SWI/SNF alterations define a subgroup with poorer outcome among patients with aggressive forms of adult T-cell leukemia/lymphoma

Aggressive forms of adult T-cell leukemia/lymphoma (ATLL) are rare T-cell malignancies that carry a dismal prognosis. ATLL is endemic in Japan (J-ATLL) and in the Caribbean and North America (NA-ATLL) where there is a high prevalence of human T-cell lymphotropic virus type 1 (HTLV-1) infection. Lymphoma and acute subtypes are more frequent in North American cases (90% of NA-ATLL patients), have a shorter overall survival (OS) (6 months), a shorter progression-free survival (93 days for acute type), and present at a younger age at diagnosis (54 years) than their Japanese (J-ATLL) counterparts[1,2]

Molecular studies on Caribbean patients are much more limited than in Japan. Whilst the major alterations identified in J-ATLL appear to be shared with NA-ATLL,[3-7] two studies suggested a higher frequency of epigenetic-targeting alterations such as *EP300* and, more recently, the transcription regulator ETS1 in NA-ATLL.[5,8] Other mutations targeting epigenetics have been described, such as DNA methylation modifiers (e.g., *TET2*, *DNMT3A*, *IDH2*), histone writers (e.g., *EP300*, *KMT2C*), and chromatin remodelers (e.g., switch/sucrose non-fermentable, SWI/SNF complex).[4] The clinical significance of these alterations is still unknown.

In this work, we analyzed the mutational profile of 33 acute and lymphoma subtypes in NA-ATLL cases diagnosed in patients of Caribbean origin and compared it to previously published data on NA-ATLL and J-ATLL. Our results showed a high prevalence of SWI/SNF alterations which seemed to be associated with a very poor outcome.

Our cohort consisted of 38 patients who were treated at the Centre Hospitalier Universitaire (CHU) de Martinique and/or Gustave Roussy between 2013 and 2024. All patients had a confirmed diagnosis of ATLL associated with the presence of HTLV-1-specific antibodies. Clinical data were available for 37/38 patients. Informed consent was obtained in accordance with institutional guidelines. This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the institutional review boards of the study centers involved. The study is registered at clinicaltrials.gov (identifier: NCT01941680).

Nineteen peripheral blood mononuclear cells, 9 blood buffy coats, and 10 FFPE samples were analyzed with targeted and whole exome sequencing (WES). This strategy offered the advantage of combining the sensitivity of a large panel of 176 genes with the exhaustivity of WES, particularly regarding epigenetic regulator genes. Amongst the 38 tested samples, 33 were informative with at least one somatic variant and were subsequently analyzed (*Online Supplementary Figure S1*).

Nineteen patients had an acute type (58%), 13 a lymphoma form (39%), and one was unknown (3%). Twenty-seven patients died with a median survival of seven months (0-40.5 months), 5 patients were lost during follow-up, and one was still alive after five years. Clinical data are summarized in Table 1.

Overall, 247 somatic mutations were detected in 95 different genes including 126 missense variants (51.0%), 60 nonsense variants (24.3%), 46 frameshift variants (18.6%), 9 splice-site variants (3.6%), and 6 in-frame insertion/deletion variants (2.4%). One hundred and seventy-four somatic variants (70.4%) were found using targeted sequencing and a further 73 additional somatic mutations were detected by WES in 45 different genes: 6 mutations in *CIC*, 5 in uncovered exons of CARD11, 4 each in *ARID2* and *HLA-A*, and 3 in *EEF1A1*. Overall, we detected a mean of 7.5 (range: 1-14) somatic variants per sample. Several patients presented multiple hits in a given gene, notably *CARD11*, *NOTCH1* (3 samples each) and *TP53* (2 samples) (Figure 1). The most frequently mutated genes were *TP53* (N=13 samples, 39.4%), *PRKCB* (N=11 samples, 33.3%), *CARD11*, *CCR4*, *IRF4*, *PLCG1* (N=10 samples, 30.3%), *CIC*, *NOTCH1* (N=7 samples, 21.2%), *CCR7*, *FAS*, *HLA-B* (N=6 samples, 18.2%).

Copy number analysis (CNA) could be performed in 23 patients out of 33 after exclusion of failed samples (heterogeneous coverage). We identified 54 deletions and 55 gains or amplifications. The most frequent deleted *loci* affected *CDKN2A* (11 samples, 47.9%), *GPR183* (6 samples, 26.0%), and *CD58*, *NFKBIA*, *TP53*, *SMARCA4* (3 samples, 13.0%). The most prevalent gains affected *CD28*, *IRF4*, *TRAF3* (7 samples each, 30.4%), *NOTCH1* (4 samples each; 17.4%), and *CARD11*, *SETDB1*, *TRAF2* (3 samples each; 13.0%). Some genes had both somatic variants and amplifications or deletions such as *IRF4* (4 samples) and *TP53* (3 samples), suggesting bi-allelic alterations.

Twenty-seven out of 33 patients (81.8%) harbored two or more mutations in the NF-κB/TCR signaling pathway. The most frequent associations of mutations were *PRKCB/CARD11*, *PRKCB/IRF4*, *PRKCB/PLCG1*, and *IRF4/CCR4*. We identified 21 samples (63.7%) with at least one mutation in other genes: 19 (57.6%) including alterations in cell-cycle genes (*TP53* excluded), 18 (54.5%) in GpCR T-cell trafficking, 18 (54.5%) in immune surveillance, and 10 (30.3%) in the JAK/STAT pathway.

Epigenetic gene alterations were found in the majority of

Table 1. Clinical characteristics of the adult T-cell leukemia/lymphoma cohort according to SWI/SNF status.

Characteristic	ATLL patients N=33	*P*	*SWI/SNF*^{WT} N=19	*SWI/SNF*^{alt} N=14	*P*
Age, mean (range)	61.4 (35-84)	-	62.11 (35-84)	60.4 (44-83)	0.720#
Female:Male sex ratio	1.75:1	0.048***	1.71:1	1.8:1	>0.999*
Female, N	21	-	12	9	-
Male, N	12	-	7	5	-
ATLL form, N	-	0.034***	-	-	>0.999*
Acute	19	-	12	7	-
Lymphoma	13	-	7	6	-
Unknown	1	-	0	1	-
Hypercalcemia, N	-	0.211***	-	-	>0.999*
Yes	19	-	11	8	-
No	13	-	8	5	-
Unknown	1	-	0	1	-
Elevated LDH, N	-	<0.0001***	-	-	0.629*
≤2N	4	-	3	1	-
>2N	28	-	16	12	-
Unknown	1	-	0	1	-
N of lines of treatment, mean (range)	2 (0-4)	-	2 (1-6)	2 (0-4)	-
First-line of treatment, N	-	-	-	-	0.535**
AZT/INF	13	-	8	5	-
Chemotherapy	11	-	8	3	-
AZT/INF + chemotherapy	5	-	3	2	-
Palliative care	1	-	0	1	-
Unknown	3	-	0	3	-
Deceased, N	-	<0.0001***	-	-	>0.999*
Yes	26	-	15	11	-
No	1	-	1	0	-
Unknown or lost to follow-up	6	-	3	3	-
5 year-OS, % (N)	3.7 (1/27)	-	6.3 (1/16)	0 (0/11)	-

#Unpaired *t* test. *Fisher exact test. **χ^2 test. ***Statistically significant. alt: altered; ATLL: adult T-cell leukemia/lymphoma; AZT/INF: zidovudine/interferon; LDH: lactate dehydrogenase; N: number; OS: overall survival; SWI/SNF: switch/sucrose non-fermentable; WT: wild-type.

patients (N=23, 69.7%) involving 23 different genes mainly belonging to the SWI/SNF complex (14 patients, 42.4%). Genes of the ARID family (*ARID1A,1B,2,4*) were the most frequently mutated, detected in 9 patients out of 14 (64.3%). Additionally, we detected CNA in the *SMARCA4 locus* in 4 patients (28.6%) (Figure 2A). Three patients (21.4%) presented multiple hits in SWI/SNF genes. We found no association with other poor prognosis genes, such as *IRF4*, *TP53* or *CDKN2A/B* (*Online Supplementary Figure S2*). There was a trend towards an increased mutational burden in SWI/SNF altered cases (two-sided Mann-Whitney test, *P*=0.0599) (Figure 2B) but no correlation was observed between the number of alterations and OS (Pearson's test, *P*=0.2418).

SWI/SNF alterations distributed equally between acute and lymphoma subtypes (Figure 2C). The presence of SWI/SNF alterations was associated with a worse outcome (*P*=0.0071) with a median OS of 5.0 months for acute *versus* 13.0 months for lymphoma subtypes, respectively (Figure 2D). This negative impact was maintained across both ATLL subtypes with a median OS of 3.0 months and 9.0 months for acute and lymphoma forms, respectively, in SWI/SNF group compared to 11.0 and 20.5 months in wild-type patients (*P*=0.0032) (Figure 2D).

It has been suggested that clinical differences between NA-ATLL and J-ATLL might be linked to more frequent alterations of *EP300*.[5] We did not confirm the high incidence of *EP300* alterations in NA-ATLL, which is consistent with the work of Marçais *et al*.[6] Globally, our results confirm a high prevalence of epigenetic alterations, in line with other reports.[6,7] As expected in this cohort of aggressive subtypes, there was an enrichment in mutations associated with a poor prognosis (*IRF4*, *TP53*) and a low frequency of *STAT3* mutations[4] (*Online Supplementary Figure S3*).

SWI/SNF gene alterations were found in 14 patients (42.4%), which is similar to the WGS J- ATLL cohort (38%), genes of the ARID family being the most frequently involved. We also found mutations in *BRD7*, *BRD9*, *DPF3* and copy number alterations in *SMARCA4*. We did not detect somatic alteration in *DPF2* or *SMARCB1*.[7] SWI/SNF is a 29-component complex that plays a crucial role in the control of chro-

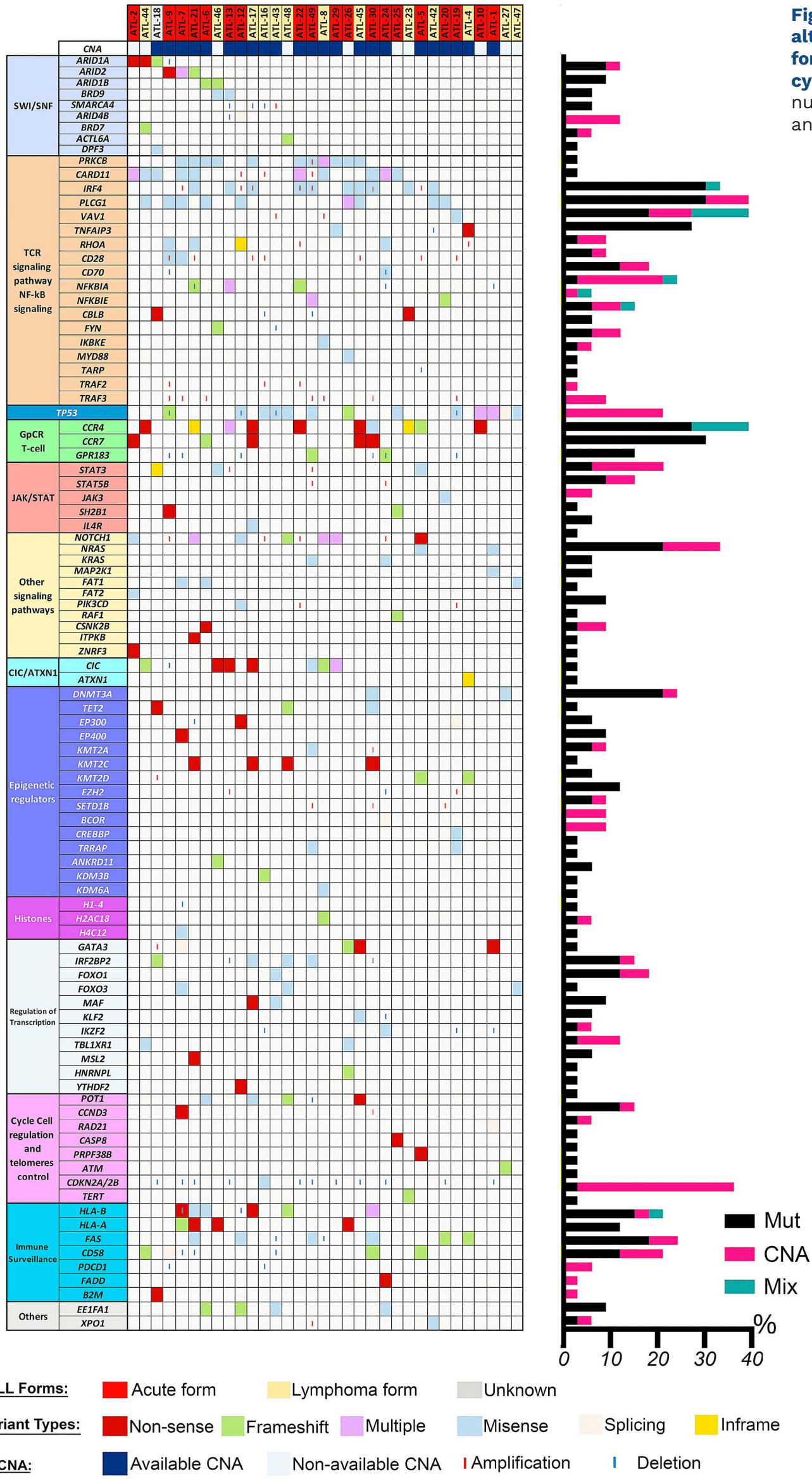


Figure 1. Heatmap of the different alterations detected in the 33 informative patients and the frequency of each gene altered. CAN: copy number alterations; mix: both mut and CAN; Mut: mutations.

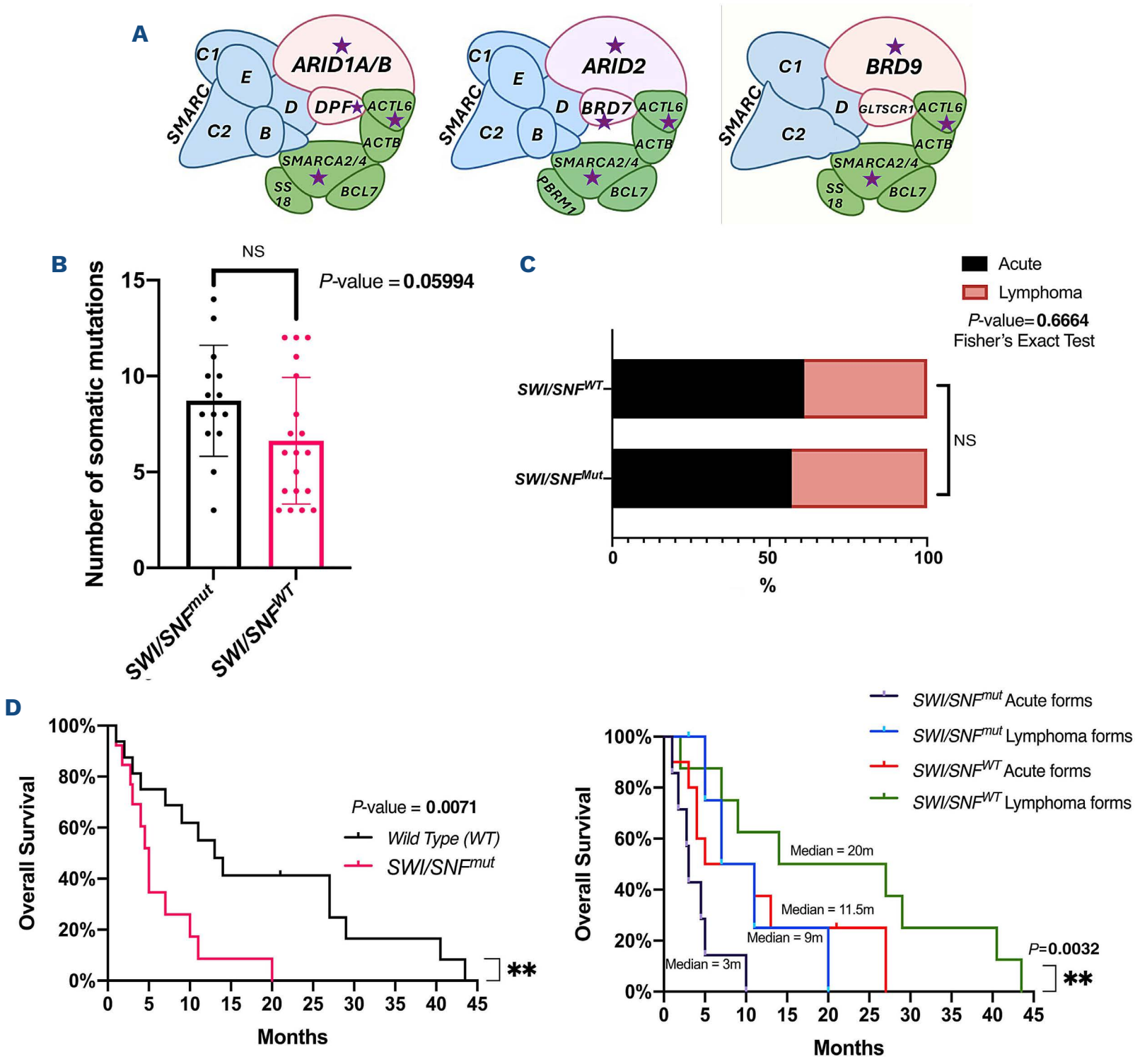


Figure 2. SWI/SNF alterations define a specific subgroup of patients with a poor prognosis. (A) Focus on the different proteins altered in the SWI/SNF complexes. (B) Somatic alteration burden according to the form of adult T-cell leukemia/lymphoma (ATLL) in SWI/SNF altered patients. (C) Prevalence of SWI/SNF alterations in the different ATLL forms. (D) Overall survival (OS) in SWI/SNF altered samples (median: 5.0 months) and wild-type (WT) patients (13.0 months). Detailed median OS of ATLL patients according to form and SWI/SNF status. NS: not significant. **Statistically significant.

matin structure and has been implicated in cancers and lymphomas.[9] SWI/SNF loss of function is believed to impair differentiation, favor cell expansion and self-renewal, and has been associated with a poor prognosis in cancer.[9,10] This could explain our observation that SWI/SNF alterations have an adverse prognostic impact in aggressive ATLL. The presence of SWI/SNF alterations was independent of other known molecular features that have a negative impact (*IRF4, TP53, CDKN2A/B)*. In addition, SWI/SNF alterations had the strongest negative prognostic impact in comparison with *IRF4*, *TP53* and *CDKN2A/B* (*Online Supplementary Figure S2*). Few data are available on the implication of the SWI/SNF complex in ATLL physiopathology. A recent work showed that Tax and HTLV-1 bZIP factor (HBZ) exert opposite effects on the regulation of HTLV-1 latency in T cells through their interaction with the SWI/SNF complex.[11] Mutations of components of the SWI/SNF complex might thus be associated with increased transcription of the HTLV-1 genome. EZH2, a subunit of the polycomb repressive complex 2 (PRC2), is frequently over-expressed in ATLL, which leads to abnormally high trimethylation at histone H3K27 (H3K27me3) and epigenetic silencing of a large number of genes.[12] This EZH2 hyperactivity is not caused either by amplification or activating mutations.[12] As SWI/SNF and PRC2 complexes play an antagonistic role and mutually inhibit each other,[9] SWI/SNF alterations could participate in EZH2 hyperactiv-

ity in ATLL. This phenomenon has been demonstrated in SMARCB1-deficient rhabdoid tumors.[13] Other recent findings suggested a role of the YY1/EZH2 axis on aggressiveness of ATLL and the potential action to targeting EZH2.[14] Dual targeting of EZH1 and EZH2 caused synthetic lethality in cancer cells harboring mutations in components of the SWI/SNF complex. The results of a phase I-II trial in ATLL with valemetostat, a dual EZH1/2 inhibitor, support these preclinical findings.[15] Whether the presence of SWI/SNF alterations correlates with sensitivity to valemetostat is not known. Functional analysis would be useful to address this question.

Though limited by its retrospective nature and small sample size, our study provides further data on the genomic landscape of a homogeneous cohort of aggressive forms of ATLL in Caribbean patients. We show that SWI/SNF complex alterations are frequent and define a very poor prognosis subgroup in this rare disease. These findings further support the concept of targeting the PRC2 complex in aggressive forms of ATLL and suggest the emerging opportunity of molecularly tailored strategies based on SWI/SNF alterations.

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Contributions

RL is responsible for the study concept, methodology, formal analysis, investigation and data curation, and reviewed and edited the manuscript. VV is responsible for the study concept and methodology. DG is responsible for the study concept, methodology and investigation, data curation, reviewed and edited the manuscript, supervised the study, and handled project administration. CM is responsible for the study concept, methodology and investigation, the formal analysis, prepared the original draft, reviewed and edited the manuscript, supervised the study, and handled project administration. MP is responsible for the methodology, investigation, and data curation. SC is responsible for the investigation, resources, and data curation. VS-P is responsible for the investigation and resources. LD, JCM, PF and AD are responsible for the resources and data curation. QH is responsible for the resources.

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Data-sharing statement

The dataset is available on request from the corresponding author.

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