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Gamma secretase inhibitors and desmoid fibromatosis: Lessons from a real world, comprehensive genomic study

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Background

- Recently, first-in-class FDA approval was granted in the U.S. for use of the gamma secretase inhibitor (GSI), nirogacestat, for adults with progressive desmoid fibromatosis (DES)[1].
- The unpredictable clinical behavior of desmoids, which ranges from local aggression to regression[2], raises consideration of whether diagnostic and molecular variability underlie their varying biological potential.
- With an aim to understand both, and to explore the potential for biomarkers for GSI therapy selection, prediction, and prognosis, we performed a retrospective review of comprehensive genomic profiling and histology of desmoids and other soft tissue tumors (STT) harboring *CTNNB1* or *APC* mutations.

Methods

- We queried the real-world Caris Life Sciences reference laboratory database of tumors submitted for clinical sequencing[3], for samples with a diagnosis of desmoid tumor, or for any samples from soft tissue harboring *CTNNB1* or *APC* pathogenic or likely pathogenic variants.
- All samples had undergone NGS of DNA (592-panel or whole exome) to identify variants/copy number alterations and of RNA (whole transcriptome for expression and fusions).
- Findings were correlated with available clinical data and whole slide images (WSIs) re-review.

Cohort Composition

- Total of 153 samples (77 DES, 76 STT*CTNNB1/APC*) were identified, 117 with WSIs for review (Figure 1).
- Final cohort of 82 DES tumors selected for study.
  - WSI re-review cohort of 66 DES tumors.
  - Additional 16 cases with prior Caris pathologist review.

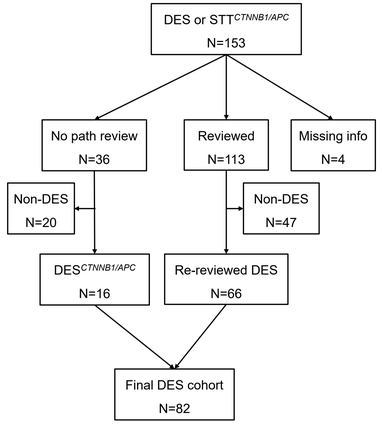


Figure 1. Overview of cohort selection process

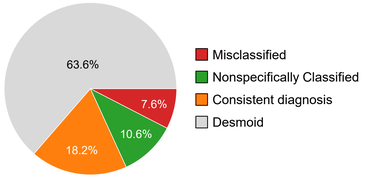
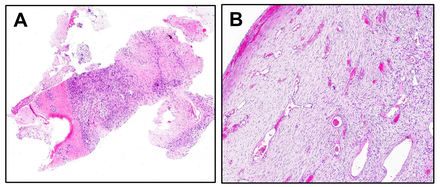


Figure 2. Desmoid reclassification assessment



A. Myositis ossificans harboring *COL1A1::USP6* rearrangement misclassified as a desmoid. **B.** *CTNNB1*-mutant desmoid tumor misclassified as a gastrointestinal stromal tumor (GIST).

Figure 3. Misclassification examples

	APC P/LP	*CTNNB1* S45F	*CTNNB1* S45P	*CTNNB1* T41A	p-value
Age					
Median age (range)	33 (14 - 61)	38 (16 - 70)	44 (32 - 68)	39 (14 - 82)	0.2842 K-W
Sex					
Female	73.3% (11/15)	76.2% (16/21)	100.0% (7/7)	74.3% (26/35)	0.5696 Fisher's Exact
Male	26.7% (4/15)	23.8% (5/21)	0.0% (0/7)	25.7% (9/35)	
Primary site					
Connective Tissue	80.0% (12/15)	85.7% (18/21)	57.1% (4/7)	68.6% (24/35)	
Abdomen	13.3% (2/15)	0.0% (0/21)	14.3% (1/7)	11.4% (4/35)	
Peritoneum/Retroperitoneum	0.0% (0/15)	4.8% (1/21)	0.0% (0/7)	8.6% (3/35)	
Jejunum	0.0% (0/15)	0.0% (0/21)	0.0% (0/7)	2.9% (1/35)	0.3714 Fisher's Exact
Lung	0.0% (0/15)	0.0% (0/21)	0.0% (0/7)	2.9% (1/35)	
Small Intestine, NOS	0.0% (0/15)	0.0% (0/21)	0.0% (0/7)	2.9% (1/35)	
Head and Neck	0.0% (0/15)	0.0% (0/21)	0.0% (0/7)	2.9% (1/35)	
Breast	6.7% (1/15)	9.5% (2/21)	14.3% (1/7)	0.0% (0/35)	
Chest/Chest Wall	0.0% (0/15)	0.0% (0/21)	14.3% (1/7)	0.0% (0/35)	
Primary pattern					
Classic	50.0% (5/10)	88.9% (16/18)	57.1% (4/7)	75.0% (21/28)	
Hypocellular	40.0% (4/10)	5.6% (1/18)	28.6% (2/7)	14.3% (4/28)	0.1993 Fisher's Exact
Keloidal	0.0% (0/10)	0.0% (0/18)	0.0% (0/7)	7.1% (2/28)	
Cellular	10.0% (1/10)	5.6% (1/18)	14.3% (1/7)	3.6% (1/28)	
Total	**15**	**21**	**7**	**35**	

Table 1. Cohort characteristics by variant group

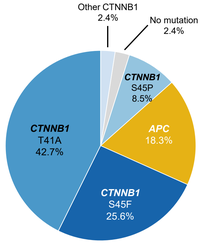


Figure 4. Desmoid *APC* and *CTNNB1* variants

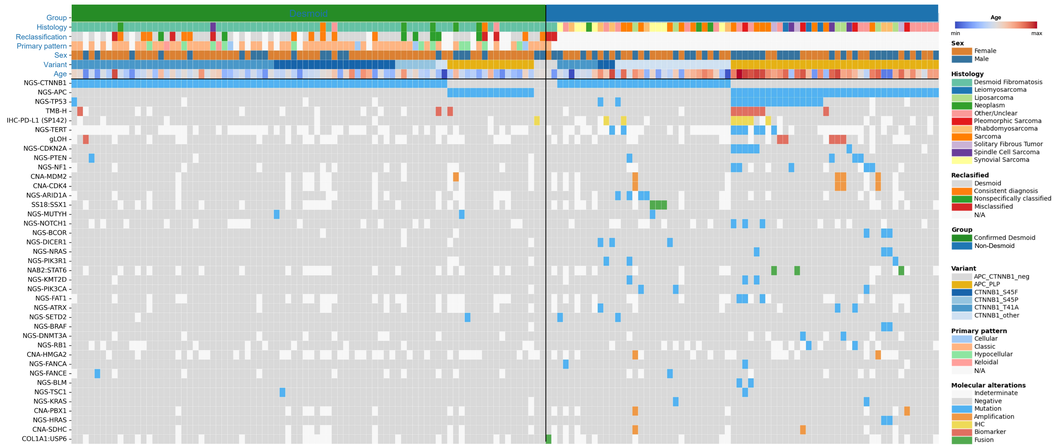


Figure 5. Mutational landscape of desmoids and *CTNNB1*/*APC*-mutated soft tissue tumors

Study highlights

- Among 66 desmoids with full re-review, ~8% had been classified as other entities, and ~11% had been diagnosed equivocally in submission reports (Figures 2-3).
- Final cohort (Table 1, n=82) was young (x̃=39y) and mostly female (~74%), with younger median age among *APC* cases (x̃=33y).
- *APC* variants were less prevalent than *CTNNB1* variants in desmoids (~18% versus ~79%) respectively, Figure 4.
  - 2 samples without mutations (1 *APC* VUS).
- Distinctly sparse desmoid genomic landscape, including 2 recurrent co-alterations: TMB-H (N=3) and *MUTYH* (N=2).
- *CTNNB1*/*APC* P/LP occur in diverse non-desmoid soft tissue entities, including synovial sarcoma, rhabdomyosarcoma, and liposarcoma (Figure 5).

Conclusions

- Correlation of genomics and histopathology may allow identification of other tumor types misclassified as desmoid fibromatosis. Conversely, genomic correlation facilitated recognition of a substantial number of desmoids among tumors submitted with other or equivocal diagnoses.
- The striking lack of secondary mutations seen in this large cohort with comprehensive sequencing implies that other mechanisms might explain their variable behavior, for which we are exploring paired transcriptome profiling data.
- Finally, subsets of diverse, other soft tissue neoplasms harbor *CTNNB1* or *APC* mutations, which may have implications for the design of future biomarker-selected Phase II basket trials.

References

1. Gounder et al. N Engl J Med. 2023
2. Gounder et al. N Engl J Med. 2018
3. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P240010