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Analysis of GNA13 Protein in Follicular Lymphoma and its Association With Poor Prognosis

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Abstract: GNA13 is a G protein involved in modulating tumor proliferative capacity, infiltration, metastasis, and migration. Genomic alteration of *GNA13* was frequently observed in follicular lymphoma (FL). In this study, we examined 167 cases of FL by immunostaining of GNA13 using tissue microarray to evaluate the clinical significance. There were 26 GNA13-positive cases (15.6%) and 141 GNA13-negative cases (84.4%). GNA13-positive cases had a higher incidence of early progression of disease for which disease progression was recognized within 2 years compared with GNA13-negative cases ($P = 0.03$). There were no significant differences in other clinicopathologic factors including histological grade, *BCL2-IGH* translocation, immunohistochemical phenotype, and Follicular Lymphoma International Prognostic Index. In addition, overall survival and progression-free survival were poorer in GNA13-positive cases than in GNA13-negative cases ($P = 0.009$ and 0.005, respectively). In multivariate analysis, GNA13 positivity was found to be a poor prognostic factor for overall survival and progression-free survival. Thus, GNA13 protein expression was an independent prognostic factor and may affect disease progression in FL.

Key Words: follicular lymphoma, GNA13, poor prognosis

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Follicular lymphoma (FL), a type of B-cell lymphoma with an indolent clinical course, is one of the most common types of non-Hodgkin lymphoma.[1] Lymphadenopathy and infiltration of the spleen and bone marrow are often observed in patients with FL.[1] Follicular Lymphoma International Prognostic Index (FLIPI)[2] and FLIPI2[3] are widely used as prognostic models for FL.

Addition of anti-CD20 antibody (rituximab) to conventional chemotherapy such as CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) improves the prognosis.[4] However, a study has shown that 19% to 20% of the FL cases who experienced progression of the disease within 2 years after initial diagnosis (early progression of disease [early POD]) and those cases had significantly poor prognosis compared with those without early POD.[5,6]

In recent years, whole genome analysis has been performed in FL and revealed the genetic landscape.[7,8] Most recently, Pastore et al[9] reported that a model based on the combination of clinical and genomic risk factors that can predict the clinical course of FL patient.

GNA13 is a G protein α subunit composed of 3 subunits (α, β, and γ). In general, α subunits play an important role in signal transmission by binding to and dissociating from GTP and GDP.[10] GNA13 expression in germinal center B cells plays an important role in signaling through sphingosine-1-phosphate receptor 2. Moreover, *GNA13* has been reported to be involved in the suppression of cell proliferation through the phosphoinositide 3-kinase-Akt pathway and in germinal center confinement through RhoA, which acts downstream of *GNA13*.[11]

GNA13 protein has been shown to be expressed in germinal center B-cell of normal tissue, and in various

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malignant tumors and is thought to be involved in modulating tumor proliferative capacity, infiltration, metastasis, and migration.[12–17] Specifically, in gastric cancer[12] and hepatocellular carcinoma,[13] patients with high expression of GNA13 protein were found to have poorer prognoses than patients with low GNA13 expression. This is thought to be related to the observation that high expression of GNA13 protein enhances Akt and extracellular signal-regulated kinase pathway as well as tumor infiltration and metastasis owing to RhoA activation.[12]

To date, *GNA13* mutations have been reported in malignant lymphoma,[18,19] particularly in B-cell lymphomas, such as FL, diffuse large B-cell lymphoma, and Burkitt lymphoma. The incidence is 9% to 20%, and the mutation causes loss of function of *GNA13*.[18–20] The mutation is considered to be a poor prognostic factor in ABC-type DLBCL cases[19], whereas not in FL.[9] Investigation of effect of GNA13 protein expression on clinicopathologic features has not been performed in FL cases.

In this study, we performed a statistical analysis of the clinicopathologic findings of FL and the expression of GNA13 using immunohistochemistry.

METHODS

Patients and Samples

We investigated 167 cases of FL from 2005 to 2015 at the Department of Pathology, Kurume University. All cases were reviewed by hematopathologists (O.K. and M.H.) and diagnosed according to the World Health Organization classification.[1] Specific FL subtypes including pediatric, primary cutaneous, and primary duodenum FL were excluded from the analyses. A tissue microarray (TMA) containing each of the 167 lymph node samples in a formalin-fixed paraffin block was prepared, with each sample occupying a 3-mm-diameter space. As described previously,[5,6] cases with early POD were defined as those with disease progression observed within 2 year after initial diagnosis. Clinical information was obtained by reviewing the patient medical charts. The use of materials and clinical information was approved by the Research Ethics Committee of Kurume University and was in accordance with the Declaration of Helsinki.

Evaluation of Expression of GNA13 Protein

Immunohistochemical (IHC) staining of GNA13 (Abcam, Cambridge, MA) was carried out using 2.5 mm thick, formalin-fixed, paraffin-embedded tissue sections from the TMA for all cases. The slides were deparaffinized with xylene and then ethanol. After rehydration with water, antigen retrieval was performed with citrate acid buffer (pH 6.0) in a microwave oven at 95°C for 20 minutes. After cooling and rinsing with buffer, the slides were placed in a Dako autostainer (Dakocytomation, Kyoto, Japan). Endogenous peroxidase activity was blocked by incubating in 3% hydrogen peroxide for 5 minutes. Slides were incubated with anti-GNA13 rabbit monoclonal antibodies (EPR 5436, 1:400 dilution, ab128900; Abcam) for 30 minutes.

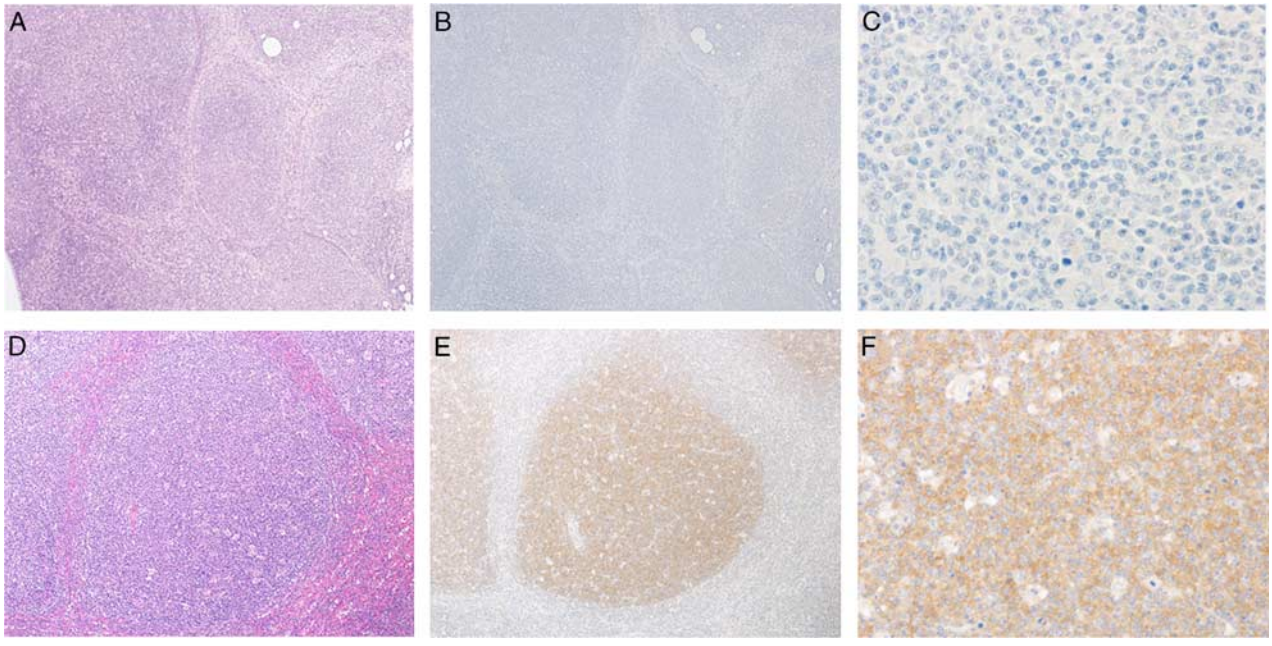

FIGURE 1. Immunohistochemical analysis of GNA13 expression in follicular lymphoma. A, GNA13-negative follicular lymphoma showed nodular proliferation (hematoxylin and eosin [HE] stain). B, GNA13-negative follicular lymphoma. Neoplastic cells presented GNA13 negativity (IHC of GNA13). C, GNA13-negative follicular lymphoma. Neoplastic cells presented GNA13 negativity (IHC of GNA13). D, GNA13-positive follicular lymphoma showed nodular proliferation (HE stain). E, GNA13-positive follicular lymphoma. Nodular proliferation of neoplastic cells was positive for GNA13 (brown staining; IHC of GNA13). F, GNA13-positive follicular lymphoma. The membranes and cytoplasm of neoplastic cells were positive for GNA13 (brown staining; IHC of GNA13).

The slides were then incubated with an EnVision1 System horseradish peroxide-labeled anti-rabbit polymer (K4003; Dakocytomation) for 30 minutes. Visualization of GNA13 was performed by staining with diaminobenzidine for 5 minutes. Slides were counterstained with hematoxylin, dehydrated with ethanol, and mounted under coverslips.

GNA13 positivity was defined when strong positivity in the membrane and/or the cytoplasm of tumor cells was estimated using an ImageJ software cell counter plugin (National Institutes of Health, Bethesda, MD).

IHC of Other Proteins

Paraffin-embedded sections of each sample were immunostained. The antibodies (clones) used for IHC were as follows: anti-CD10 (56C6; Leica Microsystems, Wetzler, Germany), anti-CD20 (L-26; Dakocytomation, Glostrup, Denmark), anti-BCL2 (124; Dakocytomation), anti-BCL6 (P1F6; Leica Microsystems), and MUM1 (MUM1p; Dakocytomation). Each case was considered positive if more than ~30% of the neoplastic cells were positive.[21]

Fluorescence In Situ Hybridization Analysis

Fluorescence in situ hybridization for the *BCL2-IGH* translocation (Leica Microsystems) was performed as previously described.[21]

Statistical Analysis

Patient clinicopathologic characteristics were compared using the χ^2 or Fisher 2-sided exact tests. The end-points of overall survival (OS) and progression-free survival (PFS) were defined as the time of all-cause death or of relapse owing to FL, respectively. OS and PFS curves were calculated using the Kaplan-Meier method. A Wilcoxon test was used to compare survival curves. Univariate and multivariate Cox proportional regression models were used to evaluate the proposed prognostic factors. Differences with *P*-values <0.05 were considered statistically significant. JMP version 11.0 was used in all analyses.

RESULTS

IHC of GNA13

In IHC, the expression of GNA13 protein was detected mainly in neoplastic follicles (Figs. 1D–F). A total of 26 cases (26/167, 15.6%) were categorized as GNA13-positive cases (Figs. 1D–F), and 141 cases (141/167, 84.4%) were categorized as GNA13-negative cases (Figs. 1A–C).

Statistical Association Between GNA13 and Clinicopathologic Features of FL

The statistical comparisons between GNA13 and each feature in FL are shown in Table 1. The incidence of early POD was significantly higher in GNA13-positive cases than in GNA13-negative cases ($P = 0.03$). However, other features, such as histologic grade, *BCL2-IGH* translocation, FLIPI, expression levels of markers (CD10, BCL2, BCL6, and MUM1), rate of complete response to initial therapy, and rate of progression or relapse, did not differ significantly between groups.

TABLE 1. GNA13 Expression in Follicular Lymphoma (167 Cases)

	GNA13 Expression (n/N [%])		
	Positive Cases (N = 26)	Negative Cases (N = 141)	*P*
Age (median [range]) (y)	61.5 (45-78)	60 (26-84)	1*
Age > 60 y	15/26 (57.7)	70/141 (49.6)	0.45
Male/female	14/12	67/74	0.55
Histologic grade			
Grade 1/2	15/26 (57.7)	78/141 (55.3)	0.82
Grade 3a	11/26 (42.3)	50/141 (35.5)	0.51
Grade 3b	0/26 (0)	13/141 (9.2)	0.22
Bulky mass > 6 cm	0/25 (0)	14/135 (10.4)	0.134
Lymph node > 4 regions	11/24 (45.8)	50/135 (37.0)	0.42
Bone marrow involvement	5/24 (20.8)	36/132 (27.3)	0.62†
Peripheral blood involvement	3/24 (12.5)	6/134 (4.5)	0.14†
Extranodal involvement	12/25 (48.0)	63/135 (46.7)	0.90
B symptoms	4/26 (15.4)	19/136 (14.0)	0.77†
Performance status, 2-4	1/26 (3.8)	13/133 (9.8)	0.47†
Ann Arbor stage III or IV	16/24 (66.7)	95/135 (70.4)	0.72
Hemoglobin level <12.0 g/dL	8/25 (32.0)	34/132 (25.8)	0.52
Elevated LDH level	5/25 (20.0)	31/137 (22.6)	1†
FLIPI, high risk	8/23 (34.8)	44/133 (33.1)	0.87
BCL2-IGH translocation	21/26 (80.8)	106/141 (75.2)	0.54
Immunohistochemistry			
CD10 expression	24/26 (92.3)	117/141 (83.0)	0.23
BCL2 expression	23/26 (88.5)	132/141 (93.6)	0.38
BCL6 expression	26/26 (100)	136/141 (96.5)	0.33
MUM1 expression	1/26 (3.8)	9/141 (6.4)	1†
Initial therapy			
Chemotherapy			
R-containing regimen	22/25 (88.0)	110/135 (81.5)	0.43
Others	1/25 (4.0)	3/135 (2.2)	0.50†
Radiation therapy			
Radiation only therapy	0/25 (0)	5/135 (3.7)	1†
Chemotherapy+radiation therapy	2/25 (8.0)	11/135 (8.1)	1†
Watchful wait	2/25 (8.0)	17/135 (12.6)	0.75†
Clinical outcome			
Early POD	8/19 (42.1)	17/93 (18.3)	0.03
CR to initial therapy	16/21 (76.2)	90/115 (78.3)	0.83
Progression or relapse	10/25 (40.0)	43/132 (36.2)	0.48
Median follow-up (median [range]) (mo)	38.5 (2–125)	54.5 (2–130)	

*Wilcoxon signed-rank test.
†Fisher exact test.
LDH indicates lactate dehydrogenase; R-containing regimen: rituximab-containing regimen.

Initial chemotherapy was administered for a total of 92.0% (23/25) of GNA13-positive cases, including 88.0% (22/25) of cases in which chemotherapy and rituximab were administered. A total of 21 cases (21/22, 95.5%) received R-CHOP therapy (composed of rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone). Of the GNA13-negative cases, 83.7% (113/135) received initial chemotherapy, 81.5% (110/135) received chemotherapy including rituximab, and 90% (99/110) received R-CHOP therapy. There were no significant differences in initial therapy between the 2 groups (Table 1). Moreover, there were no significant differences in the rate of complete response to initial therapy and rate of progression or relapse.

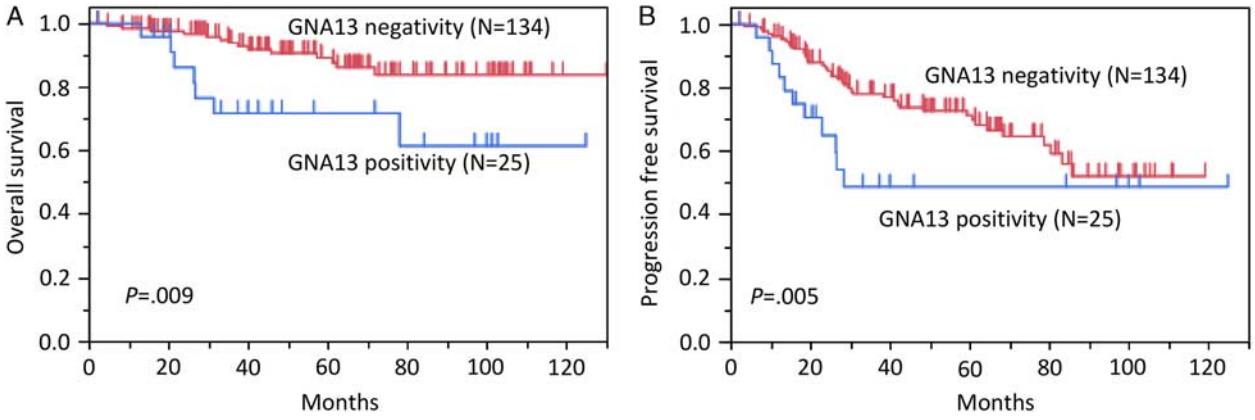

FIGURE 2. Comparison of OS and PFS between GNA13-positive and GNA13-negative FL. A, GNA13-positive cases showed significantly poorer OS than GNA13-negative cases ($P = 0.009$). B, GNA13-positive cases showed significantly worse PFS than GNA13-negative cases ($P = 0.005$).

Survival Analysis for GNA13

The results of OS and PFS curves are shown in Figures 2A and B. The OS and PFS of GNA13-positive cases were significantly poorer than those of GNA13-negative cases ($P = 0.009$ and 0.005, respectively). Even when analyses of cases treated chemotherapy and/or radiation therapy after diagnosis were performed, GNA13-positive cases showed significantly poorer OS ($P = 0.02$) and a tendency toward poorer PFS ($P = 0.05$) compared with GNA13-negative cases (Figs. 3A, B).

Univariate and Multivariate Analysis of OS and PFS

The results of univariate and multivariate analysis of OS are shown in Table 2. GNA13 positivity was a prognostic factor for OS by univariate analysis (hazard ratio [HR], 3.113; 95% confidence interval [CI], 1.254-7.727; $P = 0.04$) and multivariate analysis (HR, 4.193; 95% CI, 1.426-12.33; $P = 0.009$). The results of univariate and multivariate analysis of PFS are shown in Table 3. GNA13 positivity was a prognostic factor for PFS by univariate analysis (HR, 1.991; 95% CI, 1.041-3.807; $P = 0.04$) and multivariate analysis (HR, 2.285; 95% CI, 1.074-4.861; $P = 0.03$).

DISCUSSION

In this study, the expression of GNA13 protein was observed by IHC analysis in 15.6% of the analyzed FL cases. Expression of GNA13 protein was associated with a higher incidence of early POD and was an independent prognostic factor for OS and PFS.

GNA13 mutations have been reported in B-cell lymphoma with the germinal center origin including FL, in which the incidence of *GNA13* mutations is ~10%.[9] Previous studies showed that *GNA13* mutation was observed across all of the exons, and it has been reported that the mutation was either missense or nonsense.[22] In addition, genomic deletion of *GNA13* was also found in 4% of FL cases.[22]

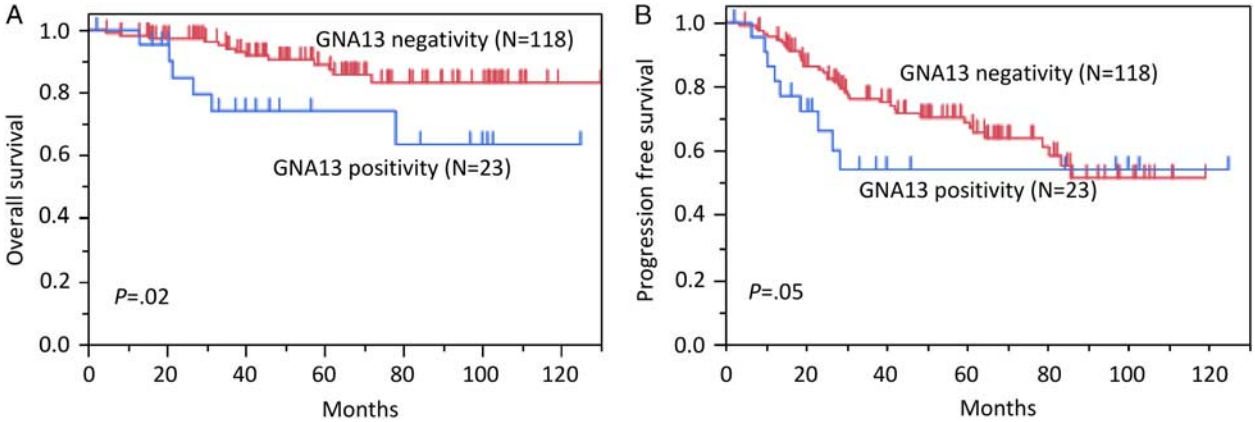

FIGURE 3. Comparison of OS and PFS between GNA13-positive and GNA13-negative FL with therapy. A, OS in GNA13-positive cases was significantly worse than that in GNA13-negative cases ($P = 0.02$). B, PFS of GNA13-positive cases tended to be worse than that in GNA13-negative cases ($P = 0.05$).

TABLE 2. Univariate and Multivariate Analysis for Overall Survival in Patients With Follicular Lymphoma

	Overall Survival			
	Univariate Analysis		Multivariate Analysis	
Parameter	HR (95% CI)	*P*	HR (95% CI)	*P*
Histologic grade 3	1.552 (0.659-3.658)	0.32		
B symptoms	1.444 (0.486-4.292)	0.51		
Bone marrow involvement	1.421 (0.567-3.565)	0.45		
Bulky mass >6 cm	0.985 (0.229-4.24)	0.98		
FLIPI, high risk	5.841 (2.207-15.46)	0.0004	7.916 (2.789-22.47)	0.0001
GNA13 positivity	3.113 (1.254-7.727)	0.01	4.193 (1.426-12.33)	0.009
BCL2-IGH translocation	1.513 (0.509-4.500)	0.46		
CD10 positivity	1.179 (0.3472-4.004)	0.79		
BCL2 positivity	1.886 (0.2529-14.07)	0.54		
BCL6 positivity	0.8193 (0.1098-6.112)	0.85		
MUM1 positivity	3.726 e−08 (0-∞)	1		

Although these mutations are considered to have a major impact on lymphoma formation by causing the loss of *GNA13* function[20,23], there was no impact of the mutation on the prognosis. Previous in vitro studies have reported that *GNA13* mutations and protein expression were not correlated with each other and the expression varied depending on the variety of mutations.[24] Further investigation into the relationship between genomic alteration of *GNA13* including genomic copy number alteration and the expression might be needed to reveal the mechanism of GNA13 expression in FL cases.

In this study, we found that there was an association between GNA13 protein expression and poor prognosis in FL. In previous studies using *GNA13*-knockout mice, deregulation of pAKT and deregulation of chemotaxis to S1P occurred in the germinal center.[20] Several reports revealed that germinal center B-cells lacking *GNA13* can survive due to impaired apoptosis and have high frequency of somatic hypermutation compared with wild type. This mechanism is thought to contribute to increase a risk of lymphoma.[22,23] These in vitro studies have suggested that GNA13 mutations may be involved in lymphomagenesis in FL.[20]

The association between GNA13 expression and poor prognosis might be caused though abnormalities of *GNA13* gene.

In contrast, an association between GNA13 expression and poor prognosis has been reported in some solid tumors, including gastric cancer[12] and hepatocellular carcinoma.[13] The OS of GNA13-positive patients with gastric cancer and hepatocellular carcinoma has been shown to be poorer than that of the GNA13-negative group.[12,13] Moreover, in gastric cancer cell lines, cells expressing GNA13 protein show greater upregulation of *c-Myc*, activation, and upregulation of *Akt* and extracellular signal-regulated kinase pathways, suppression of *FOXO1* activity, upregulation of *cyclin D1*, and downregulation of *p27*[12]; these alterations may cause tumor infiltration and promote metastasis. Further studies of these pathways are needed to confirm the findings of our study.

In this study, there was a significant association between GNA13 protein expression and early POD in FL. Early POD in FL was reported as a prognostic marker in a previous study.[5,6] Indeed, our study also showed that the early POD group (22.3% of all cases) had poorer OS

TABLE 3. Univariate and Multivariate Analysis for Progression-free Survival in Follicular Lymphoma

	Progression-free Survival			
	Univariate Analysis		Multivariate Analysis	
Parameter	HR (95% CI)	*P*	HR (95% CI)	*P*
Histologic grade 3	1.068 (0.6175-1.846)	0.81		
B symptoms	1.747 (0.8971-3.401)	0.10		
Bone marrow involvement	2.088 (1.181-3.692)	0.01	2.357 (1.277–4.349)	0.006
Bulky mass >6 cm	1.076 (0.4263-2.714)	0.88		
FLIPI, high risk	2.186 (1.23-3.883)	0.008	1.876 (1.010-3.485)	0.05
GNA13 positivity	1.991 (1.041-3.807)	0.04	2.285 (1.074-4.861)	0.03
BCL2-IGH translocation	1.417 (0.726-2.765)	0.31		
CD10 positivity	2.061 (0.8183-5.189)	0.12		
BCL2 positivity	5.348 (0.7376-38.77)	0.10		
BCL6 positivity	1.043 (0.2533-4.294)	0.95		
MUM1 positivity	0.2449 (0.03381-1.774)	0.16		

($P < 0.0001$; Online Supplementary Fig. S1, Supplemental Digital Content 1, http://links.lww.com/PAS/A561), consistent with the results of a previous report.[5,6] Most recently, early POD prognostic index that can predict early POD has been established and the index includes several clinical and genomic factors, but not pathologic factors.[25] The current study indicate that GNA13 expression is also one of the factors to predict early POD and could provide more precise predictive markers based on clinical, genomic, and pathologic factors for prognosis of FL.

There are some limitations in this study. First, the IHC analyses in this study was performed by using TMA, which might cause higher proportion of grade 3. Although analysis of whole specimens may produce more reliable results, the findings of this study could be significant because the expression of GNA13 was observed and evaluated mainly in neoplastic follicles. Second, we did not perform analyses of abnormalities at the gene and transcript levels. Such analyses may help to further elucidate the pathogenic mechanisms of FL.

In conclusion, we found that the expression of GNA13 protein was an independent prognostic factor and may affect disease progression in FL. Further studies, including genomic analysis or transcriptional investigations, are needed to confirm the associations between GNA13 and FL pathogenesis.

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