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ASSOCIATIONS OF *OTUBAIN-1, STAT, SHP* AND *NF-KB2* EXPRESSION WITH CLINICAL FEATURES IN NON-HODGKIN's LYMPHOMA PATIENTS

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ABSTRACT

Non-Hodgkin's lymphoma (NHL) is a group of lymphoproliferative disorders characterized by the abnormal proliferation and accumulation of lymphocytes in the lymphatic system. An ovarian tumor domain containing ubiquitin aldehyde binding protein 1 (*Otubain-1*) is a deubiquitinating enzyme that cleaves ubiquitin or ubiquitin-like molecules and is expressed in various human tissues. The pathogenesis of NHL is associated with activations of the nuclear transcription factor (NF-κB) and signal transducer and activator of transcription proteins (JAK/STAT) signaling pathways. In this study, all the expressions of *Otubain-1*, *NF-κB2, SHPs* and *STATs* genes, the concentrations of cytokines IL-1β, IL-6 and TNF-α and clinical features in NHL patients were examined. To the end, gene expression levels of 82 NHL patients and 56 healthy individuals were determined by quantitative real time RT-PCR and secretion of cytokines by ELISA. As a result, concentrations of IL-6 and TNF-α in the patient group were found higher than in the healthy individuals and patients with higher LDH concentrations in the clinical cutoff, 280 U/L showed increased concentrations of AST, ALT and GGT than those with normal LDH concentrations. Interestingly, NHL patients with high *Otubain-1* expression had significant elevations of GGT and ferritin concentrations as well as *STAT-5* expression compared to those with low *Otubain-1* expression. In conclusion, the present study indicates that up-regulation of *Otubain-1* led to activation of STAT5 in lymphoma cells and liver dysfunction and metabolic syndrome in NHL patients.

Keywords: NF-kB2, *Otubain-1*, non- Hodgkin's lymphoma and STAT5.

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INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is a group of lymphoproliferative disorders characterized by the abnormal proliferation and accumulation of lymphocytes in lymph nodes or extranodal lymphatic tissues (Swerdlow et al., 2016). Globally, the NHL ranked as the 11th most commonly diagnosed cancer and occurs more frequently in males (Mafra et al., 2022). The estimated incidence of NHL is 5/100,000 (nearly 545,000 new cases) and the mortality rate is about 3/100,000 (260,000 deaths) worldwide in 2020 (Mafra et al., 2022). NHL is generally divided into B-cell and T-cell lymphomas, depending on the lymphocyte lineage (Rogers et al., 2006). Among NHL, diffuse large B-cell NHL is the most common subtype and has an aggressive natural history but responds well to chemotherapy (Isshiki et al., 2021). In patients with NHL, lactate dehydrogenase (LDH), β2-microglobulin and ferritin have been documented to be inflammatory and adverse prognostic factors (Zhong et al., 2019). Among them, LDH reflects the proliferative activity of lymphoma cells and is an important prognostic factor in NHL (Dumontet et al., 1999). β2-microglobulin is a marker of tumor burden and is associated with the prognosis of most types of NHL, mainly including follicular lymphoma, mantle cell lymphoma and diffuse large cell lymphoma (Lazzarino et al., 1998). Cases with increased β2-microglobulin concentrations have a high risk of the development of NHL (Wang et al., 2015).

An ovarian tumor domain containing ubiquitin aldehyde binding protein 1 (*Otubain-1*) is considered as a deubiquitinating enzyme, which crucially regulates the ubiquitination-mediated degradation and expressed in various human tissues, such as the kidney, colon, stomach, brain, and liver (Saldana et al., 2019). *Otubain-1* is a negative regulator of cell function through the activation of several signalling molecules such as MAPK (Xuan et al., 2019). Increased *Otubain-1* expression has been reported in colorectal (Zhou et al., 2014) breast cancers (Karunarathna et al., 2016) and gastric adenocarcinoma (Weng et al., 2016). Inactivation of *Otubain-1* is observed in chronic myeloid leukemia in our study (Hoang et al., 2022). The activations of Akt-mTOR and MAPK pathways are associated with the expression levels of *Otubain-1* (Lin et al., 2009; Zhou et al., 2014).

Investigations on mechanisms underlying the modulations of functions of lymphoma cells indicated that the pathogenesis of NHL is related to activations of the nuclear transcription factor (NF-κB) and signal transducer and activator of transcription proteins (JAK/STAT) signaling pathways (Ramis-Zaldivar et al., 2021). Inactivation of SH2 domain-containing tyrosine phosphatase (SHP) 1 correlates with the advanced stages of NHL (Witkiewicz et al., 2007). *SHP1*-deficient mice display a variety of hematopoietic abnormalities including hypersensitivity of erythroid progenitors to erythropoietin and marked myeloid proliferation (Dong et al., 1999). SHP-1 is a negative regulator of, while SHP2 participates in promoting activations of JAK/STAT signaling pathways (Lorenz et al., 2009; Maroun et al., 2000; Tajan et al., 2015). Activation of the signaling molecules induces immune cells to secrete inflammatory cytokines, including IL-6, TNF-α and IL-1β, which cause chronic inflammation and the development of neoplasms and their progression (Hoermann et al., 2015). TNF-α has been demonstrated to directly contribute to the enhancement of the growth and development environment of NHL cells (D'Mello K et al., 2021).

In this study, the associations among the expressions of *Otubain-1, NF-κB2, SHPs* and *STATs* genes, the concentrations of cytokines IL-1β, IL-6 and TNF-α and clinical outcomes in 82 NHL patients and 56 healthy individuals were determined.

MATERIALS AND METHODS

Clinical samples

Fresh peripheral blood samples (4 mL) were collected from untreated 82 NHL patients based on cytomorphology and

cytochemistry according to the WHO (Swerdlow et al., 2016) classifications, at the National Institute of Haematology and Blood Transfusion, Ha Noi, Vietnam. The control group comprised 56 healthy individuals. No individuals in the control population took any medication or suffered from any known acute or chronic disease. All patients and volunteers gave written consent to participate in the study. Person care and experimental procedures were performed according to Vietnamese law for the welfare of humans and were approved by the Ethical Committee of the Institute of Genome Research, Vietnam Academy of Science and Technology.

Cytokine quantification

Serum samples were collected from both NHL patients and healthy subjects and kept at -20 ^{o}C until they were utilized for ELISA analysis. The concentrations of TNF-α, IL-6, and IL-1β were determined by using ELISA kits (Thermo Scientific) in accordance with the manufacturer's instructions.

RNA extraction and Real-time PCR

Total mRNA was isolated using the Qiashredder and RNeasy Mini Kit from Qiagen according to the manufacturer's instructions. For cDNA first-strand synthesis, 1 µg of total RNA in 12.5 µL DEPC-H_2O was mixed with 1 µL of oligo-dT primer (500 µg/mL, Invitrogen) and heated for 2 min at 70 ^{o}C. To determine transcript levels of *Otubain-1*, *NF-κB2, STAT-1, STAT-5, STAT-6, SHP-1* and *SHP-2*, the quantitative real-time PCR with the LightCycler System (Roche Diagnostics) was applied. The GenBank accession numbers, including NM_017670.3, NM_001322934.2, NM_007315.4, NM_012448.4, NM_003153.5, NM_002831.6 and NM_002834.5 were used for analysis of mRNA expressions of *Otubain-1*, *NF-κB2*, *STAT-1*, *STAT-5*, *STAT-6*, *SHP-1* and *SHP-2* genes, respectively. The following primers were indicated in Table 1.

Table 1. Primer sequences used for Real-time PCR

Gene	Forward (5'→3')	Reverse (5'→3')
Otubain-1	ACAGAAGATCAAGGACCTCCA	CAACTCCTTGCTGTCATCCA
NK-κB2	TAGCCACAGAGATGGAGGAG	CCGAGTCGCTATCAGAGGTA
STAT1	CCCTTCTGGCTTTGGATTGAA	CTTCCCGGGAGCTCTCACTGA
STAT5	CAGACCAAGTTTGCAGCCAC	CACAGCACTTTGTCAGGCAC
STAT-6	GCCCACTCACTCCAGAGGACCT	GGTGTTGGGGAAAGTCGACAT
SHP-1	GCC CAG TTC ATT GAA ACC AC	GAG GGA ACC CTT GCT CTT CT
SHP-2	GAGAGCAATGACGGCAAGTCT	CCTCCACCAACGTCGTATTTC
GAPDH	GGAGCGAGATCCCTCCAAA	GGCTGTTGTCATACTTCTCAT

PCR reactions were performed in a final volume of 20 µL containing 2 µL cDNA, 2.4 µL $MgCl_2$ (3 µM), 1 µL primer mix (0.5 µM of both primers), 2 µL cDNA Master Syber Green I mix (Roche Molecular Biochemicals), and 12.6 µL DEPC-treated water. The target DNA was amplified during 40 cycles of 95 ºC for 10 s, 62 ºC for 10 s, and 72 ºC for 16 s, each with a temperature transition rate of 20 ºC/s, a secondary target temperature of 50 ºC, and a step size of 0.5 ºC. Melting curve analysis was performed at 95 ºC, 0 s; 60 ºC, 10 s; 95 ºC, 0 s to determine the melting temperature of primer dimers and the specific PCR products. The ratio between the respective gene and corresponding *GAPDH* was calculated per sample according to the ΔΔ cycle threshold method (Livak et al., 2001).

Statistics

Statistical analysis was performed with the SPSS and GraphPad Prism 8 software. The statistical significance of the differences was determined by the Mann–Whitney U test. $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Clinical features in patients with NHL

A comprehensive correlation analysis of 82 patients with NHL showed significant increases in glucose, ferritin, AST, ALT, LDH and β2-microglobulin concentrations in the patient group (Table 2). Consistently, LDH is an important prognostic factor in patients with NHL (Dumontet et al., 1999) and cases with elevated β2-microglobulin concentrations are at increased risk of early mortality (Wang et al., 2015). Among the 82 patients with NHL at diagnosis in this study, the frequency of patients with higher LDH concentrations the clinical cutoff, 280 U/L, was 70/82 patients (85.4%), in which the patients were diagnosed in stage I in 16/70 (22.9%), 12/70 (17.1%) in stage II, 13/70 (18.6%) in stage III and 29/70 (41.4%) in stage IV. The patients with normal LDH concentrations were diagnosed in stage I in 4/12 (33.33%), 3/12 (25%) in stage II, 2/12 (16.67%) in stage III and 3/12 (25%) in stage IV. Importantly, the patients with LDH concentrations above the clinical cutoff were older and had elevations of AST, ALT and GGT concentrations than those with normal LDH concentrations, however, the differences did not reach the statistical significances (Table 3).

Table 2. Associations between *Otubain-1* expression and clinical parameters in NHL patients

Characteristic	Normal range	Total	*Otubain-1*		
Number of patients		N = 82	High (n = 52)	Low (n = 30)	*p*-value
Age (years)		56.6 (17–86)	57.9 (17–75)	54.4 (21–86)	0.34
Sex, male (n, %)		50 (61)	32 (61.5)	18 (60)	0.841
Urea (mmol/L)	3.3–6.6	6.01 ± 2.62	5.95 ± 2.03	6.11 ± 3.46	0.79
Glucose (mmol/L)	3.9–5.6	6.6 ± 2.8	6.68 ± 3.25	6.45 ± 1.81	0.728
Creatinine (µmol/L)	50–110	81.7 ± 22.13	80.03 ± 17.95	84.65 ± 28.17	0.365
Uric acid (µmol/L)	< 420	332.3 ± 128	331.8 ± 136.3	333.4 ± 114	0.955
Total bilirubin (µmol/L)	0–21	12.63 ± 10.72	11.54 ± 7.14	14.56 ± 15.09	0.219
Indirect bilirubin (µmol/L)	0–17	3.28 ± 7.51	2.68 ± 3.54	4.32 ± 11.6	0.34
Total protein (g/L)	60–80	70.92 ±8.73	70.49 ± 9.23	71.68 ± 7.84	0.555
Albumin (g/L)	35–50	36.8 ± 5.41	36.2 ± 5.24	37.9 ± 5.61	0.18
Globulin (g/L)	20–35	34.1 ± 7.44	34.28 ± 8.2	33.77 ± 5.99	0.764
Ferritin (ng/ml)	10–300	569.3 ± 508.9	659.6 ± 528.1	409.8 ± 437.1	0.031*
AST (GOT) (U/L)	5–40	46.99 ± 76.19	39.62 ± 44.52	59.99 ± 112.18	0.244
ALT (GPT) (U/L)	7–55	57.29 ± 106.7	51.15 ± 62.61	68.14 ± 158	0.489
GGT (U/L)	< 66	57.8 ±83.7	70.7 ± 101	35 ± 29	0.05*
LDH (U/L)	140–280	580.5 ± 472.7	541 ± 473.1	650.3 ± 471.8	0.315
β2 microglobulin concentration (mg/L)	0.8–2.2	2.97 ±1.99	2.82 ± 1.53	3.22 ± 2.65	0.373
Hemoglobin (g/L)	120–180	124.5 ± 19.77	122.6 ± 17.18	127.9 ± 23.6	0.243
Erythrocytes (10*12 cells/L)	3.8–5.9	4.13 ± 0.62	4.04 ± 0.53	4.29 ± 0.73	0.087

Otubain-1 is known as a negative regulator of the release of IL-6, but not TNF-α in mouse dendritic cells (Xuan et al., 2019). In this finding, the serum concentrations of IL-6 and TNF-α in the patient group were also found higher than in healthy individuals, however, these patients showed no change in the serum concentrations of IL-1β (Fig. 1). IL-6 and TNF-α are known as inflammatory mediators of cell growth, maturation/differentiation and programmed cell death (Xuan et al., 2015). The concentrations of TNF-α are elevated in cases of diffuse large B-cell lymphoma and associated with an increased risk of developing this disease (Edlefsen et al., 2014).

Table 3. Associations between LDH concentrations and clinical parameters in NHL patients

Characteristic	LDH		
Number of patients	High (n = 70)	Normal (n = 12)	*p*-value
Age (years)	57.3 (17–86)	48 (27–79)	0.1
Sex, male (n, %)	42 (60)	8 (66.67)	0.724
Urea (mmol/L)	6.06 ± 2.65	5.62 ± 2.77	0.64
Glucose (mmol/L)	6.66 ± 2.96	6.23 ± 1.68	0.674
Creatinine (µmol/L)	81.26 ± 23.19	82.92 ± 17.15	0.836
Uric acid (µmol/L)	332.6 ± 135.2	330.7 ± 86.16	0.967
Total bilirubin (µmol/L)	12.8 ± 11.55	11.9 ± 2.07	0.817
Indirect bilirubin (µmol/L)	3.41 ± 8.06	2.46 ± 0.93	0.73
Total protein (g/L)	70.59 ± 8.6	74.39 ± 10.44	0.227
Albumin (g/L)	36.6 ± 5.4	38.6 ± 6.17	0.31
Globulin (g/L)	33.98 ± 7.44	35.79 ± 8.4	0.499
Ferritin (ng/ml)	573.8 ± 529.6	482.5 ± 424.6	0.621
AST (GOT) (U/L)	50.72 ± 81.72	23.53 ± 12.97	0.325
ALT (GPT) (U/L)	62.9 ± 114.3	23.46 ± 20.76	0.307
GGT (U/L)	62.5 ± 89.7	31.9 ± 12.6	0.31
LDH (U/L)	645.17 ± 481.4	201.05 ± 76.43	0.007**
β2 microglobulin concentration (mg/L)	3.001 ± 2.1	2.97 ± 1.22	0.961
Hemoglobin (g/L)	124.8 ± 20.25	123.2 ± 19.15	0.825
Erythrocytes (10*12 cells/L)	4.15 ± 0.64	4.05 ± 0.64	0.68

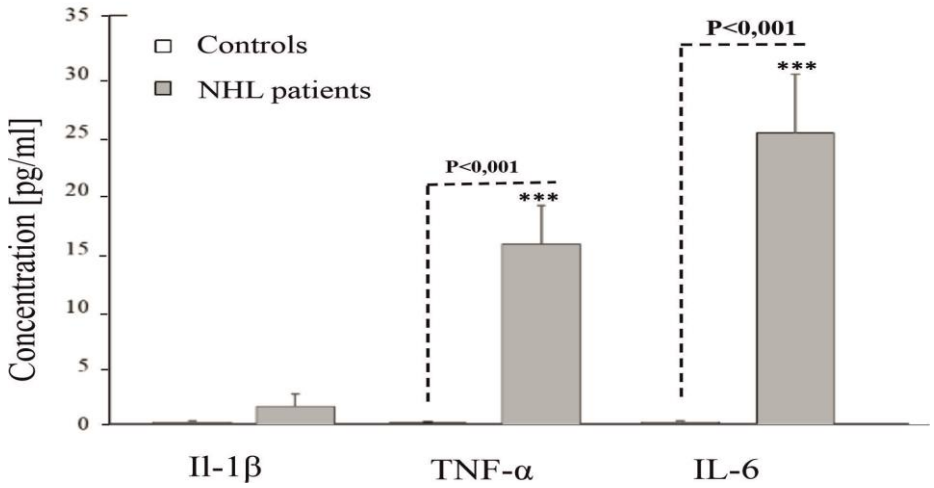

Figure 1. Arithmetic means ± SEM (n = 56–82) of IL-1β, TNF-α and IL-6 concentrations are attained from sera of healthy donors (white bars) and NHL patients (grey bars). *** ($p < 0.001$) indicates a significant difference from healthy donors (Mann–Whitney U test)

Associations of *Otubain-1* expression with clinical outcomes in NHL

The associations of *Otubain-1* expression levels and susceptibility to NHL are unknown. Recently, *Otubain-1* is downregulated in chronic myeloid leukemia (Hoang et al., 2022). In this study, we asked whether there are associations among *Otubain-1* expression levels, clinical outcomes and activations of

signalling genes including *NF-kBs*, *STATs* and *SHPs*. Accordingly, the expression levels of *Otubain-1* were examined by quantitative real time-PCR and divided into two groups based on the median *Otubain-1* expression values in healthy controls (high vs. low). A high *Otubain-1* expression group was detected in 52 samples (63.4%) and a low *Otubain-1* expression group was detected in 30 samples (36.6%) (Fig. 2 & Table 2). Importantly, NHL patients with high *Otubain-1* expression had significantly higher GGT and ferritin levels compared to those with low *Otubain-1* expression (Table 2). In addition, there were no significant differences in the other clinical indicators between the two groups (Table 1). GGT and ferritin are known to be involved in pathophysiological processes, including liver damage and metabolic syndrome (Chen et al., 2010), suggesting that patients with high *Otubain-1* expression had risks of these diseases.

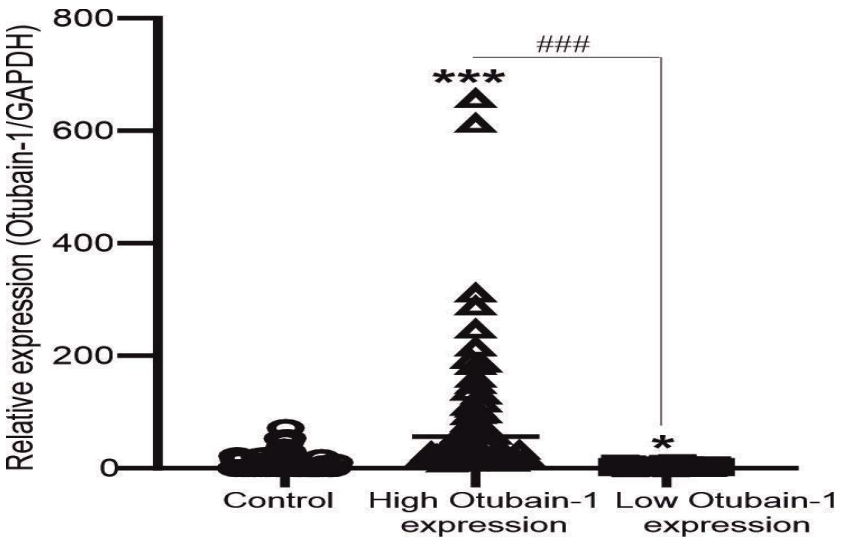

Figure 2. Otubain-1 expression in NHL patients. The graph indicates the mRNA levels of *Otubain-1* in control individuals (n = 56) and NHL patients with high *Otubain-1* expression (n = 52) and low *Otubain-1* expression (n = 30); *GAPDH* was used as a reference gene for relative quantification; each dot represents a single sample. * ($p < 0.05$) and *** ($p < 0.001$) show significant differences from healthy individuals, ### ($p < 0.001$) shows significant differences from the low *Otubain-1* expression group (Mann–Whitney U test)

Recently, activation of MAPKp38, but not NF-κB is regulated by *Otubain-1* (Xuan et al., 2019). Differently, NHL patients with high *Otubain-1* expression had significantly increased levels of *STAT-5* compared to those with low *Otubain-1* expression (Fig. 3). Activations of other signalling molecules including, *NF-kB2*, *STAT1*, *STAT6*, *SHP1* and *SHP2* were not related to *Otubain-1* expression levels (Fig. 3). Differently, *Otubain-1* interacts with NF-κB2 to control its activation in B cells (Li et al., 2019). Recently, our study indicated that downregulation of *Otubain-1* expression results in enhanced DC function mediated by prolonged phosphorylation of LPS-stimulated p38MAPK (Xuan et al., 2019). The evidences suggested that activation of STAT5 might be correlated with the regulatory effects of *Otubain-1* on the functions of lymphoma cells.

In this study, the expression levels of *NF-κB2* and *SHP-1* were notably reduced in NHL cases compared to the control group (Fig. 3). Similarly, *SHP-1* expression is the loss in hematological malignancies, leading to the activation of the JAK/STAT pathway in these patients (Chim et al., 2004; Oka et al., 2002) and activation of SHP-1 signalling is known

to induce cell apoptosis in NHL (Chen et al., 2022). Unlike the results of this study, *NF-κB2* is found to be upregulated in B-cell NHL (Savli et al., 2016) and activations of NF-κB2 and JAK-STAT pathways are involved in the pathogenesis of HL (Zhang et al., 2018). In addition, overexpression of *SHP-2* is detected in patients with leukemia (Voena et al., 2007) and the expression levels of *STAT3* and *STAT5* are enhanced in polycythemia vera and essential thrombocythemia patients (O'Sullivan et al., 2019).

In conclusion, the present study indicated that overexpression of *Otubain-1* resulted in activation of STAT5, liver dysfunction and metabolic syndrome in NHL patients. *Otubain-1* might be a good candidate for further study on its role in regulating the functional activation of lymphoma cells mediated through STAT5 signalling.

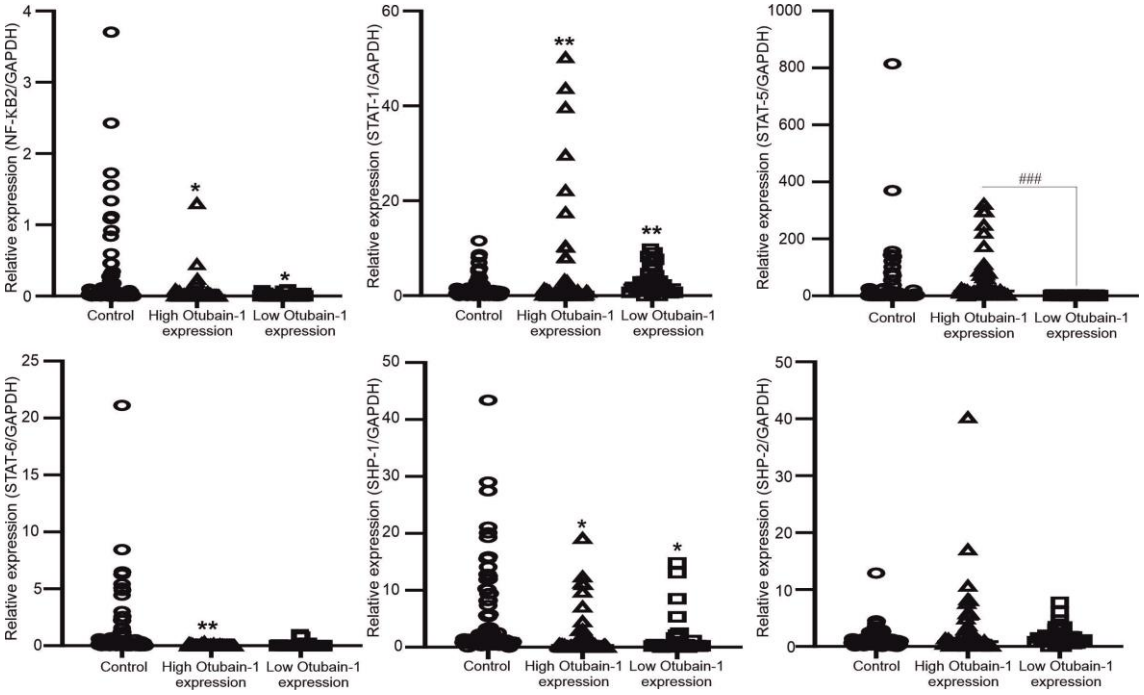

Figure 3. Associations between Otubain-1 and signalling gene expressions in NHL patients. Graphs indicate the mRNA levels of *NF-KB2, STAT-1, STAT-5, STAT-6, SHP-1* and *SHP-2* in control individuals (n = 56) and NHL patients with high *Otubain-1* expression (n = 52) and low *Otubain-1* expression (n = 30). *($p<0.05$), ** ($p < 0.01$) and *** ($p < 0.001$) show significant differences from healthy individuals, ### ($p < 0.001$) shows significant differences from low *Otubain-1* expression group (Mann–Whitney U test)

Competing interests

The authors of this paper declare that they have no financial/commercial conflicts of interest.

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