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Exploring *TBL1XR1* and *NCOR1* Expression in B-cell Lymphoma Subtypes: Interaction With DNA Damage Repair Genes

ADNAN MANSOOR[1], ARIZ AKHTER[1], MAHBOOBSADAT HAMIDI[1], TARIQ MAHMOOD ROSHAN[1], MEER-TAHER SHABANI-RAD[1] and DOUGLAS STEWART[2]

[1]*Department of Pathology & Laboratory Medicine, University of Calgary and Alberta Precision Laboratories (APL), Calgary, Alberta, Canada;*
[2]*Department of Oncology, University of Calgary, Tom Baker Cancer Centre, Calgary, Alberta, Canada*

Abstract. *Background/Aim: B-cell lymphomas are characterized by diverse genetic anomalies affecting B-cell differentiation. To expand targeted therapies, an in-depth grasp of the molecular dynamics in the germinal center (GC) is vital. Transducin β-like 1 X-linked receptor 1 (TBL1XR1) and nuclear receptor corepressor 1 (NCOR1) are instrumental within the GC, modulating myriad oncogenic pathways. Their prognostic roles in various cancers are established, yet their precise impact on B-cell lymphoma is elusive. Materials and Methods: Digital RNA quantification (Nanostring) of previously curated 188 B-cell lymphoma specimens across four subtypes, follicular lymphoma (FL), diffuse large B-cell lymphoma, not otherwise specified (DLBCL-NOS), primary testicular lymphoma (PTL), and plasmablastic lymphoma (PBL), was reanalyzed with focus on TBL1XR1 and NCOR1 expression, juxtaposing them with 730 ontogenically linked genes. Results: Notably, TBL1XR1 expression was significantly elevated in the PTL- ABC-subtype versus DLBCL-NOS- ABC-subtype (p<0.001), with no marked disparity in GCB-subtypes between them. The median TBL1XR1 expression was remarkably diminished in FL, yet, intriguingly, GCB-subtypes of DLBCL-NOS exhibited significantly enhanced expression compared to FL (p=0.001). In contrast, NCOR1's expression trajectory was consistent across DLBCL-NOS, PTL, and PBL. A strong inverse correlation between TBL1XR1 and NCOR1 was observed in PBL (p=0.001). Importantly, TBL1XR1's pronounced association with several DNA Damage repair (DDR) genes was noted suggesting influence on DNA repair. TBL1XR1-DDR gene signature was further validated employing a public data set of DLBCL-NOS. Conclusion: Our exploratory findings unravel the expression patterns of TBL1XR1/NCOR1 in B-cell lymphoma variants. The TBL1XR1-DDR genes connection offers insights into potential DNA repair roles, paving avenues for innovative therapies in B-cell lymphomas.*

Correspondence to: Adnan Mansoor, MD, FRCPC, Department of Pathology and Laboratory Medicine, University of Calgary, and Alberta Precision Laboratories (APL), Rm 7522, 7th floor McCaig Tower, 3134 Hospital Dr. NW, Calgary AB T2N5A1, Canada. Tel: +1 4039444232, e-mail: adnan.mansoor@albertaprecisionlabs.ca

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B-cell lymphomas arise from mutations affecting B-cell differentiation, particularly within germinal centers (GCs) where B-cells interact with T follicular helper cells (1). Upon antigen exposure, B-cells in the GC undergo somatic hypermutation, promoting the evolution of high-affinity antigen receptors and differentiating into memory B-cells or plasma cells (2). The complexities in B-cell lymphoma, including the common diffuse large B-cell lymphoma (DLBCL) subtype, originate from accumulated genetic anomalies during this differentiation process (3).

The protein transducin β-like 1 X-linked receptor 1 (TBL1XR1) regulates gene expression as part of the nuclear receptor corepressor (NCoR)/silencing mediator for retinoid and thyroid receptors (SMRT) corepressor complex (4). It is known to be a central component in the formation of GCs by binding and recruiting the majority of TBL1XR1/SMRT/NCOR1 complexes, a process mediated by B-cell lymphoma 6 (*BCL6*) gene expression (5). *TBL1XR1* over-expression has been linked to poor prognosis in several solid organ cancers, impacting various oncogenic signaling pathways (6). It has an essential role in B-cell development, influencing the transition of memory B-cells to plasma cells,

while mutations in the *TBL1XR1* gene have been observed to inhibit this progression and promote lymphomagenesis (7, 8). B-cell receptor diversification, essential for adaptive immunity, depends on processes like V(D)J recombination and somatic hypermutation (1). Ensuring repair of DNA lesions in these processes is vital for genomic stability and preventing oncogenic translocations. DNA damage response (DDR) plays a key role in maintaining this integrity (7, 8).

Our study examined the *TBL1XR1/NCOR1* RNA expression across B-cell lymphoma subtypes and its relationship with DDR pathway gene expression patterns, offering a foundation for future investigations into these intricate mechanisms and potential therapeutic avenues for B-cell lymphoma.

Materials and Methods

Patients and samples. Gene expression data were pooled from a previously curated heterogenous group of 188 lymphoma patients (102 FL, 27 DLBCL-NOS, 26 PTL, 33 PBL) from our institution (2008-2016), using diagnostic biopsies and excluding double-hit genetic abnormalities. Histological diagnoses followed the 2016 WHO Classification (9), and two hematopathologists reviewed all samples. For validation, we incorporated a public dataset from The Cancer Genome Atlas (TCGA) comprising 47 DLBCL and 337 normal tissues. The study conformed to the Declaration of Helsinki and secured approval from the Health Research Ethics Board of Alberta (HREBA) (HREBA study #.CC-16-0218; REN 7 dated December 15, 2022).

Gene expression analysis and determination of the Cell-of-Origin (Lymph2CX) using NanoString nCounter platform. For RNA isolation, we extracted RNA from triplicate 1 mm cores of diagnostic FFPE blocks using the Ambion Kit (ThermoFisher Scientific, Waltham, MA USA) and assessed concentrations with a Nanodrop spectrophotometer and Bio-analyzer 2100 (Nanodrop Technologies, Wilmington, DE, USA). mRNA expression was analyzed with the PanCancer pathway code set on NanoString (NanoString, Seattle, WA, USA), targeting 730 cancer genes. After a 20-h probe hybridization at 65˚C, the nCounterTM Digital Analyzer quantified expression, with normalization through nSolver Analysis Software v4.0 (NanoString). For DLBCL's cell-of-origin determination, we utilized the Lymph2Cx 20-gene expression-based assay on the NanoString platform with 250 ng of total RNA as described previously (10).

Statistical assessment: We determined the necessary sample size for each B-cell lymphoma group using a dedicated online tool (https://bioinformatics.mdanderson.org/MicroarraySampleSize/), setting our criteria at $p<0.001$, a false positive rate below 0.05, and a fold change >2.0. For our statistical evaluations, we utilized SPSS software v28.0 (IBM, Armonk, NY, USA) and normalized raw counts using nSolver software v4.0. Qlucore Omics Explorer v3.8 (Qlucore, Lund, Sweden) supported in-depth statistical analyses, setting benchmarks at a log fold change >2.0, $p<0.01$, and an FDR/q value <0.05. Furthermore, we enriched our findings using the Gene Expression Profiling Interactive Analysis (GEPIA) v2 tool, which integrates data from both The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) databases, facilitating comparisons between cancerous and normal tissue samples (11).

Results

Clinicopathological overview. We pooled data from previously curated 188 B-cell lymphoma samples, with a distribution of 54% follicular lymphoma (FL), 14% DLBCL, 14% primary testicular lymphoma (PTL), and 18% plasmablastic lymphoma (PBL). Notably, this sample distribution deviates from the typical clinical prevalence of B-cell lymphoma subtypes, a reflection of the inherent selection bias in our cohort. Nonetheless, our sample size achieved robust statistical power, ensuring the validity of findings even in instances where no differences were discerned. Examining the age distribution, DLBCL and FL cohorts showcased no significant age discrepancy, with 74% and 59% of the patients being above 60, respectively ($p=0.07$). A striking observation was made in the PBL cohort, where patients under 60 constituted a significant majority (61%), notably higher than both DLBCL and FL counterparts (23% and 41%, respectively; $p=0.002$). In terms of disease progression, patients diagnosed at advanced stages showed consistent distribution across DLBCL-NOS, FL, and PBL groups ($p=0.845$). Contrarily, PTL predominantly encompassed patients diagnosed at earlier stages (85%), a proportion significantly greater than that of DLBCL-NOS at 42% ($p<0.01$). Using the Lymph2Cx tool, we discerned that the ABC subtype was comparably prevalent in both DLBCL NOS (75%) and PTL (81%) cohorts, with no significant difference ($p=0.175$).

Expression of TBL1XR1 and NCOR1 genes across B-cell lymphoma sub-types. Through digital RNA expression analysis, we identified significant variations in *TBL1XR1* and *NCOR1* expression across different B-cell lymphoma subtypes (Figure 1). PTL-ABC subtype exhibited the highest median expression for TBL1XR1 (6,401), compared to ABC subtype in DLBCL-NOS (3,339), PBL (2,141), and FL (1,726) (Table I). Statistical analysis confirmed a significant correlation between *TBL1XR1* expression and lymphoma subtype ($p<0.001$). We noted no marked disparity in GCB-subtypes between PTL and DLBCL-NOS. However, the median *TBL1XR1* expression was significantly higher in DLBCL-GCB subtype compared to FL (2,719 *vs*. 1,733, $p=0.001$). The highest median expression of *NCOR1* was noted in FL (2,426), followed closely by DLBCL-NOS ABC subtype (2,281) and PTL-ABC subtype (2,098), with the lowest levels noted in PBL (1,555) (Table I and Figure 1A). However, *NCOR1* expression was not significantly linked to lymphoma subtype ($p=0.302$).

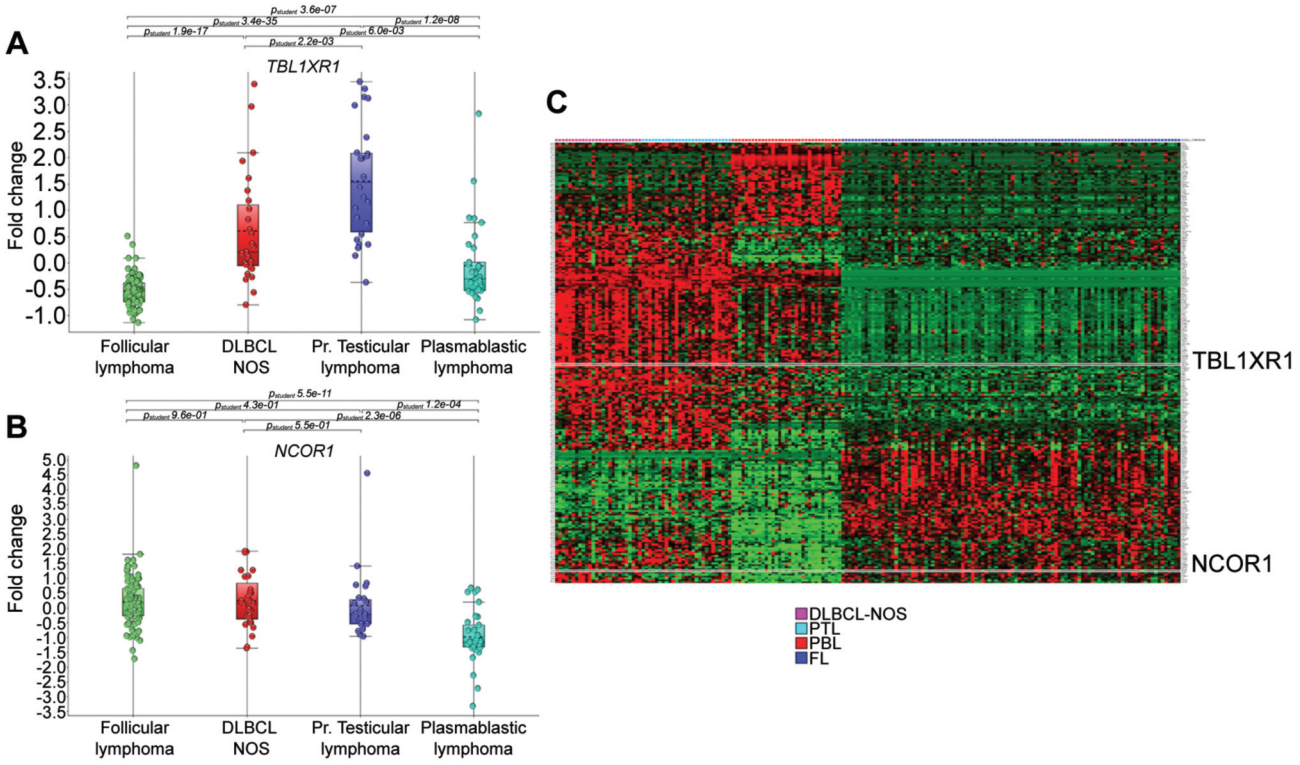

Figure 1. *Comprehensive representation of RNA expression variations across B-cell lymphoma subtypes. (A) Box plot delineating the fold change (y-axis) differential expression profile of transducin β-like 1 X-linked receptor 1 (TBL1XR1). (B) Corresponding to the fold change (y-axis) expression landscape of nuclear receptor corepressor 1 (NCOR1). (C) A heatmap detailing the differential expression signatures of 730 pertinent genes within the context of B-cell lymphoma subtypes.*

TBL1XR1 expression in FL grades and NCOR1 expression disparity. We evaluated *TBL1XR1* expression in low- and high-grade FLs, finding comparable mean and median levels between the two grades (p=0.809). Additionally, upon analyzing *TBL1XR1* and *NCOR1* expression in relation to FL stages, there were no discernible differences between early and advanced stages (p=0.862). A correlation study between *TBL1XR1* and *NCOR1* expression across both lymphoma grades revealed no significant association (Pearson r=0.15; 95%CI=0.53 to –0.21; p=0.489).

TBL1XR1 and NCOR1 expression in PBL. PBL showcased notably lower median *TBL1XR1* expression levels (2,141) than both DLBCL-NOS (3,086) and PTL (5,562) (p=0.001). However, *NCOR1* expression was consistent across PBL, DLBCL-NOS, and PTL. Within PBL samples, *TBL1XR1* and *NCOR1* demonstrated a significant negative correlation (Pearson r=–0.600; 95%CI=–0.778 to 0.315; p=0.001), hinting at divergent roles for these genes in PBL pathology.

Investigation of TBL1XR1 function and its association with DNA damage response (DDR) in B-cell lymphoma. We investigated the elevated expression of TBL1XR1 in B-cell lymphoma to discern its potential roles. Utilizing stringent criteria, we identified genes showing significant correlation with *TBL1XR1*. Remarkably, we found a pronounced association with key DNA damage response (DDR) genes, including R*AD50, RAD51, FN1, RFC4, FANCA, MCM4, HELLS, STAG2,* and *RAC1*. Bivariate analysis reinforced a significant tie between TBL1XR1 and these DDR genes (Pearson correlation r=0.496-0.770; p≤0.01) (Table II). A network plot (Figure 2A) visually represents these intricate relationships, emphasizing *TBL1XR1*'s potential interaction with critical DNA repair mechanisms in B-cell lymphoma.

Validation of the distinct expression of TBL1XR1-DDR pathway genes signature in a second cohort. In a second set of analysis, we probed the expression levels of *TBL1XR1*-DDR gene signature, namely *TBL1XR1*, *FANCA, FN1, HDAC2, RFC4, RAC1, RAD50,* and *RAD51*, across three cancer types namely, DLBCL, breast carcinoma, and gastric cancer. Leveraging data from the publicly available TCGA and GTEx databases, we juxtaposed these findings against their respective normal tissue controls. Remarkably, only DLBCL samples exhibited a statistically significant expression of

Table I. *Comparison of median expression levels and significance analysis for TBL1XR1 and NCOR1 in B-cell lymphoma subtypes.*

	FL-Low grade	FL-High grade	PBL	DLBCL-NOS ABC subtype	PTL ABC subtype	*p*-Value
TBL1XR1						
Mean	1,699	1,732	2,601	4,042	5,894	
Median	1,726	1,726	2,141	3,339	6,401	0.001
NCORI						
Mean	2,461	2,164	1,658	2,313	2,171	
Median	2,426	2,225	1,555	2,281	2,098	0.302

FL: Follicular lymphoma; DLBCL-NOS ABC: diffuse large B-cell. lymphoma NOS, activated B-cell type; PBL: plasmablastic lymphoma; PTL: primary testicular lymphoma.

Table II. *Pearson's correlation between TBL1XR1 gene expression and genes associated with the DNA damage repair (DDR) pathway.*

Primary variable	Secondary variable	Pearson correlation	Lower 95%CI	Upper 95%CI
TBL1XR1				
RAC1	0.565	0.459	0.655	0.001
FN1	0.644	0.552	0.721	0.001
FANCA	0.666	0.578	0.739	0.001
HDAC2	0.435	0.311	0.544	0.001
HELLS	0.793	0.674	0.912	0.001
RAD51	0.719	0.641	0.781	0.001
RAD50	0.605	0.506	0.689	0.001
RFC4	0.716	0.639	0.78	0.001
NBN	0.639	0.546	0.717	0.001
STAG2	0.484	0.366	0.587	0.001

CI: Confidence interval.

TBL1XR1-DDR signature genes. In contrast, the solid tumors from breast and gastric origins showed no discernible association between *TBL1XR1* and DDR gene expression (Figure 2B).

Discussion

TBL1XR1 and *NCOR1,* components of the nuclear receptor corepressor complex, are vital for cell differentiation and metabolism, modulating gene expression through chromatin modifications. In various cancers, aberrant expression, especially elevated *TBL1XR1*, is linked to poor prognosis, tumor growth, and therapy resistance. Their role, dependent on context, either inhibits tumor suppressor genes or activates oncogenic genes. Genomic aberrations disrupt this balance, enabling cancerous growth. While understood in solid tumors, knowledge about their dynamics in B-cell lymphoma remains scant. Disruptions in these proteins can impede B-cell differentiation, fostering lymphoid malignancies. Deciphering their roles can shed light on B-cell transformation mechanisms. TBL1XR1 and NCOR1 are key components of the nuclear receptor corepressor complex, pivotal in embryogenesis, cell differentiation, and metabolism by regulating transcription and modifying chromatin structure (12). In various cancers, including colorectal and breast, dysregulated expression, especially increased *TBL1XR1*, is linked to worse outcomes and increased resistance to treatment (13). The intricate interplay of *TBL1XR1* and *NCOR1* in cancer can either suppress tumor suppressor genes or amplify oncogenic ones (14). Genomic changes, like mutations, can disrupt this balance, enabling cancer cells to bypass growth control (15). However, knowledge about their roles in B-cell lymphoma remains rudimentary.

TBL1XR1 and *NCOR1*, integral to the corepressor complex, are pivotal in lymphohematopoietic processes. Their absence in hematopoietic stem cells (HSC) hampers lymphoid differentiation, as they shape gene expression and chromatin structure during cellular maturation (16). However, aberrations in these proteins can disturb lymphohematopoietic equilibrium, particularly in mature B-cell differentiation, potentially leading to lymphoid malignancies (8). *TBL1XR1* has been associated with abnormal memory B cell formation and plasma cell differentiation hindrance, linking it to

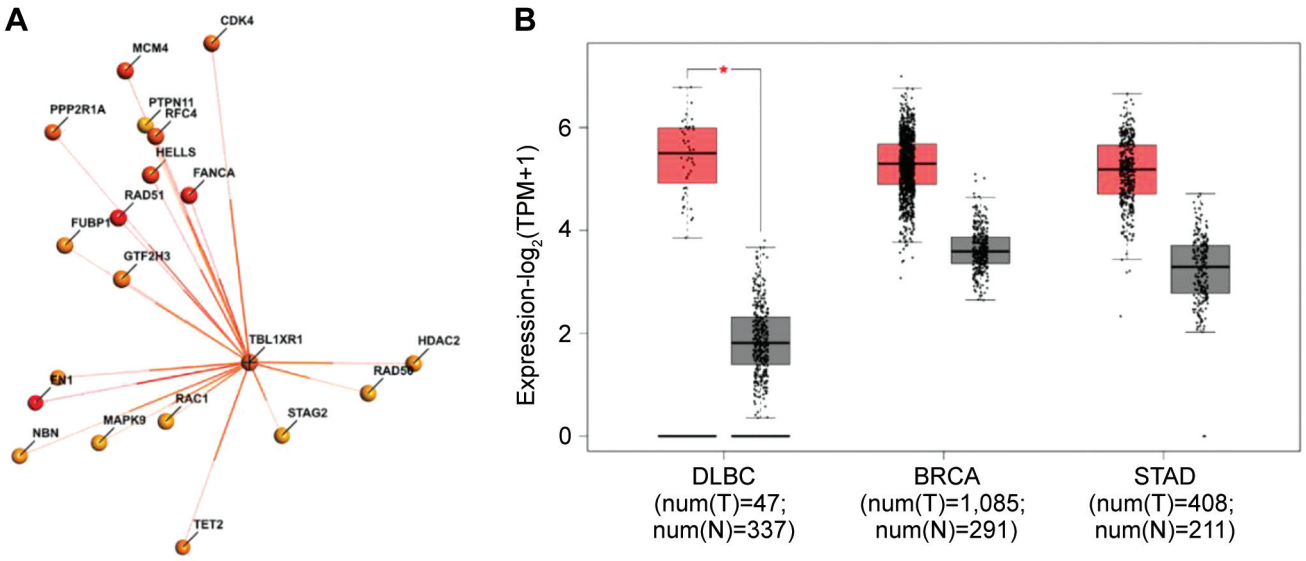

Figure 2. *Detailed visualization of TBL1XR1's interplay with DNA repair genes and its expression landscape across diverse cancers. (A) Network plot illustrating the intricate associations between transducin β-like 1 X-linked receptor 1 (TBL1XR1) expression and key DNA repair genes in the context of B-cell lymphoma. (B) Box plot contrasting the TBL1XR1-DNA damage response (DDR) gene signature's expression profiles in normal versus tumor tissues, spotlighting diffuse large B-cell lymphoma (DLBCL), breast carcinoma (BRCA), and stomach cancer (STAD) using data sourced from the TCGA public dataset.*

lymphoma development. Notably, *TBL1XR1* mutations have been found in lymphomas including DLBCL and among *MYD88* wild-type Waldenstrom's macroglobulinemia, imparting aggressive behavior (3, 17), emphasizing the critical need to unravel their roles for understanding B-cell malignancies' underpinnings.

In this study, we delve into the distinct expression profiles of *TBL1XR1* and *NCOR1* genes across B-cell lymphoma subtypes, aiming to uncover their associations with disease pathology and DNA repair mechanisms. We identified a specific expression pattern of *TBL1XR1* in Activated B-cell-like (ABC) subsets of PTL compared to ABC- subtype of DLBCL-NOS, a distinction that holds promise for individualized therapeutic approaches and improved patient outcomes. Previous work by Youssef *et al*. found *TBL1X* (a homolog of *TBL1XR1*) to influence DLBCL prognosis, suggesting *TBL1XR1*'s potential as a biomarker or therapeutic pivot in ABC-DLBCL in preclinical model (18). While *TBL1XR1*'s oncogene-rich genomic region is implicated in driving aggressive malignancies, *NCOR1* remains consistently expressed across DLBCL subsets. The observed inverse relationship between *TBL1XR1* and *NCOR1* in ABC-DLBCL underscores the necessity for further investigation, paving the way for enhanced understanding and innovative treatments.

TBL1XR1, known to stabilize G-protein pathway suppressor 2 (GPS2) *via* SUMOylation, is implicated in diverse physiological activities, ranging from DNA repair and cell proliferation to apoptosis and brain development (19). While the explicit role of TBL1XR1 in DDR within cancers such as B-cell lymphoma is still being deciphered, its encoding of an F-box-like/WD repeat-containing protein aligns it with the WD40 repeat protein family, previously associated with DNA damage pathways and cellular reactions to genotoxic stress (20). In our detailed analysis of B-cell lymphoma, we identified a compelling association between *TBL1XR1* and a cluster of DDR genes (including RAD50, RAD51, and others). This elevated *TBL1XR1*-DDR gene signature in DLBCL was cross-verified using public databases (TCGA and GTEx). The intricate interactions of *TBL1XR1* with pivotal DNA repair pathway components like XPA and BRCA1 accentuate its potential significance in DNA repair, illuminating its possible contributions to DDR and the ensuing ramifications for B-cell lymphoma pathogenesis.

In conclusion, our investigation revealed differential expression patterns of *TBL1XR1* and *NCOR1* across various B-cell lymphoma subtypes, particularly within the ABC-DLBCL subset of PTL and DLBCL-NOS. We observed a notably elevated expression of *TBL1XR1*, suggesting potential therapeutic avenues for customized treatments. Furthermore, we established a strong association between high *TBL1XR1* expression and the DDR gene signature, a finding further substantiated in a separate validation cohort.

While *TBL1XR1* may have a pro-proliferative role, *NCOR1* exhibited no significant differential expression between germinal centre and post-germinal centre derived B-cell lymphomas. Intriguingly, an inverse relationship between *TBL1XR1* and *NCOR1* expressions was evident in ABC-subtypes of PTL and DLBCL-NOS. These insights underscore the potential of *TBL1XR1* as a therapeutic target in DLBCL and set the stage for subsequent investigations.

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Conflicts of Interest

The Authors declare no competing financial interests concerning this work.

Authors' Contributions

DS and AM, conceived and designed the study, devised all the protocols, and edited the final manuscript. MH performed data collection and analysis. AA performed experimental work and QA. TMR, MTSR contributed samples/clinical data and reviewed pathology.

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