Desmoid tumours in 2016

Molecular pathology tools

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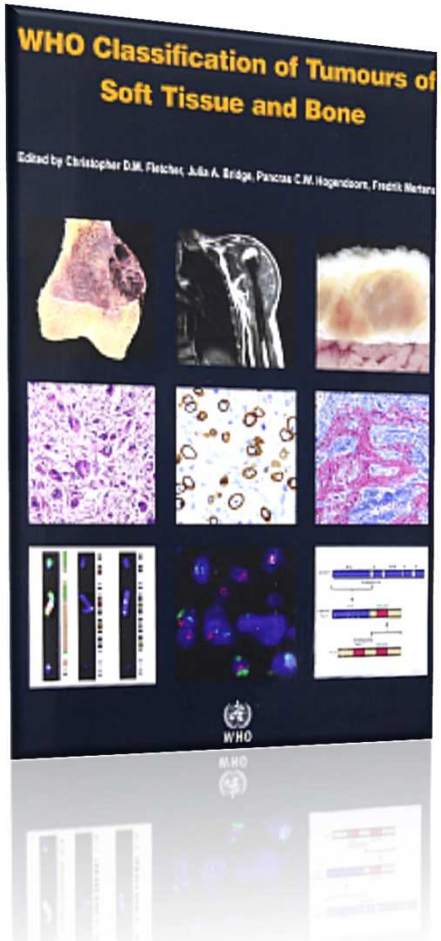
What is desmoid tumour ?



« Locally aggressive (myo)fibroblastic neoplasm that usually arises in deep soft tissues and is characterized by infiltrative growth and a tendency toward local recurrence, but lacks metastatic potential »

J.R. Goldblum
J.A. Fletcher

First genetic description ?

[CANCER RESEARCH 53, 5079–5082, November 1, 1993]

Advances in Brief

Coexistence of Somatic and Germ-Line Mutations of *APC* Gene in Desmoid Tumors from Patients with Familial Adenomatous Polyposis[1]

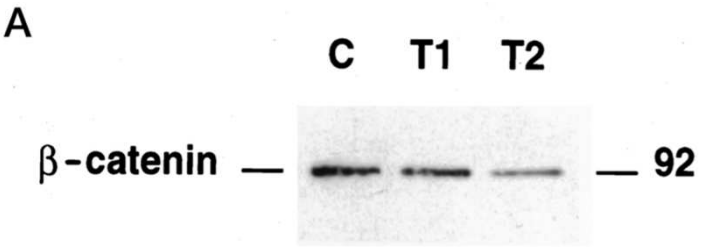
Michiko Miyaki,[2] Motoko Konishi, Rei Kikuchi-Yanoshita, Masayuki Enomoto, Kiyoko Tanaka, Hiromi Takahashi, Masatoshi Muraoka, Takeo Mori, Fumio Konishi, and Takeo Iwama

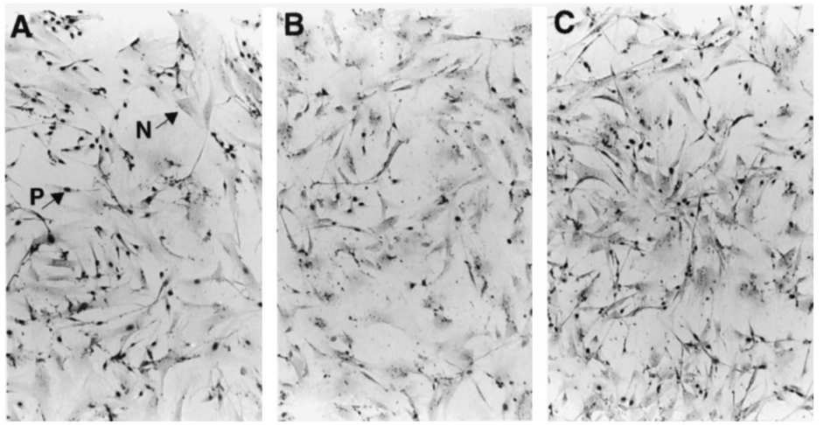
Department of Biochemistry, The Tokyo Metropolitan Institute of Medical Science, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo, 113 [M. Mi., M. K., R. K-Y., M. E., K. T., H. T., M. Mu.], Department of Surgery, Tokyo Medical and Dental University [M. E., T. I.], and Department of Surgery, Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Tokyo, 113, Japan [T. M.]; and Department of Surgery, Jichi Medical School, Tochigi, 329-04, Japan [F. K.]

Table 2 *Germ-line and somatic mutations of the APC gene in desmoid tumors from FAP patients*[a]

	Germ-line mutation		Somatic mutation	
Tumor	Codon	Mutation	Codon	Mutation
PLK42-Desmoid	1462–1465	(AGAG) del		Loss of normal allele[b]
PLK56-Desmoid	1105–1106	(G) del	1461–1462	(AA) del
PLK59-Desmoid	1061–1063	(AACA) del	1581–1584	(TGCCATGC) del
PLK111-Desmoid	1110	T(C)A→T(G)A	1399–1426	(C····A) 82-base pair repeat[c]
PLK124-Desmoid	1309–1311	(AAAGA) del	1452	(G) del
PLK126-Desmoid	848	(A)AA→(T)AA	1458–1561	(TACTGCTGAA) del
PLK150-Desmoid			1458–1464	(TACTGCTGAAAAGAGAGAG) del
PLK150-Desmoid-R			1470	(T) del

APC mutations trigger β-Catenin nuclear accumulation





APC truncating mutations give aggressive fibromatosis cells a proliferative advantage through β-catenin and suggest that β-catenin acts to transactivate transcription.

(Li et al; Am J Pathol 1998, 153:709–714)

β-catenin (CTNNB1) is mutated in Desmoid tumours?

Oncogene (1999) 18, 6615–6620

http://www.stockton-press.co.uk/onc

SHORT REPORT

Predominance of beta-catenin mutations and beta-catenin dysregulation i sporadic aggressive fibromatosis (desmoid tumor)

Sabine Tejpar[1,2,8], Friedel Nollet[3,8], Catherine Li[1,8], Jay S Wunder[4], Genevieve Michils[2], Paola dal Cin[2], Eric Van Cutsem[5], Bharati Bapat[6], Frans van Roy[3], Jean Jacques Cassiman[2] an Benjamin A Alman*[,1,7,8]

[1]Programme in Development Biology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G1X8 Canada; [2]Center for Human Genetics, Katholieke Universiteit Leuven, Herestraat 49, 3000 Leuven, Belgium; [3]V.I.B.-University of Ghent, Department of Molecular Biology, Molecular Cell Biology Unit, Ledeganckstraat 35, 9000 Ghent, Belgium; [4]Department of Surgery, Division of Orthopaedic Surgery, The Mount Sinai Hospital and the University of Toronto, 600 University Avenue, Toronto, Ontario M5G1X5 Canada; [5]Department of Gastroenterology, Katholieke Universiteit Leuven, Herestraat 49, 3000 Leuven, Belgium; [6]Department of Laboratory Medicine and Pathobiology, The Mount Sinai Hospital and the University of Toronto, 600 University Avenue, Toronto, Ontario M5G1X5 Canada; [7]Department of Surgery, Division of Orthopaedic Surgery,

REPORT

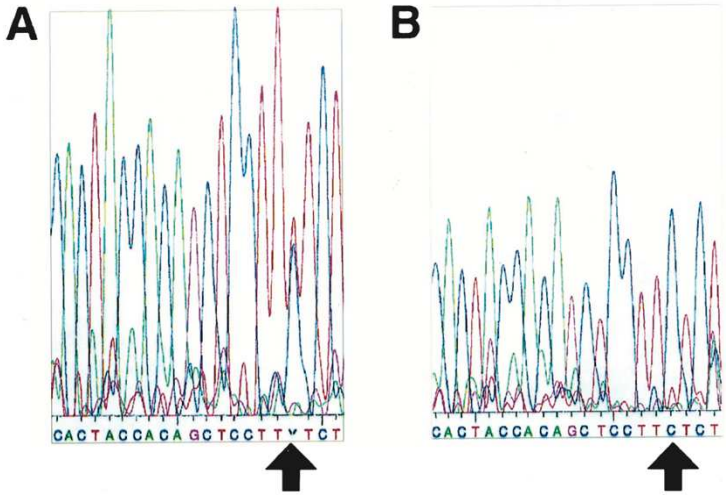
Stabilization of β-Catenin by Genetic Defects in Melanoma Cell Lines

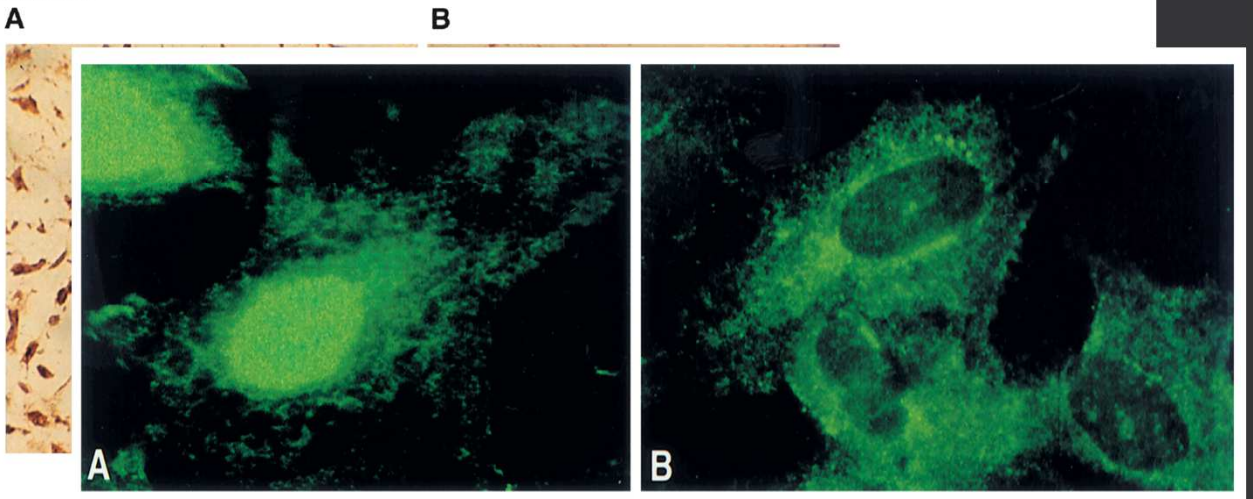
Bonnee Rubinfeld, Paul Robbins, Mona El-Gamil, Iris Albert, Emilio Porfiri, Paul Polakis*

+ Author Affiliations

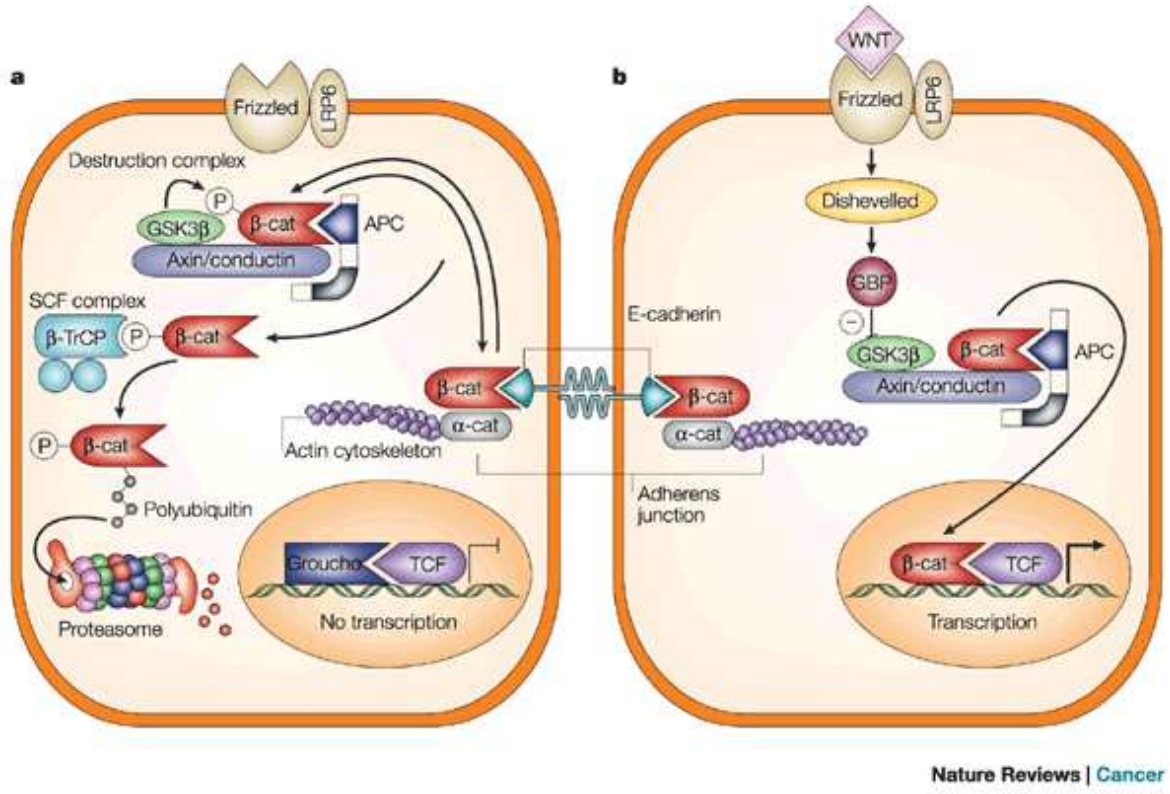
↵* To whom correspondence should be addressed. E-mail: paul@onyx-pharm.com

Science 21 Mar 1997:
Vol. 275, Issue 5307, pp. 1790-1792
DOI: 10.1126/science.275.5307.1790





APC and β-catenin pathway



Fodde et al; Nature Reviews Cancer 1, 55-67 (October 2001)

β-catenin mutations: a molecular pathology tool?

Diagnosis!

Detection of β-Catenin Mutations in Paraffin-embedded Sporadic Desmoid-type Fibromatosis by Mutation-specific Restriction Enzyme Digestion (MSRED): an Ancillary Diagnostic Tool

Maria Fernanda C. Amary, MD,† Patrick Pauwels, MD,‡ Els Meulemans, PhD,§ Guido M. Roemen, PhD,§ Lily Islam, MD,† Bernadine Idowu, PhD,† Konstantinos Bousdras, MD,‖ Timothy C. Diss, PhD,‖ Paul O'Donnell, MD,¶ and Adrienne M. Flanagan, MD, PhD†‖#*

(*Am J Surg Pathol* 2007;31:1299–1309)

	Cases (n)	β-Catenin Point Mutation	β-Catenin Expression by Immunohistochemistry	
			Positive Cases (n)	Total Cases Tested (n)
Desmoid-type fibromatosis	76	66 (87%)	66	66
Superficial fibromatosis	18	—	8	16
Low grade fibromyxoid sarcoma	10	—	8	8
Fibroma of tendon sheath	6	—	5	6
Solitary fibrous tumor	6	—	3	5
Nodular fasciitis	4	—	2	3
Desmoplastic fibroblastoma	3	—	3	3
Myofibroma	3	—	1	1
Perineurioma	3	—	0	2
Desmoplastic fibroma	1	—	1	1
Infantile digital fibromatosis	1	—	0	0
Periosteal fasciitis	1	—	1	1
Osteosarcoma	1	—	1	1
Total n number	133		99	112

β-Catenin mutations: a molecular pathology tool?

Prognosis?

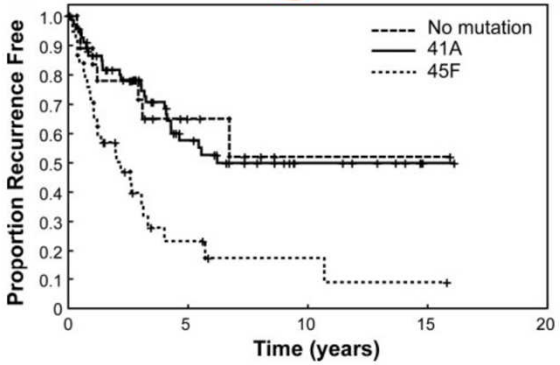
The American Journal of Pathology, Vol. 173, No. 5, November 2008

DOI: 10.2353/ajpath.2008.080475

Tumorigenesis and Neoplastic Progression

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*§



Variable	Total		WT		41A		45F		45P	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Gender										
Female	86	62	19	22	36	42	25	29	6	7
Male	52	38	2	4	33	63	14	27	3	6
Age at diagnosis										
<30 years	61	44	12	20	31	51	14	23	4	7
>30 years	77	56	9	12	38	49	25	32	5	7
Tumor site										
Superficial trunk	54	39	10	19	27	50	11	20	6	11
Extremity	53	38	5	9	27	51	20	38	1	2
Deep trunk/viscera	18	13	3	17	11	61	2	11	2	11
Head and neck	13	10	3	23	4	31	6	46	0	0
Tumor size*										
<6 cm	56*	52	11	20	24	43	16	29	5	9
>6 cm	52*	48	6	11	30	58	14	27	2	4
Total	138		21	15	69	50	39	28	9	7

β-Catenin mutations: a molecular pathology tool?

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

www.bjcancer.com

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 Brouste[2], P Saulnier[3], P Terrier[1], D Ranchère[5], A Neuville[6], A Leroux[7], L Guillou[8], R Sciot[9], F Collin[10], A Dufresne[5], J-Y Blay[5], A Le Cesne[1], J-M Coindre[*,2,11], S Bonvalot[*,1] and J Bénard[*,1,4,12]

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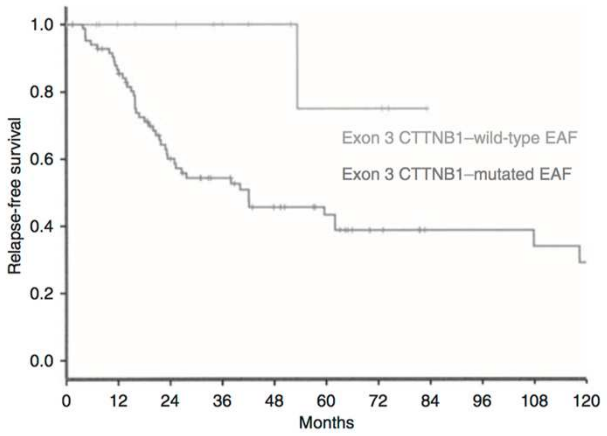
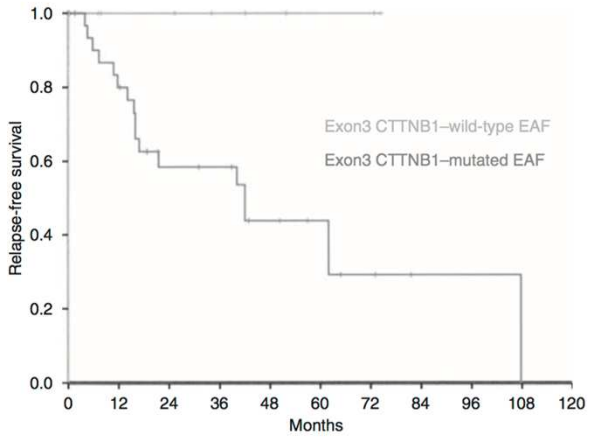




Prognosis?

CTNNB1 characteristics	Total	WT *n*	Mutated *n*	41A *n*	45F *n*	45P *n*	del *n*
N	101	13	88	40	37	9	2
Age							
Median, years	37	39.5	37.5	36.7	37	45.5	43
Range	0.1–77	0.5–66	0.1–77	10–73	0.1–77	14–65	19–68
Sex							
Male	36	4	32	14	15	3	—
Female	65	9	56	26	22	6	2
Presentation							
Primary	57	12	45	16	20	8	1
Relapse	40	1	39	22	15	1	1
NA	4	—	4	2	2	—	—
Tumour site							
Head/Neck	8	1	7	2	5	—	—
Trunk	54	5	49	20	19	8	2
Limb	37	7	30	17	12	1	—
NA	2	—	2	1	1	—	—
Tumour size, mm							
Median, mm	80	40	80	80	85	75	40
Range	10–300	15–120	10–300	21–300	25–200	25–190	10–70
Therapy							
Surgery	101	13	88	40	37	9	2
Radiation therapy	18	1	17	7	8	1	1
Medical therapy	8	1	7	3	4	—	—
Surgical margin							
R0	42	9	33	14	13	5	1
R1	33	3	30	15	12	3	—
R2	8	—	8	1	5	1	1
NA	18	1	17	10	7	—	—
Outcome							
Relapse	51	1	50	22	23	4	1

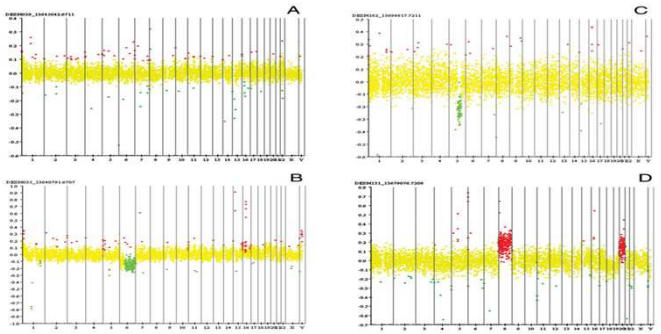
And what about the whole genome?

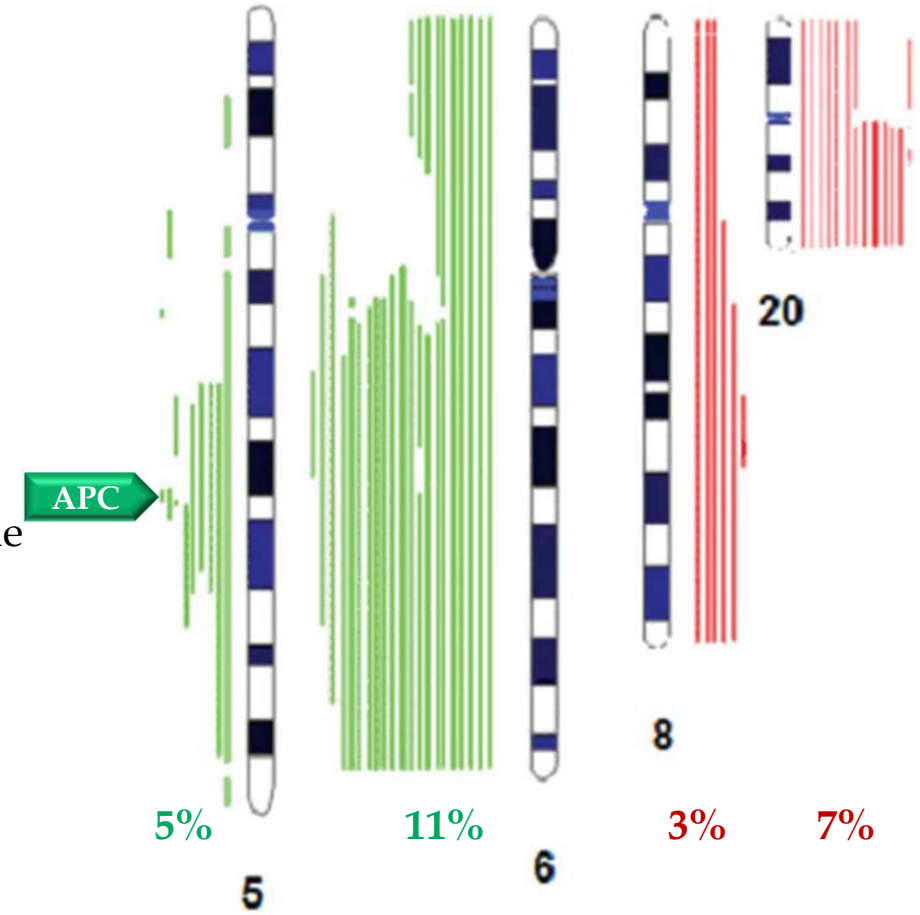
GENES, CHROMOSOMES & CANCER 49:560–568 (2010)

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

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] Agnes 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]

- Flat in ¾ of DT and when rearranged, very simple





NGS applied to Desmoid genome

GENES, CHROMOSOMES & CANCER 54:606–615 (2015)

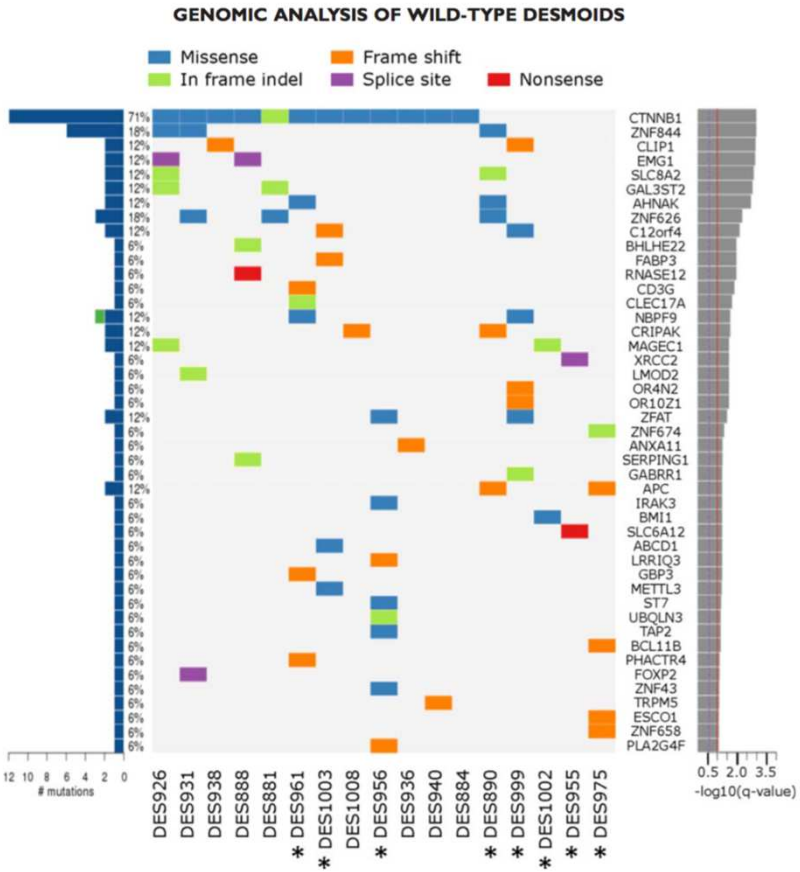
Near Universal Detection of Alterations in *CTNNB1* and Wnt Pathway Regulators in Desmoid-Type Fibromatosis by Whole-Exome Sequencing and Genomic Analysis

Aimee M. Crago,[1,2]* Juliann Chmielecki,[3,4] Mara Rosenberg,[4] Rachael O'Connor,[1] Caitlin Byrne,[5] Fatima G. Wilder,[1] Katherine Thorn,[1] Phaedra Agius,[5] Deborah Kuk,[6] Nicholas D. Socci,[5] Li-Xuan Qin,[6] Matthew Meyerson,[3,4,7] Meera Hameed,[8] and Samuel Singer[1,2]

[1]Sarcoma Biology Laboratory and Sarcoma Disease Management Program, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY
[2]Department of Surgery, Weill Cornell Medical College, New York, NY
[3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
[4]Cancer Program, Broad Institute of Harvard and MIT, Cambridge, MA
[5]Bioinformatics Core, Memorial Sloan Kettering Cancer Center, New York, NY
[6]Biostatistics and Epidemiology, Memorial Sloan Kettering Cancer Center, New York, NY
[7]Department of Pathology, Harvard Medical School, Boston, MA
[8]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

Sanger sequencing:
Mut. CTNNB1: 98/117 = 82%

Whole-Exome sequencing of Sanger WT cases:
Mut. CTNNB1 : 7 / 16 cases
Mut. APC: 3
Mut. BMI1: 1 cases



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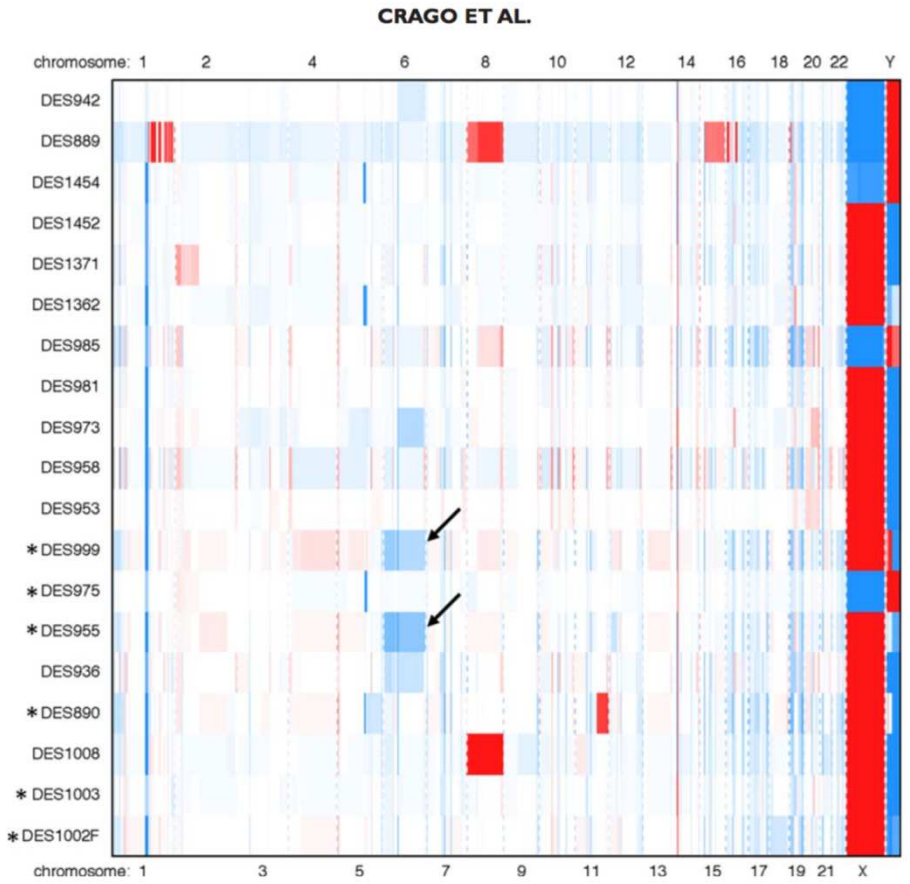

Sanger sequencing:
Mut. CTNNB1: 98/117 = 82

Whole-Exome sequencing of Sanger WT cases:
Mut. CTTNB1 : 7 / 16 cases
Mut. APC: 3
Mut. BMI1: 1 cases

CGH:
Chromosome 6 loss: 2 WT cases

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[7]Department of Pathology, Harvard Medical School, Boston, MA
[8]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

TABLE 2. Whole-Exome Sequencing of Desmoids

		Whole-exome sequencing results (allele frequency)		
Sample	*CTNNB1* mutation by Sanger	*CTNNB1* mutation	*APC* mutation	Other event noted
DES1008	S45F	S45F (32%)	None	
DES931	S45F	S45F (32%)	None	
DES938	S45F	S45F (46%)	None	
DES926	S45F	S45F (38%)	None	
DES884	T41A	T41A (36%)	None	
DES888	T41A	T41A (33%)	None	
DES936	T41A	T41A (22%)	None	
DES940	T41A	T41A (54%)	None	
DES881	H36del	H36del (30%)	None	
DES1003	None	T41A (10%)	None	
DES956	None	T41A (21%)	None	
DES961	None	T41A (10%)	None	
DES890	None	None	I1918fs (61%)	*APC* loss
DES975	None	None	K1462fs (70%)	*APC* loss
DES955	None	None	None	Chr 6 loss
DES999	None	None	None	Chr 6 loss
DES1002	None	None	None	*BMI1* Q59E (8%)

Sanger sequencing:
Mut. CTNNB1: 98/117 = 82

Whole-Exome sequencing of Sanger WT cases:
Mut. CTTNB1 : 7 / 16 cases
Mut. APC: 3
Mut. BMI1: 1 cases

CGH:
Chromosome 6 loss: 2 WT cases

95% of desmoid tumours are mutated for CTNNB1 or APC

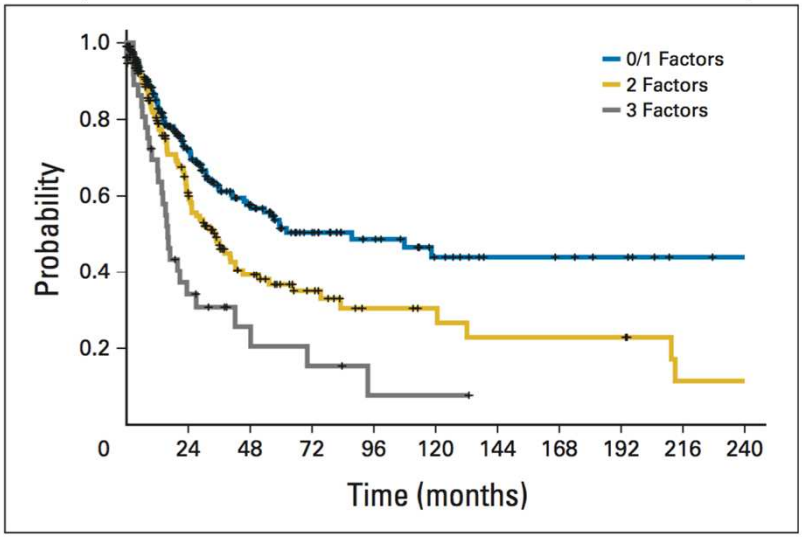
Clinical prognosis factor

Table 3. Univariate Analysis for Prognostic Factors in Progression-Free Survival

Factor	No. of Patients	Progression-Free Survival Rate 2-Year	5-Year	10-Year	Log-Rank *P*
Age, years					
≤ 37	199	57.4	36.3	28.7	.005
> 37	205	70.9	49.5	42.1	
Sex					
Male	130	63.1	41.3	23	.35
Female	276	64.4	43.3	39.9	
Context of abdominal wall desmoids in women of child-bearing age during or shortly after pregnancy					
No	374	63.1	41.2	32.9	.06
Yes	32	75	62.3	62.3	
Previous history of surgery in area of primary tumor					
No	371	63.3	41.4	34	.264
Yes	35	70.5	54.5	48.5	
Previous history of trauma in area of primary tumor					
No	389	64.3	42.9	35	.456
Yes	17	55.1	44.1		
Tumor localization					
Abdominal wall	91	78.2	61.7	57.2	< .001
Abdominal cavity	43	70	50.2	50.2	
Extra-abdominal	267	59.2	36.5	26.9	
Extra-abdominal localization					
Trunk	93	65.5	53.9	42.6	< .001
Upper and lower limbs	105	50.3	23.9	21.7	
Head and neck	28	71.9	60.4	—	
Buttocks	20	62.3	16.6	—	
Limb localization					
Proximal	52	68.8	54.5	49.5	.006
Distal	59	54.4	22.8	18.3	
Delay between first symptoms and diagnosis, months					
≤ 4.74	114	69.3	54.9	47.8	.942
> 4.74	114	71.9	52.7	46.2	
Tumor size, cm					
≤ 7	181	75.1	57.4	47	.004
> 7	136	58.3	40.6	32.8	
Surgical margins (R0 *v* R1 *v* R2)					
R0	110	76.5	62.5	47.5	< .001
R1	107	73.7	60.5	48.1	
R2	35	43.4	22	16.5	
Surgical margins (R0 *v* R1)					
R0	110	76.5	62.5	47.5	.867
R1	107	73.7	60.5	48.1	

Table 1. Patient and Disease Characteristics at Baseline

Characteristic	Overall Patients (N = 426) No.	%
Age at diagnosis, years		
Median	37	
Range	0.3-83	
Sex		
Proximal	52	47.7
Distal	57	52.3
Context of abdominal wall desmoids in women of child-bearing age during or shortly after pregnancy		
Yes	33	7.7
Previous history of surgery in area of primary tumor		
Yes	36	8.4
Previous history of trauma in area of primary tumor		
Yes	17	3.9



Molecular prognosis signature ?

Published OnlineFirst April 15, 2015; DOI: 10.1158/1078-0432.CCR-14-2910

Biology of Human Tumors

Clinical Cancer Research

Gene Expression Profiling of Desmoid Tumors by cDNA Microarrays and Correlation with Progression-Free Survival

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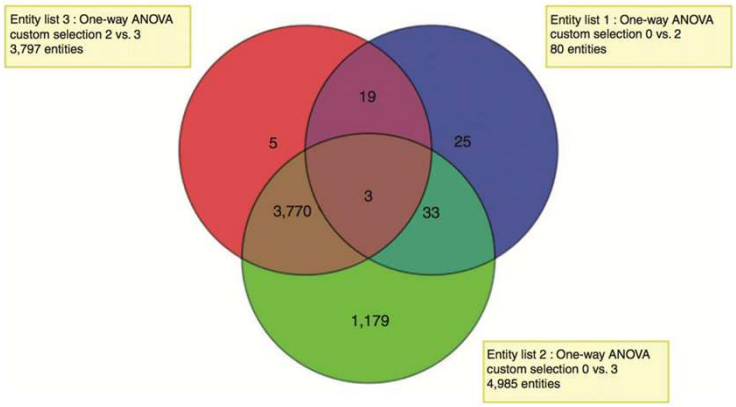

Characteristics	Cohort A ($n = 66$)	Cohort B ($n = 49$)	Cohorts A + B ($n = 115$)
Median follow-up (years) (IC 95)	2.36 (0.03–12.04)	1.43 (0.33–11.07)	1.82 (0.08–11.97)
Age at diagnosis (%)			
≤37 years	27 (41)	25 (50)	52 (45)
>37 years	37 (56)	24 (50)	61 (53)
Nd	2 (3)		2 (2)
Male sex (%)	23 (35)	20 (41)	43 (37)
Location (%)			
Intra-abdominal	4 (6)	8 (16)	12 (10)
Abdominal wall	13 (20)	9 (18)	22 (18)
Extra-abdominal	49 (74)	32 (66)	71 (62)
Size (%)			
≥7 cm	35 (53)	20 (41)	55 (48)
<7 cm	17 (26)	22 (45)	39 (34)
Nd	14 (21)	7 (14)	21 (18)
Progression number (%)			
0	48 (72)	14 (29)	62 (54)
1	0	30 (61)	30 (26)
2	13 (20)	1 (2)	14 (12)
3	5 (8)	1 (2)	6 (5)
>3	0	3 (6)	3 (3)
Mutations *CTNNB1* (%)	66 (100)	29 (60)	95(82)

Molecular prognosis signature !

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Biology of Human Tumors

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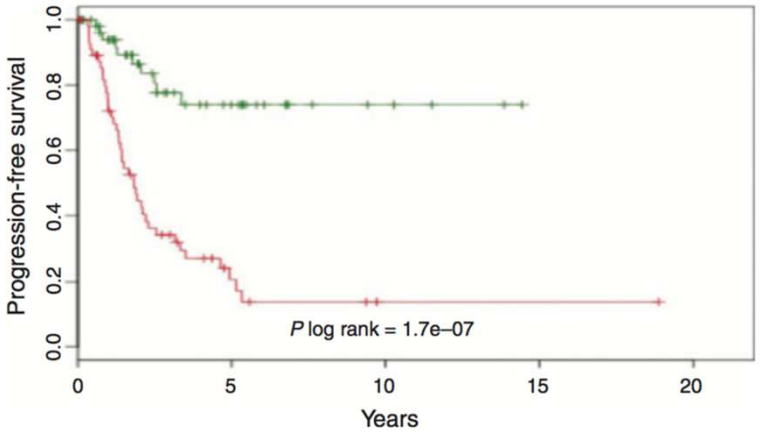

Downregulated genes in recurrence			Upregulated genes in recurrence		
Probe set id	Corrected *P* value	Gene symbol	Probe set id	Corrected *P* value	Gene symbol
209129_at	8.93e−05	*TRIP6*	203116_s_at	3.23e−07	*FECH*
226728_at	1.17e−04	*SLC27A1*	215416_s_at	1.09e−05	*STOML2*
204986_s_at	1.77e−04	*TAOK2*	225439_at	2.49e−05	*NUDCD1*
229377_at	2.55e−04	*GRTP1*	200014_s_at	1.34e−05	*HNRNPC*
206846_s_at	4.27e−04	*HDAC6*	226312_at	2.26−e05	*RICTOR*
220128_s_at	5.22e−04	*NPAL2*	230465_at	2.73e−05	*HS2ST1*
231767_at	6.35e−04	*HOXB4*	202854_at	3.58e−04	*HPRT1*
236229_at	8.01e−04	*Hs.661286*	211727_s_at	3.66e−04	*COX11*
203204_s_at	8.22e−04	*JMJD2A*	227211_at	3.70e−04	*PHF19*
214251_s_at	9.82e−04	*NUMA1*	229253_at	7.60e−04	*THEM4*
215692_s_at	9.93e−04	*MPPED2*	200006_at	8.07e−04	*PARK7*
236123_at	1.01e−03	*ST7L*	226776_at	8.22e−04	*ENY2*
228929_at	1.05e−03	*DNASE1*	203312_x_at	8.27e−04	*ARF6*
244614_at	1.48e−03	*TFG*	203606_at	1.40e−03	*NDUFS6*
232463_at	1.62e−03	*CXYorf10*	200749_at	1.47e−03	*RAN*
237317_at	1.68e−03	*Hs.127312.0*	217880_at	2.69e−03	*CDC27*
232331_at	2.26e−03	*Hs.25717.0*	202121_s_at	3.17e−03	*CHMP2A*
234106_s_at	2.43e−03	*FLYWCH1*	226596_x_at	3.32e−03	*LOC729852*

Energy metabolism!

LETTER

Mechanical induction of the tu pathway by tumour growth pr

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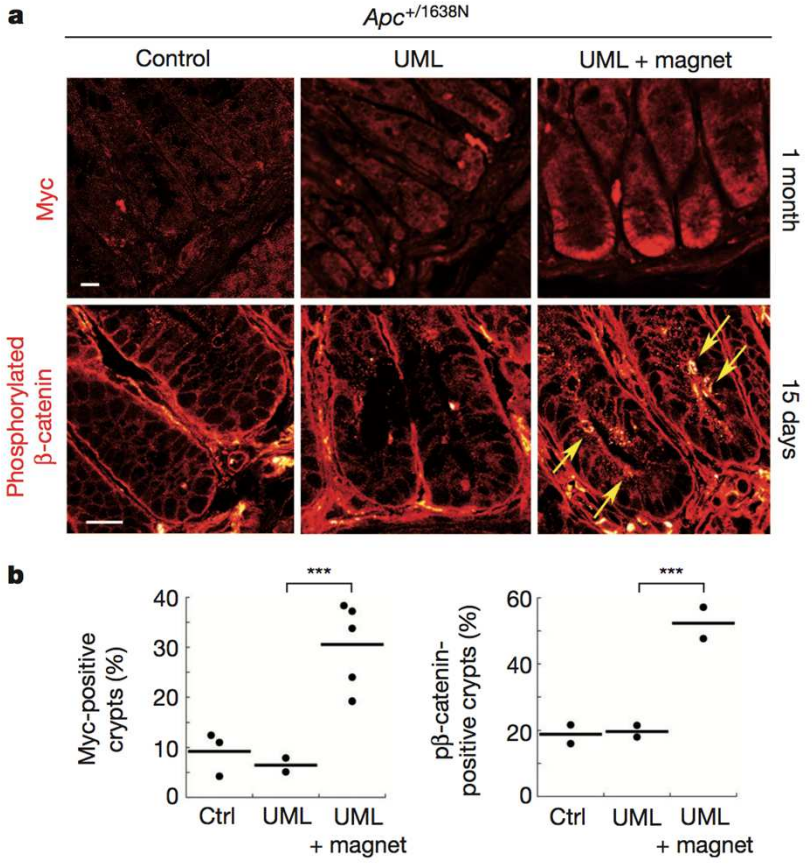
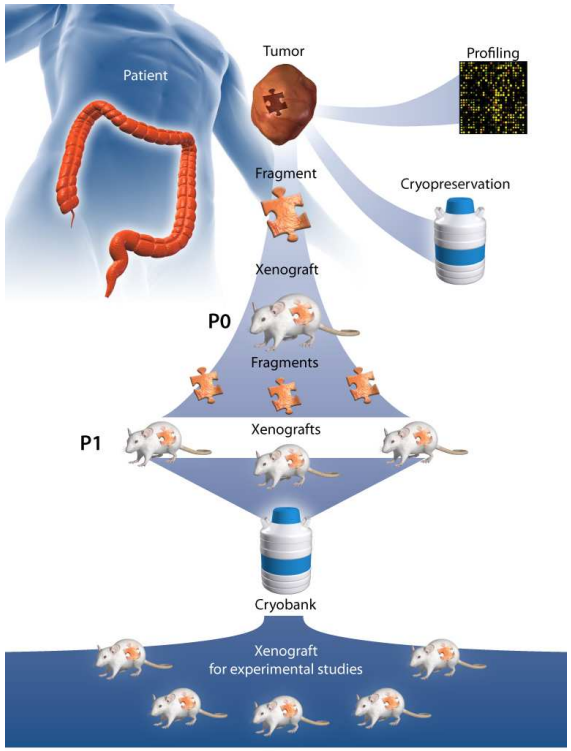


Des models… DES MODELS…DES MODELS !!!

- Lignées
  - Primaires oui mais ne dépassent pas les dix passages!

- PDX
  - Plateforme d'établissement de PDX de Montpellier
    - Greffe et suivit: Laetita Linares IRCM
    - Caractérisation génétique et bases de données: F. Chibon (INSERM U1218)



Take home messages !

- La plupart des desmoïdes sont sporadiques
- 10% des patients avec une PAF vont développer une desmoïde
- 85% des desmoïdes ont une mutation activatrice de l'exon 3 de CTNNB1
  - Le **séquençage Sanger** reste le meilleur moyen de détecter de telles mutations et de confirmer le diagnostic histologique (à partir de blocks **FFPE**!)
  - Les patients WT pour CTNNB1 peuvent etre évalués pour APC par séquençage Sanger ou Exon seq (tissus congelé)
  - Desmoïdes WT n'existent vraisemblablement pas!
- La valeur pronostique de la mutation n'est toujours pas établie.
- Le génome des desmoïdes n'est que très peu réarrangé et seulement dans 25% des cas sans que ce soit relié à une agressivité particulière.
- La valeur pronostique de la signature moléculaire doit être cliniquement validée.
- La génétique des desmoides est maintenant bien connue mais reste sans impact sur la prise en charge thérapeutique des patients. Nous devons explorer d'autres pistes: Métabolisme et immunité anti-tumorale.
- Le besoin de MODELS pour des études FONCTIONNELLES est immense:
  - Nous recevons tous les échantillons frais!

Merci…