



Article

BDP1 Expression Correlates with Clinical Outcomes in Activated B-Cell Diffuse Large B-Cell Lymphoma

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Abstract: The RNA polymerase III-specific TFIIB complex is targeted by oncogenes and tumor suppressors, specifically the TFIIB subunits BRF1, BRF2, and TBP. Currently, it is unclear if the TFIIB subunit BDP1 is universally deregulated in human cancers. We performed a meta-analysis of patient data in the OncoPrint database to analyze BDP1 alterations in human cancers. Herein, we report a possible role for BDP1 in non-Hodgkin's lymphoma (NHL) for the first time. To the best of our knowledge, this is the first study to report a statistically significant decrease in BDP1 expression in patients with anaplastic lymphoma kinase-positive (ALK+) anaplastic large-cell lymphoma (ALCL) ($p = 1.67 \times 10^{-6}$) and Burkitt's lymphoma (BL) ($p = 1.54 \times 10^{-11}$). Analysis of the BDP1 promoter identified putative binding sites for MYC, BCL6, E2F4, and KLF4 transcription factors, which were previously demonstrated to be deregulated in lymphomas. MYC and BDP1 expression were inversely correlated in ALK+ ALCL, suggesting a possible mechanism for the significant and specific decrease in BDP1 expression. In activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL), decreased BDP1 expression correlated with clinical outcomes, including recurrence at 1 year ($p = 0.021$) and 3 years ($p = 0.005$). Mortality at 1 ($p = 0.030$) and 3 ($p = 0.012$) years correlated with decreased BDP1 expression in ABC DLBCL. Together, these data suggest that BDP1 alterations may be of clinical significance in specific NHL subtypes and warrant further investigation.

Keywords: TFIIB; BDP1; BRF1; BRF2; RNA polymerase III transcription; lymphoma; cancer



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1. Introduction

Lymphoma is characterized by the deregulated growth of lymphocytes, including natural killer, B-, and T-cells. It is anticipated that, in 2021, 8830 individuals will be diagnosed with Hodgkin's lymphoma (HL), and 81,560 individuals will be diagnosed with non-Hodgkin's lymphoma (NHL) in the United States (US) [1]. Thus, NHL accounts for approximately 80% of all lymphoma diagnoses in the US. Subtypes of aggressive (fast-growing) NHL include: diffuse large B-cell lymphoma (DLBCL), anaplastic large-cell lymphoma (ALCL), Burkitt's lymphoma (BL), lymphoblastic lymphoma (LBL), mantle cell lymphoma (MCL), and peripheral T-cell lymphoma (PTCL) [2].

Uncontrolled cell proliferation is a common characteristic of many human cancers, including aggressive forms of lymphoma [2]. The regulation of eukaryotic cell proliferation is controlled by three distinct RNA polymerases (pol) [3], including RNA pol III, which controls transcription of untranslated small RNA molecules involved in processing and translation. Together, these regulate the biosynthetic capacity of a cell. Accurate transcription by RNA pol III requires general and gene-specific transcription factors [3], including the RNA pol III-specific TFIIB complex (3, 4). To date, two forms of TFIIB have been well characterized in humans [4,5], with both forms of human TFIIB requiring BDP1 [4,6]. In humans, multiple BDP1 isoforms have been identified [4]. The identified eukaryotic BDP1 isoforms contain a conserved SANT domain (Swi3, Ada2, N-Cor, and TFIIB) involved in

chromatin remodeling and transcription regulation [3,4]. The isolated BDP1 isoforms vary in the length of c-terminal extensions characterized by a 55-residue repetitive motif [3–7].

TFIIIB activity, via the TBP, BRF1, and BRF2 subunit(s), is targeted both directly and indirectly by various oncogenes and tumor suppressors [7,8]. For example, the oncogenes MAP kinase ERK and MYC [9,10] stimulate TFIIIB activity *in vitro*. The tumor suppressors p53 [10,11], PTEN [12,13], BRCA1 [14], the retinoblastoma protein (RB) [10], and the Rb family members p107 and p130 [15] inhibit TFIIIB activity. The TFIIIB subunit BRF2 is deregulated in various human cancers and is an oncogene in lung squamous cell carcinoma [8,16–18]. To date, alterations in BDP1 have been demonstrated in nonsyndromic hereditary hearing loss [17] and have been shown to promote tumorigenicity in TP53-mutated prostate cancers [18]. Additionally, BDP1 is overexpressed in cells transformed by papovaviruses [19]. However, specific BDP1 alterations in human cancers have not been investigated.

In this study, we queried patient data from the OncoPrint database and an integrated data-mining platform to analyze BDP1 alterations in human cancers using publicly available datasets. Herein, we report a possible role for decreased BDP1 expression in lymphoma for the first time. To the best of our knowledge, this is the first study to report a statistically significant decrease in BDP1 expression in patients with anaplastic lymphoma kinase-positive (ALK+) anaplastic large-cell lymphoma (ALCL) ($p = 1.67 \times 10^{-6}$) and Burkitt's lymphoma (BL) ($p = 1.54 \times 10^{-11}$). An analysis of the BDP1 promoter identified putative binding sites for myelocytomatosis oncogene (MYC), B-cell lymphoma 6 protein (BCL6), E2 factor transcription factor 4 (E2F4), and Krüppel-like factor 4 (KLF4) transcription factors. MYC, BCL-6, E2, and E2F4 are demonstrated to be deregulated in lymphomas. Specifically, MYC and BDP1 expression are inversely correlated in ALK+ ALCL, suggesting a possible mechanism for the significant and specific decrease in BDP1 expression. In activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL), decreased BDP1 expression correlated with clinical outcomes, including recurrence at 1 year ($p = 0.021$) and 3 years ($p = 0.005$). Mortality at 1 ($p = 0.030$) and 3 ($p = 0.012$) years correlated with decreased BDP1 expression in ABC DLBCL. Together, these data suggest that BDP1 alterations may be of clinical significance in lymphoma and warrant further investigation.

2. Materials and Methods

2.1. OncoPrint Analyses

From September 2019 through December 2021, we performed comprehensive queries of the OncoPrint Research Premium Edition platform [20,21]. The OncoPrint Research Premium Edition platform is a cancer microarray database and web-based data-mining platform [20] containing 729 datasets (91,866 samples) to determine the frequency of BDP1 alterations in human cancers. The OncoPrint Research Premium Edition platform uses statistical tests conducted both as two-sided for differential expression analysis and as one-sided for specific over- and underexpression analysis [20,21]. For the overall study analysis, *p*-values were corrected for multiple comparisons by the false discovery rate method [20,21]. For BDP1 expression analyses in specific datasets, cutoff values, sample numbers, and *p*-values are indicated in the figure legends. The OncoPrint™ Platform (Thermo Fisher, Ann Arbor, MI, USA) was used for analysis and visualization. The public datasets used are noted in Table 1, with study descriptions and hyperlinks to the available datasets, and are cited in figure legends.

Table 1. Public datasets used in this study. Study descriptions and hyperlinks to datasets are provided.

Dataset (Hyperlink to Public Dataset)	Study Description	Reference
Brune	Forty-two (42) malignant lymphoma samples, including 11 Hodgkin's lymphoma, 11 diffuse large B-cell lymphoma, 5 nodular lymphocyte predominant Hodgkin's lymphoma, 5 follicular lymphomas, 5 Burkitt's lymphoma, and 4 T-cell/histiocyte-rich large B-cell lymphoma samples, were analyzed. In addition, 25 normal B-cell samples of various types were included in this analysis.	[22]
Eckerle	Twenty-three (23) lymphoma samples, including 4 classical Hodgkin's lymphoma, 7 primary cutaneous anaplastic large-cell lymphoma, and 12 anaplastic large-cell lymphoma samples (including 3 cell lines), were analyzed.	[23]
Shaknovich	Forty (40) germinal center B-cell-like diffuse large B-cell lymphoma, 20 activated B-cell-like diffuse large B-cell lymphoma, and 9 diffuse large B-cell lymphoma samples were analyzed.	[24]

2.2. BDP1 Promoter Analysis

The Eukaryotic Promoter Database [25] (<https://epd.epfl.ch//index.php>, accessed on 5 January 2022) was queried to identify putative transcription factor binding sites within the BDP1 promoter, specifically targeting transcription factors known to be deregulated in NHL. A threshold *p*-value of 0.001 was used while querying the Eukaryotic Promoter Database [25].

3. Results

3.1. BDP1 Expression Is Significantly Altered in a Subset of Human Cancers

Recently, it was observed that p53-deficient prostate cancer cells display high levels of BDP1 [18], suggesting that deregulation of BDP1 may be of functional significance in human cancers. Deregulation of the human TFIIIB subunits BRF1 [26–30] and BRF2 [7,16,27,31–37] has been well documented in human cancers. The primary aim of this study was to determine if the TFIIIB subunit BDP1 is specifically altered in human cancers and if the observed alterations correlate with clinical outcomes. OncoPrint 4.5 was queried for BDP1 expression in 729 datasets (91,866 samples) based on cancer type, cancer versus normal, and cancer versus cancer, including histology and multicancer analysis and outlier analyses. The disease summary analysis for BDP1 is presented in Figure 1. Red shading of boxes denotes gene overexpression; blue shading represents decreased gene expression. This disease summary was performed using the following criteria: a minimum 2-fold change in BDP1 gene expression, a *p*-value of 1×10^{-4} , and a gene rank percentile of 10%. BDP1 was overexpressed in breast and colorectal cancer versus normal datasets but underexpressed in breast and lymphoma cancer versus normal datasets (Figure 1A). In cancer versus cancer datasets, BDP1 was over- and underexpressed in kidney cancer (cancer histology dataset) (Figure 1A). In a cancer subtype analysis, BDP1 was overexpressed in castrate-resistant metastatic prostate cancer [38] ($n = 122$, $p = 2.60 \times 10^{-11}$), suggesting that alterations in BDP1 may be of clinical significance, as previously reported [18]. Interestingly, BDP1 expression was decreased in the pathway and drug analysis in lung cancers (Figure 1A). Specifically, BDP1 expression decreased in the HCC 1299 lung cancer cell line transfected with the epidermal growth factor receptor (EGFR) and treated with the EGFR signal transduction inhibitor gefitinib ($p = 2.40 \times 10^{-5}$) [39]. The disease summary analysis for BDP1 includes an OncoPrint outlier analysis reporting the number of unique datasets in which BDP1 had the highest-ranking cancer outlier profile analysis (COPA) score [20]. The outlier analysis demonstrated that BDP1 was both over- and underexpressed across the analyzed cancer datasets.

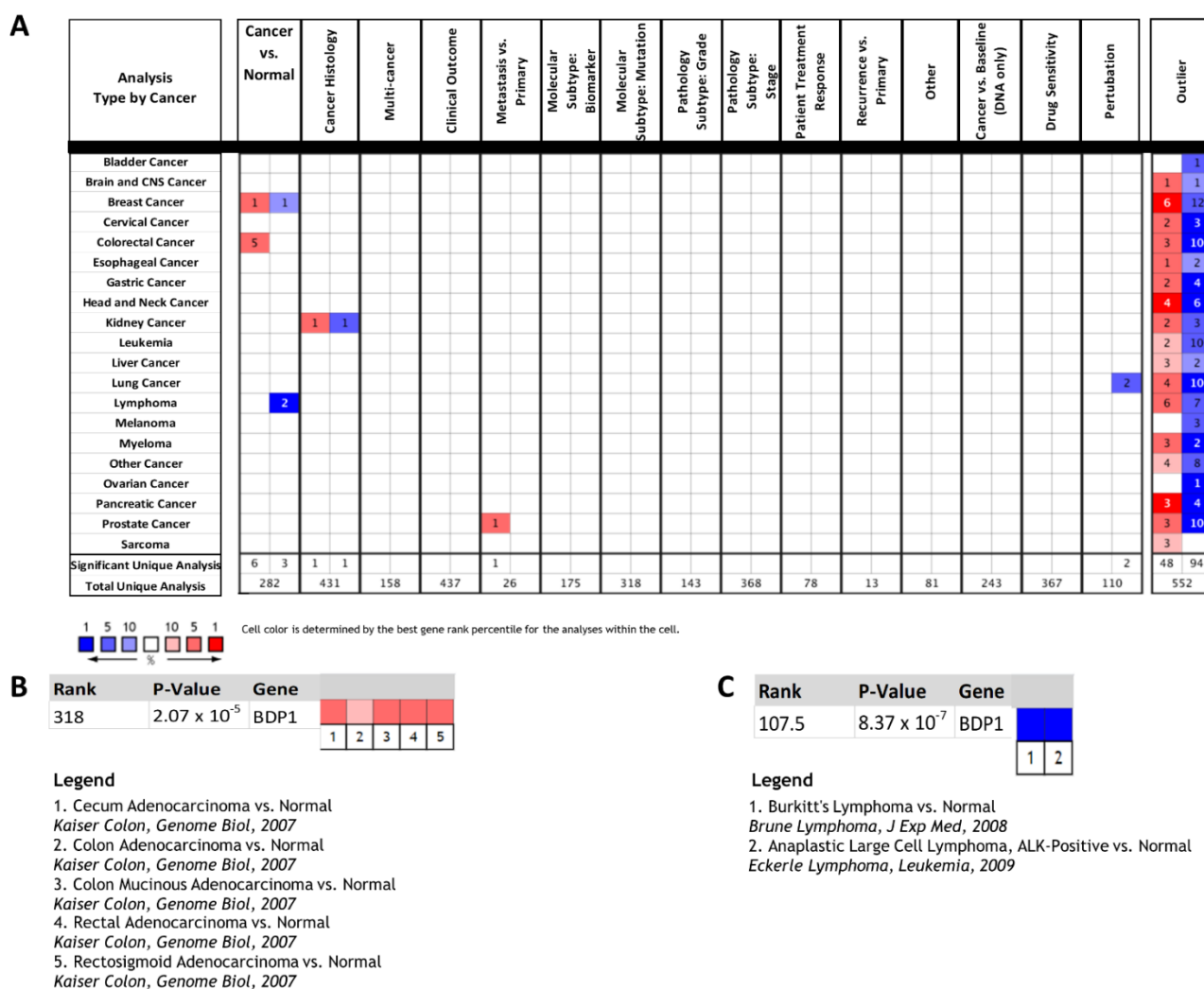


Figure 1. BDP1 expression is significantly altered in a subset of human cancers. (A) OncoPrint 4.5 database disease summary for BDP1. OncoPrint 4.5 was queried for BDP1 expression in 729 datasets (91,866 samples) based on cancer type, cancer versus normal, and cancer versus cancer, including histology and multicancer analysis types and outlier analyses. Red shading of boxes denotes gene overexpression; blue shading represents decreased gene expression. This disease summary was performed using the following criteria: a 2-fold change for gene expression, a p -value of 1×10^{-4} , and a gene rank percentile of 10%. BDP1 was overexpressed in breast and colorectal cancer vs. normal datasets but underexpressed in breast and lymphoma cancer vs. normal datasets. In cancer vs. cancer datasets, BDP1 was over- and underexpressed in kidney cancer (cancer histology dataset). BDP1 was overexpressed in prostate cancer (metastasis vs. primary) in a cancer subtype analysis but decreased in drug and perturbation analysis in lung cancers. The outlier analysis demonstrated that BDP1 was both over- and underexpressed across analyzed cancers. (B) BDP1 was significantly overexpressed in colorectal cancer ($p = 2.07 \times 10^{-5}$, 105 patients) across 5 datasets (10%). (C) BDP1 was significantly underexpressed in lymphoma ($p = 8.37 \times 10^{-7}$, 131 patients) across 2 datasets (28.5%). The OncoPrint™ Platform (Thermo Fisher, Ann Arbor, MI, USA) was used for analysis and visualization.

Interestingly, BDP1 was significantly overexpressed in colorectal cancer ($p = 2.07 \times 10^{-5}$, 105 patients, median gene rank of 318) across five datasets (10%) (Figure 1B). However, further analysis did not identify any correlation with clinical outcomes (unpublished data). In contrast, BDP1 was significantly underexpressed in lymphoma ($p = 8.37 \times 10^{-7}$, 131 patients, median gene rank of 107) across two datasets (28.5%) (Figure 1C). To the best of our knowledge, BDP1 alterations in lymphoma have not been investigated previously. Thus, the observed

statistically significant BDP1 underexpression in lymphoma datasets (Figure 1A,C) warranted further in-depth analysis.

3.2. BDP1 mRNA Is Significantly and Specifically Underexpressed in Lymphoma

In Figure 2A, we show BDP1 expression in the Brune lymphoma dataset [38]; BDP1 expression was significantly decreased in BL (normal versus cancer; gene rank of 25, $p = 1.54 \times 10^{-11}$, fold change of -2.148 , $n = 67$). In Figure 2B, we show BDP1 expression in the Eckerle lymphoma dataset [39]; BDP1 expression was significantly decreased in ALK+ ALCL, an ALCL subtype that responds well to standard chemotherapy treatment (gene rank of 190, $p = 1.67 \times 10^{-6}$, fold change of -2.635 , $n = 64$) [23].

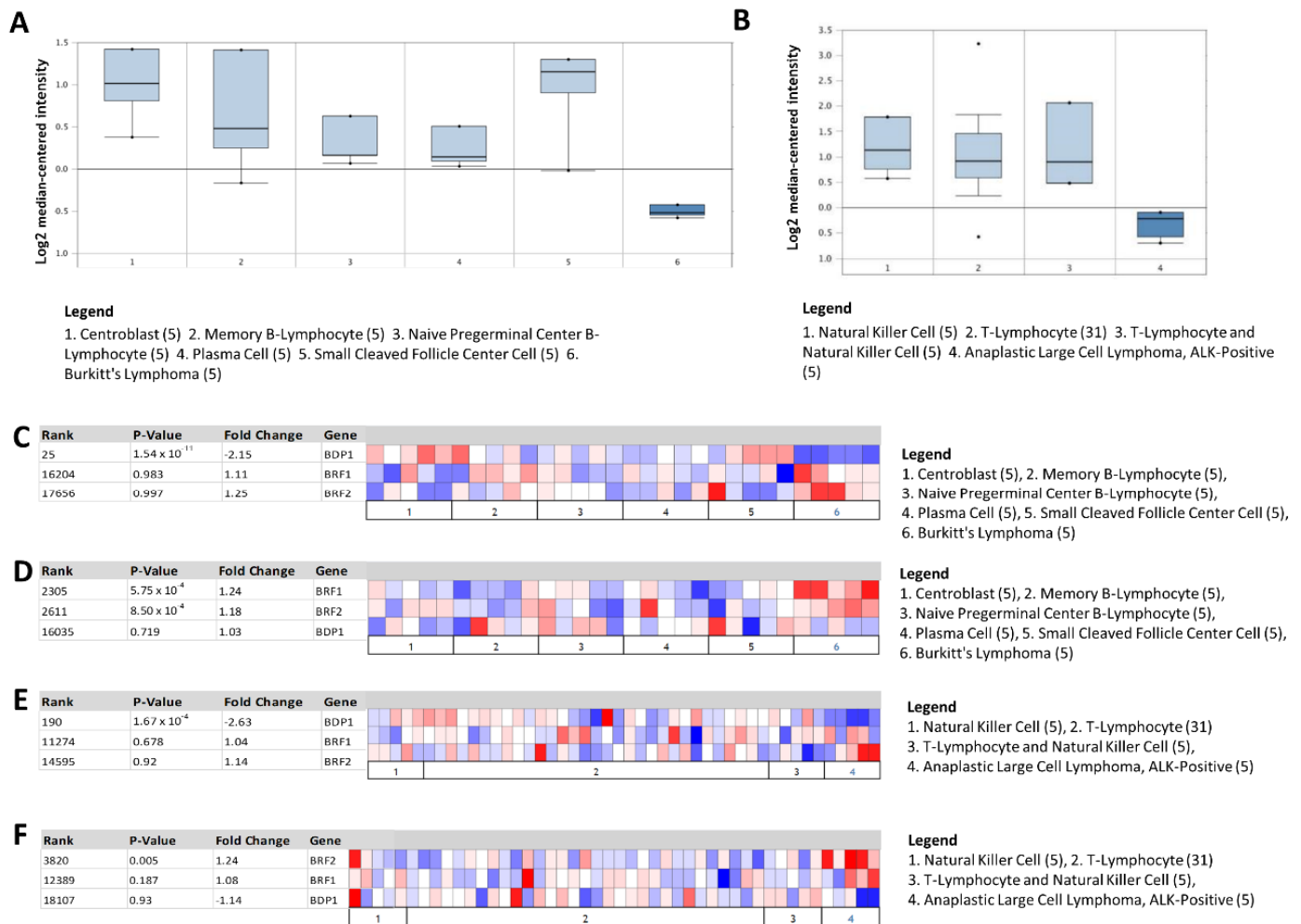


Figure 2. BDP1 mRNA is significantly and specifically underexpressed in lymphoma. (A) BDP1 expression in Brune lymphoma [22] (Burkitt's lymphoma vs. normal), gene rank of 25 (top 1%), p -value = 1.54×10^{-11} , fold change of -2.148 , $n = 67$. (B) BDP1 expression in Eckerle lymphoma [23] (anaplastic large-cell lymphoma, ALK-positive vs. normal), gene rank of 190 (top 1%), p -value = 1.67×10^{-6} , fold change of -2.635 , $n = 64$. Heat maps denoting underexpression of the TFIIB subunit BDP1 (C,E) in the Brune [22] and Eckerle [23] lymphoma datasets are specific. BRF1 and BRF2 were significantly overexpressed exclusively in the Brune dataset (D). Only BRF2 was significantly overexpressed in the Eckerle dataset (F). The OncoPrint™ Platform (Thermo Fisher, Ann Arbor, MI, USA) was used for analysis and visualization.

Subsequently, we determined if the observed statistically significant decrease in BDP1 expression in lymphoma patients was unique to BDP1 or was common to the TFIIB subunits BRF1 and BRF2. The heat maps depict TFIIB expression in BL (Figure 2C,D) and ALK+ ALCL (Figure 2E,F). There was no significant decrease in BRF1 or BRF2 expression

concurrent with the significant decrease in BDP1 expression (Figure 2C,E). However, BRF1 ($p = 5.75 \times 10^{-4}$) and BRF2 ($p = 8.50 \times 10^{-4}$) were significantly and specifically overexpressed exclusively in the Brune lymphoma dataset (Figure 2D) [22]. Only BRF2 ($p = 0.005$) was overexpressed in the Eckerle lymphoma dataset (Figure 2F) [23].

3.3. Heat Map Identifies BDP1 Expression as Significantly Underexpressed in BL and ALK+ ALCL

Gene expression profiling identifying molecular heterogeneity in various lymphomas has provided additional genetic information with the potential to develop targeted therapies [40]. As such, we re-examined the Brune [22] and Eckerle [23] lymphoma datasets to identify the top over- and underexpressed genes in BL and ALK+ ALCL to determine the potential significance of BDP1 underexpression in the context of these NHL subtypes (Figure 3). Using the Steidl lymphoma [41] concept cluster (Oncomine cluster-ID n9239), we queried the Brune [22] and Eckerle [23] lymphoma datasets to identify genes with the top median gene rank that were significantly over- and underexpressed. The top genes identified as significantly under- or overexpressed are labeled with median gene rank, p -value, and fold change in gene expression. Analysis of the Brune dataset (Figure 3A,B) identified BDP1 ($p = 1.54 \times 10^{-11}$) as significantly underexpressed in BL vs. normal (log2 median-centered intensity), with a median gene rank of 25 and -2.15 -fold change (Figure 3A). The significantly overexpressed genes in BL are presented in Figure 3B using the same parameters utilized in Figure 3A. Analysis of the Eckerle dataset (Figure 3C,D) identified BDP1 ($p = 1.67 \times 10^{-6}$) as significantly underexpressed in ALK+ ALCL vs. normal (log2 median-centered intensity), with a median gene rank of 190 and -2.63 -fold change (Figure 3C). The identification of significantly overexpressed genes in ALK+ ALCL is presented in Figure 3D using the same criteria as in Figure 3C.

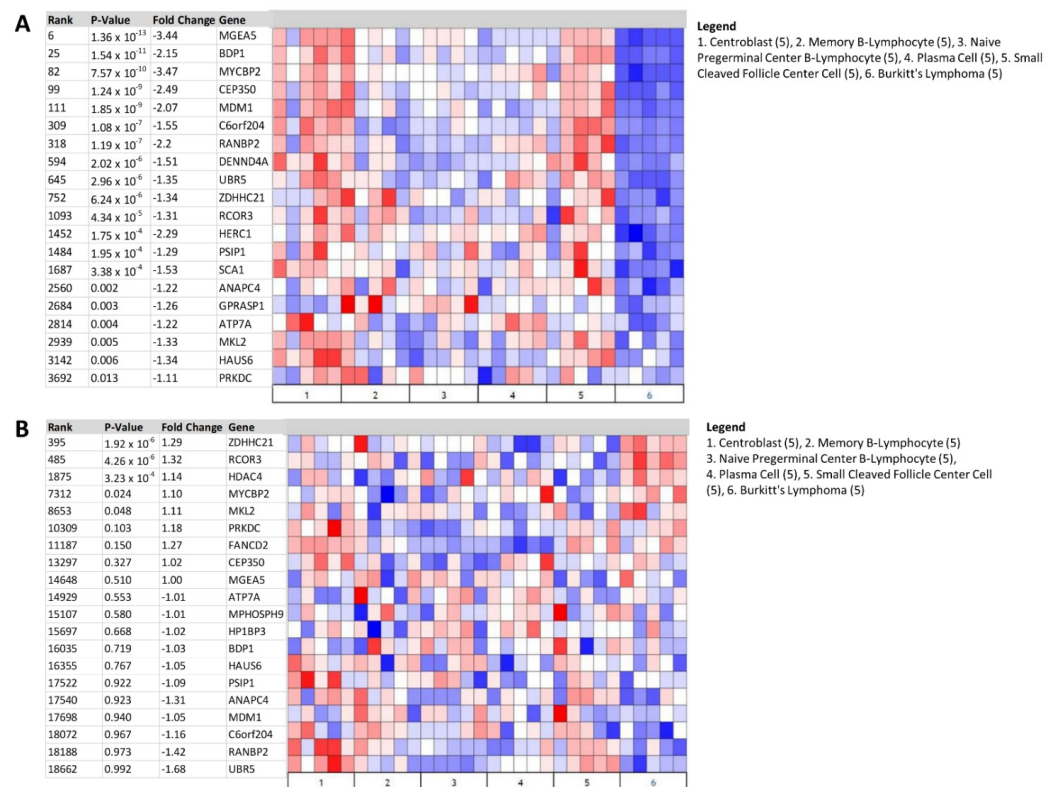


Figure 3. Cont.

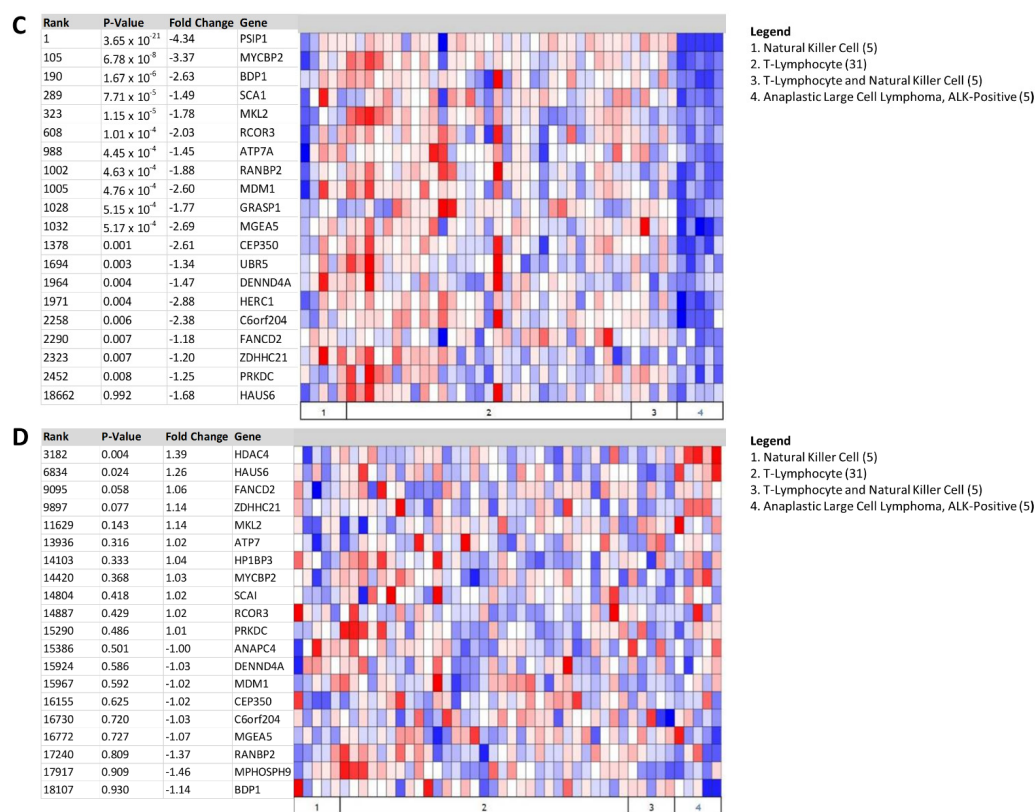


Figure 3. Heat map identifies BDP1 expression as significantly underexpressed in BL and ALK+ ALCL. Using the Steidl lymphoma [41] concept cluster (Oncomine cluster-ID n9239), we queried the Brune [22] and Eckerle [23] lymphoma datasets to identify genes with the top median gene rank that are significantly over- and underexpressed. (A) BDP1 ($p = 1.54 \times 10^{-11}$) was significantly underexpressed in BL vs. normal (log2 median-centered intensity), with a median gene rank of 25 and -2.15 -fold change. The top genes identified as significantly underexpressed are labeled with median gene rank, p -value, and fold change in gene expression. (B) Identification of significantly overexpressed genes in BL using the same parameters identified in (A). (C) BDP1 ($p = 1.67 \times 10^{-6}$) was significantly underexpressed in ALK+ ALCL vs. normal (log2 median-centered intensity), with a median gene rank of 190 and -2.63 -fold change. The top genes identified as significantly underexpressed are labeled with median gene rank, p -value, and fold change in gene expression. (D) Identification of significantly overexpressed genes in ALK+ ALCL using the same criteria applied in (C). The Oncomine™ Platform (Thermo Fisher, Ann Arbor, MI, USA) was used for analysis and visualization.

3.4. In Silico Identification of Putative Transcription Factor Binding Sites in the BDP1 Promoter for Transcription Factors Deregulated in NHL

The results in Figure 3 prompted an in silico analysis to determine if the transcription factors with significantly altered expression have the potential to deregulate BDP1 activity and expression. The BDP1 protein contains a highly conserved SANT domain, originally identified in Swi3, Ada2, N-Cor, and TFIIB (yeast BDP1) [3,4]. The SANT domain has been implicated in DNA binding and chromatin remodeling [42]. Of the transcription factors with significantly altered expression in BL and ALK+ ALCL identified in Figure 3, we identified two transcription factors with the potential to regulate BDP1 activity via the SANT domain (Table 2).

Table 2. Transcription factors significantly altered in BL and ALK+ ALCL known to interact with the SANT domain of BDP1.

Transcription Factor	Over- or Underexpressed	Interaction with SANT Domain	References
HDAC4	Overexpressed	Y	[43]
RCOR3	Overexpressed/Underexpressed	Y	[44]

Further analysis of deregulated transcription factors in BL and ALK+ ALCL identified histone deacetylase 4 (HDAC4) as specifically and significantly overexpressed in both BL and ALK+ ALCL (Figure 3). Previously, SANT domain proteins were identified in chromatin remodeling complexes [45]. In addition, corepressor of nuclear receptors (*n*-CoR) is a SANT domain protein known to interact with and activate histone deacetylase 3 (HDAC3) [46]. In esophageal carcinoma, HDAC4 overexpression has been associated with poor survival and promotes tumor progression [47]. It was recently demonstrated that the miRNA miR-155 targets HDAC4 and indirectly regulates B-cell lymphoma 6 (BCL6) expression, a key event in B-cell leukemia development [48]. A meta-analysis of the diffuse large B-cell lymphoma patient microarray data demonstrated that miR-155 expression inversely correlates with HDAC4 and BCL6 [48]. More experiments are required to determine if BDP1, potentially via the SANT domain, interacts with HDAC4, playing a regulatory role in NHL. In addition, we noted that the REST corepressor 3 (RCOR3) was both significantly over- and underexpressed in both BL and ALK+ ALCL.

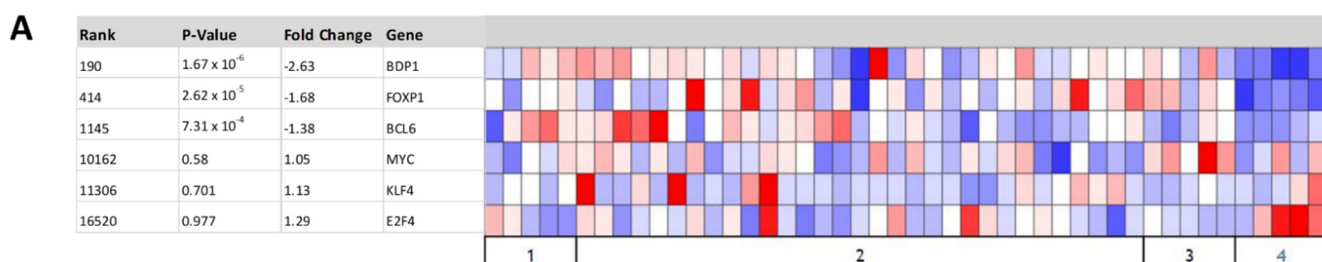
There are three REST corepressor family members (1–3), each with two SANT domains [44]. Deletions in RCOR1 are associated with unfavorable survival outcomes in patients with DLBCL [49]. RCOR1 and RCOR2 facilitate nucleosome demethylation during blood cell maturation, whereas RCOR3 inhibits this process [50]. It is unclear if RCOR3 plays a role in NHL.

We could not determine whether the observed significant decrease in BDP1 mRNA expression in BL and ALK+ ALCL is the result of decreased transcription from the BDP1 promoter or decreased BDP1 mRNA stability. Thus, we examined the BDP1 promoter for putative transcription factor binding sites known to play a role in lymphoma. Thus, we performed a query of the Eukaryotic Promoter Database [25] for lymphoma-associated putative transcription factor binding sites in the BDP1 promoter, located –1000 to +100 relative to the transcriptional start site (TSS), using a cutoff *p*-value of 0.001 [25]. Table 3 summarizes the location of putative binding sites in the BDP1 promoter for lymphoma-associated transcription factors.

Table 3. Identification of transcription factors deregulated in NHL with putative transcription factor binding sites in the BDP1 promoter.

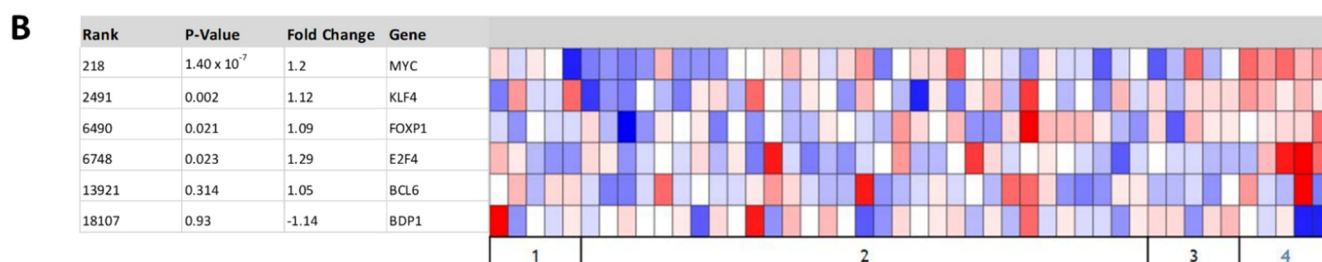
Transcription Factor	Location in the BDP1 Promoter Relative to TSS	References
KLF4	–734, –593, –553, –459, –291,	[51]
MYC	–582, –581	[52]
BCL6	–985, –936, –384, –362, –287, –276, –173	[53]
FOXP1	–876, –802, –747, –427, –388	[54]
E2F4	526, –470, –15, 54, 74	[55]

In NHL, Krüppel-like factor 4 (KLF4) has been characterized as a tumor suppressor, and overexpression inhibits cell proliferation in BL cell lines [51]. In ALK+ ALCL, KLF4 overexpression is significant ($p = 0.002$, gene rank 2491) and BDP1 expression is significantly decreased ($p = 1.67 \times 10^{-6}$, gene rank 190) (Figure 4). Thus, the KLF4 binding sites identified at –734, –593, –553, –459, and –291 may partially explain the significant decrease in BDP1 observed in subtypes of NHL [51].



Legend

1. Natural Killer Cell (5), 2. T-Lymphocyte (31), 3. T-Lymphocyte and Natural Killer Cell (5), 4. Anaplastic Large Cell Lymphoma, ALK-Positive (5)



Legend

1. Natural Killer Cell (5), 2. T-Lymphocyte (31), 3. T-Lymphocyte and Natural Killer Cell (5), 4. Anaplastic Large Cell Lymphoma, ALK-Positive (5)

Figure 4. Coexpression analysis of BDP1, KLF4, MYC, BCL6, FOXP1, and E3F4 in ALK+ ALCL. Under (A,B) overexpression of BDP1, KLF4, MYC, BCL6, FOXP1, and E3F4 in ALK+ ALCL. The analysis was performed using the Eckerle lymphoma dataset [23]. Gene rank, fold change in expression, and *p*-values are indicated. The OncoPrint™ Platform (Thermo Fisher, Ann Arbor, MI, USA) was used for analysis and visualization.

3.5. Decreased BDP1 Expression Correlates with FOXP1 and BCL6 Expression

In NHL, MYC amplification is associated with poor prognosis [52]. It is plausible that MYC binding to the BDP1 promoter, located at -582 and -581 , may permit the recruitment of MYC-associated proteins to silence BDP1 expression. MYC is significantly overexpressed ($p = 1.4 \times 10^{-7}$, gene rank 218) and BDP1 expression is significantly decreased ($p = 1.67 \times 10^{-6}$, gene rank 190) in ALK+ ALCL (Figure 4). BCL6 overexpression has been implicated in lymphoma [53]. We identified BCL6 binding sites in the BDP1 promoter at -985 , -936 , -384 , -362 , -287 , -276 , and -173 , relative to the transcription start site (TSS). Overexpression of BCL6 has been implicated in lymphoma [53]. However, both BCL ($p = 7.31 \times 10^{-4}$, gene rank 1145) and BDP1 ($p = 1.67 \times 10^{-6}$, gene rank 190) expression are significantly decreased in ALK+ ALCL (Figure 4A) [53]. We did not observe the same correlation in Burkitt's lymphoma using the Brune dataset (data not shown) [22].

We identified several putative Forkhead box protein P1 (FOXP1) and E2 factor transcription factor 4 (E2F4) binding sites in the BDP1 promoter (Table 3). FOXP1 is overexpressed in a subset of DLBCL patients [54]. In ALK+ ALCL, both FOXP1 ($p = 2.62 \times 10^{-5}$, gene rank 414) and BDP1 ($p = 1.67 \times 10^{-6}$, gene rank 190) expression is significantly decreased (Figure 4). Decreased E2F4 protein expression in BL tumor samples has been reported [55]. However, our analysis of E2F4 expression shows that it remains relatively unchanged in ALK+ ALCL (Figure 4). Analyses of these putative binding sites suggest that the MYC binding sites at -582 and -581 in the BDP1 promoter may play a key role in regulating BDP1 mRNA expression in ALK+ ALCL.

3.6. Decreased BDP1 Expression Correlates with Clinical Outcomes in Activated B-Cell Diffuse Large B-Cell Lymphoma

Together, these data suggest a role for BDP1 alterations in NHL patients. To determine if the decreased BDP1 expression in lymphoma subtypes is clinically relevant, we examined whether BDP1 expression changes correlated with clinical outcomes. Clinical outcomes analyses, depicted in Figure 5, were performed using the Shaknovich lymphoma dataset [24] ($n = 69$). In activated B-cell (ABC) DLBCL [40], decreased BDP1 expression correlated with clinical outcomes, including recurrence at 1 year ($p = 0.021$) and 3 years ($p = 0.005$) (Figure 5A,B).

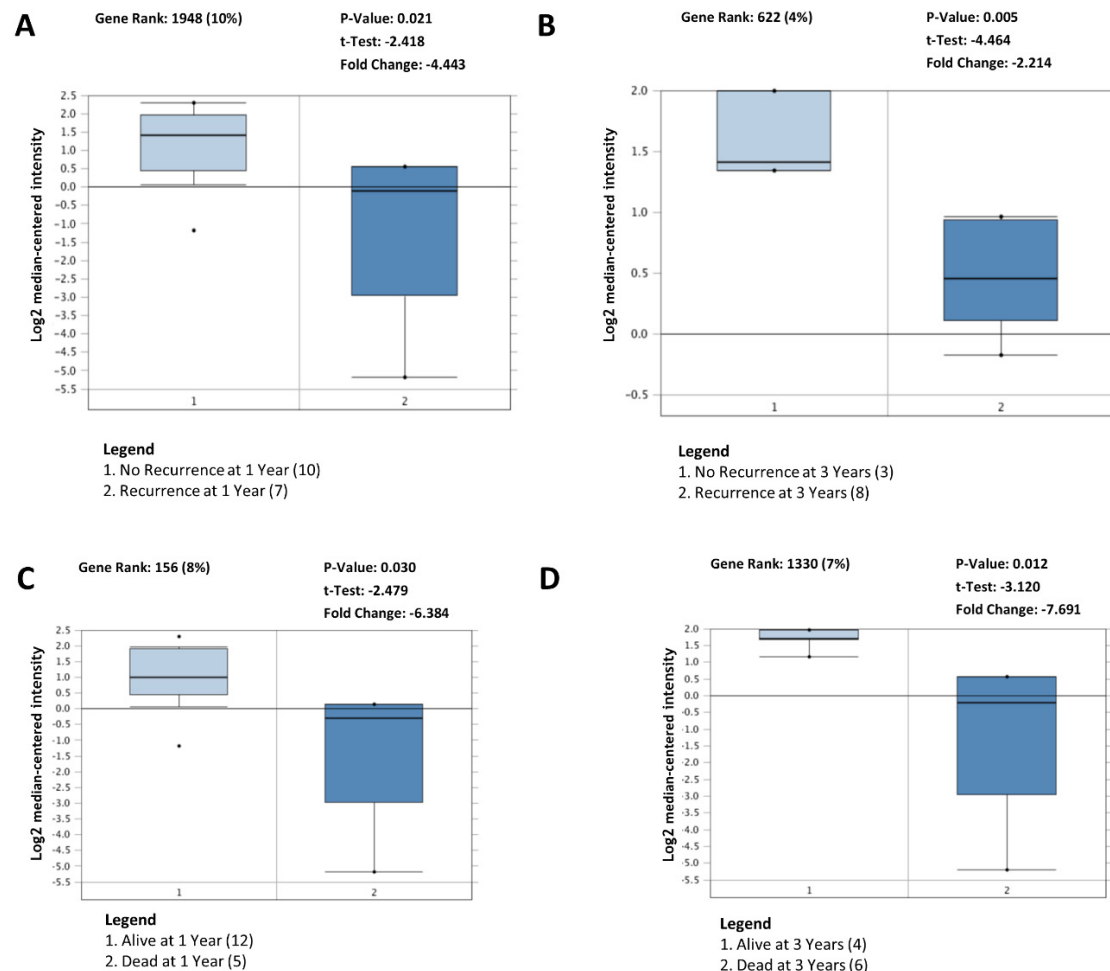


Figure 5. BDP1 expression in activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL) correlates with clinical outcomes. BDP1 expression was significantly altered in ABC DLBCL recurrence at 1 (A) and 3 (B) years. In addition, in ABC DLBCL, BDP1 expression was significantly altered in patients who died in year 1 (C) and year 3 (D). Clinical outcomes analyses were performed using the Shaknovich lymphoma dataset [24], $n = 69$. The OncoPrint™ Platform (Thermo Fisher, Ann Arbor, MI, USA) was used for analysis and visualization.

DLBCL patients can be divided into two groups based on expression profiling: ABC DLBCL and germinal center B-cell (GCB) DLBCL subtypes [56]. Patients with ABC DLBCL have poorer clinical outcomes than GCB patients [56]. Consequently, we carried out an analysis to determine if BDP1 expression and mortality were correlated in ABC DLBCL. Mortality at 1 ($p = 0.030$) and 3 ($p = 0.012$) years correlated with a decrease in BDP1 expression in ABC DLBCL (Figure 5C,D). Using the Shaknovich lymphoma dataset [24], recurrence ($p = 0.614$) and mortality ($p = 0.858$) outcomes in Figure 5 did not correlate with BDP1 expression in patients with GCB DLBCL (data not shown). However, BDP1

underexpression correlated with mortality at 1 ($p = 0.023$) and 3 ($p = 0.009$) years in the Lenz DLBCL dataset [56] (data not shown).

A variety of predictive and diagnostic biomarkers have been defined in ABC DLBCL [57], including the following common loss-of-function ABC DLBCL molecular biomarkers: beta-2-microglobulin (B2M), CD58 molecule (CD58), cyclin-dependent kinase inhibitor 2A (CDKN2A), CREB-binding protein (CREBBP), E1A-binding protein p300 (EP300), myeloid/lymphoid or mixed-lineage leukemia 2 (MLL2), and the myeloid differentiation primary response gene (88) (MYD88) [57]. FOXP1 [57] and the melanoma-associated antigen (mutated) 1 (MUM1) are immunohistochemical biomarkers in ABC DLBCL [57]. We queried the Shaknovich [24] lymphoma dataset in OncoPrint to determine if BDP1 and established ABC DLBCL biomarkers correlate with clinical outcomes, and the results are shown in Figure 6. The expression heat maps represent recurrence at one year (Figure 6A) and three years (Figure 6B) and ABC DLBCL patients who died at one year (Figure 6C) and three years (Figure 6D); p -value and fold-change are indicated. BDP1 expression was significantly decreased, as were many of the established ABC DLBCL biomarkers. This significant correlation of BDP1 expression with both clinical outcomes and identified biomarkers in lymphoma suggests that more extensive analyses are warranted to determine if decreased BDP1 expression is a global feature of DLBCL or specific to DLBCL subtypes.

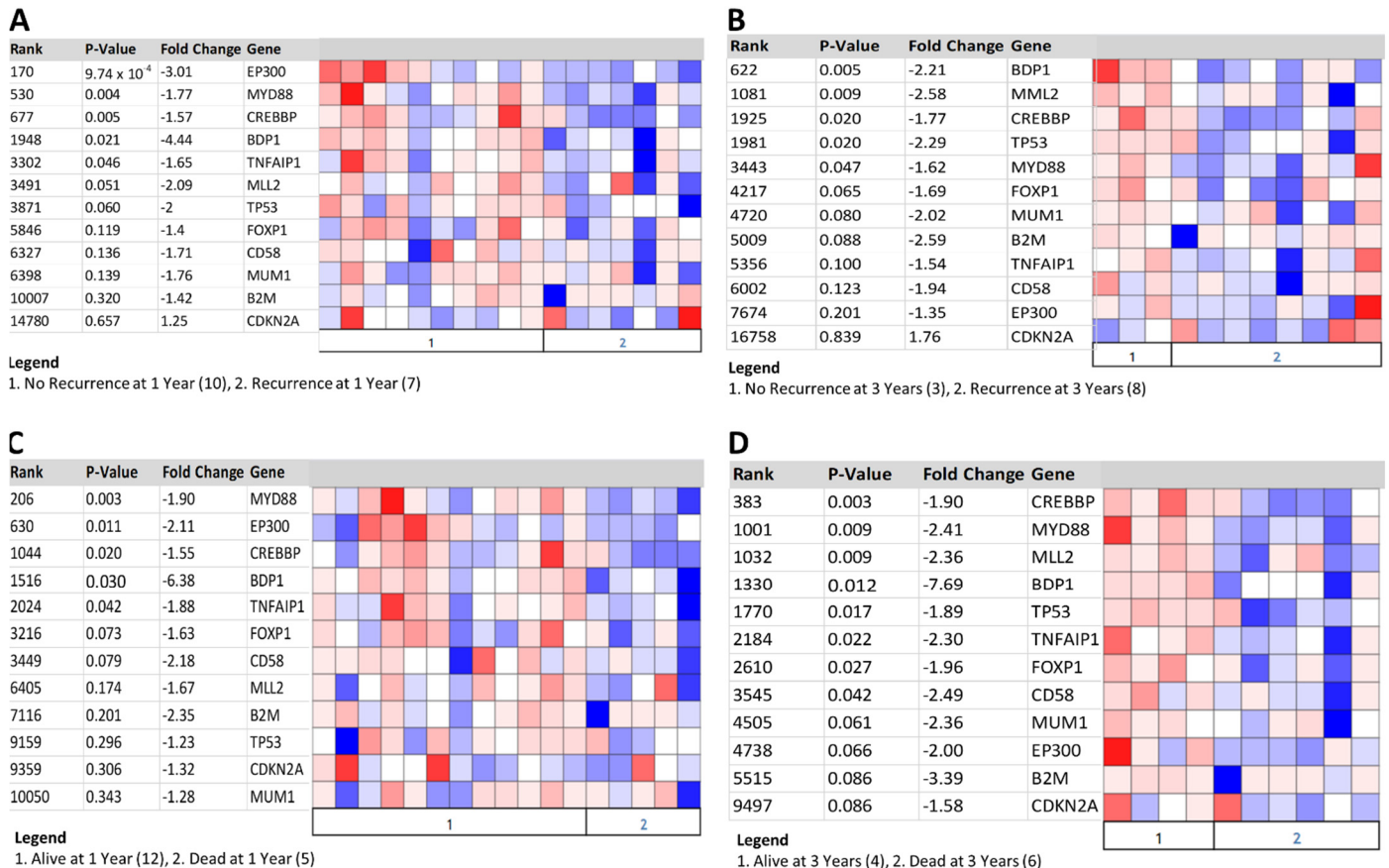


Figure 6. Correlation of ABC DLBCL biomarkers and BDP1 expression with clinical outcomes. BDP1 expression and ABC DLBCL biomarker expression were significantly altered in ABC DLBCL recurrence at 1 (A) and 3 (B) years. ABC DLBCL biomarker and BDP1 expression were significantly altered in patients who died in year 1 (C) and year 3 (D). Clinical outcomes analyses were performed using the Shaknovich lymphoma dataset [24], $n = 69$. The OncoPrint Platform (Thermo Fisher, Ann Arbor, MI, USA) was used for analysis and visualization.

4. Discussion

To the best of our knowledge, this is the first study to identify BDP1 alterations in NHL. In this study, we performed a meta-analysis of cancer patient data from the OncoPrint web-based data-mining platform to analyze BDP1 alterations in human cancers. Interestingly, there is a statistically significant decrease in BDP1 expression in patients with ALK+ ALCL ($p = 1.67 \times 10^{-6}$) and BL ($p = 1.54 \times 10^{-11}$). To potentially identify mechanisms that drive the decrease in BDP1 mRNA expression, we analyzed the BDP1 promoter for transcription factor binding sites with relevance in NHL. Analysis of the BDP1 promoter identified putative binding sites for MYC, BCL6, E2F4, and KLF4 transcription factors, which were previously demonstrated to be deregulated in lymphomas. MYC and BDP1 expression are inversely correlated in ALK+ ALCL, suggesting a possible mechanism for the significant and specific decrease in BDP1 expression. In ABC DLBCL, decreased BDP1 expression correlated with clinical outcomes, including recurrence at 1 year ($p = 0.021$) and 3 years ($p = 0.005$). Mortality at 1 ($p = 0.030$) and 3 ($p = 0.012$) years correlated with decreased BDP1 expression in ABC DLBCL. Lastly, BDP1 underexpression correlates with previously identified biomarkers in ABC DLBCL patient clinical data. DCBCL is the most common lymphoma diagnosed in adults, with ABC DCBCL having a poor prognosis [58].

All microarray dataset analyses have limitations and should be interpreted with caution. In this study, we examined BDP1 alterations in NHL and clinical outcomes. We exclusively used publicly available microarray datasets from the NCBI Gene Expression Omnibus repository containing clinical outcome data identified using the OncoPrint Research Platform in Figure 1. We believe that larger studies of NHL patients using RNA-seq analysis would provide an unbiased approach to analyzing all transcripts in a genome.

Additional clinical studies are required to determine if the observed correlation between BDP1 expression and clinical outcomes is specific to ABC DCBCL, potentially identifying BDP1 as a predictive biomarker in ABC DCBCL, or a general observation in NHL. Together, the data presented suggest that BDP1, a unique factor in the RNA pol III machinery, may be a novel target for therapeutic intervention for patients with NHL and warrants further investigation in the clinic.

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