Journal of clinical and experimental hematopathology
Vol. 61 No.2, 71-77, 2021

Original Article

Detection of novel and recurrent conjoined genes in non-Hodgkin B-cell lymphoma

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For this study, we investigated comprehensive expression of conjoined genes (CGs) in non-Hodgkin B-cell lymphoma (B-NHL) cell line KPUM-UH1 by using paired-end RNA sequencing. Furthermore, we analyzed the expression of these transcripts in an additional 21 cell lines, 37 primary samples of various malignancies and peripheral blood mononuclear cells of four normal individuals. Seventeen CGs were detected in KPUM-UH1: *CTBS-GNG5*, *SRP9-EPHX1*, *RMND5A-ANAPC*, *OTX1-EHBP1*, *ATF2-CHN1*, *PRKAA1-TTC33*, *LARP1-MRPL22*, *LOC105379697-BAK1*, *TIAM2-SCAF8*, *SPAG1-VPS13B*, *WBP1L-CNNM2*, *NARS2-GAB2*, *CTSC-RAB38*, *VAMP1-CD27-AS1*, *LRRC37A2-NSF*, *UBA2-WTIP* and *ZNF600-ZNF611*. To our knowledge, 10 of these genes have not been previously reported. The various characteristics of the CGs included in- and out-of-frame fusions, chimeras involving non-coding RNA and transcript variants. A finding of note was that *LARP1-MRPL2* was characterized as in-frame fusion and was recurrently expressed in B-NHL samples. In this study, variety of CGs was expressed both in malignant and normal cells, some of which might be specific to lymphoma.

Keywords: Conjoined genes, *LARP1*, *MRPL2*, non-Hodgkin B-cell lymphoma

INTRODUCTION

A conjoined gene (CG), a read-through transcript, or cis-splicing between adjacent genes (cis-SAGe) is defined as a fusion gene resulting from the splicing of two neighboring genes in the same coding orientation.[1,2] A CG is a novel gene expression mechanism and interest in its presence in both normal and cancer cells has been on the increase. Many CGs have been discovered only recently and listed on a database (ConjoinG, http://metasystems.riken.jp/conjoing/). Some CGs have been identified in several types of cancers and their tumorigenesis of them has been studied intensively. However, few reports have dealt with CGs in lymphoma.[3]

The genetic pathogenesis of non-Hodgkin B-cell lymphoma (B-NHL) is highly heterogeneous. By and large, two types of genetic pathogenesis of B-NHL have been researched. One is dysregulated expression of oncogenes, cyclins, transcription factors and other entities resulting from the translocation of immunoglobulin heavy and light chain genes on chromosomes 14q32, 2p12, and 22q11.[4-7] The other is a number of genetic mutations, which lead to dysregulation of various signaling pathways including NFκB, PI3K/MTOR, JAK-STAT, B-cell differentiation and focal adhesion, as well as of epigenetic modification and other consequences.[8] Furthermore, though in rare cases, fusion transcripts resulted from chromosomal rearrangements in B-NHL have been reported, as exemplified by *API2-MALT1* or *TBL1XR1-TP63*.[9,10] In addition to researching these pathogeneses, we also considered the possibility that the expression of lymphoma-specific CGs might create a novel genetic pathogenesis and be useful as a genetic biomarker of lymphoma.

In this study, we used paired-end RNA sequencing (RNA-Seq) to reveal the comprehensive expression of CGs in the diffuse large B-cell lymphoma (DLBCL) cell line KPUM-UH1. Furthermore, we analyzed by means of

Received: July 31, 2020. Revised: October 21, 2020. Accepted: January 27, 2021. J-STAGE Advance Published: April 20, 2021
DOI: 10.3960/jslrt.20033

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reverse transcription polymerase chain reaction (RT-PCR) the expression of these transcripts in additional 21 cell lines, 37 primary samples of various malignancies and peripheral blood mononuclear cells (PBMCs) of four healthy individuals.

MATERIALS AND METHODS

Cell lines and primary samples

The study population included two B-NHL cell lines (KPUM-UH1 and -MS3) established at our institute,[11] 20 purchased cell lines (B-NHL: JeKo-1, Mino, JVM, Z-138, MLMA, P32/ISH, Namalwa, A3/KAW and RAJI; hematological malignancies other than B-NHL: DND-41, YNH-1, MOLM-13, MOLM-1 and K562; solid tumors: GOTO, NB-1, COLO-320, MeWo, MKN45 and KATO-III), and primary samples from 37 Japanese patients with various malignancies who were diagnosed at the KPUM hospital between May 2005 and October 2014 and were previously described[12] (Supplementary Table 1). PBMCs of four healthy individuals were also studied. Informed consent was obtained from each patient and healthy individual in accordance with our institutional guidelines.

To detect recurrent CGs specific to the histological subtype of lymphoma we applied DLBCL cell line to paired-end RNA sequencing because DLBCL is the most common subtype of B-NHL. KPUM-UH1 was established from pleural effusion lymphoma cells of 77 years old female patient with DLBCL. Cytogenetic features of this cell line were previously reported.[11] Flow cytometric analysis of the lymphoma cells immunophenotype showed positivity for CD10, CD19, CD20, CD25, and negativity for CD5 and CD23. Light chain restriction was detected (κ:λ=0.5%:95.4%).

DNA and RNA extraction

Genomic DNA was extracted using the Wizard Genomic DNA Purification kit (Promega Corporation, Madison, WI, USA). Total RNA was extracted using the AllPrep DNA/RNA/Protein Mini Kit (QIAGEN, Venlo, The Netherlands), and reverse transcribed into cDNA with the aid of QuantiTect Reverse Transcription (QIAGEN).

Sample collection, library preparation and RNA-Seq

Total RNA was extracted from KPUM-UH1. The quality and quantity of total RNA were evaluated by using RNA 6000 Nano Kit of Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). The library for next generation sequencing (NGS) was prepared with the Ribo-Zero Gold LT Sample Prep Kit (Illumina, San Diego, CA, USA) from 1.0 μg of total RNA using TruSeq Stranded Total RNA. In brief, after depletion of ribosomal RNA, the remaining RNA was purified, fragmented, and subjected to first and second strand cDNA synthesis. The cDNA was then end-repaired, adenylated at the 3' end, and ligated with paired-end sequencing adaptors. After amplification by polymerase chain reaction (PCR) and removal of unligated adaptors using Agencourt AMPure XP beads (Beckman Coulter, Tokyo, Japan), the quality and quantity of the generated library was assessed by using both the Agilent DNA 1000 Kit of the Agilent 2100 Bioanalyzer (Agilent Technologies) and the KAPA NGS qPCR Kit (Kapa Biosystems, Wilmington, MA). Finally, sequencing was performed in the NGS Core Facility at Kyoto Prefectural University of Medicine with the HiScanSQ instrument (Illumina) by the 100-bp paired-end method.

Detection of fusion transcripts with the RNA-Seq data

NGS raw data was converted into FASTQ files using CASAVA software (version 1.8.2). For quality control, we removed the low quality reads if 1) over 80% of the sequences consisted of bases with a quality score below 20 and 2) lengths were shorter than 30 bps. In addition, 3' end bases with a quality score less than 20 were trimmed with the aid of PRINSEQ (version 0.20.4) and FASTX (version 0.0.13). For the alignment to the human genome reference (UCSC hg19) and detection of the fusion transcripts *in silico*, the following programs were used: deFuse (version 0.6.1), FusionHunter (version 1.4), and TopHat-Fusion (version 2.0.9).

Genomic copy number analysis

Genomic copy number in KPUM-UH1 was analyzed by means of GeneChip Human mapping SNP 6.0 array (Affymetrix, Santa Clara, CA, USA) according to the manufacturer's instructions. Chromosome copy numbers were calculated using the Affymetrix Genotyping Console Browser.

RT-PCR and primers

To confirm the presence of CGs detected by RNA-Seq and to detect these genes in the cell lines and the primary samples listed above, RT-PCR was performed and followed by nucleotide sequencing. To show conserved and constant expression of CGs, mRNA was extracted from KPUM-UH1 for RNA-Seq and for RT-PCR independently and at different times. For conventional 35-cycle RT-PCR analysis (30 s at 94 °C, 30 s at 55 °C, 30 s at 72 °C), the AmpliTaq Gold 360 Master Mix (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA) was used, and 5 μl of the RT-PCR product was electrophoresed in a 3% agarose gel. The primer sets were designed to detect each of the CGs as shown in Supplementary Table 2.

Nucleotide sequencing

After purification of the above mentioned RT-PCR products and cycle sequencing, capillary electrophoresis was performed on an Applied Biosystems 3130 Genetic Analyser. The RT-PCR products were then sequenced in both directions by using forward and reverse specific primers.

RESULTS

The paired-end RNA sequencing of KPUM-UH1

revealed 2,929 fusion gene transcripts, of which only 24 (0.8%) genes between coding regions. Of these 24, 17 (71%) were CGs: *CTBS-GNG5*, *SRP9-EPHX1*, *RMND5A-ANAPC*, *OTX1-EHBP1*, *ATF2-CHN1*, *PRKAA1-TTC33*, *LARP1-MRPL22*, *LOC105379697-BAK1*, *TIAM2-SCAF8*, *SPAG1-VPS13B*, *WBP1L-CNNM2*, *NARS2-GAB2*, *CTSC-RAB38*, *VAMP1-CD27-AS1*, *LRRC37A2-NSF*, *UBA2-WTIP* and *ZNF600-ZNF611* (Fig. 1-3, Supplementary Fig. 1, Supplementary Table 3). DNA copy number SNP arrays confirmed that none of these genes in KPUM-UH1 had a genomic deletion between the two adjacent genes (Fig. 1b). The base sequences of these chimeric transcripts were verified by RT-PCR and the subsequent sequencing analysis. The expression of these chimeric transcripts in various tumor cell lines, primary samples and normal PBMCs are listed in Table 1. Of the search results listed by ConjoinG and in previous reports, 10 CGs were novel. The CGs showed in- and out-of-frame fusions, chimeras involving non-coding RNA and transcript variants. These representative characteristics verified by RT-PCR and the subsequent sequence analysis are listed in Table 2.

DISCUSSION

In this study, fusion transcripts in the DLBCL cell line KPUM-UH1 were comprehensively analyzed by means of RNA-Seq. While numerous fusion transcripts were detected, very few were found between coding regions (24/2929, 0.8%). In addition, most of these fusion transcripts were CGs (17/24, 71%). We detected ten novel CGs in a lymphoma cell line KPUM-UH1. These results suggest that many novel CGs and their functions are still unknown and may be discovered in the future.

The 12 CGs (*CTBS-GNG5*, *SRP9-EPHX1*, *RMND5A-ANAPC*, *ATF2-CHN1*, *PRKAA1-TTC33*, *LOC105379697-BAK1*, *TIAM2-SCAF8*, *CTSC-RAB38*, *VAMP1-CD27-AS1*, *LRRC37A2-NSF*, *UBA2-WTIP* and *ZNF600-ZNF611*) were detected in both various tumor cell lines and PBMCs of all four normal individuals (Table 1). The expression of these CGs was not analyzed in the primary samples in this study because these samples might have been contaminated by normal PBMCs. Of these 12 CGs, *CTBS-GNG5*,[13-15] *CTSC-RAB38*,[16,17] *VAMP1-CD27-AS1*[14] and *UBA2-WTIP*[17,18] were previously reported to be expressed in several cancer types and normal tissue, and might therefore be associated with cell functions common to both various tumor populations and in normal cells. On the other hand, *OTX1-EHBP1*, *SPAG1-VPS13B* and *WBP1L-CNNM2* were detected only in KPUM-UH1, and *LARP1-MRPL22* in KPUM-UH1 and one primary DLBCL sample (L-1840) (Fig. 1). In contrast to the CGs widely expressed in both normal and tumor cells, the expression of these CGs in the limited number of lymphoma samples points to the heterogeneity and specificity of each malignant tumor.

In KPUM-UH1, seven CGs (Table 2) were found to be formed by in-frame fusion, which might be translated to the chimeric proteins and have a certain function. Although we did not analyze the expression of chimeric proteins and function of the CGs in this study, other studies have investigated the functions of some in-frame fusion genes. For example, *CTBS-GNG5* was reported to show a growth inhibitory function in some cancer cell lines through the analysis of

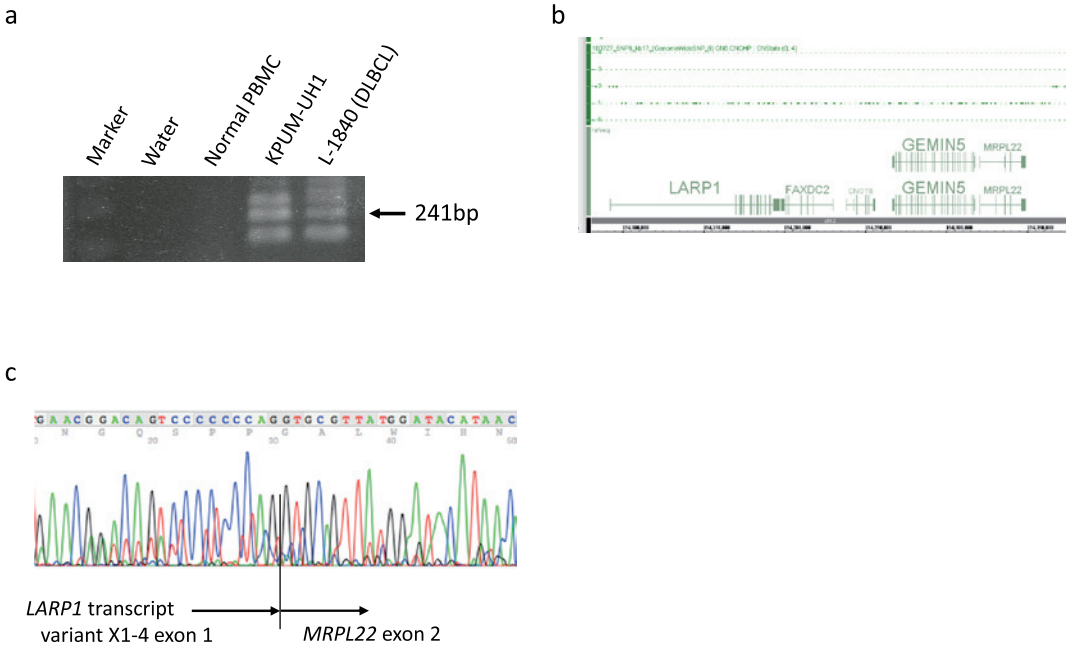

Fig. 1. Expression and base sequence of *LARP1-MRPL22*. ***a*** Expression of a chimeric transcript of *LARP1-MRPL22* shown by RT-PCR. ***b*** High-density SNP genotyping arrays showed no genomic deletion between *LARP1* and *MRPL22*. The base sequences of *LARP1* transcript variant X1-4 are listed on https://www.ncbi.nlm.nih.gov/gene/23367. ***c*** Sequencing analysis of 241bp RT-PCR product of *LARP1-MRPL22*. PBMCs, peripheral blood mononuclear cells; DLBCL, diffuse large B-cell lymphoma.

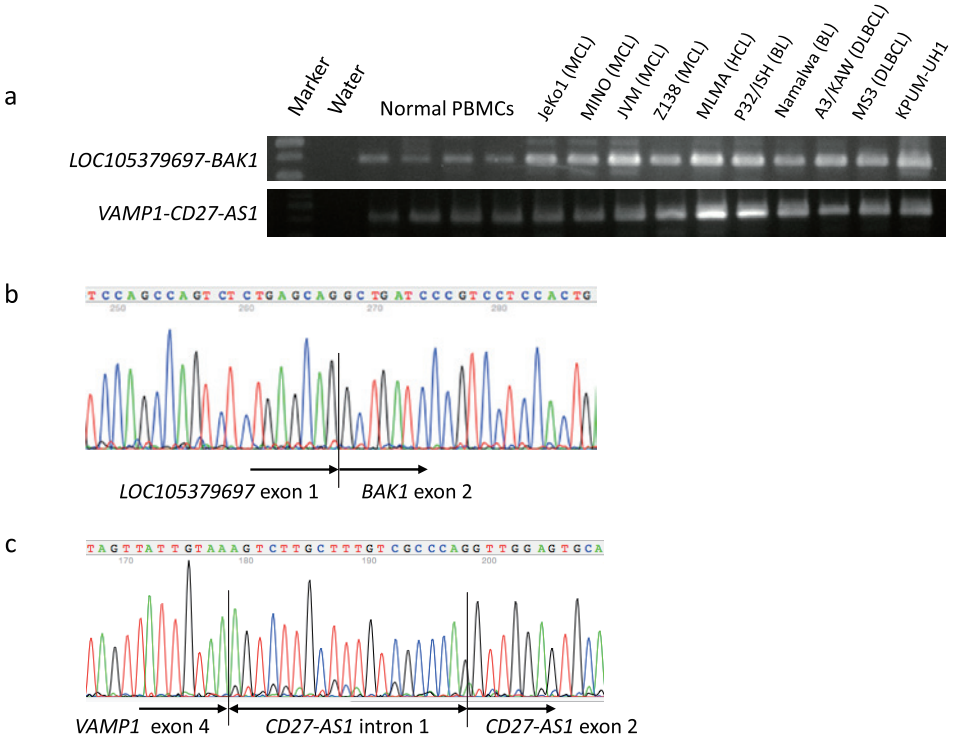

Fig. 2. Expression shown by RT-PCR (***a***) and subsequent sequencing analysis (***b*** and ***c***) of conjoined genes involving non-coding RNA, *LOC105379697* and *CD27-AS1*. *LOC105379697* is listed on https://www.ncbi.nlm.nih.gov/gene/105379697, and https://www.ncbi.nlm.nih.gov/nuccore/XR_954461.1?report=genbank. MCL, mantle cell lymphoma; HCL, hairy cell leukemia; BL, Burkitt lymphoma.

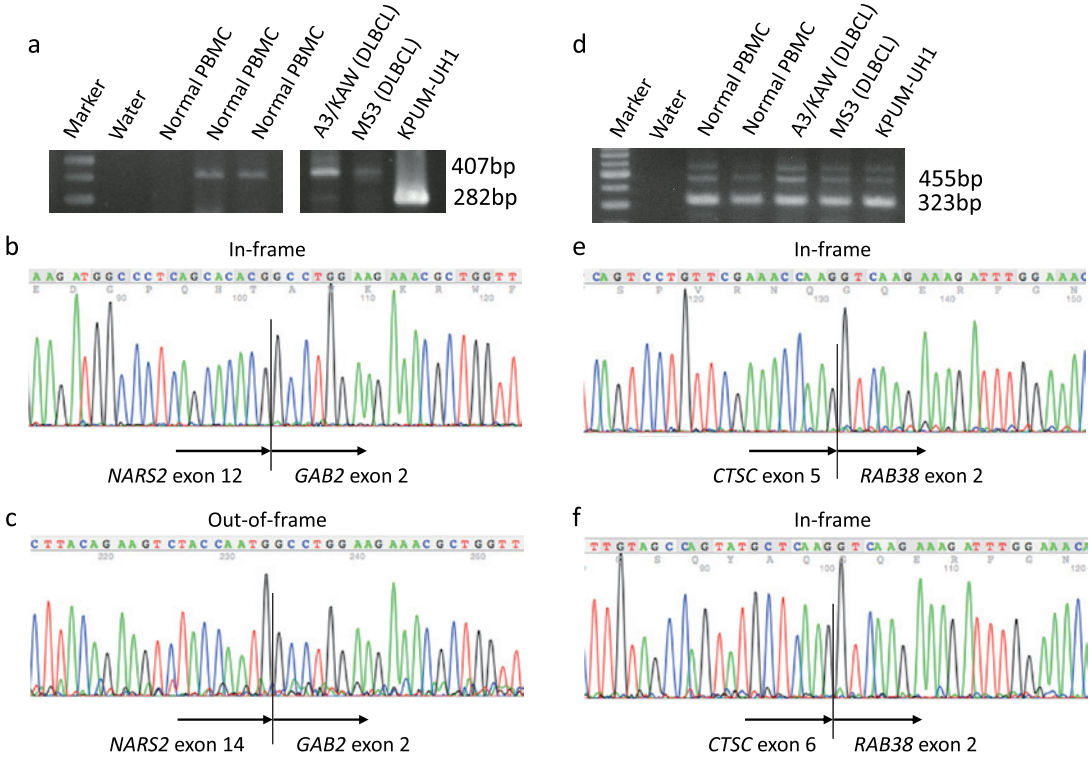

Fig. 3. Expression verified by RT-PCR and subsequent sequencing analysis of transcript variants of conjoined genes. ***a*** PCR products of *NARS2-GAB2*. ***b*** Sequencing analysis of 282bp RT-PCR product of *NARS2-GAB2*. ***c*** Sequencing analysis of 407bp RT-PCR product of *NARS2-GAB2*. ***d*** PCR products of *CTSC-RAB38*. ***e*** Sequencing analysis of 323bp RT-PCR product of *CTSC-RAB38*. ***f*** Sequencing analysis of 425bp RT-PCR product of *CTSC-RAB38*. MM, multiple myeloma; APL, acute promyelocytic leukemia.

Table 1. Expression of the conjoined genes in various tumor cell lines, primary samples and normal peripheral blood mononuclear cells.

Conjoined genes	Chromosome	Cell lines				Primary samples					
		B-NHL	T-ALL	AML /CML	Solid tumors	B-ALL	B-NHL	MM	T-NHL	AML /CML	Normal PBMCs
CTBS-GNG5	1p22	10/11 (91%)	1/1 (100%)	4/4 (100%)	6/6 (100%)	NA	NA	NA	NA	NA	4/4 (100%)
SRP9-EPHX1	1q42.1	11/11 (100%)	1/1 (100%)	4/4 (100%)	6/6 (100%)	NA	NA	NA	NA	NA	4/4 (100%)
RMND5A-ANAPC1	2p11.2	11/11 (100%)	1/1 (100%)	4/4 (100%)	6/6 (100%)	NA	NA	NA	NA	NA	4/4 (100%)
OTX1-EHBP1	2p13	1/11 (9%)	0/1 (0%)	0/4 (0%)	0/6 (0%)	0/1 (0%)	0/16 (0%)	0/4 (0%)	0/3 (0%)	0/13 (0%)	0/4 (0%)
ATF2-CHN1	2q31	10/11 (91%)	1/1 (100%)	2/4 (50%)	5/6 (83%)	NA	NA	NA	NA	NA	4/4 (100%)
PRKAA1-TTC33	5p12-13.1	11/11 (100%)	1/1 (100%)	4/4 (100%)	6/6 (100%)	NA	NA	NA	NA	NA	4/4 (100%)
LARP1-MRPPL22	5q33.2	1/11 (9%)	0/1 (0%)	0/4 (0%)	0/6 (0%)	0/1 (0%)	1/16 (6%)	0/4 (0%)	0/3 (0%)	0/13 (0%)	0/4 (0%)
LOC105379697-BAK1	6p21	11/11 (100%)	1/1 (100%)	4/4 (100%)	6/6 (100%)	NA	NA	NA	NA	NA	4/4 (100%)
TIAM2-SCAF8	6q25.1-25.3	10/11 (91%)	1/1 (100%)	2/4 (50%)	5/6 (83%)	NA	NA	NA	NA	NA	4/4 (100%)
SPAG1-VPS13B	8q22.2	1/11 (9%)	0/1 (0%)	0/4 (0%)	0/6 (0%)	0/1 (0%)	0/16 (0%)	0/4 (0%)	0/3 (0%)	0/13 (0%)	0/4 (0%)
WBP1L-CNNM2	10q24	1/11 (9%)	0/1 (0%)	0/4 (0%)	0/6 (0%)	0/1 (0%)	0/16 (0%)	0/4 (0%)	0/3 (0%)	0/13 (0%)	0/4 (0%)
NARS2-GAB2	11q14.1	3/11 (27%)	0/1 (0%)	0/4 (0%)	0/6 (0%)	0/1 (0%)	0/16 (0%)	2/4 (50%)	0/3 (0%)	2/13 (15%)	2/4 (50%)
CTSC-RAB38	11q14.2	11/11 (100%)	1/1 (100%)	4/4 (100%)	6/6 (100%)	NA	NA	NA	NA	NA	4/4 (100%)
VAMP1-CD27-AS1	12p13	11/11 (100%)	1/1 (100%)	4/4 (100%)	6/6 (100%)	NA	NA	NA	NA	NA	4/4 (100%)
LRRC37A2-NSF	17q21	11/11 (100%)	1/1 (100%)	2/4 (50%)	3/6 (50%)	NA	NA	NA	NA	NA	4/4 (100%)
UBA2-WTIP	19q12-13.11	11/11 (100%)	1/1 (100%)	4/4 (100%)	6/6 (100%)	NA	NA	NA	NA	NA	4/4 (100%)
ZNF600-ZNF611	19q13.41	11/11 (100%)	1/1 (100%)	4/4 (100%)	6/6 (100%)	NA	NA	NA	NA	NA	4/4 (100%)

B-NHL, B-cell non-Hodgkin lymphoma; T-ALL, T-cell acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myelogeneous leukemia; B-ALL, T-cell acute lymphoblastic leukemia; MM, multiple myeloma; T-NHL, T-cell non-Hodgkin lymphoma; PBMCs, peripheral blood mononuclear cells; NA, not analyzed.

Table 2. Characteristics of the conjoined genes detected in KPUM-UH1.

Conjoined genes	Frame	Transcript Variants	Previous Reports
CTBS-GNG5	In-frame		ConjoinG ID CGHSA0321
SRP9-EPHX1	Out-of-frame	+	ConjoinG ID CGHSA0324
RMND5A-ANAPC1	Out-of-frame		
OTX1-EHBP1	In-frame		
ATF2-CHN1	In-frame		ConjoinG ID CGHSA0556
PRKAA1-TTC33	Out-of-frame		
LARP1-MRPPL22	In frame		
LOC105379697-BAK1	-		
TIAM2-SCAF8	Not determined	+	ConjoinG ID CGHSA0279
SPAG1-VPS13B	Out-of-frame		
WBP1L-CNNM2	Out-of-frame		
NARS2-GAB2	In-frame	+	
CTSC-RAB38	In-frame	+	Ref. 16, 17
VAMP1-CD27-AS1	-		Ref. 14
LRRC37A2-NSF	Out-of-frame	+	
UBA2-WTIP	In-frame		Ref. 17, 18
ZNF600-ZNF611	-		

Only transcript variants confirmed by means of sequencing analysis are listed in this table.

chimera-targeting small inhibitory RNA.[13] Moreover, UBA2-WTIP chimeric protein reportedly could alter SUMOylation activity.[18] A noteworthy finding of our study was that *LARP1-MRPL22* is an in-frame fusion gene and recurrently expressed in DLBCL samples (Fig. 1). LARP1 plays a role in ribosomal translation through interaction with mammalian target of rapamycin complex 1 (mTORC1),[19] and is highly expressed in various epithelial cancers.[20] *MRPL22* gene encodes 39S mitochondrial ribosomal protein (MRP) L22. MRPs regulate not only cellular respiration but also apoptosis as well as modify tumorigenesis and metastasis in numerous cancers.[21] Because *LARP1-MRPL22* fusion transcript did not contain the base sequences translated into the functional domains of LARP1, this fusion gene might have lymphomagenic function mainly originated from the MRP. To detect recurrent CGs specific to each histological subtype of lymphoma, analysis of further number of patient specimens is needed.

LOC105379697-BAK1 and *VAMP1-CD27-AS1* were identified as CGs associated with non-coding RNA (Fig. 2). Although discoveries of chimeric transcripts involving non-coding RNA have been on the increase, their function in normal and malignant cells remains unknown. Recently, we reported finding novel chimeric transcripts involving non-coding RNA, *PVT1* in multiple myeloma (MM) and acute myeloid leukemia (AML), which could lead to dysregulation of the expression of fusion partner genes.[22,23]

CGs were found to express transcript variants as well as conventional genes (Fig. 3). In this study, the presence of transcript variants in *SRP9-EPHX1*, *TIAM2-SCAF8*, *NARS2-GAB2*, *CTSC-RAB38*, and *LRRC37A2-NSF* were confirmed by means of sequencing analysis. We also established there were two types of the transcript variant expression in the CGs. Expression of the transcripts of *NARS2-GAB2* was seen to vary among the samples including normal PBMCs. While an out-of-frame chimeric transcript between *NARS2* exon 14 and *GAB2* exon 2 was detected in two normal PBMCs, two DLBCL cell lines (A3/KAW and KPUM-MS3), two primary MM samples, and two primary acute promyelocytic leukemia samples, an in-frame chimeric transcript between *NARS2* exon 12 and *GAB2* exon 2 was detected only in two DLBCL cell lines KPUM-UH1 and A3/KAW. The transcript variants of the other CGs, on the other hand, were detected concurrently in the same samples.

In conclusion, we detected 17 CGs in the DLBCL cell line KPUM-UH1, 10 of which were novel. These genes show various characteristics including in- and out-of-frame fusions, chimeras involving non-coding RNA and transcript variants. In our study, while most CGs were detected both in normal PBMCs and malignant cells, in-frame fusion CG, *LARP1-MRPL2* was specifically and recurrently expressed in B-NHL samples. CGs are one of gene expression mechanisms commonly found in normal and malignant cells, some of which might be specific to malignancies. Clarification of oncogenesis associated with lymphoma-specific CGs and establishment of novel genetic biomarkers using CGs are the next challenges.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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