), the cytokine receptor for erythropoietin (EPOR) (5), the type I cytokine receptor CRLF2 (6) and IL3 (7). In most cases, translocations involving IGH result in the transcriptional activation of its partner genes (8). For example, the IGH/CRLF2 translocation produces an overexpression of the CRLF2 protein, resulting in the constitutive activation of the JAK/SAT signaling pathways in leukemic blast cells (9).
In this study, we found new IGH rearrangements in three B-ALL patients with recurrent novel P2RY8/IGH translocations. The noncoding exon 1 of the purinergic receptor P2Y, G protein coupled, 8 (P2RY8) gene was translocated with different sites of IGHD, resulting in P2RY8/IGHM, P2RY8/IGHV, and P2RY8/IGHD transcripts. A high expression level of P2RY8 was found in two patients with an aggressive clinical course and poor prognosis, indicating that high levels of P2RY8 may contribute to leukemogenesis or disease progression.

MATERIALS AND METHODS

Fluorescence In Situ Hybridization

FISH analyses were performed according to our institutional protocols (10). Accordingly, a commercial panel of FISH probes covering Philadelphia chromosome-like B-lymphoblastic leukemia (Ph-like ALL), including ABL1, ABL2, CRLF2, EPOR, and JAK2, was purchased (Vysis, Abbott/IL/USA). A positive rearrangement was reported when at least 3% of the nuclei showed break-apart split signals. Bone marrow (BM) samples at diagnosis or relapse were analyzed by FISH (Olympus IX 71, Tokyo, Japan).

RNA Sequencing and Reverse Transcription-Polymerase Chain Reaction (RT–PCR)

Total RNA was extracted from the BM samples taken at the time of diagnosis or relapse using an RNAeasy Mini Kit (Qiagen, Hilden, Germany). RNA sequencing libraries were prepared using 20-100 ng total RNA of BM samples with the TruSeq RNA library preparation kit v2 (Illumina, CA, USA). Paired-end sequencing with a read length of 150 bp was performed on Illumina NovaSeq platforms to at least 12 G raw data per sample according to the manufacturer’s protocol. The prediction of fusion genes was analyzed by STAR-fusion software (version: 1.9.0) and Fusion catcher (version:1.33) and aligned to the human reference genome GRCh38 (hg38). SNVs/indels were analyzed by following the Gatk best practices for variant calling on RNA sequencing. GRCh38 (hg38). SNVs/indels were analyzed by following the Gatk best practices for variant calling on RNA sequencing.

RESULTS

In Case 1, a 17-year-old female was admitted due to fatigue and worsening asthenia. Her blood tests showed a white blood count of 1.56×10^9/L, hemoglobin 84 g/L, and platelets 54×10^9/L. Bone marrow (BM) smears showed break-apart split signals. Bone marrow (BM) samples at diagnosis or relapse were analyzed by FISH (Olympus IX 71, Tokyo, Japan).

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In Case 2, a 22-year-old male presented with fever, stomach ache, and dizziness. Blood tests showed a white blood count of 24.22×10^9/L, hemoglobin 90 g/L, and platelets 93×10^9/L. BM morphology analysis detected 87.5% blasts (Figure 1A). The blasts were positive for CD34, HLA-DR, CD10, CD19, and CD123 and partially positive for CD22 (Table 1). Conventional karyotyping was normal. The results of multiplex RT–PCR covering 43 acute leukemia-related fusion genes were negative. FISH analysis with split signal probes covering ABL1, JAK2, CRLF2, and EPOR all tested negative (Figure 1B). Next-generation sequencing (NGS) targeting 172 leukemia- and lymphoma-related genes identified ANKR2D6-p.Asn267Ser, PTTPN11-p.Glu76Lys, CIITA-p.His1119Asn and FAT1-p.Phe765Tyr mutations. The patient was treated with conventional induction therapy (IVP regimen, containing idarubicin, vincristine, and dexamethasone) and achieved complete remission. Subsequently, she received consolidation therapy with cyclophosphamide, 6-MP, and arabinoside cytosine for one cycle and high-dose methotrexate (MTX) for one cycle. Then, she received anti-CD19 chimeric antigen receptor-modified T-cell therapy bridging to haploidential allogeneic hematopoietic stem cell transplantation (allo-HSCT) and remained in complete remission until the last follow-up in October 2021.

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burden. Then, 1.0×10^7/L tandem CD19/CD22 CAR T cells were infused via a dose-escalation schedule for three consecutive days. BM smears showed no response after infusion. The patient received salvaged allo-HSCT in January 2021. He remained in complete remission until the last follow-up in August 2021.

Case 3 involved a 40-year-old female who was a patient with refractory and relapsed B-ALL. At the initial consultation in January 2018, her blood tests showed a white blood count of 3.62×10^9/L, hemoglobin 59 g/L, and platelets 63×10^9/L. BM morphology analysis detected 95% blasts, which were positive for CD19, CD34, cCD22, and HLA-DR (Table 1). BM karyotyping showed 46, XX, del (9) (p22) [10]/46, XX [10]. She achieved complete remission after receiving conventional induction chemotherapy and then received three courses of consolidation therapy. The treatment was not administered continuously, and the patient was admitted to the local hospital for recurrence in October 2018. A screen for 33 fusion genes associated with Ph-like ALL was negative. The BM smear

![FIGURE 1](image-url) | Identification of novel recurrent P2RY8/IGH fusions. (A) Bone marrow aspirate at diagnosis or relapse (Wright’s staining ×1,000). (B) Fluorescence in situ hybridization results with a CRLF2 break-apart probe, which detected split signals of CRLF2. (C) Immunophenotyping of bone marrow cells at diagnosis or relapse. Flow cytometric analyses of leukemic cells revealed that the blast cells in Case 2 were positive for CRLF2. (D) RNA sequencing analysis revealed one breakpoint in exon 1 of the P2RY8 gene and breakpoints in different exons of the IGH gene in three patients. (E) A 139 bp product for Case 1 and a 508 bp product for Case 2 were detected by RT–PCR in samples taken at diagnosis. A product of 504 bp for Case 3 was detected by RT–PCR in samples taken at relapse. (F) Sequence alignment of the amplified product revealed breakpoints between exon 1 of the P2RY8 gene and different exons of the IGH gene at diagnosis or relapse. (G) Structure of the primers designed for the RT-qPCR of P2RY8. The amount of P2RY8 mRNA in BMNC cell fractions purified from P2RY8-IGH patients, healthy volunteers (normal) and B-ALL patients was determined by real-time RT-PCR analysis. Each fold change was calculated by the 2^(-ΔCt) method (left) and 2^(-ΔΔCt) method (right). Values are the mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001.
| Case | Age/Gender | Time | Blast (%) | Phenotype | Karyotype | Fusiongene | Mutation | Treatment | Clinical outcome |
|------|------------|------|-----------|-----------|-----------|------------|----------|-----------|-----------------|
| 1    | 17/F       | Initial diagnosis | 75 |  +  +  - | Normal | P2RY8/IGHD | ANKRD26-p.Asn267Ser | IVP—CR—consolidation chemotherapy—CD19-CAR T—allo-HSCT | Alive |
|      |            |       |           |           |           |            | PTPN11-p.Glu76Lys |            |                 |
|      |            |       |           |           |           |            | CIITA-p.His1119Asn |            |                 |
|      |            |       |           |           |           |            | FAT1-p.Phe765Tyr |            |                 |
|      |            |       |           |           |           |            | P2RY8/IGHD | N/A        |                 |
| 2    | 22/M       | Initial diagnosis | 81.5 |  +  +  + | Normal | P2RY8/IGHV | CIITA-p.Asp206Asn | CIVP+Dasatinib—CR—consolidation chemotherapy—relapse—CD19/CD22-CAR T—NR—allo-HSCT | Alive |
|      |            |       |           |           |           |            | SMC2-p.Asp655Val |            |                 |
|      |            |       |           |           |           |            | TET1-p.Ser1845Pro |            |                 |
|      |            |       |           |           |           |            | TNFAIP3-p.Ala648Val |            |                 |
| 3    | 40/F       | Initial diagnosis | 95 |  N/A  +  - | 46, XX, del (9) (p22) [10]/46, XX | Normal | N/A        | treatment in local hospital—relapse—VLP—NR—IA—NR—Blinatumomab—NR—local hospital | Dead |
|      |            | Relapse | 90 |  +  +  - | 47, XX, +X,9p- [9]/46, XX | P2RY8/IGHM | N/RAS-p.Gly12Asp |            |                 |
|      |            |       |           |           |           |            | PTPN11-p.Asp61Val |            |                 |
|      |            |       |           |           |           |            | PTPN11-p.Thr68Met |            |                 |
|      |            |       |           |           |           |            | KRAS-p.Gly12Val |            |                 |
|      |            |       |           |           |           |            | CALR-p.Gly108Arg |            |                 |

**Note:** Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CAR T, chimeric antigen receptor T-cell therapy; CIVP, Cyclophosphamide, Idarubicin, Vincristine, Dexamethasone; CR, complete remission; F, female; IA, Idarubicin, Cytarabine; IVP, Idarubicin, Vincristine, Dexamethasone; M, male; N/A, not available; NR, non remission; PR, partial remission; VLP, Vincristine, Idarubicin, L-asparaginase, Dexamethasone.
showed no remission after two courses of induction chemotherapy. The patient was admitted to our hospital in March 2019. BM morphology analysis detected 90% blasts (Figure 1A). The blasts were positive for CD34, HLA-DR, CD10, CD19, CD13, CD38, CD79a, and CD117 and partially positive for CD22. BM karyotyping showed 47, XX, +X.9p- [9]/ 46, XX [1]. No fusion gene was identified by multiplex RT–PCR. NGS covering 51 genes related to hematological malignancies revealed NRAS-p.Gly12Asp, PTPN11-p.Asp61Val, PTPN11-p.Thr468Met, KRAS-p.Gly12Val, and CALR-p.Gly108Arg mutations. She underwent induction chemotherapy with the IVP regimen in our hospital, but her BM smear showed no response. Subsequently, she was enrolled in the Blinatumomab clinical trial (CTR201701176) for relapsed/refractory (R/R) ALL. Because of severe cytokine release syndrome, she withdrew from the clinical trial, and blinatumomab was administered for two days (9 µg, d1–d2). A total of 99.8% blast cells were detected in bone marrow aspirates by flow cytometry. She refused further therapy and died of progression in May 2019.

RNA sequencing of bone marrow cells from these three patients was performed, and P2RY8/IGH translocations (Figure 1D) were identified. RT–PCR and Sanger sequencing further confirmed three different P2RY8/IGH transcripts (Figures 1E, F). In the three patients, exon 1 of the P2RY8 gene was fused with the IGH gene. However, the fused IGH fragments were different. Case 1 and Case 3 have unique transcripts, while Case 2 has two different transcripts. In Case 1, exon 1 of P2RY8 was fused with exon 1 of immunoglobulin heavy constant delta (IGHD). RT–PCR and Sanger sequencing showed a sharp band of 139 bp, which is consistent with P2RY8/IGHD fusion. In Case 2, exon 1 of P2RY8 was fused with exon 2 of immunoglobulin heavy variable 3-74 (IGHV3-74) with 2 different fusion sites, resulting in IGHV3-74/P2RY8 fusion. The two IGHV3-74 fragments fusion were different by 15 bases in length. In Case 3, exon 1 of P2RY8 was fused with exon 1 of immunoglobulin heavy constant mu (IGHM). A sharp band of 504 bp was observed, which is consistent with P2RY8/IGHM fusion.

IGH translocations always lead to the overexpression of partner genes. To determine whether P2RY8 transcription was influenced by the P2RY8/IGH translocation, two pairs of primers were designed (Figure 1G). P1 covered P2RY8 exon 2, and the cDNA of both unbroken and truncated P2RY8 could be detected. P2 spanned P2RY8 exon 1, intron 1, and exon 2, representing the unbroken mRNA of P2RY8. There was no significant difference in the abundance of P2RY8 mRNA from healthy donors by quantitative RT–PCR (RT-qPCR) using P1 and P2. However, RT-qPCR results from Case 2 and Case 3 showed that the products of P1 were remarkably higher than those of P2. These findings indicated that truncated P2RY8, the derivative of the P2RY8/IGH translocation, may be transcribed with an unknown promoter or enhancer. We tried to identify the truncated P2RY8 transcripts that contain some intron 1 sequence as a suggestion of cryptic promoter activation by IGH. RT-PCR was performed in cDNA and genomic DNA from case 2 and 3 by P0 primers, which spanned the junction of exon 2 and intron 1 of P2RY8 (Supplementary Figure 2A). As a result, a sharp band of 846bp, which is consistent with P2RY8, was found in the product of genomic PCR. However, no consistent bands were found in the products by cDNA samples (Supplementary Figures 2B, C). One possible reason for this failure is that the transcript start sites may be further downstream of the intron primer.

We further detected P2RY8 mRNA expression in BM MNCs using primer P1 in Case 2 and Case 3 compared with that in healthy donors and B-ALL patients. The results suggested that the expression level of P2RY8 was increased in P2RY8/IGH patients compared with healthy donors (p=0.0004) and B-ALL patients (p=0.03), indicating that high levels of P2RY8 may contribute to leukemogenesis or disease progression.

**DISCUSSION**

The IGH gene plays an important role in B-cell development. To produce antibody diversity and enhance the affinity of immunoglobulins to recognize and bind to foreign antigens, DNA undergoes a series of genetic events, including V(D)J rearrangement, somatic hypermutation, and class switch recombination (11–13). This system results in a diversity of high-affinity antibodies but also leaves B cells vulnerable to potentially oncogenic translocations. It has been reported that more than 40 genes can be fused with IGH. The common genes are of the CRLF2, ID4, EPOR, IL3, and CEBP gene families, which are seen in ALL. Recently, two IGH rearrangements were found in myeloid tumors, including an IGH-MECOM in myelodysplastic syndrome (MDS) and an IGH-CCNG1 in acute myeloid leukemia (14). IGH translocation juxtaposes the promoters of oncogenes with transcriptional enhancers within the IGH locus, resulting in the transcriptional activation of oncogenes (3).

The P2RY8 gene is located on both chromosomes X and Y. It belongs to the P2Y family of G-protein coupled receptors that mediate migration inhibition and the growth regulation of B cells in lymphoid tissues. P2RY8 was reported to have oncogenic potential. Loss of function somatic mutations were reported in GC-derived diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL) (15–17). P2RY8 expression was always increased in leukemia patients, especially in those with refractory disease. A high level of P2RY8 expression was associated with a poorer prognosis than a lower level (18, 19). Thus, overexpression of P2RY8 may contribute to leukemogenesis or progression.

Here, we found recurrent novel P2RY8/IGH translocations in three B-ALL samples by transcriptome sequencing. Although we confirmed the existence of three transcripts by RT-PCR, we failed to observe the translocations by whole genome sequencing. It seems that these P2RY8/IGH transcripts might be special products in the RNA splicing process. The same noncoding exon 1 of P2RY8 fused with different sites of the IGH gene, resulting in P2RY8/IGHM, P2RY8/IGHV, and P2RY8/IGHD transcripts. P2RY8 may use the exon/intron 1 splice junction while IGH may have different splicing sites. However, these results do not completely exclude the possibility of complex
genomic events occurring in a small proportion of the tumor cells and generating the RNA chimera.

It has been reported that IGH translocations always result in high expression of partner genes by juxtaposing the promoters of the partner gene with transcriptional enhancers within the IGH locus. We then designed the two pairs of primers to distinguish the full length of the P2RY8 transcript and the truncated P2RY8 transcript (coding region). Interestingly, in these three cases, truncated P2RY8 transcript was examined with high expression, while full-length of P2RY8 transcript was detected at a low level. Moreover, the P2RY8 mRNA expression level was also higher than that in healthy donors and B-ALL patients. Thus, we speculated that the cryptic promoter of P2RY8 might be activated by IGH, resulting in the overexpression of the truncated P2RY8 transcripts. To explore the existence of a truncated P2RY8 transcript that contains some intron 1 sequence as a suggestion of cryptic promoter activation by IGH, RT-PCR was performed in both cDNA and genomic DNA from case 2 and 3. A sharp band of 846bp was observed in the product using genomic DNA sample other than that using cDNA samples. The results might be due to the fact that the start sites of the truncated transcripts were downstream of the intron primer. In summary, P2RY8/IGH transcripts are not capable of producing P2RY8 protein. These fusion transcripts are simply an indication of the IGH/P2RY8 translocation and are not pathogenic. We considered that the pathogenicity is mediated by the overexpression of the truncated P2RY8 transcripts that are capable of generating the P2RY8 protein.

Another interesting phenomenon was observed in one of three patients: IGH/CRLF2 transcript and P2RY8/IGH transcript were coexistent in case 2, and that was not been reported before. Relapse occurred when he was treated with conventional chemotherapy and tyrosine kinase inhibitor (TKI) therapy. Tandem CD19/CD22 CAR T infusion also didn’t work. Finally, he received salvaged allo-HSCT. The overexpression of P2RY8 was also observed in this case. It remains a problem if P2RY8 overexpression here could be a diver fact when coexisting with IGH/CRLF2. Meanwhile, there is a possibility that P2RY8 overexpression might be a second hit in this subtype of B-ALL.

In summary, we described recurrent novel P2RY8/IGH translocations with high expression levels of P2RY8. Future studies are needed to define the biological significance of this event in leukemogenesis and may provide contributions to the guidelines for clinical diagnosis and treatment.

**DATA AVAILABILITY STATEMENT**

The data presented in the study are deposited in the NCBI Sequence Read Archive (SRA) repository, accession number PRJNA816342.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Soochow University. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)’ legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

**AUTHOR CONTRIBUTIONS**

YW, HQ, and XT treated the patients. MW and SC performed the molecular studies and analysis. YF and SH designed the genetic analysis and wrote the manuscript. TW, YL, JX, and YC analyzed the clinical data. YX and TL critically read and revised the manuscript. All authors approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.896858/full#supplementary-material

Supplementary Figure 1 | (A) Circos plot displaying the interconnectivity between CRLF2 and IGH, (B) The expression levels of CRLF2, P2RY8, IL3RA, CSF2RA, and ASMTL were detected in our RNA sequencing. FPKM: fragments per kilobase of transcript sequence per millions base pairs sequenced.

Supplementary Figure 2 | (A) P0 Primers designed to identify the truncated P2RY8 transcript with intron 1 sequence, (B) Products of RT-PCR using cDNA samples from patients. No consistent bands of P2RY8 were found. (C) Products of RT-PCR using genomic DNA samples from patients. An 846 bp product consistent with P2RY8 was detected.
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