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Non-small cell lung cancer with loss of expression of the SWI/SNF complex is associated with aggressive clinicopathological features, PD-L1-positive status, and high tumor mutation burden

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ABSTRACT

Objectives: Loss of the chromatin remodeling SWItch/Sucrose Non-fermentable (SWI/SNF) complex is implicated in the pathogenesis of several types of neoplasms. The aim of this study was to examine the clinicopathological features of non-small cell lung cancer (NSCLC) with loss of expression of the SWI/SNF complex.

Materials and methods: Specimens from a total 1013 NSCLC cases used for tissue microarrays (TMAs) were immunohistochemically examined for expression of SWI/SNF complex (BAF) subunits, namely SMARCA4, SMARCA2, ARID1A, and ARID1B. We examined the clinicopathological features and PD-L1 expression status in NSCLC cases with loss of expression of one or more subunits of the SWI/SNF complex (BAF-Loss). Moreover, we compared the tumor mutation burden (TMB) between NSCLC cases with BAF-Loss and those with intact expression of the four subunits (BAF-Intact).

Results: Using TMA, BAF-Loss was observed in 5.4% of cases (SMARCA4: 2.4%, SMARCA2: 2.4%, ARID1A: 1.3%, and ARID1B: 0.3%). Concurrent loss of expression of two or more subunits of the SWI/SNF complex was detected in 0.7% of cases. BAF-Loss was significantly associated with smoking history, young age, male sex, pulmonary emphysema/bullae, large invasive tumor size, pleural invasion, vascular invasion, solid-predominant morphology, and absence of a lepidic growth component. A higher proportion of PD-L1-positive cases was observed among NSCLC patients with BAF-Loss than BAF-Intact (42% vs 26%, $P < 0.01$). In stage I NSCLC, SWI/SNF-Loss (n = 23) was associated with shorter overall survival (HR: 2.43; 95% CI: 1.18–5.01; $P = 0.01$) and recurrence-free survival (HR: 2.22; 95% CI: 1.17–4.24; $P < 0.01$) compared to BAF-Intact (n = 563). The degree of TMB was significantly higher among NSCLC patients with BAF-Loss (n = 3) than BAF-Intact (n = 7) (median 437 vs 113 mutations/whole-exome, $P = 0.02$).

Conclusion: The current results suggest that loss of SWI/SNF expression in NSCLC is associated with aggressive clinicopathological features, PD-L1-positive status and high TMB.

1. Introduction

Chromatin remodeling involves dynamic modification of the chromatin architecture to allow access to the condensed genomic DNA for control of gene expression and regulation by transcription machinery proteins [1]. SWItch/Sucrose Non-Fermentable (SWI/SNF) is a large complex involved in chromatin remodeling. Mammalian SWI/SNF complexes exist in three distinct, final-form assemblies: canonical BRG1/BRM-associated factor (BAF), polybromo-associated BAF complexes (PBAF) and a newly characterized non-canonical complex (ncBAF), with specific subunits specifying distinct complexes, such as PBRM1, ARID2 and BRD7 in PBAF, ARID1A/ARID1B and DPF2 in BAF and GLTSCR1/GLTSCR1L and BRD9 in ncBAF [2,3].

Inactivation mutations in several subunits of SWI/SNF (e.g.,

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SMARCA4, SMARCA2, ARID1A) have been identified in a significant proportion of lung tumors [4–6]. In the Catalogue of Somatic Mutations in Cancer database, several subunits of the SWI/SNF complex were mutated in 282 of 803 (35%) lung carcinoma samples, ranking second to *Tumor Protein 53* (*TP53)* [4]. Recently, NSCLC with loss of expression of SMARCA4 has been considered a distinct subtype of NSCLC with a heterogeneous spectrum due to its morphological features, such as the absence of a lepidic growth pattern [7,8], immunohistochemically TTF-1-negative HepPar-1-positive phenotype [9,10], lack of actionable gene alterations (e.g., *EGFR* mutation, rearrangement of *ROS1*, *EML/ALK*) [7–9], and poor prognosis [11–13].

Immune checkpoint inhibitors (ICI) have shown encouraging results as treatments in patients with advanced NSCLC. Reports have demonstrated that programmed cell death ligand 1 (PD-L1) expression, DNA mismatch-repair (MMR) deficiency, and tumor mutation burden (TMB) are predictive biomarkers of response to ICI [14–16]. While a few studies have reported correlations between a response to ICI and the SWI/SNF complex [17–19], little is known about PD-L1 expression and TMB in NSCLC with loss of expression of the SWI/SNF complex. Further, although there are clinicopathological studies with limited case numbers, analysis using large cohorts is still lacking. In addition, the association between NSCLC with loss of expression of the SWI/SNF complex and TMB has not been clarified.

The purpose of the current study was to examine the clinicopathological features of NSCLC with loss of expression of the SWI/SNF complex using a large cohort and whole-exome sequencing data.

2. Material and methods

2.1. Case selection

The tissue microarray (TMA) cohort included a total of 1098 patients with NSCLC resected from May 2010 to March 2015 at the National Cancer Center Hospital East. Clinicopathological features, including age, sex, smoking history, medical history, invasive tumor size, pleural invasion, vascular invasion, intrapulmonary metastasis, lymphatic permeation, lymph node metastasis, pathological stage, tumor morphology, and status of EGFR mutation, were determined from medical records. Histologic classification of NSCLC was based on the 4th edition of the World Health Organization Classification of Lung Tumors. The 8th edition of the TNM classification for lung cancer (International Association for the Study of Lung Cancer) was used for pathological staging.

2.2. Pathologic studies

The specimens were fixed with 10% formalin and embedded in paraffin. Serial 4-μm-thick sections were prepared and used for hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC). Sections were reviewed by two pulmonary pathologists (T.N. and G.I.).

2.3. Construction of tumor TMAs

The most representative tumor areas were carefully selected and marked on H&E-stained slides for the construction of microarrays. TMAs were assembled with a tissue-arraying instrument (KIN-2; Azumaya, Tokyo, Japan). The microarray system consists of thin-walled stainless steel needles approximately 2 mm in diameter and a stylet for transferring and removing the contents of the needle. A normal control TMA that included samples from nonmalignant specimens from various organs was used as a positive control. Of the 1098 patients in the TMA cohort, 85 cases for which an adequate tissue sample was not available for pathologic review were excluded from the study. Data from the remaining 1013 cases were analyzed.

2.4. Antibodies and immunohistochemical staining

Immunohistochemical staining for four representative BAF components, SMARCA4, SMARCA2, ARID1A, and ARID1B, was performed according to a previously described procedure [20] (Supplemental Table 1). Immunohistochemical staining for PD-L1 was performed with an anti-PD-L1 22C3 (Dako) rabbit monoclonal primary antibody using the EnVision FLEX visualization system on a Dako Autostainer Link 48 system [21]. In addition, H&E staining was performed to help orient the sections.

2.5. Immunohistochemical evaluation

All stained slides were digitized with a NanoZoomer HT scan system (Hamamatsu Photonics, Japan). For SMARCA4, SMARCA2, ARID1A, and ARID1B, a “loss” of reactivity was defined as complete absence of nuclear staining compared to the background in an intact positive control (stromal fibroblasts, inflammatory cells, vascular endothelial cells, or normal epithelial cells) as reported recently [10,22]. We defined loss of expression of one or more subunits of the SWI/SNF complex as “BAF-Loss” and intact of expression of the all four subunits of the SWI/SNF complex as “BAF-Intact”. For PD-L1, the proportion of viable tumor cells exhibiting membranous staining of any intensity was evaluated. PD-L1 scores were categorized as $< 1\%$ or $\geq 1\%$ tumor cells, and $< 50\%$ or $\geq 50\%$ tumor cells [23,24].

2.6. Whole-exome sequencing

We used whole-exome sequencing (WES) data from 10 Japanese NSCLC cases that were previously part of the Lung Cancer Genomic Screening Project for Individualized Medicine Immuno-Oncology Biomarker Study (LC-SCRUM-IBIS, UMIN000026425). WES data were used to calculate the TMB, which was defined as the total number of non-synonymous somatic mutations present in a baseline tumor sample.

Comprehensive informed consent to use the samples for this research was obtained from all patients. Further, this study was conducted with the approval of the Institutional Review Boards of the National Cancer Center (approval number 2018-134).

2.7. Statistical analysis

The chi-squared test and t test were used to compare the clinicopathological features, PD-L1 expression status, and TMB between BAF-Loss and BAF-Intact. Fisher’s exact test was used to compare clinicopathological features and PD-L1 expression status between cases in which there was loss versus intact expression of each subunit of the SWI/SNF complex. Overall survival (OS) was defined as the time from the date of surgery to the date of death from any cause or the last follow-up. Recurrence-free survival (RFS) was defined as the time from the date of surgery to the date of tumor recurrence, death, or the last follow-up. Survival curves were estimated using the Kaplan-Meier method, and differences in OS and RFS were compared using the log-rank test. Hazard ratios (HRs) were estimated using the Cox proportional hazards model. All P-values were two sided, and P-values of < 0.05 were considered statistically significant. All statistical analyses were performed using the JMP statistical software package for Mac, Ver.13 (SAS Institute, Cary, NC).

3. Results

3.1. Frequency of NSCLC with loss of SWI/SNF complex

Representative images showing the expression of individual SWI/SNF complex subunits are shown in Fig. 1. NSCLC cells with BAF-Loss were devoid of nuclear staining, while infiltrating lymphocytes within the same section showed specific nuclear staining.

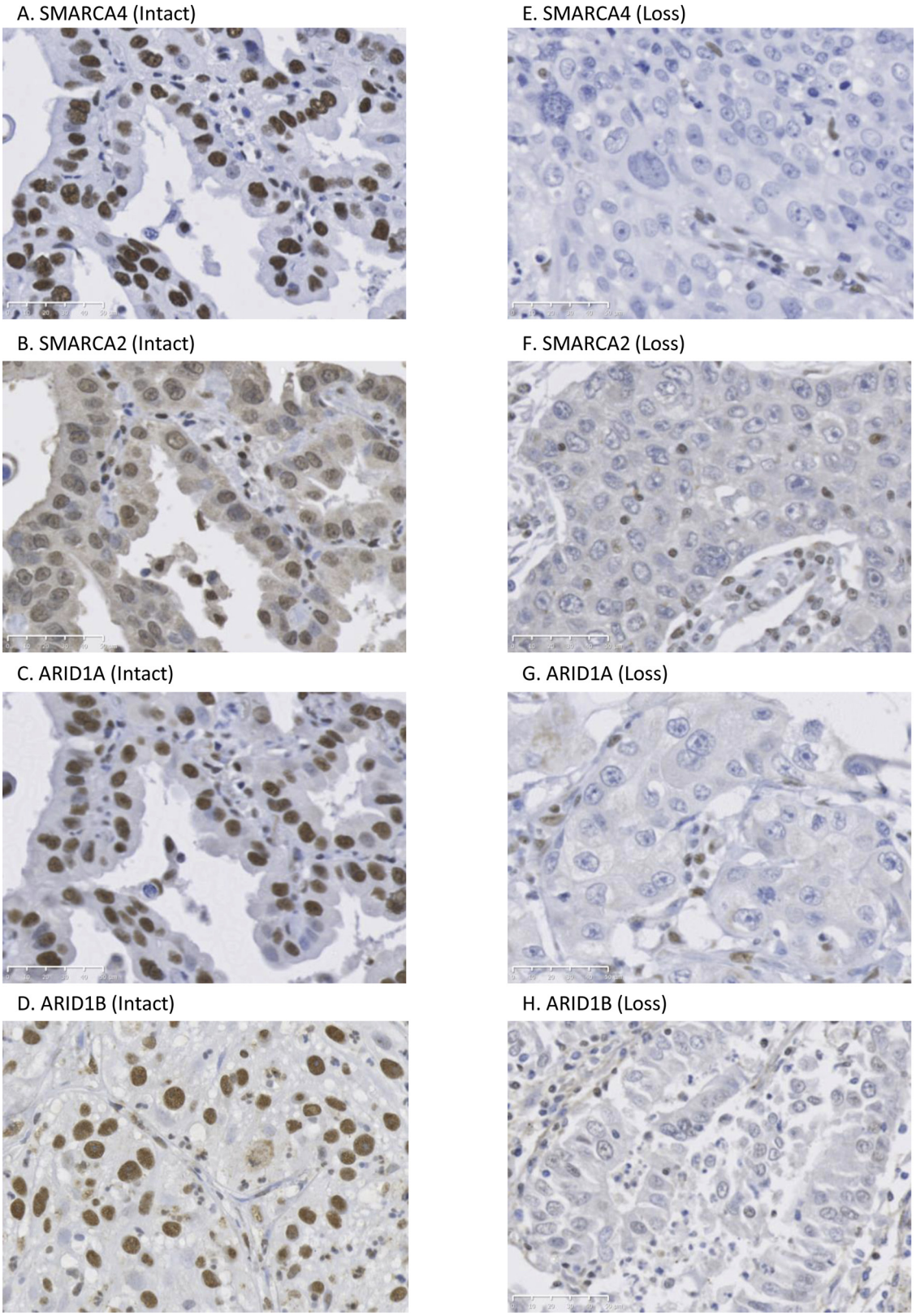

Fig. 1. Representative images showing SMARCA4, SMARCA2, ARID1A, and ARID1B expression in NSCLC. (A) Intact expression of SMARCA4, (B) SMARCA2, (C) ARID1A, and (D) ARID1B. (E) Loss of SMARCA4, (F) SMARCA2, (G) ARID1A, and (H) ARID1B.

In the TMA cohort, BAF-Loss was observed in 5.4% of the 1013 NSCLC cases (5.5% of 744 adenocarcinomas, 4.7% of 254 squamous cell carcinomas, and 13.3% of 15 other histological types; Table 1). The frequency of loss of expression of each subunit was 2.4% (2.7% of 744 adenocarcinomas, 1.2% of 254 squamous cell carcinomas, and 6.7% of 15 other histological types) for SMARCA4, 2.4% (2.6% of 744 adenocarcinomas, 1.2% of 254 squamous cell carcinomas, and 13.3% of 15 other histological types) for SMARCA2, 1.3% (0.9% of 744

Table 1
Frequency of loss of expression of the SWI/SNF complex (BAF) in 1013 patients with NSCLC.

Histology	Loss of expression of the SWI/SNF complex (BAF)					
	All	SMARCA4	SMARCA2	ARID1A	ARID1B	One or more subunits
	n	n (%)	n (%)	n (%)	n (%)	n (%)
AD	744	20 (2.7)	19 (2.6)	7 (0.9)	1 (0.1)	41 (5.5)
SQ	254	3 (1.2)	3 (1.2)	6 (2.4)	2 (0.8)	12 (4.7)
AS	7	0	0	0	0	0
LC	7	1 (14.3)	1 (14.3)	0	0	1 (14.3)
PL	1	0	1 (100)	0	0	1 (100)
Total	1013	24 (2.4)	24 (2.4)	13 (1.3)	3 (0.3)	55 (5.4)

SWI/SNF: switch sucrose nonfermentable, BAF: canonical BRG1/BRM-associated factor, NSCLC: non-small cell lung carcinoma, AD: adenocarcinoma, SQ: squamous cell carcinoma, AS: adenosquamous carcinoma, LC: large cell carcinoma, PL: pleomorphic carcinoma.

adenocarcinomas and 12.4% of 254 squamous cell carcinomas) for ARID1A, and 0.3% (0.1% of 744 adenocarcinomas and 0.2% of 254 squamous cell carcinomas) for ARID1B. Concurrent loss of expression of two or more subunits of the SWI/SNF complex was detected in 0.7% of cases (7/1013): 3 cases for SMARCA4 and SMARCA2; 1 case for SMARCA2 and ARID1A; 2 cases for SMARCA2, ARID1A and ARID1B; and 1 case for ARID1A and ARID1B (Supplemental Table 2).

3.2. Clinicopathological features

Comparison of clinicopathological features between BAF-Loss and BAF-Intact is shown in Table 2. BAF-Loss (n = 55) was significantly associated with younger age (median [range]: 66 [42–93] vs 70 [33–91] years; $P = 0.04$), male sex (80% vs 64%; $P = 0.01$), smoking history (87% vs 69%; $P < 0.01$), pulmonary emphysema or bulla (69% vs 26%; $P < 0.01$), larger invasive tumor size (median [range]: 3.2 [0.1–13.5] vs 2.4 [0.1–18.0] cm; $P < 0.01$), pleural invasion (55% vs 37%, $P = 0.01$), vascular invasion (67% vs 47%; $P < 0.01$), solid predominant histologic subtype (71% vs 40%; $P < 0.01$), and absence of a lepidic growth component (69% vs 43%; $P < 0.01$) compared to BAF-Intact.

3.3. Survival analysis

BAF-Loss was associated with shorter OS (HR: 1.60; 95% confidence interval: 1.04-2.45; $P = 0.03$) compared to BAF-Intact. On the other hands, there is no differences in RFS between the BAF-Loss NSCLC and BAF-Intact NSCLC (HR: 1.33 [95% CI: 0.91-1.95], $P = 0.13$) (Fig. 2). When patients were divided based on pathological stage (588 patients in stage I, 192 patients in stage II, 218 patients in stage III, and 15 patients in stage IV), stage I NSCLC with BAF-Loss was associated with shorter OS (HR: 2.43; 95% CI: 1.18–5.01; $P = 0.01$) and RFS (HR: 2.22; 95% CI: 1.17–4.24; $P < 0.01$) compared to stage I NSCLC with BAF-Intact (Fig. 2). In contrast, there was no statistically significant difference in OS or RFS in stage II (OS: HR: 0.78; 95% CI: 0.31–1.95; $P = 0.48$, RFS: HR: 0.76; 95% CI: 0.37–1.58; $P = 0.47$), stage III (OS: HR: 1.33; 95% CI: 0.64–2.72; $P = 0.44$, RFS: 0.84; 95% CI: 0.43–1.65; $P = 0.27$), or stage IV (OS: HR: 0.83; 95% CI: 0.16–4.28; $P = 0.81$, RFS: HR: 0.30; 95% CI: 0.06–1.49; $P = 0.12$) between BAF-Loss and BAF-Intact (Supplemental Fig. 1).

In stage I NSCLC, BAF-Loss was correlated with pulmonary emphysema/bulla (57% vs 21%; $P < 0.01$), vascular invasion (48% vs 27%; $P = 0.03$), and solid predominant histologic subtype (57% vs 25%; $P < 0.01$) compared to BAF-Intact (Supplemental Table 4). Multivariate analysis (age ≥70/ < 70 years old, sex, smoking history, histology, invasive tumor size > 3.0/ ≤ 3.0, pleural invasion, lymphatic permeation, solid predominant morphology, and loss of expression of the SWI/SNF complex) showed that there was no statistically significant difference in OS (HR:1.75; 95% CI: 0.77–3.50; $P = 0.17$) or RFS (HR: 1.42; 95% CI: 0.68–2.66; $P = 0.33$) between BAF-Loss and BAF-Intact in stage I NSCLC (Supplemental Table 4).

3.4. PD-L1 expression analysis

A higher proportion of cases with PD-L1 ≥ 1% was observed among

Table 2
Correlation between loss of expression of the SWI/SNF complex (BAF) and clinicopathological features in 1013 patients with NSCLC.

	Expression of the SWI/SNF complex (BAF)					
	Intact n (%)	Loss n (%)	*P*		Intact n (%)	Loss n (%)	*P*
Age, years				Lymphatic Permeation			
Median	70	66	0.04	Positive	168 (18)	7 (13)	0.36
Range	33–91	42–93		Negative	790 (82)	48 (87)	
Sex				Lymph Node Metastasis			
Male	610 (64)	44 (80)	0.01	Positive	278 (29)	18 (33)	0.56
Female	348 (36)	11 (20)		Negative	680 (71)	37 (67)	
Smoking History				Pathological Stage			
Ever	660 (69)	48 (87)	< 0.01	Stage I	565 (59)	23 (42)	< 0.01
Never	297 (31)	7 (13)		Stage II	177 (19)	15 (27)	
Emphysema/Bulla				Stage III	205 (21)	13 (24)	
Present	246 (26)	38 (69)	< 0.01	Stage IV	11 (1)	4 (7)	
Absent	712 (74)	17 (31)		Predominant Morphology			
Invasive Tumor Size, cm				Solid	381 (40)	39 (71)	< 0.01
Median	2.4	3.2	< 0.01	Other	577 (60)	16 (29)	
Range	0.1–18.0	0.1–13.5		Lepidic Growth Component			
Pleural Invasion				Present	546 (57)	17 (31)	< 0.01
Positive	358 (37)	30 (55)	0.04	Absent	412 (43)	38 (69)	
Negative	600 (63)	25 (45)		EGFR Mutation			
Vascular Invasion				Positive	188 (43)	7 (29)	< 0.01
Positive	453 (47)	37 (67)	< 0.01	Negative	250 (57)	17 (71)	
Negative	505 (53)	18 (33)		NE	524	31	
Intrapulmonary Metastasis							
Positive	53 (6)	6 (11)	0.10				
Negative	905 (94)	49 (89)					

SWI/SNF: switch sucrose nonfermentable, BAF: canonical BRG1/BRM-associated factor, NSCLC: non-small cell lung carcinoma, EGFR: Epidermal Growth Factor Receptor, NE: Not evaluated.

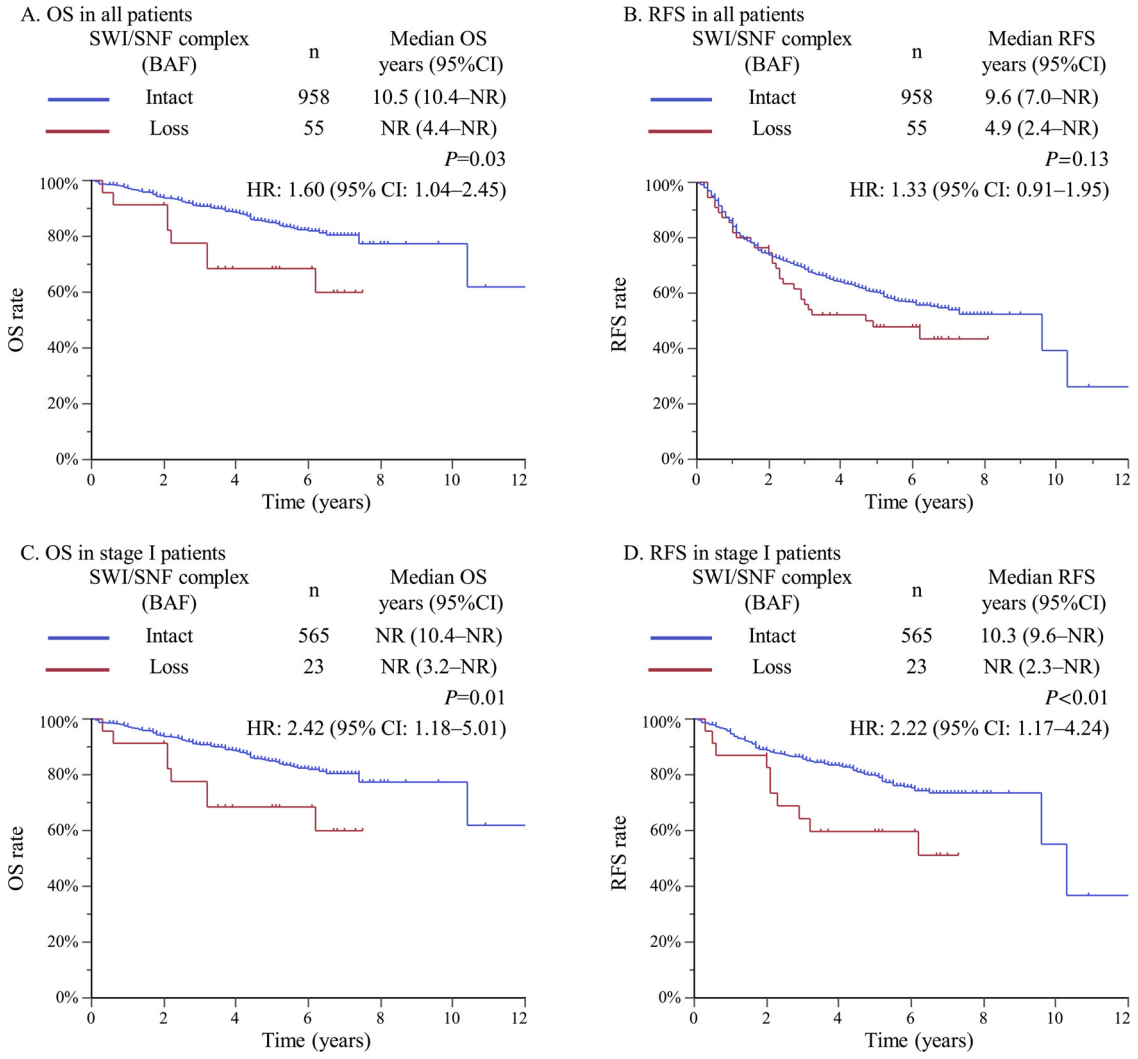

Fig. 2. Kaplan-Meier curves for overall survival (OS) and recurrence-free survival (RFS) according to expression of the SWI/SNF complex in 1013 patients with non-small cell lung carcinoma (NSCLC). (A) OS in all patients, and (B) RFS in all patients, (C) OS in stage I patients, and (D) RFS in stage I patients. HR: hazard ratio, CI: confidence interval, NR: not reached.

Table 3
Correlation between loss of expression of the SWI/SNF complex (BAF) and PD-L1 expression.

PD-L1 expression	Expression of the SWI/SNF complex (BAF)		
	Intact n (%)	Loss n (%)	P
≥1%	247 (26)	23 (42)	< 0.01
< 1%	711 (74)	32 (58)	
≥50%	103 (11)	7 (13)	0.65
< 50%	855 (89)	48 (87)	

SWI/SNF: switch sucrose nonfermentable, BAF: canonical BRG1/BRM-associated factor, PD-L1: Programmed cell death ligand 1.

patients with BAF-Loss than BAF-Intact (42% vs 26%; $P < 0.01$). In contrast, there was no difference in the proportion of cases with PD-L1 ≥50% (13% vs 11%; $P = 0.64$) between BAF-Loss and BAF-Intact (Table 3).

3.5. Tumor mutation burden analysis

In the WES cohort, BAF-Loss was observed in three of ten NSCLC cases. All three of these patients showed loss of expression of the SMARCA4 subunit. Two of three NSCLC cases harbored a SMARCA4 mutation (two frameshift deletions). The degree of TMB was significantly higher among patients with BAF-Loss (n = 3) than BAF-Intact (n = 7) (median 437 vs 113 mutations/whole-exome; $P = 0.02$; Fig. 3).

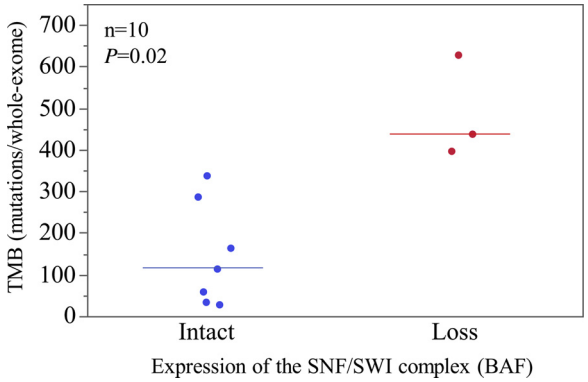

Fig. 3. Correlation between expression of the SWI/SNF complex and tumor mutation burden (TMB).

4. Discussion

To our knowledge, this study, which examined 1013 NSCLC patients in the TMA cohort and 10 NSCLC patients in the WES cohort, is the largest study to evaluate the clinicopathological features of NSCLC with loss of expression of the SWI/SNF complex. Our results showed that BAF-Loss was associated with younger age, male sex, smoking history, pulmonary emphysema or bulla, larger invasive tumor size, pleural invasion, vascular invasion, solid predominant histologic subtype, and absence of a lepidic component compared to BAF-Intact. In addition, this is the first report to show associations between NSCLC with BAF-Loss and PD-L1 ≥1%, and between NSCLC with BAF-Loss and high TMB.

Previous studies have shown that NSCLC with loss of expression of the SMARCA4 subunit is prevalent in poorly differentiated tumors without a lepidic pattern in males and smokers [8,25], features that are similar to those identified in this study. In addition, NSCLC with BAF-Loss was prevalent in cases with younger age, pulmonary emphysema or bulla, and larger invasive tumor size, features that are similar to those of SMARCA4-deficient thoracic sarcomas [26,27]. Most studies have demonstrated that loss of expression of the SWI/SNF complex correlates with aggressive clinicopathological features in several types of cancer, including breast cancer [28,29], ovarian cancer [30], endometrial cancer [31,32], renal cancer [33,34], colorectal cancer [35,36], gastric cancer [37], and pancreatic cancer [38,39]. Inactivation of SMARCA4 enables cancer cells to maintain undifferentiated gene expression programs [40]. The SWI/SNF complex has roles in regulating the actin cytoskeleton [41,42] and has also been implicated in regulating the transmembrane glycoprotein CD44 [43,44]. Therefore, aberrant activation of the SWI/SNF complex that causes changes in cellular motility may contribute to invasion and metastasis [45]. We speculate that these aggressive features of malignant tumors with loss of expression of the SWI/SNF complex may be universally observed across various organs.

Our study showed that BAF-Loss was associated with shorter OS compared to BAF-Intact in all stages. One previous study (n = 60) showed that loss of expression of SMARCA4 and SMARCA2 was correlated with poor prognosis compared to intact expression [11]. Another study (n = 193) showed that NSCLC with low expression of SMARCA2 correlated with a worse prognosis in NSCLC patients (5-year survival: 32.3% vs 53.5%) [12]. In the other study using a gene expression microarray (n = 460), multivariate analysis (SMARCA4 expression, Age ≥65/ < 65, Sex, Stage I/II–III, pathological differentiation) indicated that low expression of SMARCA4 was an independent prognostic factor [46]. Our result supported these previous reports in the point that low expression of subunits of the SWI/SNF complex correlated with a worse prognosis compared to high expression in all stages. However, NSCLC cases with the BAF-Loss had a higher proportion of stage II, stage III, and stage IV in comparison to NSCLC cases with the BAF-Intact. Although stage I NSCLC with BAF-Loss was associated with shorter OS and RFS compared to stage I NSCLC with BAF-Intact, there were no statistically significant differences in OS or RFS between BAF-Loss and BAF-Intact in stage II, stage III, or stage IV. In addition, multivariate analysis of our study showed that BAF-Loss was not an independent prognostic factor in stage I NSCLC. The reason for the difference between our study and the past previous study might be because they evaluated only SMARCA4 expression using a different method and they did not include the other prognostic factors, such as histology, pleural invasion, or vascular invasion. A strength of our report is that we compared prognosis between NSCLC with BAF-Loss and BAF-Intact in a large cohort with stratification for pathological stage and other prognostic factors.

Studies have demonstrated that loss of expression or mutation of the SWI/SNF complex is correlated with PD-L1-positive status in gastric cancer [37] and ovarian cancer [47,48]. However, the association between NSCLC with loss of expression of the SWI/SNF complex and PD-L1 status has not been clarified. We are the first to demonstrate that NSCLC with loss of expression of the SWI/SNF complex is correlated with PD-L1-positive status, suggesting that the phenomenon is common to many types of cancers.

Our results demonstrate that NSCLC with loss of expression of the SWI/SNF complex was correlated with high TMB. Activation of ARID1A and SMARCA4 is required for DNA MMR [48]. High TMB is associated with a deficiency in the DNA MMR pathway via either an inherited or acquired mutation in DNA MMR enzymes [49], or via somatic epigenetic modifications that result in decreased expression of key DNA MMR enzymes [50] or mutations in genes encoding DNA polymerase proofreading domains [51]. In fact, past study using the COSMIC database of lung carcinoma demonstrated a positive correlation between the sum of the mutation values from the SNF/SWI genes and the numbers of mutated genes ($R^2 = 0.72$, $P < 0.01$) or simple mutations ($R^2 = 0.68$, $P < 0.01$) [4]. In addition, we validated our result using the data of the TCGA for lung adenocarcinoma (TCGA-LUAD: n = 549) and lung squamous cell carcinoma (TCGA-LUSC: n = 504). Lung carcinoma case with a SMARCA4 mutation (n = 149) exhibit statistically higher TMB than that with SMARCA4 wild-type (n = 904) (median 385 vs 285 mutations/whole-exome; $P < 0.01$). Similar results were obtained from lung carcinoma case with a SMARCA2 (Mutant [n = 130] vs Wild type [n = 923]: 383 vs 287 mutations/whole-exome; $P < 0.01$), ARID1A (Mutant [n = 176] vs Wild type [n = 877]: median 360 vs 287 mutations/whole-exome; $P < 0.01$), and ARID1B mutation (Mutant [n = 142] vs Wild type [n = 911]: median 419 vs 280 mutations/whole-exome; $P < 0.01$). Shen et al. showed that tumors formed by an ARID1A-deficient ovarian cancer cell line in syngeneic mice displayed increased TMB, elevated numbers of tumor-infiltrating lymphocytes (89% vs 29%), and PD-L1 expression (100% vs 14%) [48]. Our IHC study using human lung carcinoma samples was the first to demonstrate a clear correlation between loss of expression of the SWI/SNF complex and higher TMB.

BAF-Loss was observed in 5.5% of the 1013 NSCLC cases (SMARCA4 in 2.4%, SMARCA2 in 2.4%, ARID1A in 1.3%, and ARID1B in 0.3%). A previous large cohort study that analyzed a total of 316 NSCLC patients showed immunohistochemical loss of expression of SMARCA4 in 5.1% and SMARCA2 in 4.8% [10]. The frequency of loss of expression of the SWI/SNF complex in the present study was therefore of similar magnitude to that in the previous large cohort study. Our result showed a much higher frequency of loss of SMARCA4 and SMARCA2 in adenocarcinoma than squamous cell carcinoma, and loss of ARID1A and ARID1B appear more frequently in squamous cell carcinoma than adenocarcinoma. These results of IHC were the same as previous studies of genetic analysis [52,53].

Several reports have shown that SMARCA4 mutations can cause defects in its chromatin remodeling activity, however, SMARCA4 mutations identified in previous NGS studies do not result in loss of protein expression [54,55]. From this reason, we need to recognize that mutations of the SWI/SNF complex do not always correspond to loss of protein expressions of the SWI/SNF complex. Immunohistochemistry staining for the SWI/SNF complex might be more helpful for predicting the inactivation of the SWI/SNF complex.

Several limitations of this study warrant consideration. First, the study was conducted under a retrospective design at one institution. Second, TMA has limited power for quantifying antigen expression in whole tumor sections. However, a large sample size (n = 1013) may compensate for the level of precision at the individual level [56]. In addition, we used samples in the shape of 2-mm high cylinders, which is three- to four-fold higher than 0.6-mm high cylinders (3.1 vs 0.84 mm^2) [57]. Third, the sample size in the WES cohort was relatively small.

5. Conclusion

We demonstrated that NSCLC with loss of expression of the SWI/SNF complex was associated with distinct clinicopathological features,

PD-L1-positive status, and high TMB.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.10.009.

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