DISTINCT SECONDARY MUTATIONAL LANDSCAPES ARE ASSOCIATED WITH *NAB2–STAT6* FUSION BREAKPOINTS IN SOLITARY FIBROUS TUMORS

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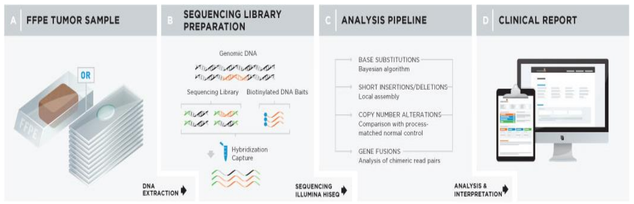
BACKGROUND

- Solitary fibrous tumor (SFT) is a mesenchymal neoplasm driven by a *NAB2-STAT6* fusion and exhibits variable clinical behavior.
- Emerging evidence suggests that specific fusion breakpoints carry prognostic significance.
- The *NAB2* exon 6-*STAT6* exon 16 (ex6-ex16) fusion is linked to younger age, aggressive behavior, and extrapulmonary location, while *NAB2* exon 4-*STAT6* exon 2 (ex4-ex2) is associated with older age, indolent course, and pulmonary origin.
- However, fusion-specific patterns of secondary genomic alterations remain largely unexplored.

DESIGN

- We sought to assess the genomics of a cohort of SFTs, to identify if there are any distinct co-occurring genomic alterations based on fusion breakpoints.
- FFPE tissue from 471 clinically advanced SFT patient tumors underwent comprehensive genomic profiling by a next-generation sequencing based in vitro diagnostic test (clinical trial assay based on FoundationOne®Heme) to evaluate all classes of genomic alterations (GAs) and tumor mutational burden (TMB, mutations/Mb).
- Overall, 54% were male and median age was 62 years.



RESULTS

- Seven distinct *NAB2-STAT6* exon fusion configurations were identified in over 10 patients each (Table 1). The most prevalent was *NAB2* exon 6-*STAT6* exon 16 (ex6-ex16; n = 202), followed by ex4-ex2 (n = 56) and ex7-ex2 (n = 37).
- Patients with ex6-ex16 fusion were significantly younger (median age 55 years) compared to those with ex4-ex2 (66 years, p = 5.3×10^{-9}) or ex7-ex2 (67 years, *p* = 7.6×10^{-8}).
- Compared to the ex6-ex16 fusion, both ex4-ex2 and ex7-ex2 fusion variants were more commonly associated with lung primaries.
- Ex4-ex2 cases demonstrated a higher frequency of *TP53* mutations (46% vs. 24%, *p* = 0.0014), whereas ex7-ex2 cases were enriched for *CDKN2A/CDKN2B* homozygous loss (19% vs. 2%, *p* = 0.0001) (Tables 2, 3).

		***NAB2-STAT6* exon breakpoints**						
	All cases	**Ex6-Ex16**	**Ex4-Ex2**	**Ex7-Ex2**	**Ex6-Ex17**	**Ex4-Ex1**	**Ex7-Ex1**	**Ex5-Ex16**
Number of patients	471	202	56	37	28	16	14	13
Median age (range), years	62 (13-89)	55 (13-89)	66 (41-89)	67 (41-86)	61 (31-86)	67 (55-89)	71 (32-84)	53 (15-81)
% male (n)	54% (252)	54% (108)	59% (33)	59.5% (22)	50% (14)	31% (5)	57% (8)	46% (6)
% lung SFT		5% (9)	21% (12)	29.7% (11)	3.6% (1)	44% (7)	36% (5)	0
Median TMB (Q1-Q3)	1.6 (0.8-2.4)	0.8 (0.8-1.6)	1.6 (0.8-3.2)	2.0 (0.8-3.2)	1.6 (0.8-2.4)	2.0 (1.6-2.4)	1.2 (0.8-2.4)	1.2 (0.8-2.4)
TP53	28.7%	23.8%	46.4%	27.0%	17.9%	31.3%	14.3%	15.4%
RB1	7.9%	4.0%	10.7%	16.2%	14.3%	18.8%	0.0%	7.7%
***CDKN2A/B* loss**	5.5%	1.0%	8.9%	18.9%	0.0%	6.3%	7.1%	0.0%

Table 1. Comparative demographics and percent frequency of genomic alterations stratified by *NAB2-STAT6* exon breakpoint. Displayed are data for specific exon breakpoints affecting more than 10 patients. Exon breakpoints are based on *NAB2* NM_005967 and *STAT6* NM_003153 transcript variants. Abbreviations: Ex, exon; TMB, tumor mutational burden.

	All cases	**Ex6-Ex16**	**Ex4-Ex2**	***p* value**
Number of patients	471	202	56	
Median age (range), years	62 (13-89)	55 (13-89)	66 (41-89)	**5.25E-09**
% male (n)	54% (252)	54% (108)	59% (33)	0.55
Median TMB (Q1-Q3), mut/Mb	1.6 (0.8-2.4)	0.8 (0.8-1.6)	1.6 (0.8-3.2)	0.79
TP53	28.7%	23.8%	46.4%	**0.0014**
RB1	7.9%	4.0%	10.7%	0.0866
***CDKN2A/B* loss**	5.5%	1.0%	8.9%	**0.0057**

Table 2. Comparative demographics and percent frequency of genomic alterations stratified by common *NAB2-STAT6* ex6-ex16 and ex4-ex2 breakpoints. The Bonferroni correction for six simultaneous comparisons was applied; significant *P* values (<0.008) are in bold.

	All cases	**Ex6-Ex16**	**Ex7-Ex2**	***p* value**
Number of patients	471	202	37	
Median age (range), years	62 (13-89)	55 (13-89)	67 (41-86)	**7.56E-08**
% male (n)	54% (252)	54% (108)	59.5% (22)	0.59
Median TMB (Q1-Q3), mut/Mb	1.6 (0.8-2.4)	0.8 (0.8-1.6)	2.0 (0.8-3.2)	0.022
TP53	28.7%	23.8%	27.0%	0.68
RB1	7.9%	4.0%	16.2%	0.011
***CDKN2A/B* loss**	5.5%	1.0%	18.9%	**<0.0001**

Table 3. Comparative demographics and percent frequency of genomic alterations stratified by common *NAB2-STAT6* ex6-ex16 and ex7-ex2 breakpoints. The Bonferroni correction for six simultaneous comparisons was applied; significant *P* values (<0.008) are in bold.

RESULTS

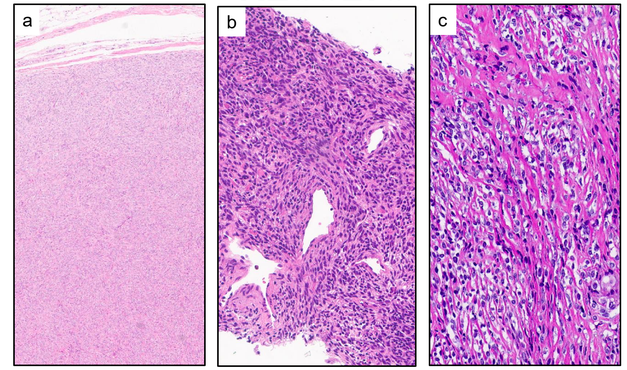


Figure 1. Characteristic histopathological features of a Solitary Fibrous Tumor (SFT). (A) Low-power view showing a well-circumscribed patternless spindle cell proliferation set in a collagen-rich stroma (H&E, ×40x). (B) Higher magnification revealing bland spindle cells with oval nuclei and indistinct cytoplasm arranged around branching, thin-walled, "staghorn"-type vessels (H&E, ×200). (C) Area showing dense, keloid-like collagen deposition and focal hyalinization, typical of SFT (H&E, ×100).

CONCLUSIONS

- SFTs demonstrate distinct molecular profiles based on *NAB2-STAT6* fusion breakpoints.
- Specifically, ex4-ex2 cases are enriched for *TP53* mutations, while ex7-ex2 cases show a higher frequency of *CDKN2A/B* alterations.
- The ex6-ex16 fusion is associated with younger patient age and extrapulmonary tumor location, consistent with prior reports.
- These findings suggest that fusion subtype and genomic profiling may inform diagnosis, prognosis, and potentially treatment frameworks.

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ACKNOWLEDGMENTS

This work was made possible by the Horowitz Solitary Fibrous Tumor Initiative Fund.