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

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Running heads : SWI/SNF alterations, a poorer subgroup in ATLL.

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Aggressive forms of Adult T-cell Leukemia/Lymphoma (ATLL) are rare T-cell malignancies of dismal prognosis. ATLL is endemic, in Japan (J-ATLL) and in Caribbean/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 (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 yet unknown.

In this work, we analyzed the mutational profile of 33 acute and lymphoma subtypes 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 in 38 patients who were treated at 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 Declaration of Helsinki and approved by institutional review board. Nineteen peripheral blood mononuclear cells, nine blood buffy coats and ten 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 subsequently analyzed (Supplementary Fig.1).

Nineteen had an acute type (58%), 13 a lymphoma form (39%) and one was unknown (3%). Twenty-seven died with a median survival of 7 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%), nine splice-site variants (3.6%) and six 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: six mutations in *CIC*, five in uncovered exons of CARD11, four in *ARID2* and *HLA-A* and three in *EEF1A1*. Overall, we detected a mean of 7.5 (1-14) somatic variants per sample. Several patients presented multiple hits in a given gene, notably *CARD11*, *NOTCH1* (3 samples each) and *TP53* (2) (Fig.1). The most frequently mutated genes were *TP53* (n=13 samples, 39.4%), *PRKCB* (11; 33.3%), *CARD11*, *CCR4, IRF4, PLCG1* (10; 30.3%), *CIC*, *NOTCH1* (7; 21.2%), *CCR7, FAS, HLA-B* (6; 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 each, 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-kB/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 a majority of patients (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 nine patients out of 14 (64.3%). Additionally, we detected CNA in the *SMARCA4 locus* in four patients (28.6%) (Fig.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* (Supplementary Fig.2). There was a trend towards an increased mutational burden in SWI/SNF altered cases (Mann-Whitney test, two sided, *P*=0.0599) (Fig.2.B) 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 (Fig.2C). The presence of SWI/SNF alterations was associated with a pejorative outcome (*P*=0.0071) with a median overall survival (OS) of 5.0 months *versus* 13.0 months (Fig 2.D). This pejorative 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, Fig.2.D).

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]. (Supplementary Fig.3)

SWI/SNF genes 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 chromatin 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 pejorative molecular features (*IRF4, TP53, CDKN2A/B*). In addition, SWI/SNF

alterations had the strongest negative prognostic impact in comparison with *IRF4*, *TP53* and *CDKN2A/B* (Supplementary Fig.2).

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 SWI/SNF complex[11]. Mutations of components of the SWI/SNF complex might thus be associated with increased transcription of HTLV-1 genome. EZH2, a subunit of the polycomb repressive complex 2 (PRC2), is frequently overexpressed 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 neither caused by amplification nor activating mutations [12]. As SWI/SNF and PRC2 complexes play antagonistic role and mutually inhibit each other[9], SWI/SNF alterations could participate to EZH2 hyperactivity 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 1-2 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 an 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 provide further support to target 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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Figure and Table legends

Table 1. Clinical characteristics of ATLL cohort, depending on SWI/SNF status.

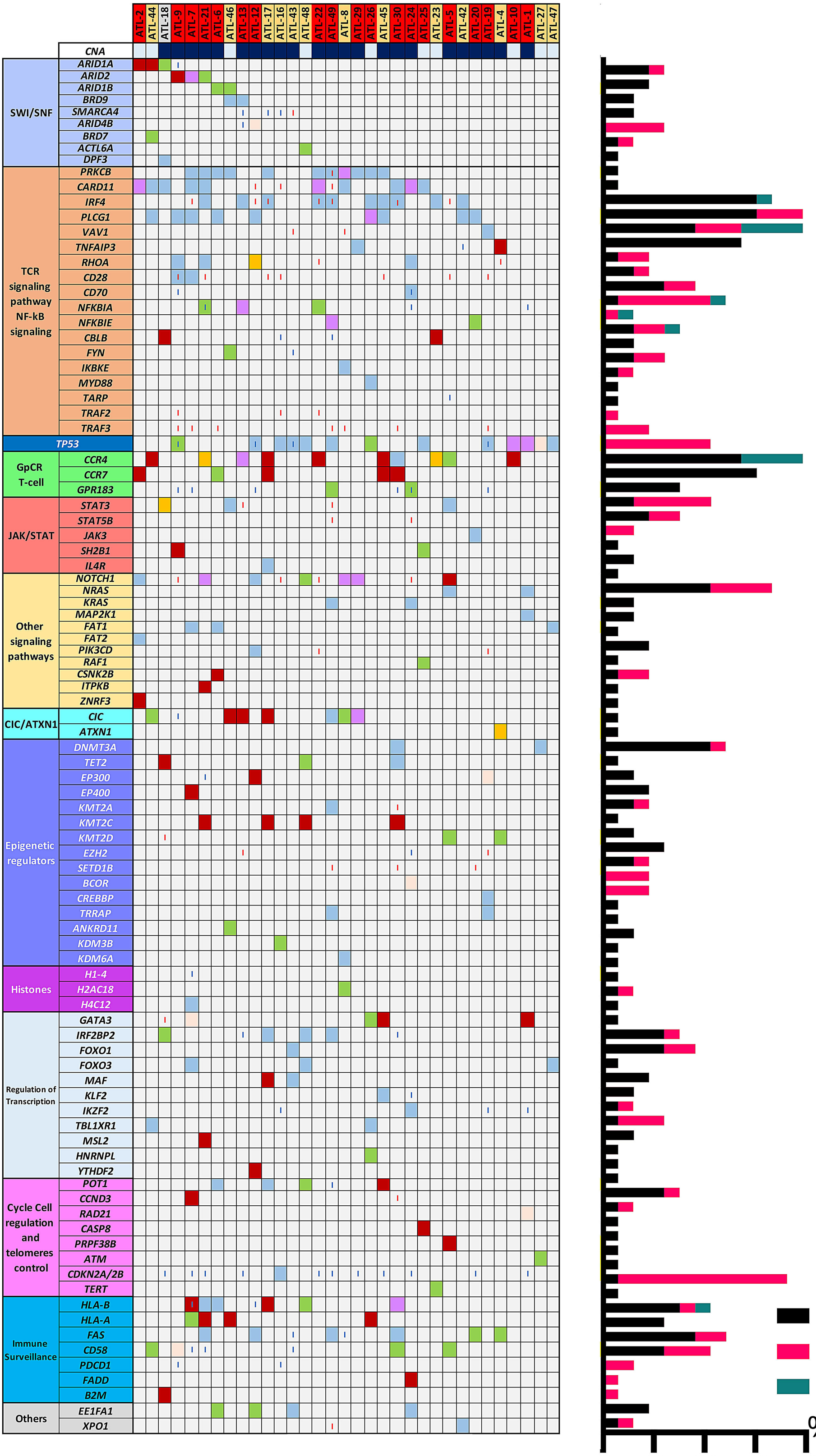
WT = Wild type; alt=altered; AZT/INF=Zidovudine/Interferon; *Fisher's exact test; **Chi-Square test; #Unpaired t test

Table 1

	ATLL Patients n = 33	***P*-value**	***SWI/SNF^{WT}* n = 19**	***SWI/SNF^{alt}* n = 14**	***P*-value**
Age (Mean)	61.4 (35-84) years		62.11 (35-84) years	60.4 (44-83) years	0.720#
Sex ratio	1.75:1	**0.048***	1.71:1	1.8:1	>0.999*
Female	21		12	9	
Male	12		7	5	
ATLL form		**0.034***			>0.999*
Acute	19		12	7	
Lymphoma	13		7	6	
Unknown	1		0	1	
Hypercalcemia		0.211*			>0.999*
Yes	19		11	8	
No	13		8	5	
Unknown	1		0	1	
Elevate LDH		**<0.0001***			0.629*
≤ 2N	4		3	1	
> 2N	28		16	12	
Unknown	1		0	1	
Line of treatment (Mean)	2 (0-4)		2 (1-6)	2 (0-4)	
First line of treatment					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		**<0.0001***			>0.999*
Yes	26		15	11	
No	1		1	0	
Unknown or lost to follow-up	6		3	3	
5 years-Overall Survival	3.7% (1/27)		6.3% (1/16)	0% (0/11)	

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

Figure 2. – SWI/SNF alterations define a specific subgroup of patients with a poor prognosis.
(A) Focus on the different protein altered in the SWI/SNF complexes (B) Somatic alterations burden depending on the form of 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 patients (13.0 months). Detailed median OS of ATL patients depending on the forms and SWI/SNF status


ATL-2
ATL-44
ATL-18
ATL-9
ATL-7
ATL-21
ATL-6
ATL-46
ATL-13
ATL-12
ATL-17
ATL-16
ATL-43
ATL-48
ATL-22
ATL-49
ATL-8
ATL-29
ATL-26
ATL-45
ATL-30
ATL-24
ATL-25
ATL-23
ATL-5
ATL-42
ATL-20
ATL-19
ATL-4
ATL-10
ATL-1
ATL-27
ATL-47
CNA
SWI/SNF
ARID1A
ARID2
ARID1B
BRD9
SMARCA4
ARID4B
BRD7
ACTL6A
DPF3
TCR signaling pathway NF-kB signaling
PRKCB
CARD11
IRF4
PLCG1
VAV1
TNFAIP3
RHOA
CD28
CD70
NFKBIA
NFKBIE
CBLB
FYN
IKBKE
MYD88
TARP
TRAF2
TRAF3
TP53
GpCR T-cell
CCR4
CCR7
GPR183
JAK/STAT
STAT3
STAT5B
JAK3
SH2B1
IL4R
Other signaling pathways
NOTCH1
NRAS
KRAS
MAP2K1
FAT1
FAT2
PIK3CD
RAF1
CSNK2B
ITPKB
ZNRF3
CIC/ATXN1
CIC
ATXN1
Epigenetic regulators
DNMT3A
TET2
EP300
EP400
KMT2A
KMT2C
KMT2D
EZH2
SETD1B
BCOR
CREBBP
TRRAP
ANKRD11
KDM3B
KDM6A
Histones
H1-4
H2AC18
H4C12
Regulation of Transcription
GATA3
IRF2BP2
FOXO1
FOXO3
MAF
KLF2
IKZF2
TBL1XR1
MSL2
HNRNPL
YTHDF2
Cycle Cell regulation and telomeres control
POT1
CCND3
RAD21
CASP8
PRPF38B
ATM
CDKN2A/2B
TERT
Immune Surveillance
HLA-B
HLA-A
FAS
CD58
PDCD1
FADD
B2M
Others
EE1FA1
XPO1
Mut
CNA
Mix
%
0
10
20
30
40
ATLL Forms:
Acute form
Lymphoma form
Unknown
Variant Types:
Non-sense
Frameshift
Multiple
Misense
Splicing
Inframe
CNA:
Available CNA
Non-available CNA
Amplification
Deletion

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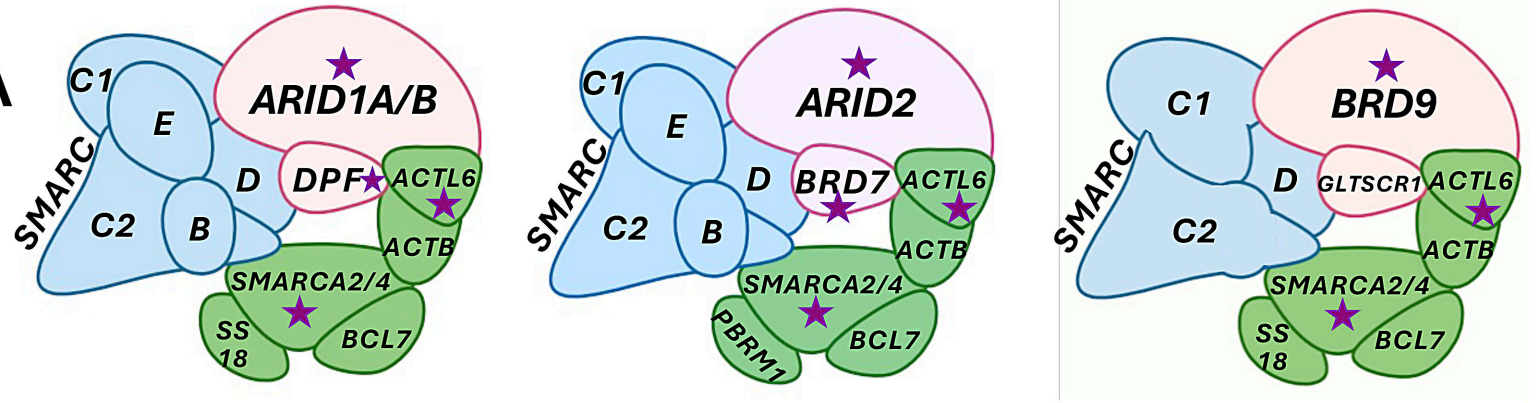
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ACTB
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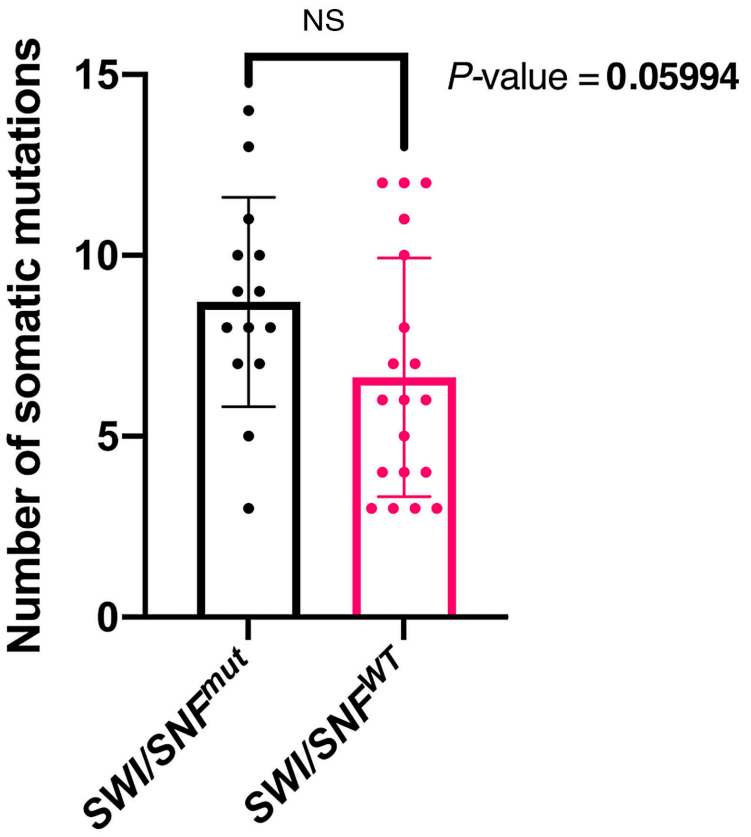
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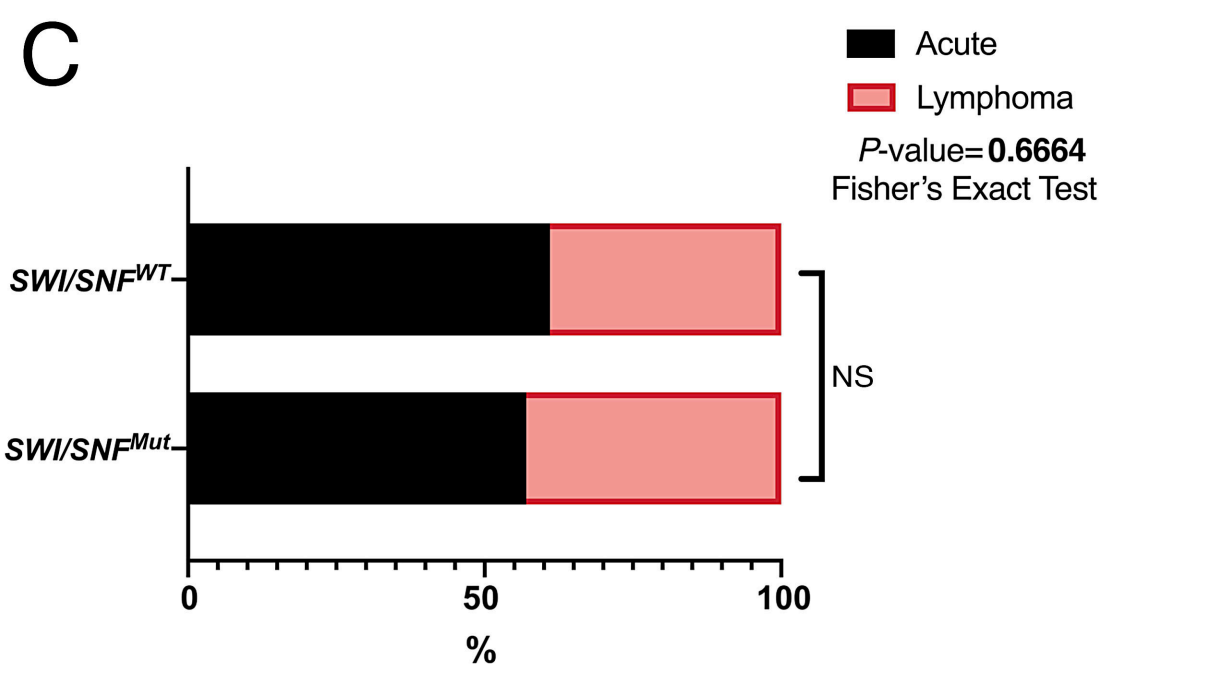
15
10
5
0
Number of somatic mutations
SWI/SNFmut
SWI/SNFWT

C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Lymphoma
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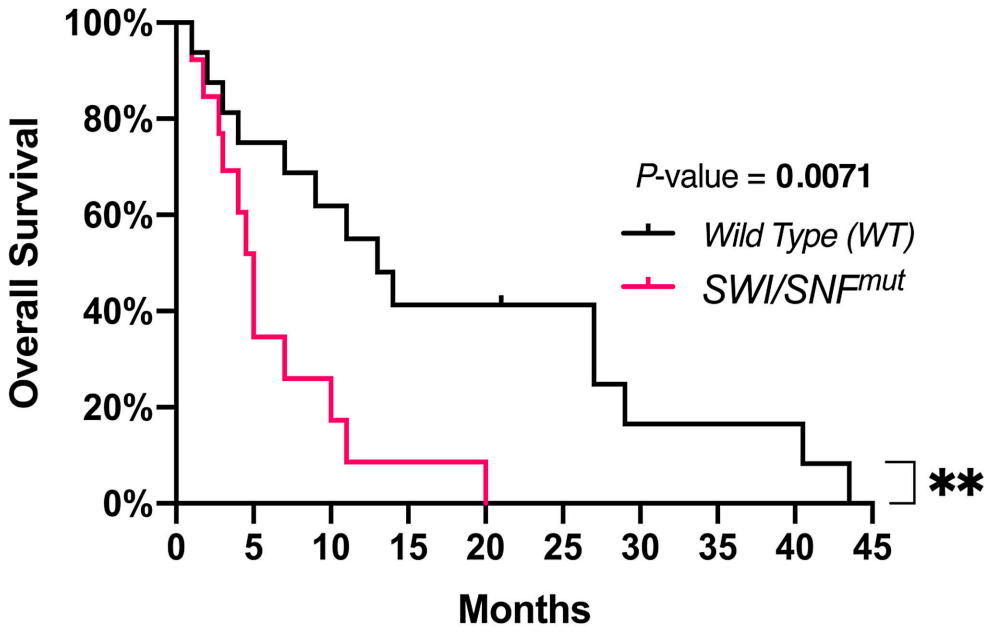
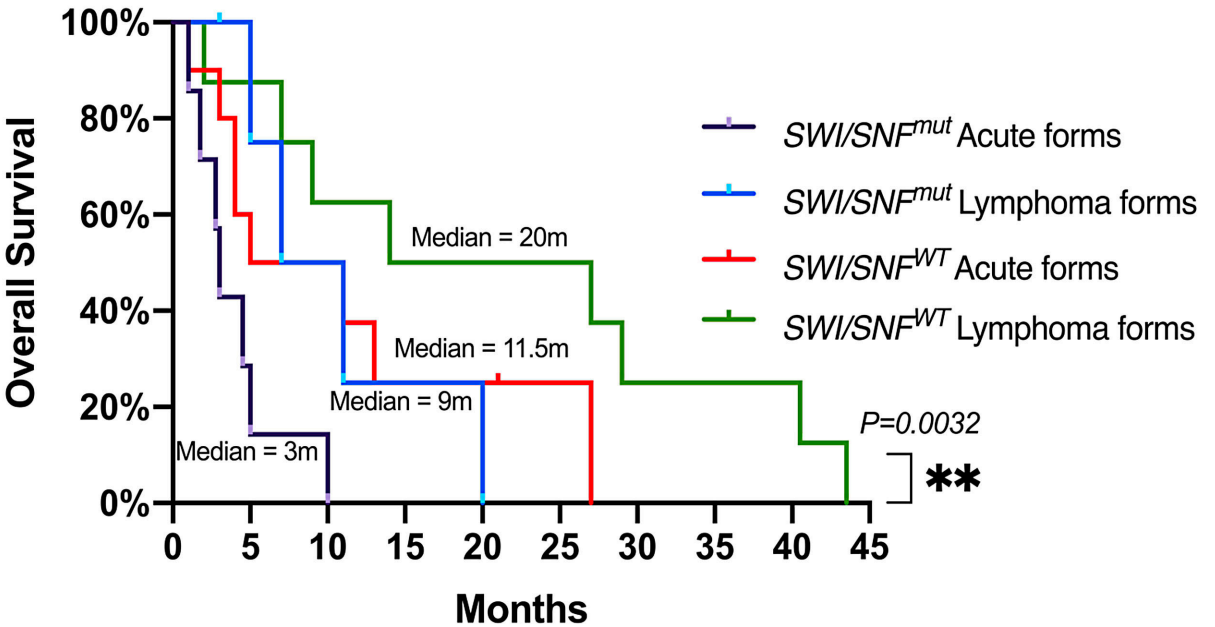
Fisher's Exact Test
SWI/SNFWT
SWI/SNFMut
NS
0
50
100
%

D


100%
80%
60%
40%
20%
0%
Overall Survival
P-value = 0.0071
Wild Type (WT)
SWI/SNFmut
**
0
5
10
15
20
25
30
35
40
45
Months


100%
80%
60%
40%
20%
0%
Overall Survival
SWI/SNFmut Acute forms
SWI/SNFmut Lymphoma forms
SWI/SNFWT Acute forms
SWI/SNFWT Lymphoma forms
Median = 20m
Median = 11.5m
Median = 9m
Median = 3m
P=0.0032
**
0
5
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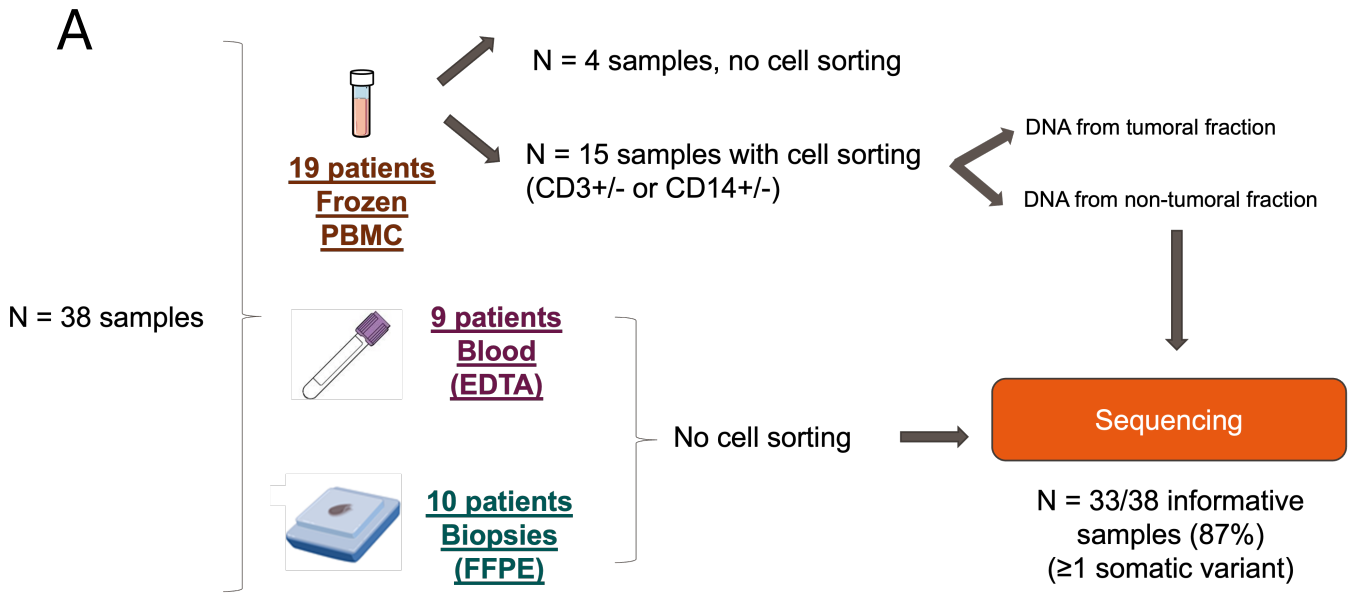
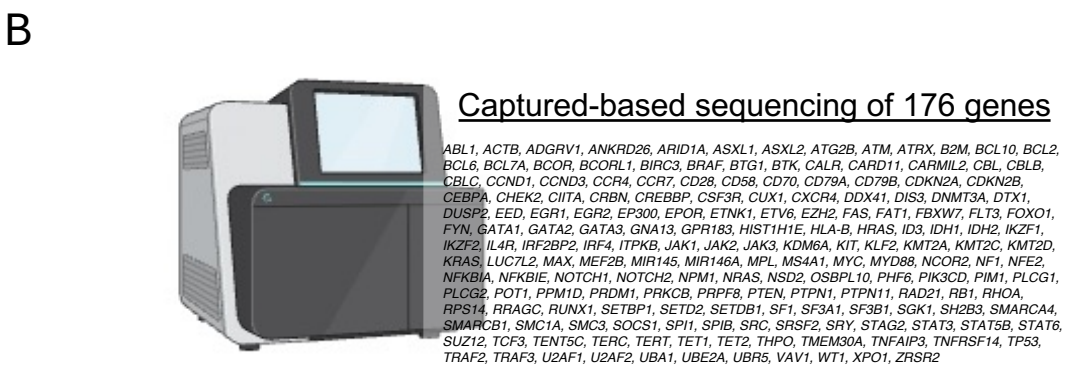
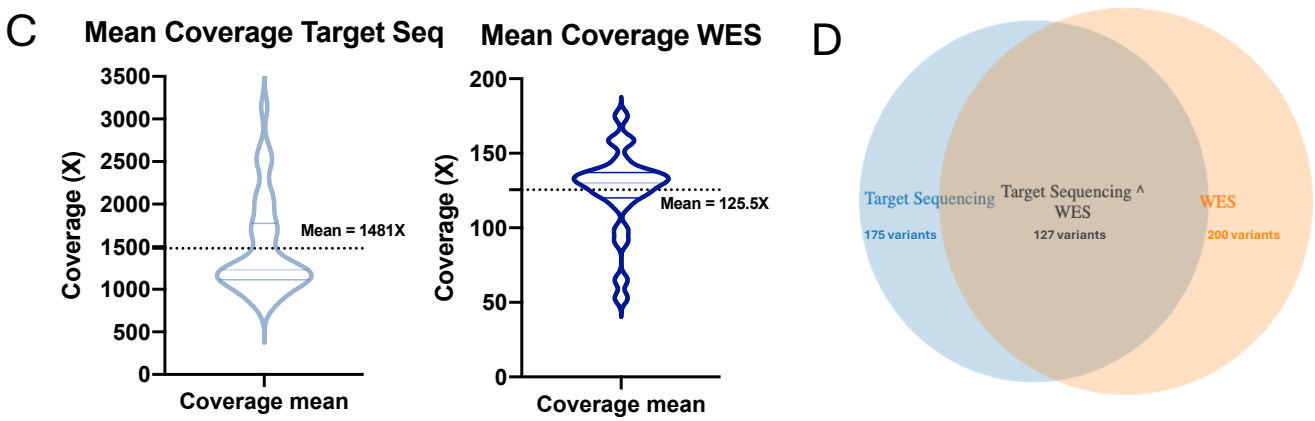
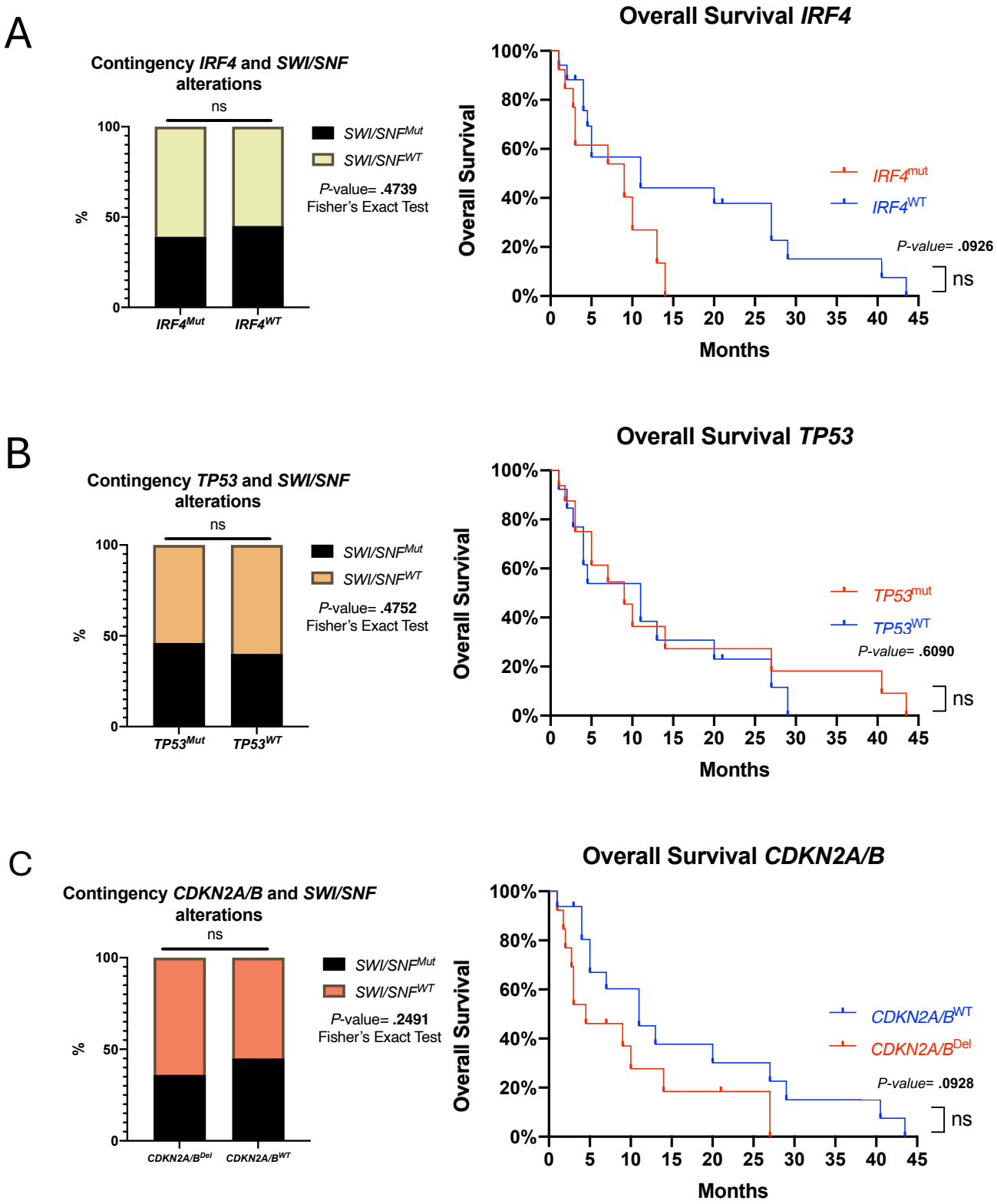
Months



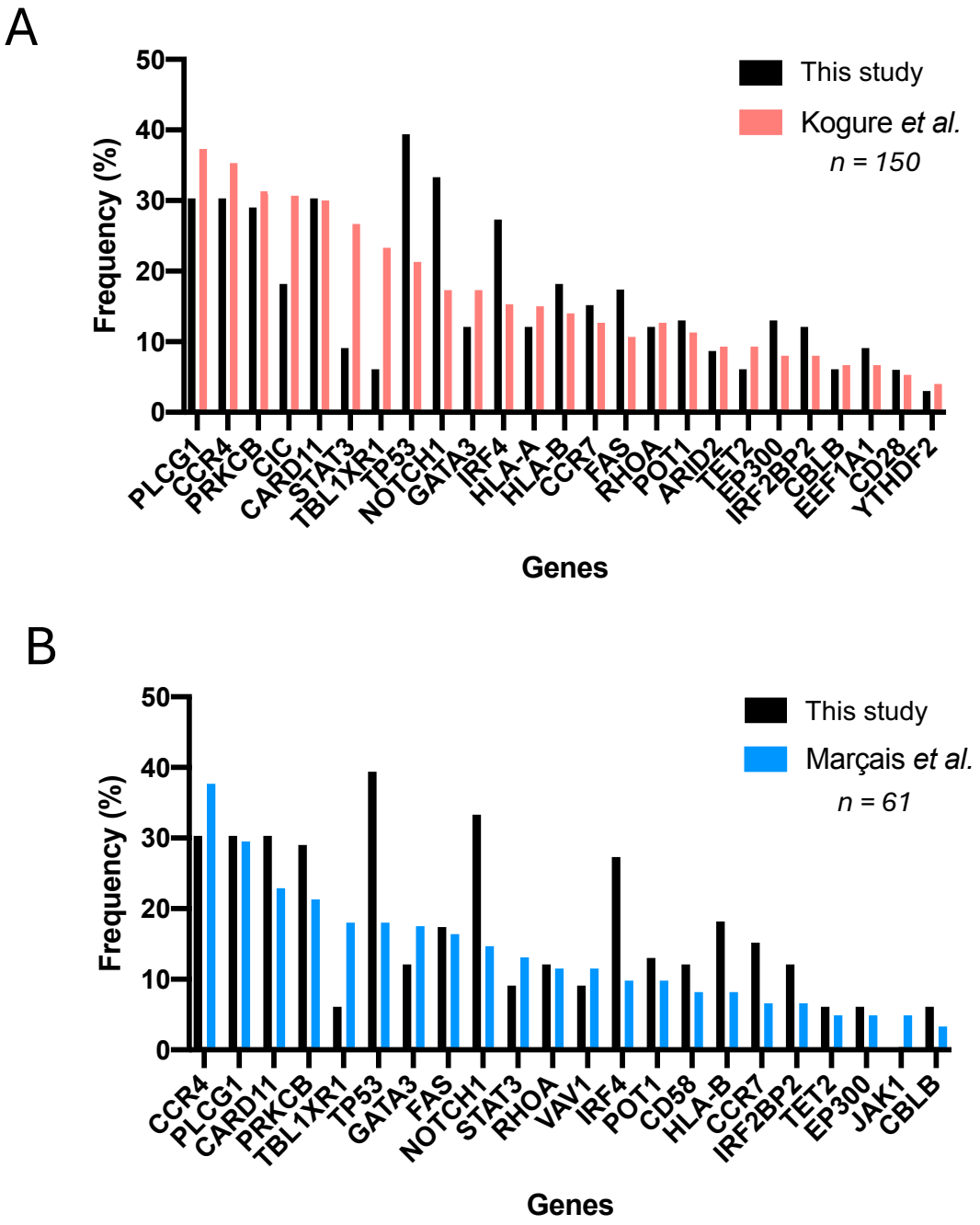




Supplementary Fig.1. Details and results of the sequencing strategy. (A) The sequencing strategy of the 38 samples - 33 were informative. (B) The capture-based panel of 176 genes. (C) Mean coverage of target sequencing and WES. (D) Venn diagram of variants detected by target sequencing and WES.



Supplementary Fig.2. Prevalence of co-altered mutations with SWI/SNF mutated samples (contingency with Fisher's exact test) and overall survival of principle known pejorative factors : *IRF4* (A), *TP53* (B) and *CDKN2A/B* (C).



Supplementary Fig.3.

Prevalence of the different alterations compared to other studies

(A) Prevalence of the cohort compared to Kogure Y *et al.*, Blood, 2022. (B) Prevalence of the cohort compared to Marçais A *et al.*, Leukemia, 2021