



Desmoid tumours

Chairs: Ionnis Bukovinas, Thessaloniki, Greece &
Franco Gherlinzoni, Udine, Italy

Can Molecular Biology Help?

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Faculty, Sarcoma Research Center

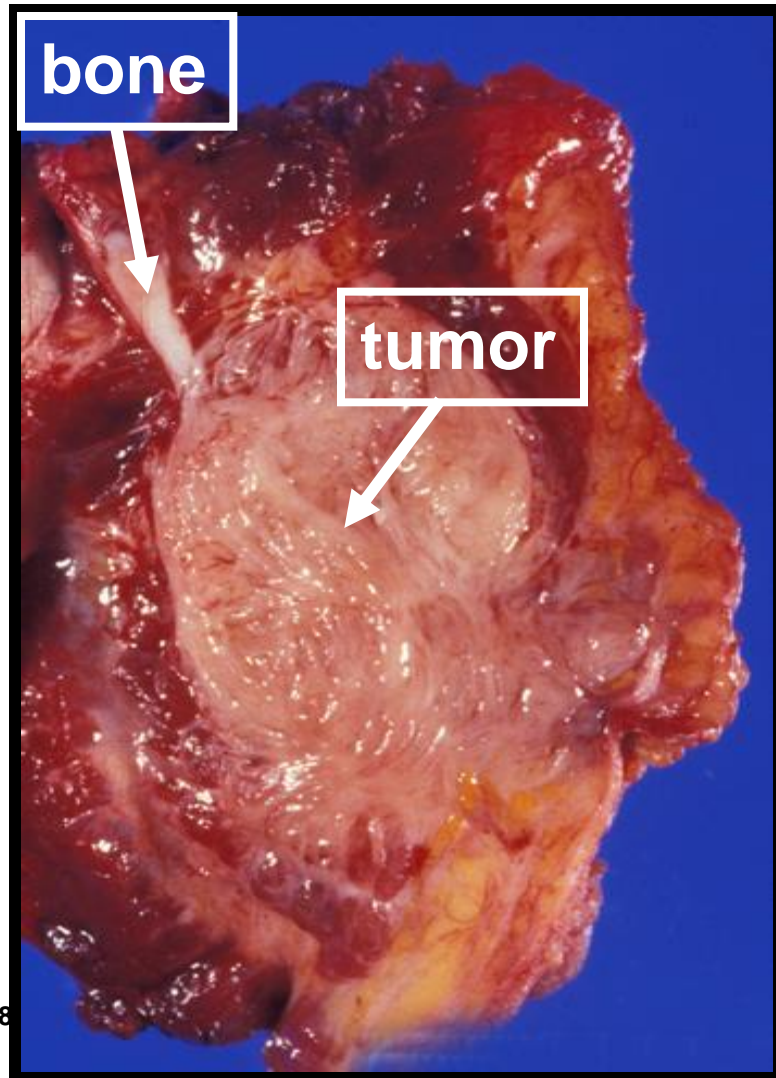
The University of Texas MD Anderson Cancer Center



Disclosure slide

- I do **not** have disclosures relevant to the topic(s) of this lecture.

Desmoid - Clinical Features

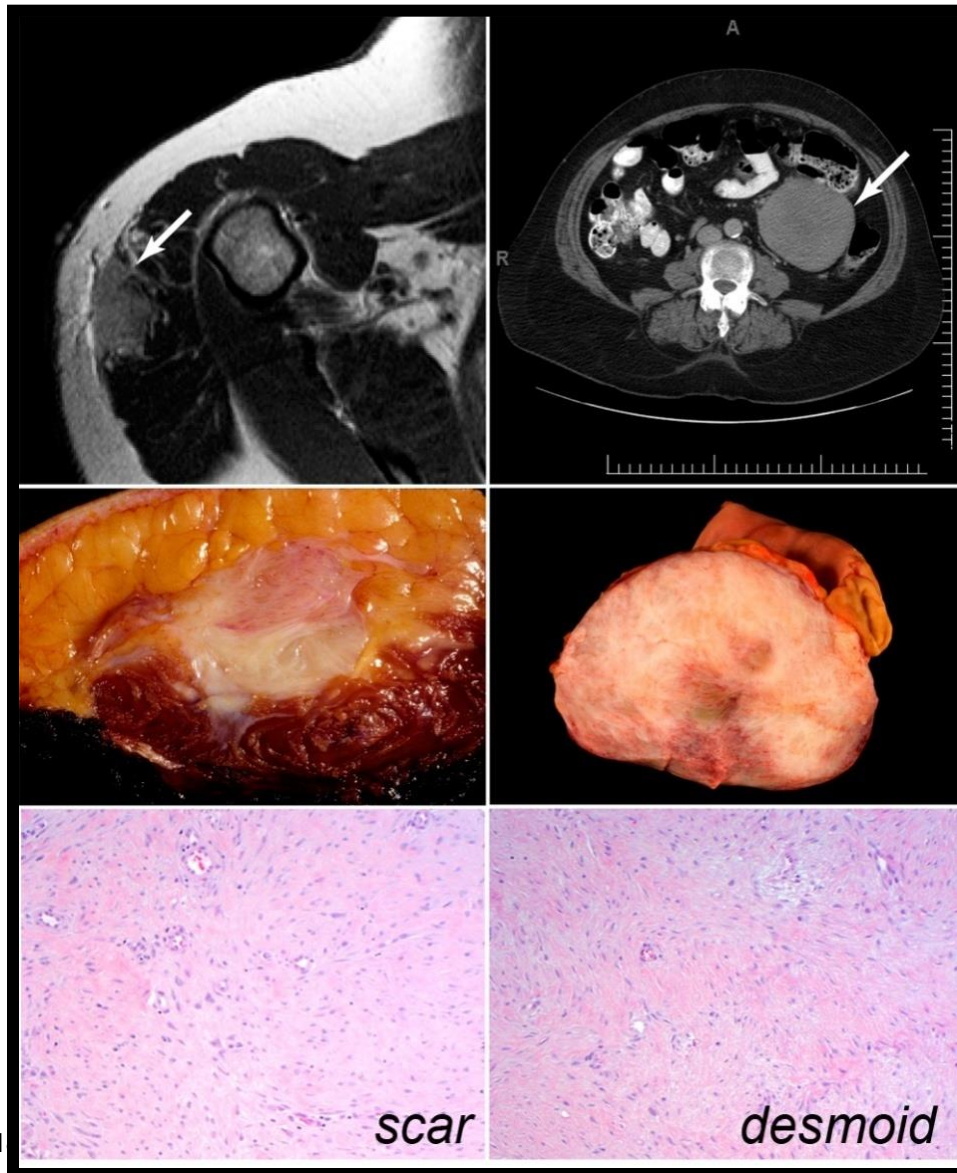


Low-grade
Locally infiltrative
Lack ability to metastasize
Local recurrence



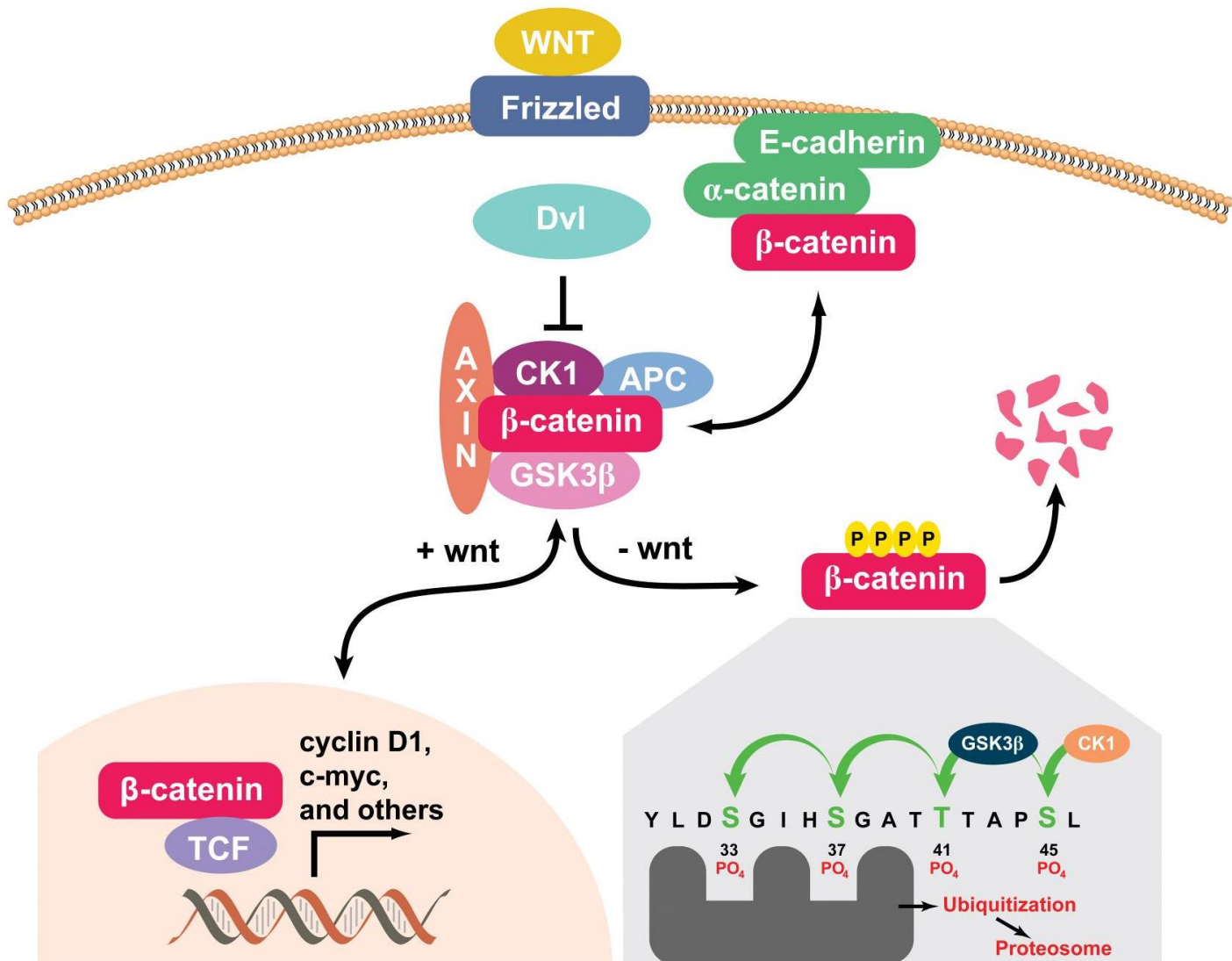
Epidemiology

- **Incidence ~2-4 / million / year**
 - 700 to 1,500 new cases per year
 - Prevalence is much higher
- **Mostly Sporadic**
 - Also, familial adenomatous polyposis (FAP) = Gardner Syndrome
- **Young Adults**
 - Females > Males



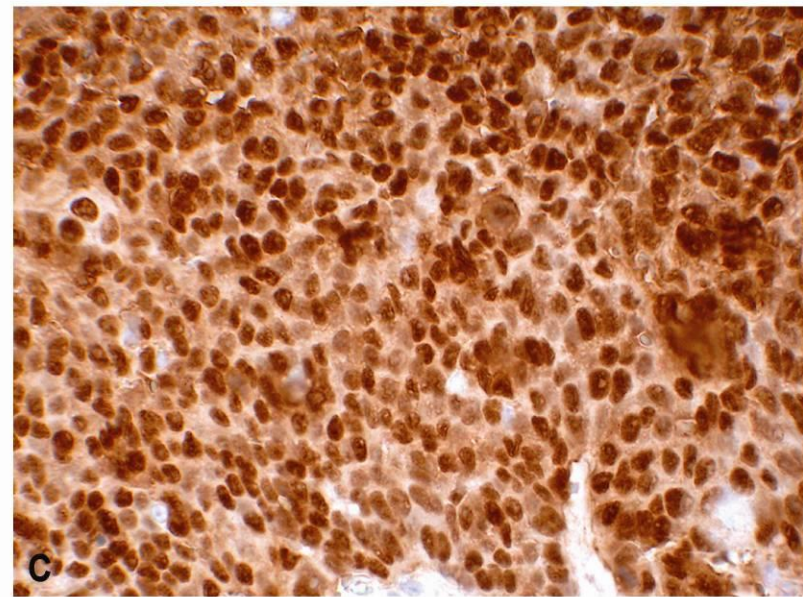
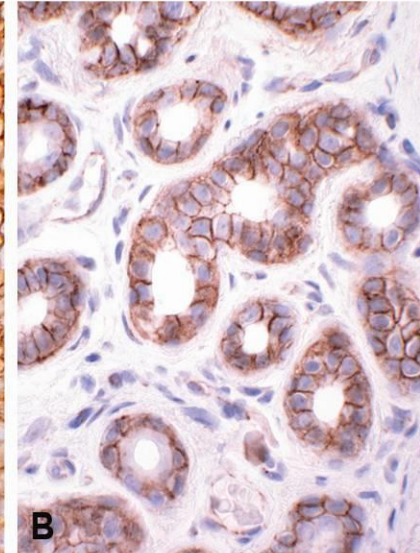
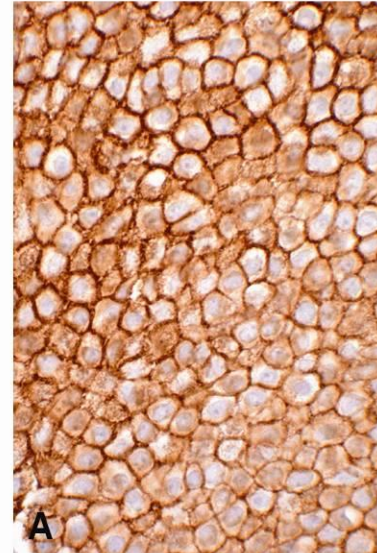
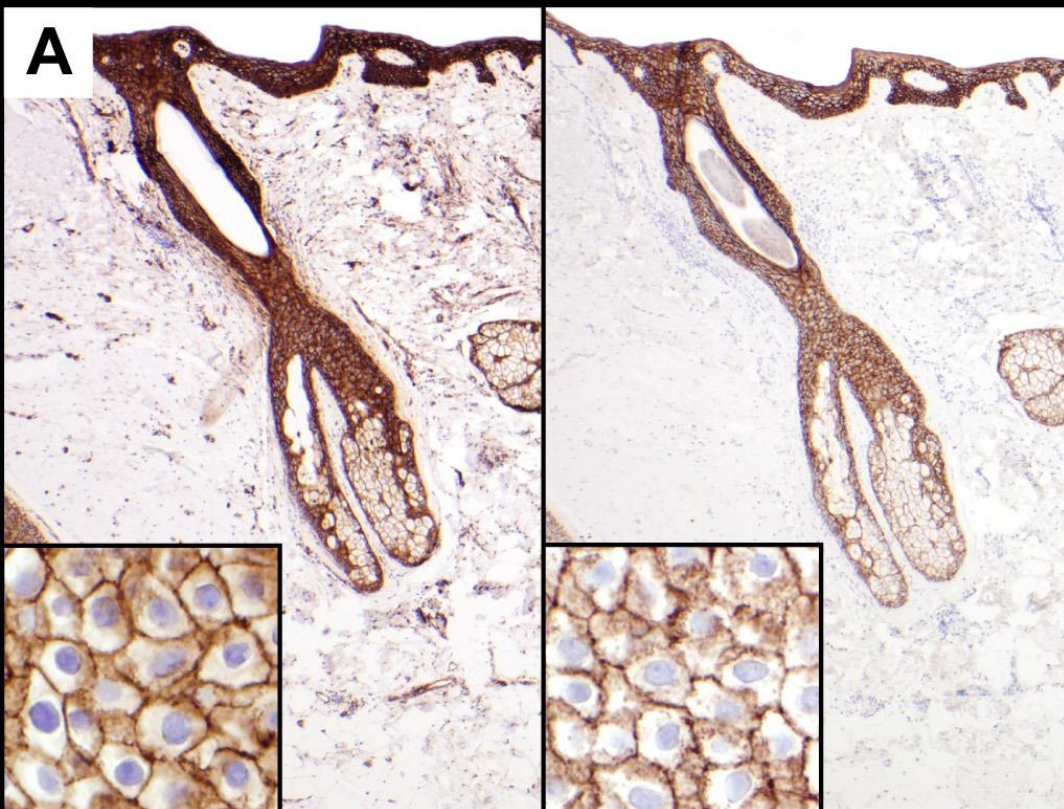
**Mesenchymal
fibroblastic/
myofibroblastic
proliferations**

**Cell of Origin:
UNKNOWN**

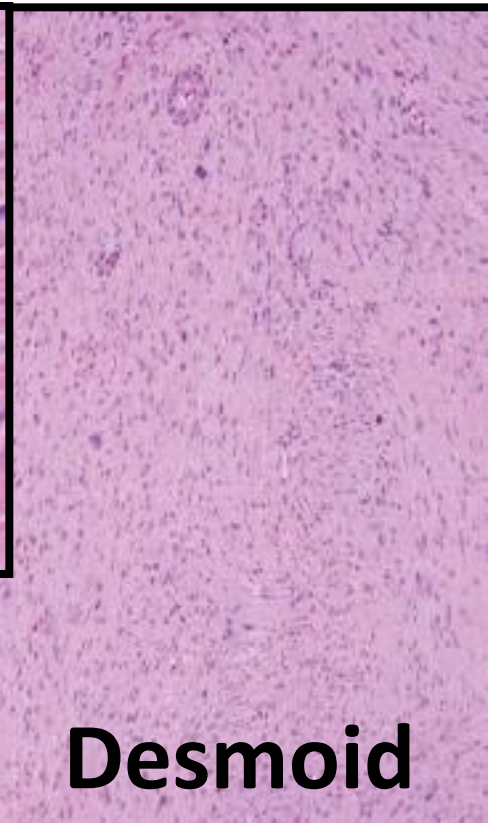
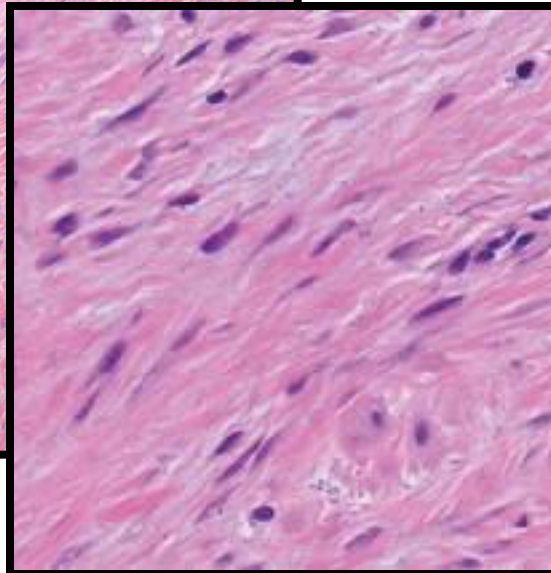
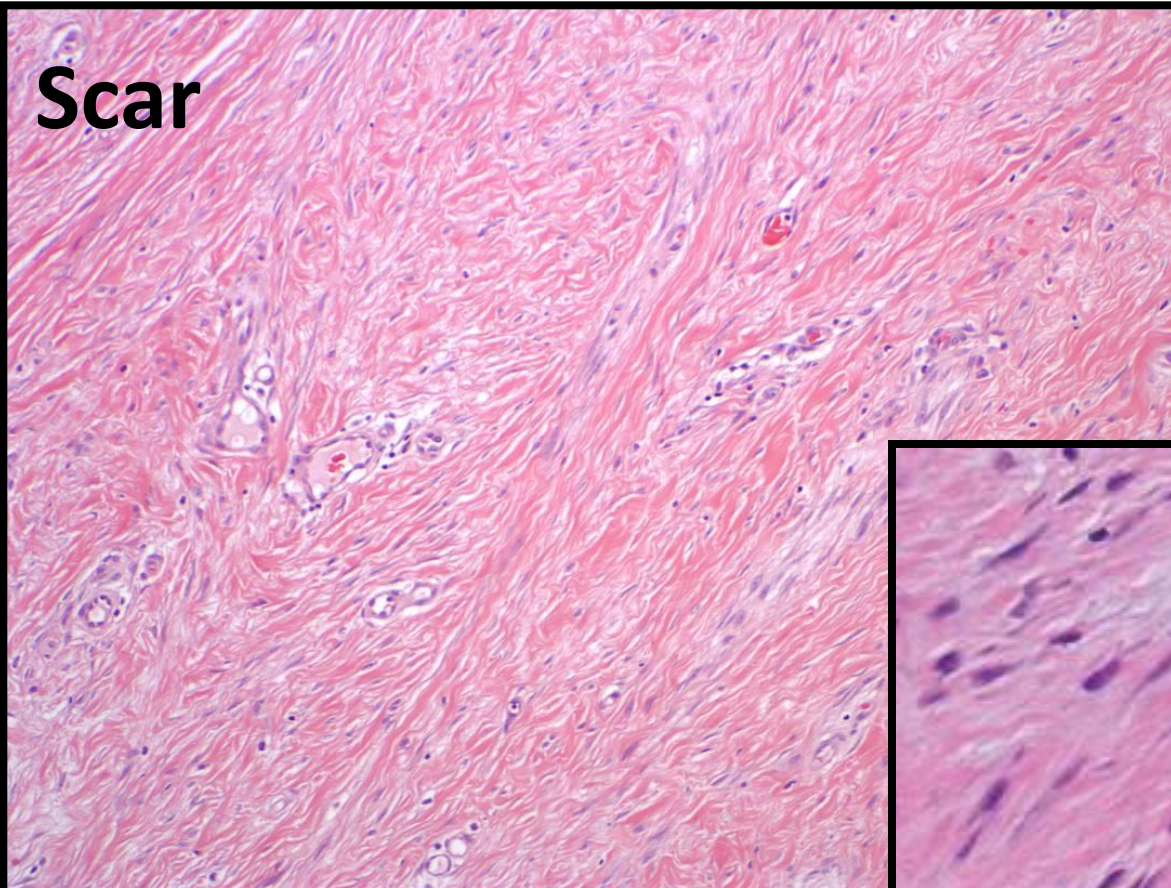


β -catenin

Adherens junctions:
E-cadherin to the actin-
based cytoskeleton

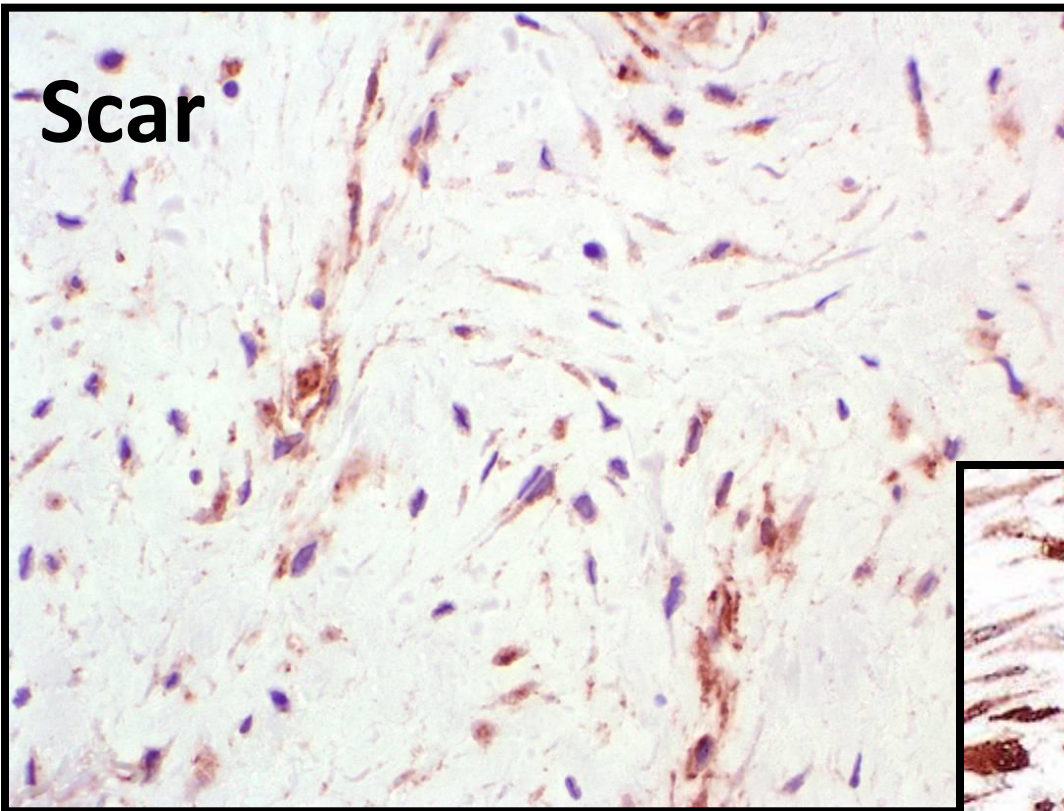


Scar



Desmoid

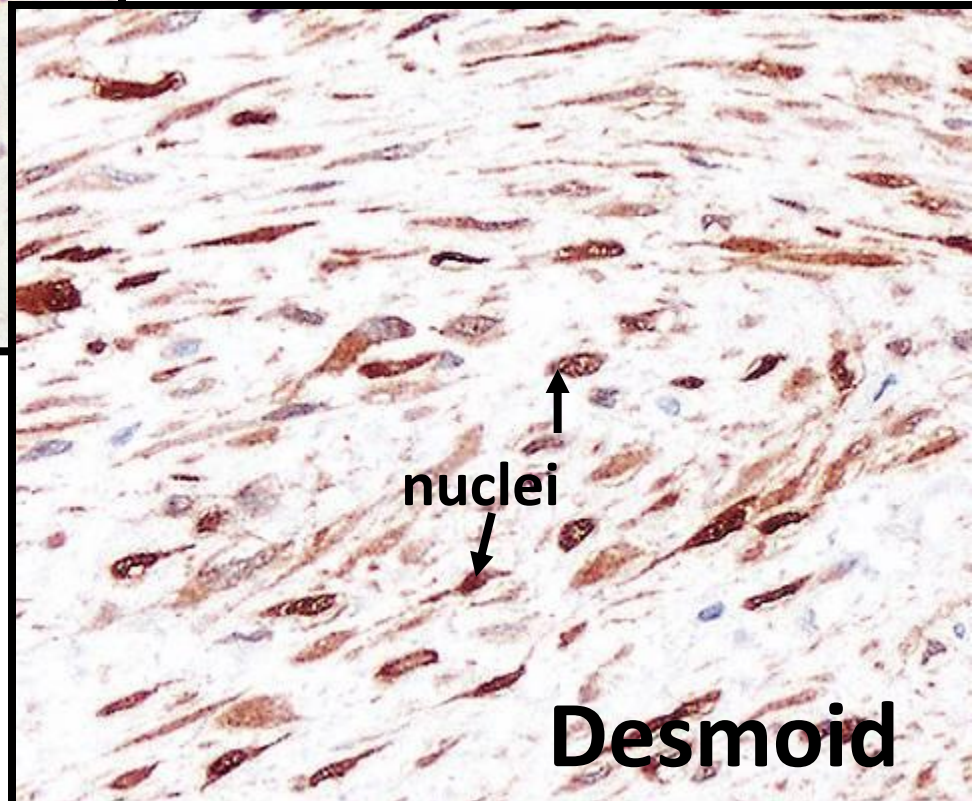
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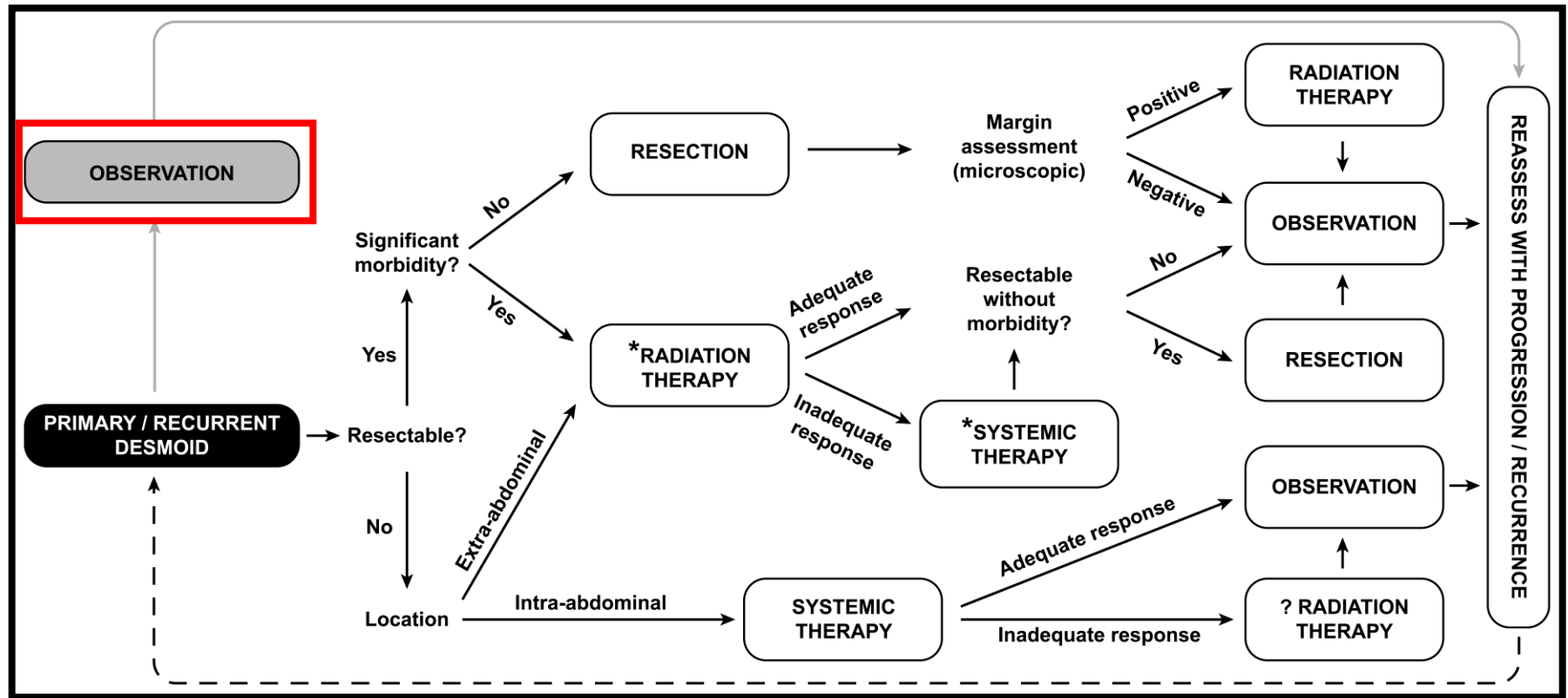


β -catenin
impoz

nuclei

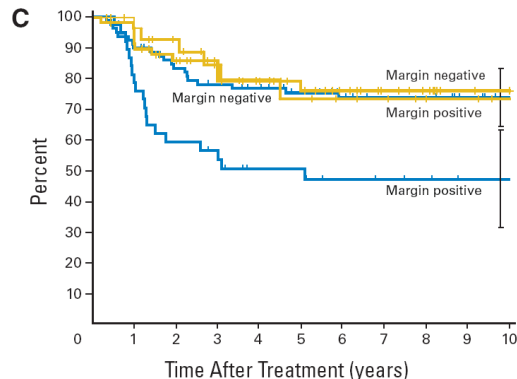
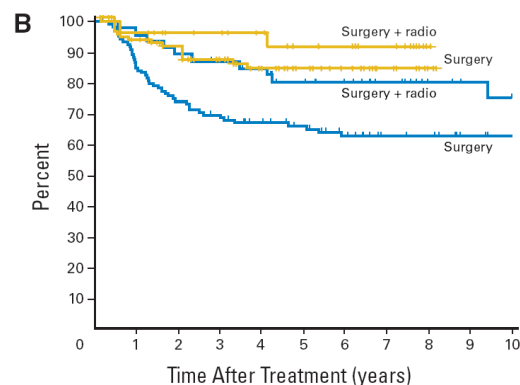
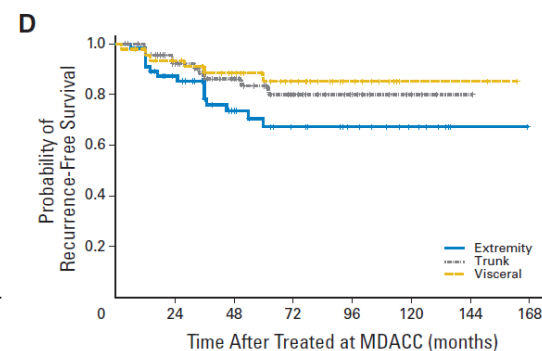
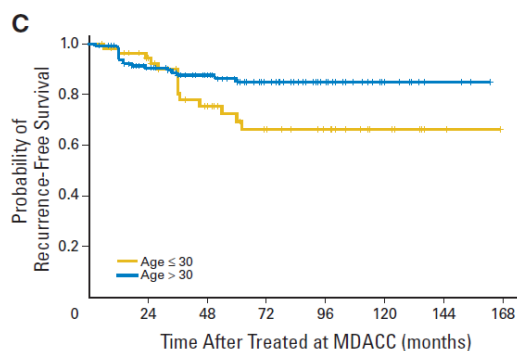
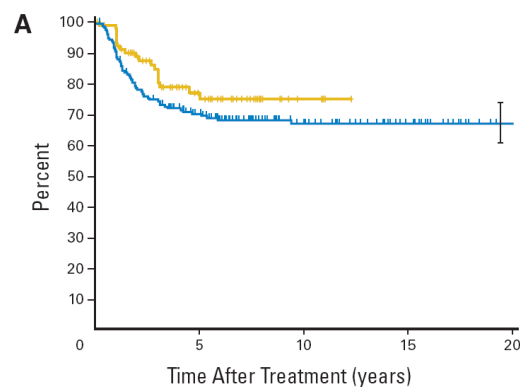
Desmoid





Optimizing Treatment of Desmoid Tumors

Dina Lev, Dhanasekaran Kotilingam, Caimiao Wei, Matthew T. Ballo, Gunar K. Zagars, Peter W.T. Pisters, Alexander A. Lazar, Shreyaskumar R. Patel, Robert S. Benjamin, and Raphael E. Pollock



Prognostic Factors Influencing Progression-Free Survival Determined From a Series of Sporadic Desmoid Tumors: A Wait-and-See Policy According to Tumor Presentation

Sébastien Salas, Armelle Dufresne, Binh Bui, Jean-Yves Blay, Philippe Terrier, Dominique Ranchere-Vince, Sylvie Bonvalot, Eberhard Stoeckle, Louis Guillou, Axel Le Cesne, Odile Oberlin, Véronique Brouste, and Jean-Michel Coindre

Table 4. Multivariate Progression-Free Survival Analysis

Variable	Crude HR	95% CI	P
Median age	1.97	1.36 to 2.84	< .001
Median size	1.64	1.13 to 2.36	.008
Tumor site			
Abdominal wall			
Intra-abdominal tumor	1.95	0.92 to 4.15	.084*
Extra-abdominal tumor	2.55	1.48 to 4.4	< .001

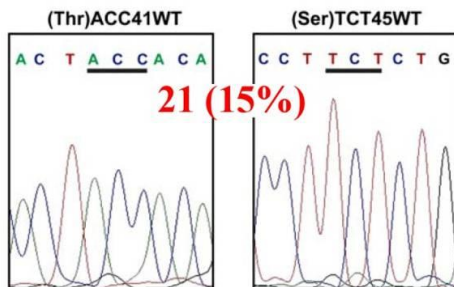
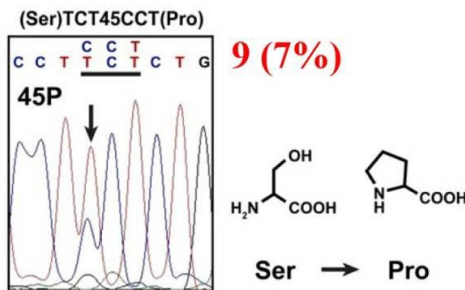
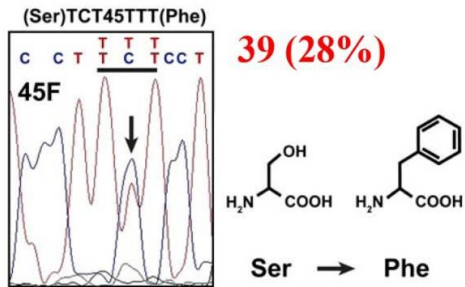
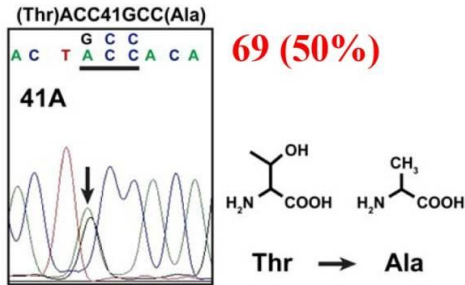
Abbreviation: HR, hazard ratio.

*Not significant.

CTNNB1 Mutations

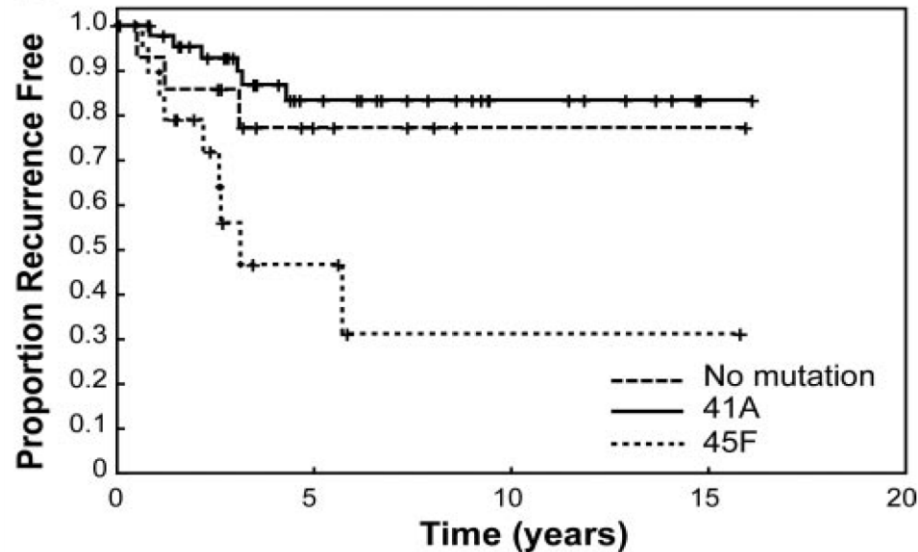
138 Patients

- 85% Mutated
- 15% WT

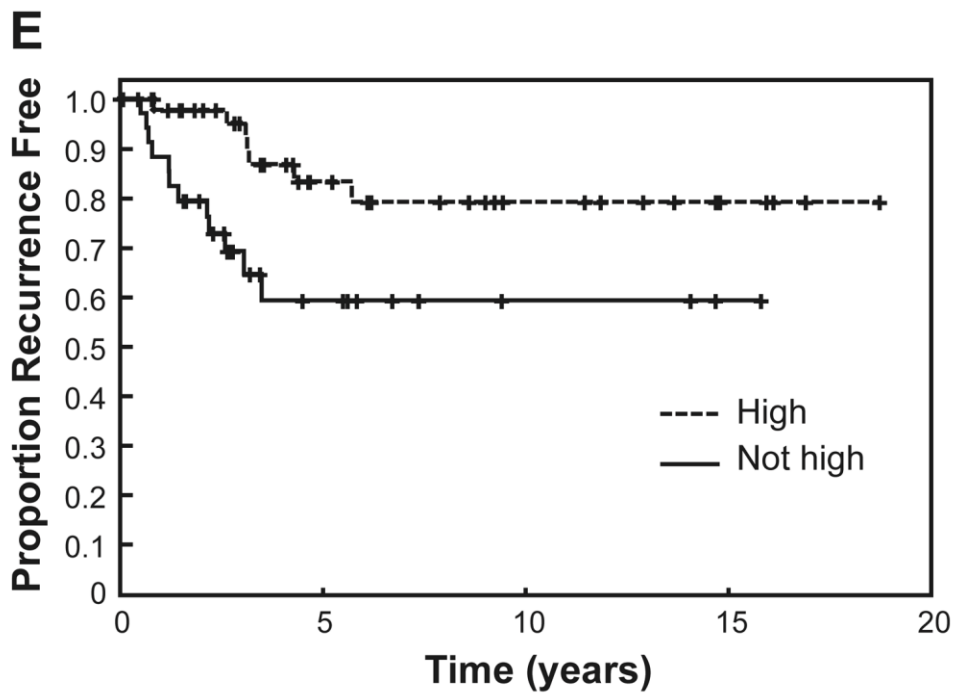
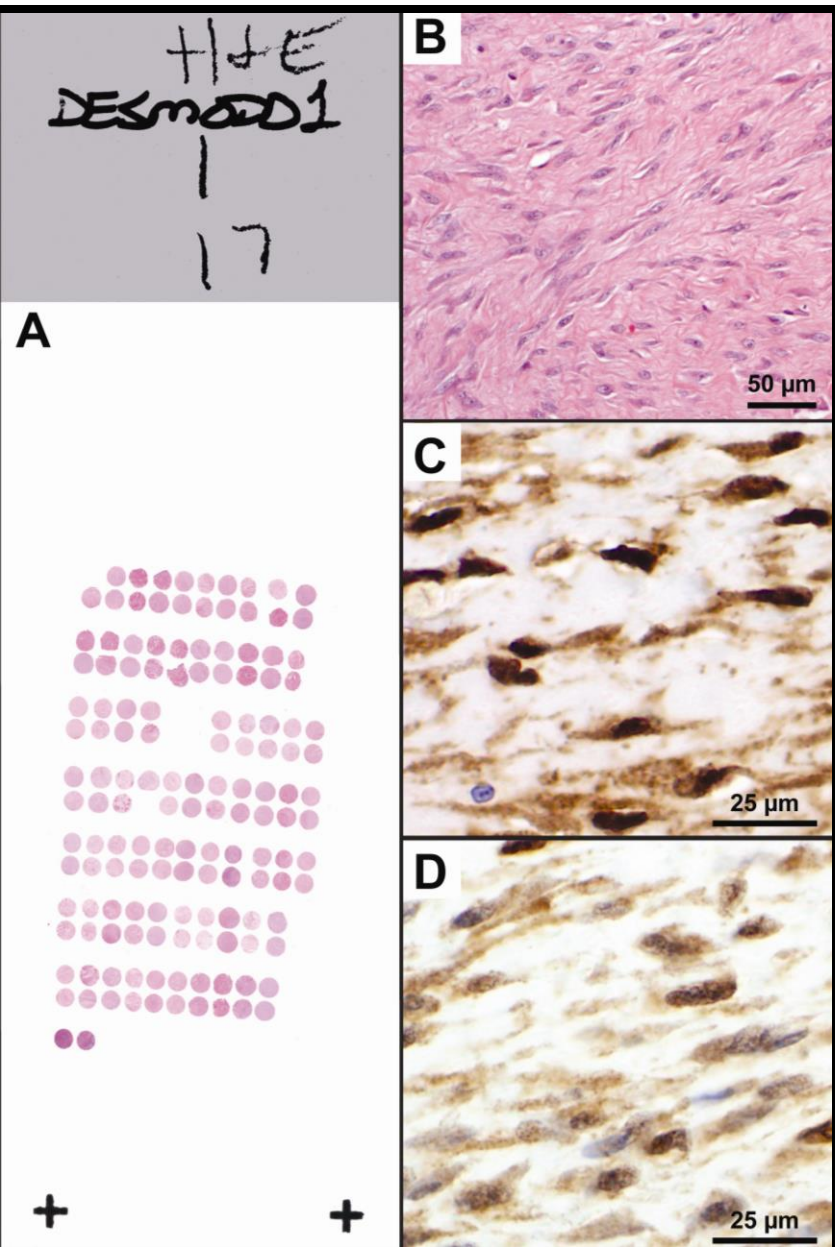


Specific Mutations in the β -Catenin Gene (*CTNNB1*) Correlate with Local Recurrence in Sporadic Desmoid Tumors

Alexander J.F. Lazar,^{*†} Daniel Tuvin,^{*‡}
Shohrae Hajibashi,^{*§} Sultan Habeeb,[¶]
Svetlana Bolshakov,^{*‡} Empar Mayordomo-Aranda,[¶]
Carla L. Warneke,^{||} Dolores Lopez-Terrada,[¶]
Raphael E. Pollock,^{*‡} and Dina Lev^{*§}



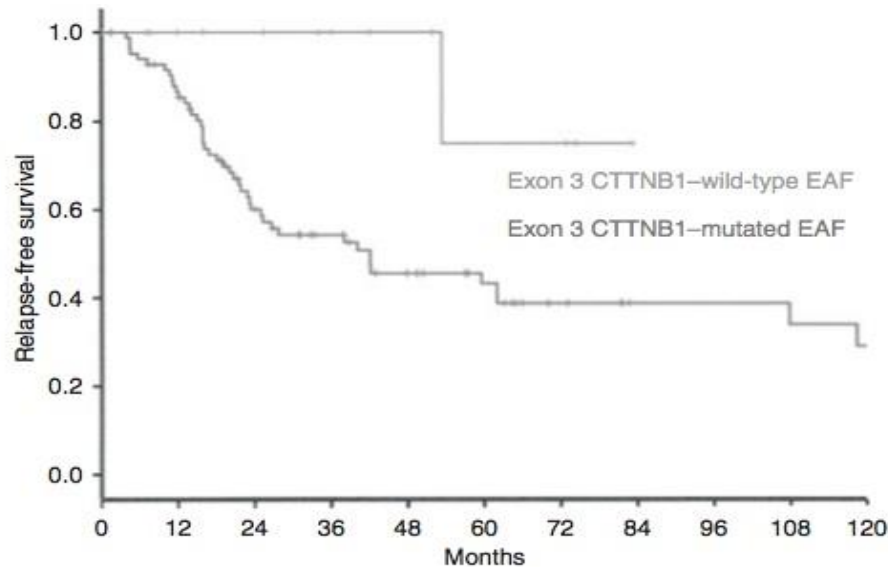
The American Journal of Pathology, Vol. 173, No. 5, November 2008
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DOI: 10.2353/ajpath.2008.080475



Lazar, et al: *Am J Pathol*, 2008.

High frequency of β -catenin heterozygous mutations in extra-abdominal fibromatosis: a potential molecular tool for disease management

J Dômont^{1,13}, S Salas^{2,13}, L Lacroix^{3,4}, V Brouste², P Saulnier³, P Terrier¹, D Ranchère⁵, A Neuville⁶, A Leroux⁷, L Guillou⁸, R Sciot⁹, F Collin¹⁰, A Dufresne⁵, J-Y Blay⁵, A Le Cesne¹, J-M Coindre^{*,2,11}, S Bonvalot^{*,1} and J Bénard^{*,1,4,12}

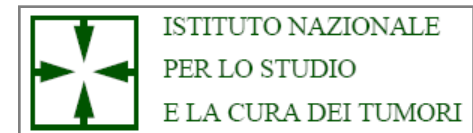


British Journal of Cancer (2010) 102, 1032–1036

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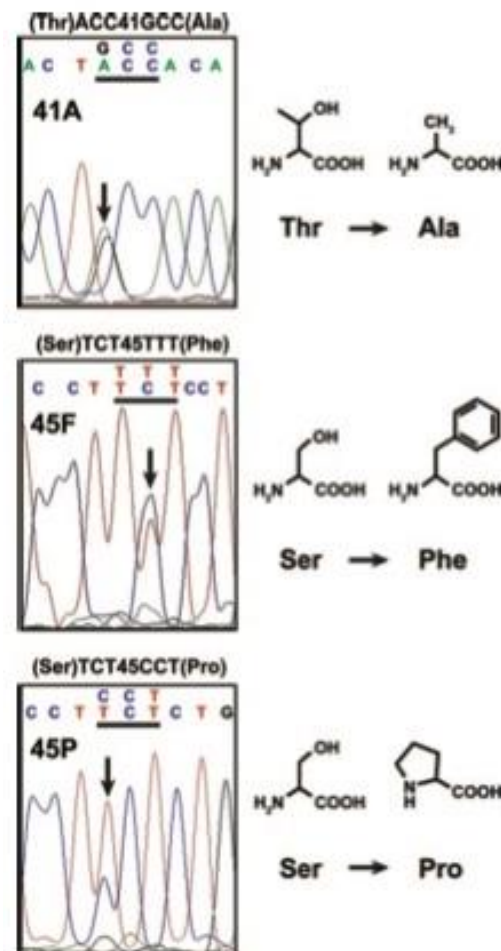
New Cohort: Patient characteristics

- >200 patients (April 1998-March 2010)
- Female predominance (65% F vs 35% M)
- Young patients (38y, 5-78)
- Site
 - Abdominal/chest wall 49%
 - Extremity 20%,
 - Head/neck 6%
 - Intra-abdominal 23%



Mutation in 69% of DTs

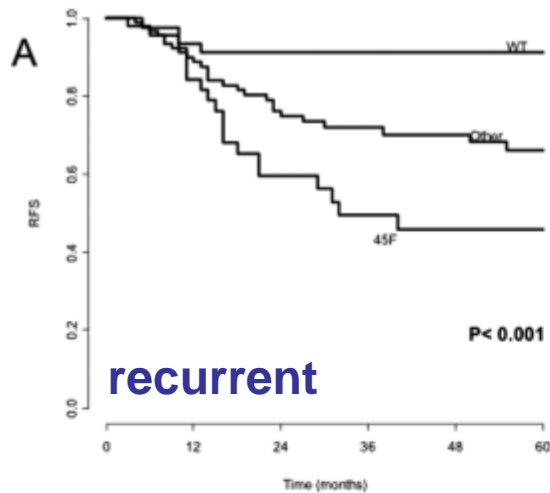
- 41A: 47%
- 45F: 16%
- 45P: 6%
- WT: 31%



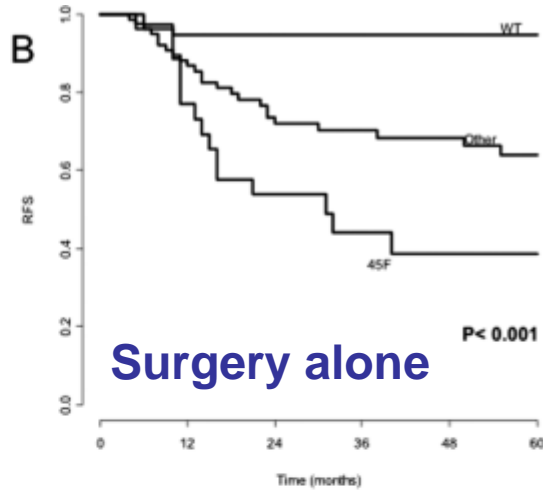
S45F mutation more prevalent in the extremity ($p= 0.013$)

Site					
	Abd/chest wall	Extremity	Head/neck	Intra-abdominal	Total
45F	12	7	1	0	20
	20%	29%	14%	0%	16%
WT	18	8	3	9	38
	30%	33%	43%	29%	31%
Others	30	9	3	22	64
	50%	38%	43%	71%	53%
Total	60	24	7	31	122
	100%	100%	100%	100%	100%

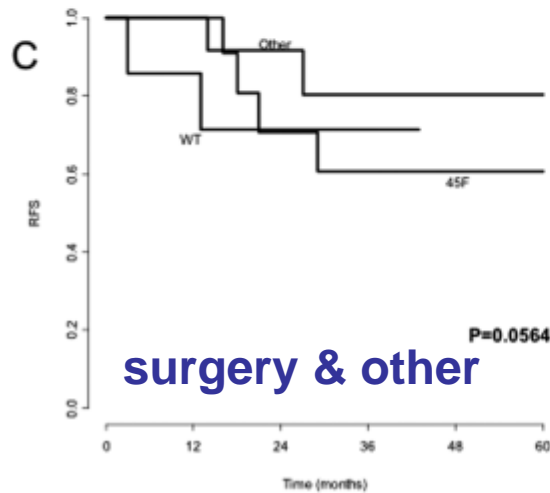
International Study



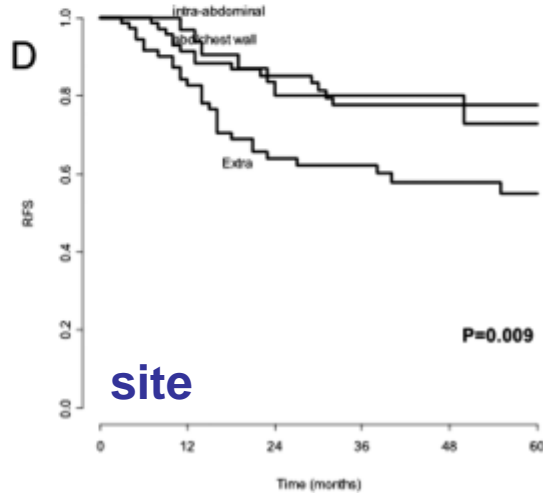
recurrent



Surgery alone



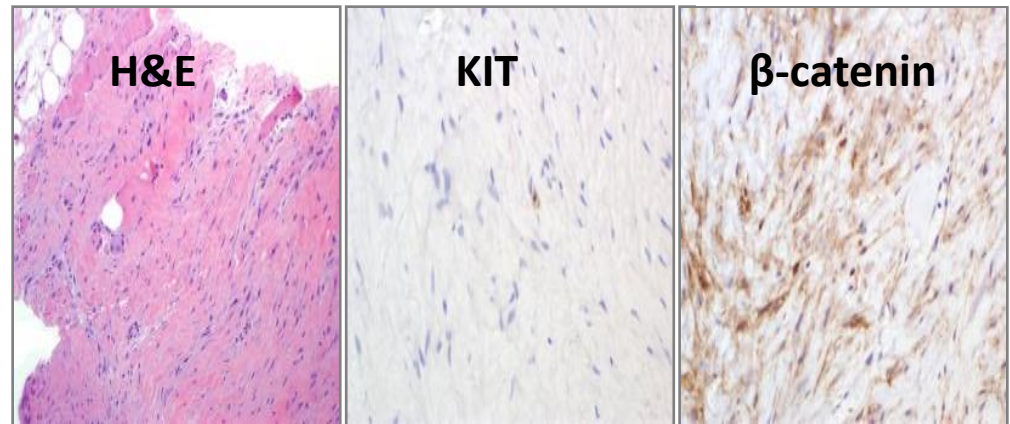
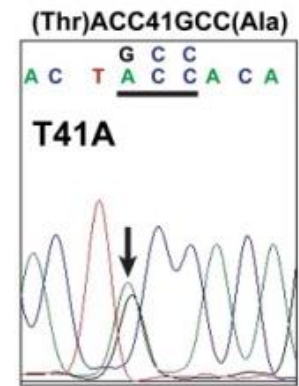
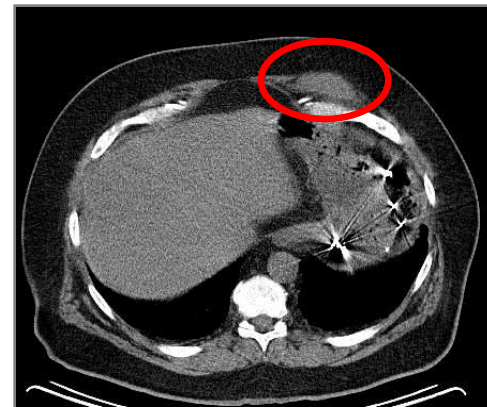
surgery & other



site

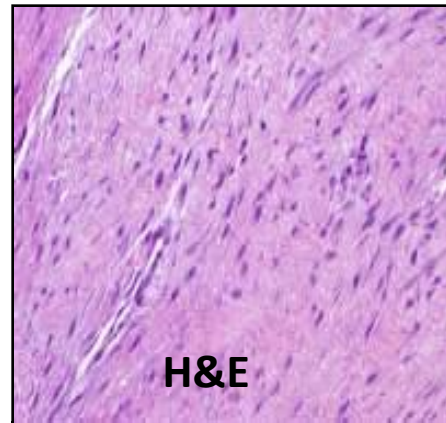
Clinical vignette (desmoid positive)

- ❑ Male, aged 66
- ❑ GIST (2005): laparoscopic partial gastrectomy
- ❑ CT (03/08): mass in abdominal wall scar
- ❑ Core needle biopsy

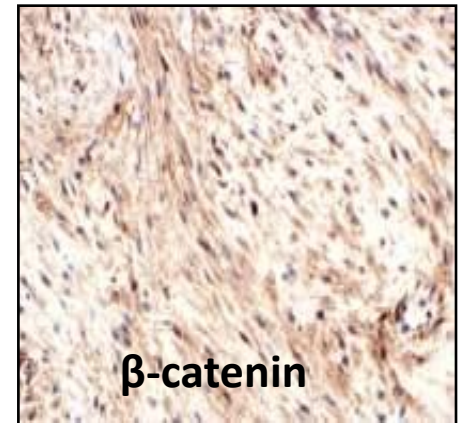


Clinical vignette #2 (desmoid positive)

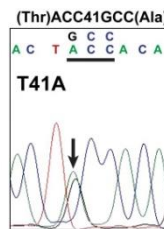
- ❑ Female, aged 41
- ❑ Lymphoma (7/2003):
treated to complete
remission
- ❑ 08/2008: upper back
swelling
- ❑ Core needle biopsy



H&E



β-catenin



Pediatric Desmoids – FAP Connection?



▪If *CTNNB1* mutation present, then there is no germline *APC*

▪If no *CTNNB1* mutation, then reasonable to test for germline *APC*

Molecular Characterization by Array Comparative Genomic Hybridization and DNA Sequencing of 194 Desmoid Tumors

GENES, CHROMOSOMES & CANCER 49:560–568 (2010)

Sébastien Salas,^{1,*†} Frederic Chibon,^{1†} Tetsuro Noguchi,² Philippe Terrier,³ Dominique Ranchere-Vince,⁴ Pauline Lagarde,¹ Jean Benard,⁵ Sébastien Forget,⁵ Camille Blanchard,¹ Julien Dômont,⁵ Sylvie Bonvalot,⁶ Louis Guillou,⁷ Agnès Leroux,⁸ Agnès Mechine-Neuville,⁹ Patrick Schöffski,¹⁰ Marik Laë,¹¹ Françoise Collin,¹² Olivier Verola,¹³ Amelie Carbonnelle,¹⁴ Laure Vescovo,¹⁵ Binh Bui,¹⁶ Véronique Brouste,¹⁷ Hagay Sobol,² Alain Aurias,¹⁸ and Jean-Michel Coindre^{1,19}

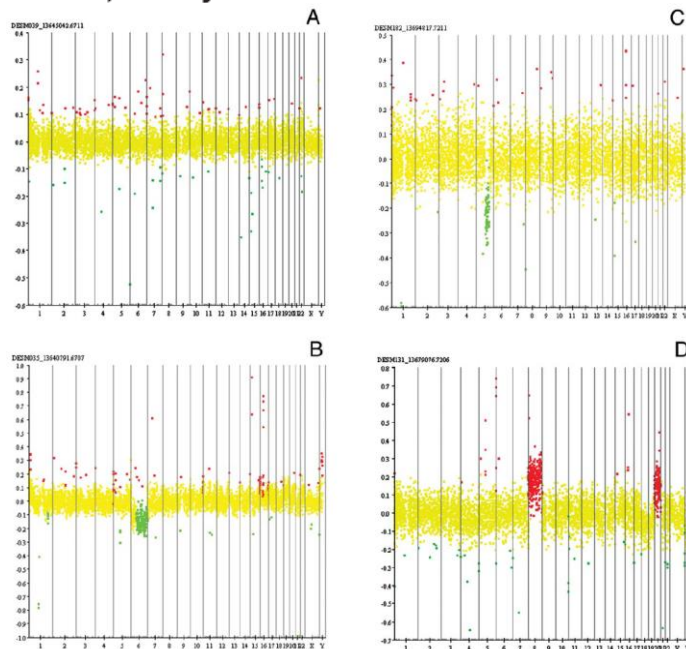


Figure 1. Examples of genomic alterations. BACs are aligned along the X-axis from chr 1p telomere to chr Yq telomere. BAC status (Cy5/Cy3 ratio) is indicated as follows: gain in red, loss in green, and normal in yellow. (a) No gains, losses, or amplifications of genomic

material were seen in 151 cases (Patient 39); (b) loss of 6p12-q27 (Patient 35); (c) loss of 5q14-q31 (Patient 182); (d) gain of Chromosomes 8 and 20 (Patient 131).

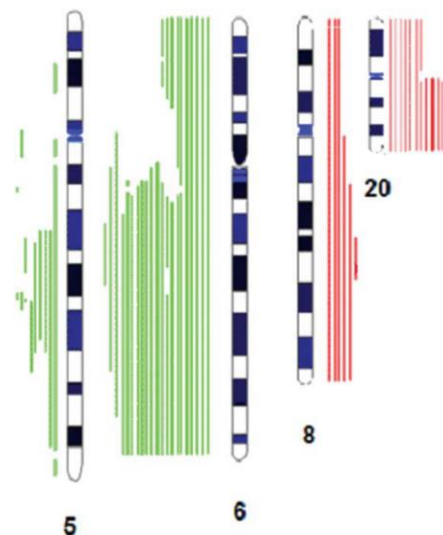


Figure 2. Summary of DNA copy number changes in 46 desmoid tumors. Losses are shown on the left (green) and gains on the right (red) of each chromosome. Each line represents a change seen in one sample.

A gene expression signature that distinguishes desmoid tumours from nodular fasciitis

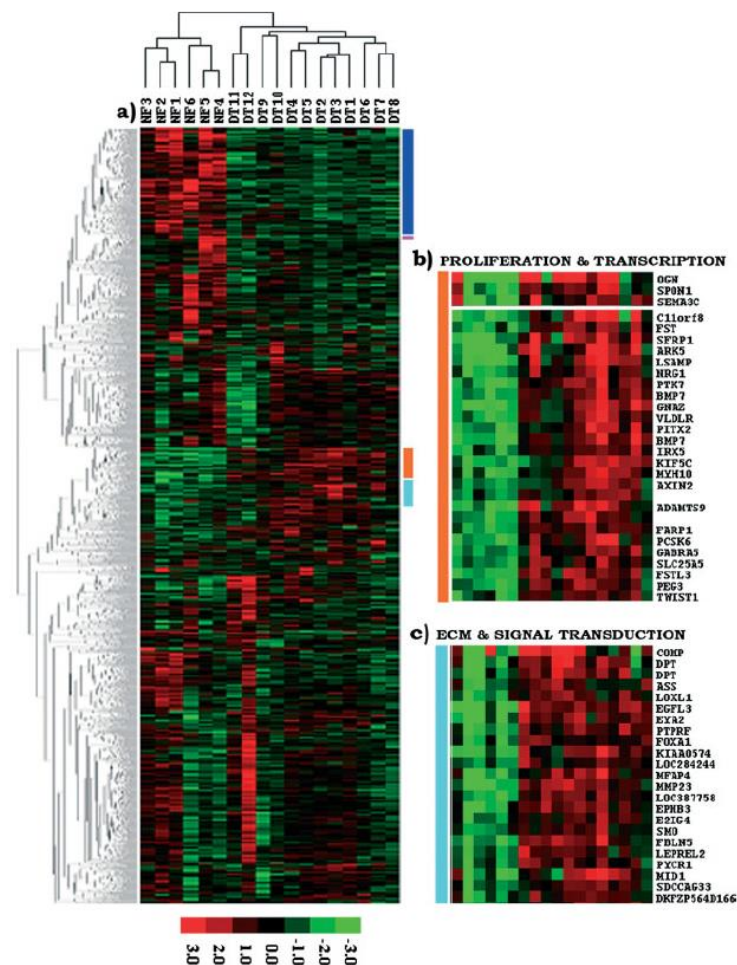
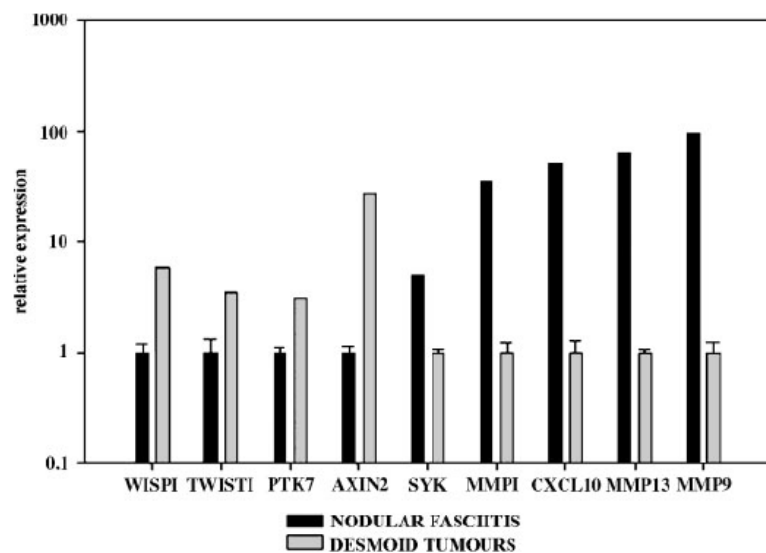
M Bacac,¹ E Migliavacca,² J-C Stehle,¹ T McKee,^{1,3} M Delorenzi,² J-M Coindre,⁴ L Guillou³ and I Stamenkovic^{1*}

¹Division of Experimental Pathology, University Institute of Pathology, Lausanne, Switzerland

²National Center of Competence in Research, Swiss Institute of Experimental Cancer Research and Swiss Institute of Bioinformatics, Epalinges, Switzerland

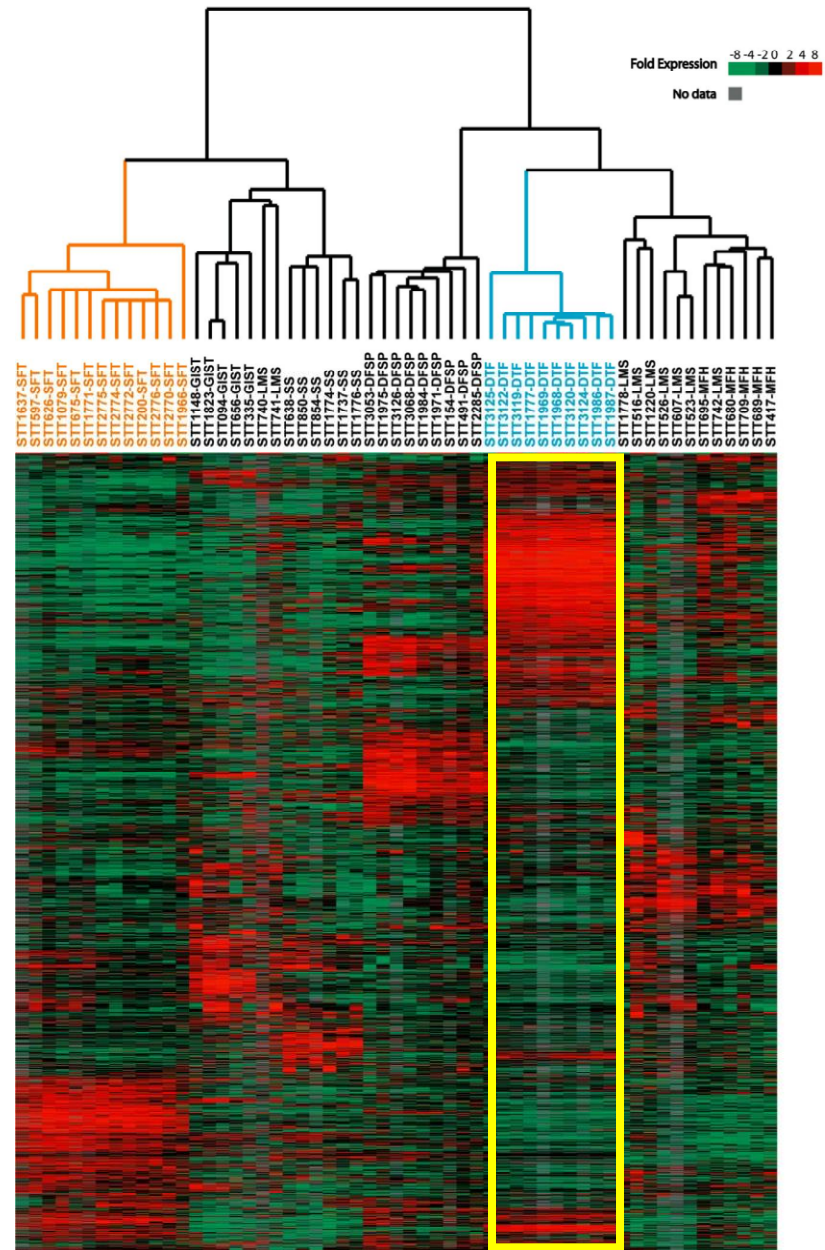
³Division of Anatomic Pathology, University Institute of Pathology, Lausanne, Switzerland

⁴Institut Bergonié and University Victor Segalen, Bordeaux, France



Gene Expression Array

- Initial 10 desmoids
- Human Exonic Evidence Based Oligonucleotide (HEEBO Chip) microarray
- SFT, GIST, SS, DFSP, DT, LMS, UPS/MFH



Expression Signature Rich in β -catenin/TCF Responsive Genes

- Many proposed IHC markers
for clinical behavior

- All retrospective

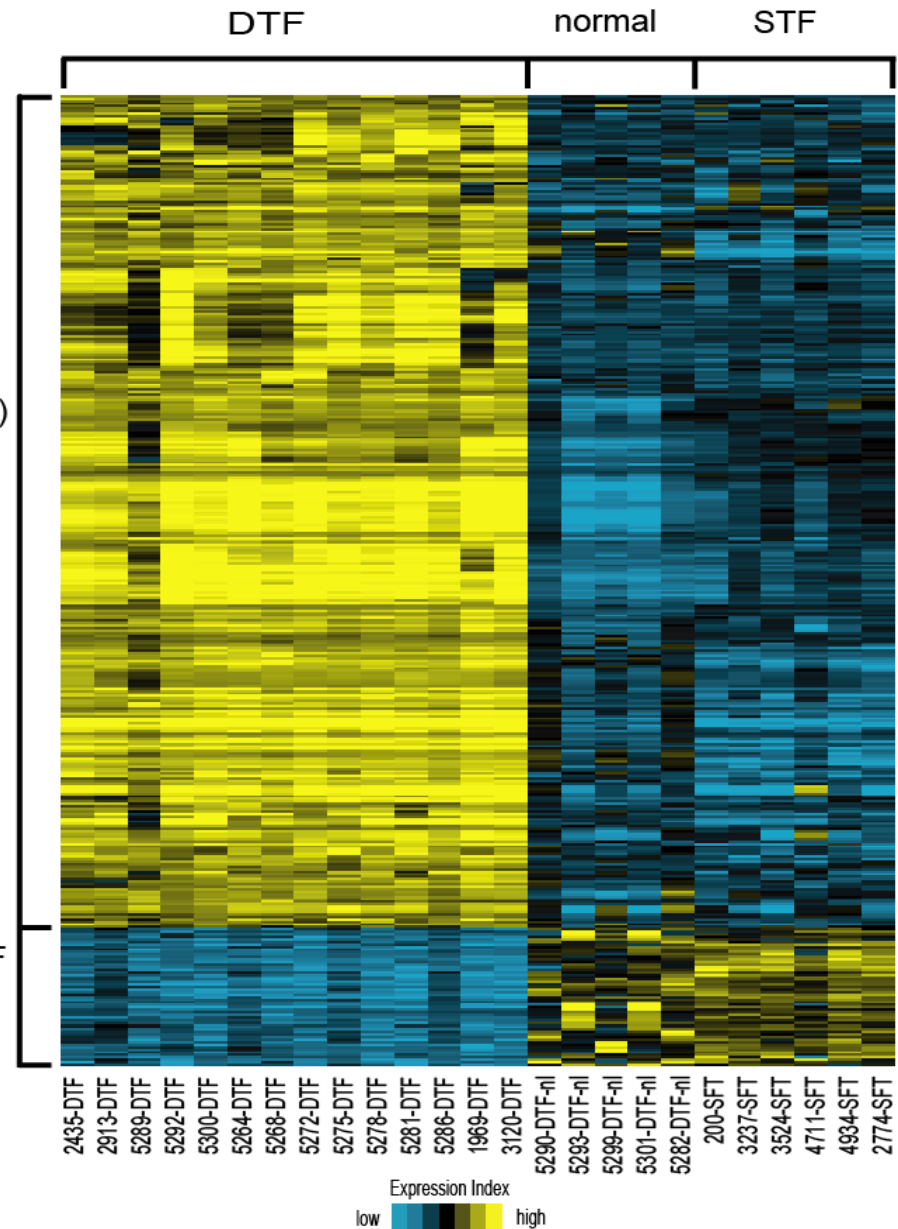
- None robust for clinical

(REMARK)

18-19 February 2014, Milan, Italy

Up DTF
(N=1109)

Down DTF
(N=184)



Prospective Trial for Desmoid Progression

- Prospectively genotype patients from biopsy material
- Wait and see / observation cohort (n=100)
- Correlate outcome (PFS)
- Does *CTNNB1* S45F predict progression?
- Immunological factors (host)
- Prior retrospective studies: post-resection recurrence
- Does test provide clinically actionable information?

So, Can Molecular Biology Help?

- **Confirm primary diagnosis**
- **Assess for recurrence**
- **Evaluate for FAP**

- **Prognosticate???.....wait and see**

Acknowledgements

- Chiara Colombo
- Alessandro Gronchi
- Rosalba Miceli
- Svetlana Bolshakov
- Federica Perrone
- Lola Lopez-Terrada
- Silvana Pilotti
- Julien Domont
- Sylvie Bonvalot
- Isabela Warnecke-Cunha
- Matt van de Rijn
- Rob West
- Dina Lev
- Raph Pollock
- Shohrae Hajibashi
- Quan Sheng Zhu
- Svetlana Bolshakov
- Theresa Nguyen
- Billy Wang
- Daniel Tuvin
- Judith Bovee
- Hans Geldenblom
- Robin Jones

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Ricerca sul Cancro (AIRC)**

18-19 February 2014, Milan, Italy