Mutations in SWI/SNF subunits have context-specific prognostic effects in driver subsets of NSCLC

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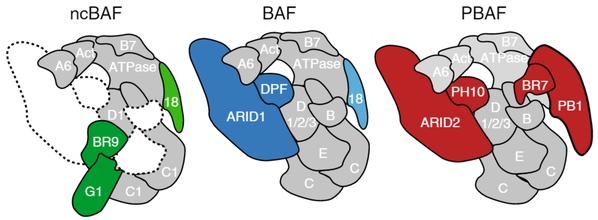
BACKGROUND AND HYPOTHESIS

The Switch/Sucrose-Nonfermentable (SWI/SNF) complex remodels chromatin to modify gene expression

- There are multiple SWI/SNF complexes in cells who play a role in regulating gene expression, chromatin structure, DNA repair, and more
- ncBAF, BAF, and pBAF have different DNA binding and modifying domains. Each contains a central ATPase (SMARCA4 or SMARCA2).



C: SMARCC1/C2
B7: BCL7A/B/C
PH10: PHF10
ARID1: ARID1A/B

G1: GLTSCR1/1L
D: SMARCD1/D2/D3
A6: ACTL6A
BR7: BRD7

DPF: DPF1/2/3
BR9: BRD9
B: SMARCB1
Act: B-actin

PB1: PBRM1
18: SS18/L1
E: SMARCE1
ATPase: SMARCA2/4

Mutations in SWI/SNF complex subunits are common in non-small cell lung cancer (NSCLC)

- After known oncogenic drivers (KRAS, EGFR, etc) and well-studied tumor suppressors (TP53, STK11, KEAP1), SWI/SNF complex genes are among the most commonly mutated in NSCLC
- Despite this, the oncogenic function of these mutations remains poorly understood
- There may be specific vulnerabilities associated with some SWI/SNF mutations, but utilizing these will require a detailed understanding of different mutational contexts

Prior attempts to understand the prognostic roles of SWI/SNF mutations has led to conflicting results in different datasets

- In some published datasets[2], some SWI/SNF mutations are associated with immunotherapy sensitivity; in others, immunotherapy resistance[3,4]

Therefore, we sought to comprehensively understand the prevalence and prognostic effects of all evaluable SWI/SNF mutations in a large cohort, both independently and in association with different classical NSCLC drivers

- We wanted to understand the distribution of mutations across different SWI/SNF subunits; the relationship to other markers of poor prognosis in NSCLC; the interactions with different classical driver oncogenes; the relationship with traditional markers of response to immunotherapy, and more

METHODS

- 42,329 NSCLC tumor specimens were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-gene or whole-exome sequencing).
- Based on the observed frequency of likely pathogenic/pathogenic (LP/P) mts, the four most commonly-altered SWI/SNF subunits – ARID1A (8.29%), SMARCA4 (6.29%), ARID2 (3.05%) and PBRM1 (1.98%) – were further analyzed.
- We divided the cohort by driver mutation status, specifically LP/P mts in KRAS, EGFR, BRAF, ERBB2 or MET; METex14 skipping; ERBB2 amplification, LP/P fusions in ALK (including IHC overexpression), RET, ROS1, NTRK (1-3) & NRG1.Driver- tumors were devoid of mts/amplifications/fusions in all genes mentioned above.
- Kaplan-Meier analysis was performed on real world survival data obtained from insurance claims.
- Statistical significance was determined using chi-square and Mann-Whitney U test adjusted for multiple comparisons (q<0.05).

RESULTS

Table 1: Frequency of overall and LP/P mutations among SWI/SNF genes

SWI/SNF Genes	Any Mutation (% Prevalence)	Pathogenic/ Likely Pathogenic Mutations (% Prevalence)
ARID1A (n=30550)	**17.03**	**8.30**
SMARCA4 (n=41956)	**12.08**	**6.29**
ARID1B (n=23814)	11.18	0.00
ARID2 (n=41208)	**8.53**	**3.05**
PBRM1 (n=41717)	**5.67**	**1.98**
SS18 (n=33892)	1.78	0.00
SS18L1 (n=18335)	1.65	0.00
SMARCE1 (n=35469)	1.25	0.23
SMARCB1 (n=42245)	0.90	0.22
BCL7A (n=18294)	0.75	0.00

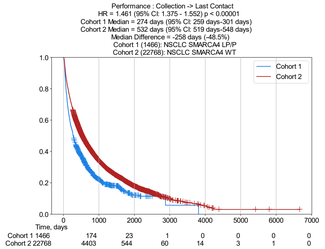
Fig 2: Co-mutational landscape of SWI/SNF mutations in NSCLC

LP/P mutations in ARID1A, SMARCA4, ARID2 and PBRM1 were among the most prevalent (Table 1). LP/P mutations in SWI/SNF genes were mutually exclusive for a vast majority of NSCLC tumors (Fig 2)

RESULTS

Fig 3: Prognostic role of SMARCA4 & PBRM1 mutations in NSCLC

SMARCA4 MT vs WT



PBRM1 MT vs WT

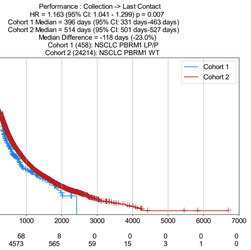


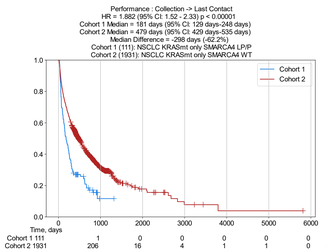
Table 2: Prevalence of Driver alterations in SMARCA4 MT vs WT NSCLC

Driver Alterations	SMARCA4 MT (% Prevalence)	SMARCA4 WT (% Prevalence)
mt-KRAS	29.35	30.89
mt-BRAF	2.98	4.48
mt-EGFR	1.8	14.47
cna-ERBB2	1.6	1.04
mt-ERBB2	0.97	1.75
fus-RET	0.76	0.88
mt-MET	0.56	2.8
METex14skip+	0.49	2.91
oe-ALK	0.21	2.8
fus-ROS1	0.21	0.67
fus-ALK	0.14	2.51
fus-NRG1	0.07	0.25
fus-NTRK1	0	0.05
fus-NTRK2	0	0.02
fus-NTRK3	0	0.03
Driver-	63.36	42.4

Of all SWI/SNF genes, only SMARCA4 (HR=1.46) and PBRM1(HR=1.16) LP/P mutations were associated with worse survival (Fig 3). While KRAS is the predominant driver in both SMARCA4 MT and WT tumors, alterations in EGFR constitute a significant proportion of driver altered SMARCA4 WT tumors (Table 2)

Fig 4: Prognostic role of SMARCA4 in KRAS driven and Driver- NSCLC

KRASmt SMARCA4 MT vs WT



Driver- SMARCA4 MT vs WT

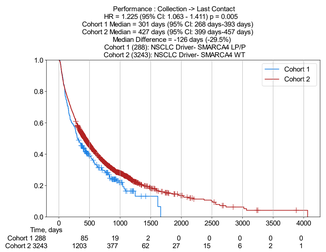
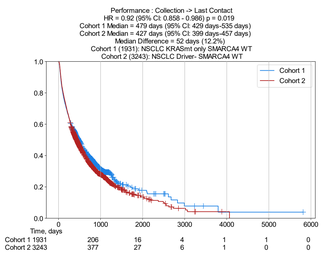
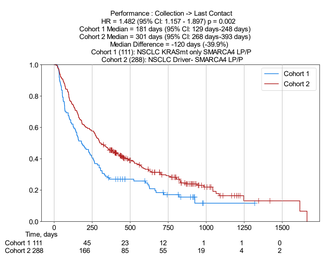


Fig 5: Prognostic cooperation of SMARCA4 and KRAS mutations in NSCLC

SMARCA4 WT KRASmt vs Driver-



SMARCA4 MT KRASmt vs Driver-



SMARCA4 mutations were prognostic in KRASmt driven as well as in Driver- NSCLC. The prognostic role of SMARCA4 mutations remained even after accounting for KEAP1 and STK11 mutations in the Driver- cohort (Fig 4). When comparing KRASmt vs Driver- tumors. KRASmt tumors have a favorable prognosis in the SMARCA4 WT cohort and a worse prognosis in the SMARCA4 MT cohort (Fig 5).

CONCLUSIONS

- In this largest-ever retrospective cohort of NSCLC patients with SWI/SNF mutations, SMARCA4 mutation and to a lesser extent PBRM1 mutation are the only SWI/SNF alterations associated with worse survival.
- SMARCA4 mutation is overrepresented in KRASmut NSCLC and in NSCLC without a known classical strong driver (such as EGFR mutation, ALK fusion)
- SMARCA4 mutation is associated with particularly short survival in KRASmt tumors indicating a potential cooperation of KRASmt and SMARCA4mt to drive poor prognosis in NSCLC.
- These effects are robust to control for KEAP1, and STK11 status.
- The cooperativity with KRAS may explain why different datasets have shown varying effects and in particular differing effects of immunotherapy in SMARCA4 mutant NSCLC

References

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