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Supplemental Data

Germline *BAP1* Mutations Predispose to Renal Cell Carcinomas

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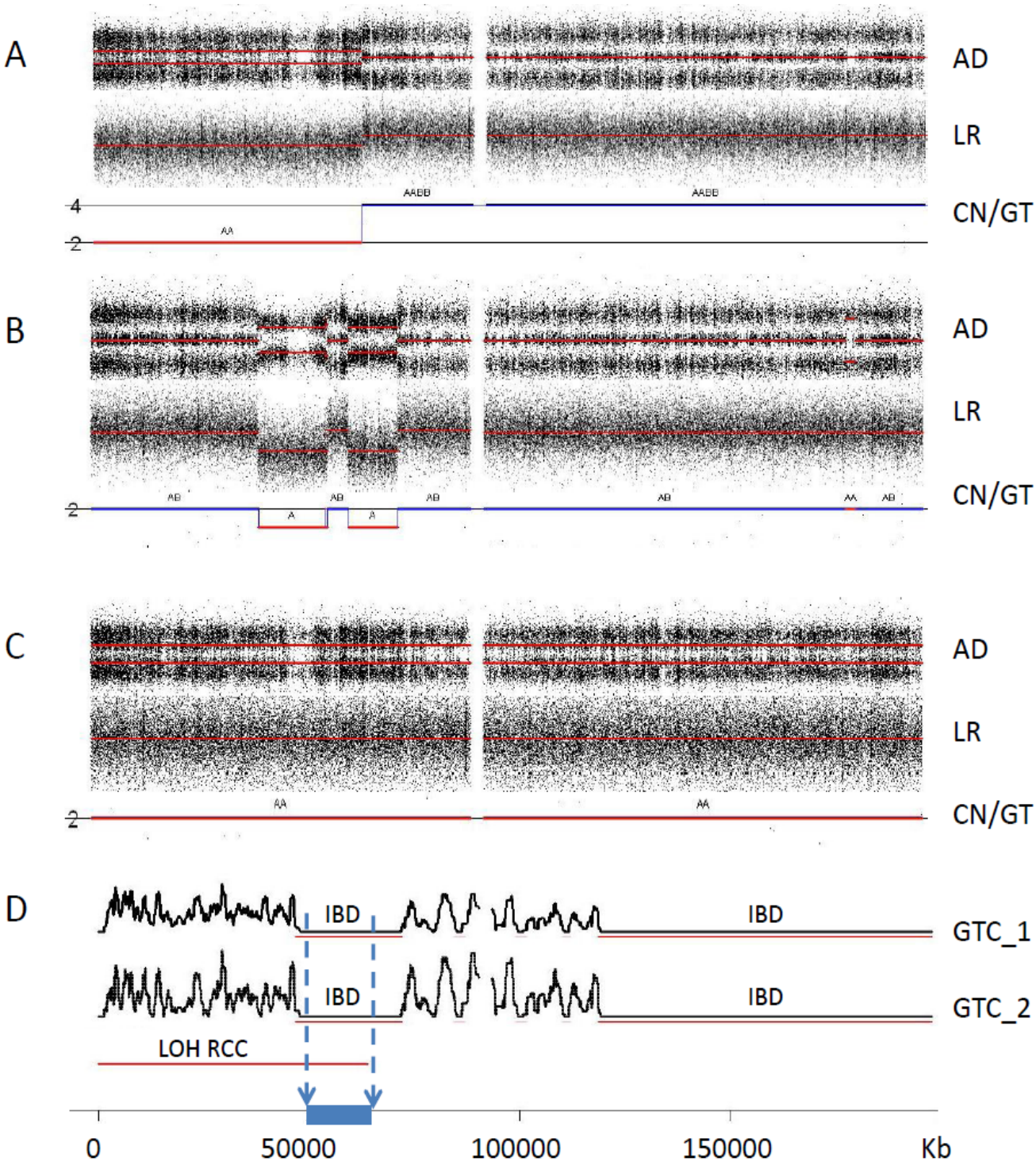
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AD
LR
CN/GT
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2
AABB
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C
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D
IBD
IBD
GTC_1
IBD
IBD
GTC_2
LOH RCC
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50000
100000
150000
Kb

Figure S1. Delimitation of candidate predisposition gene region by tumor genome profiling and detection of Identical By Descent (IBD) regions in family A.

A-C. Genomic profiles of RCC from III-1 (A), breast tumors from III-1 (B) and III-3 (C). SNP arrays were normalized and genotyped with Genotyping Console (v.3). Tumor samples were processed by the GAP method (Popova T, 2009) in order to obtain absolute allele specific copy numbers. Loss of Heterozygosity (LOH) status was called for the segments with identical copy number and major allele counts.

D. Genotype inconsistency plots calculated for genotype profiles of renal cell carcinoma (RCC) versus III-5 (GTC_1) and III-1 versus III-5 (GTC_2). SNP genotype calls for tumor samples were estimated from Allelic Difference profiles based on the thresholds adjusted by the actual segmental copy number and allelic content. Genotype calls from the LOH region were used to confirm persistence of shared allele in tumor.

AD, LR, CN/GT stand for allelic difference, copy number variation and detected Copy Number and Genotype profiles; LOH is designated on CN/GT profiles by the red color; blue arrows indicate intersection between Identical by descent (IBD) and LOH.

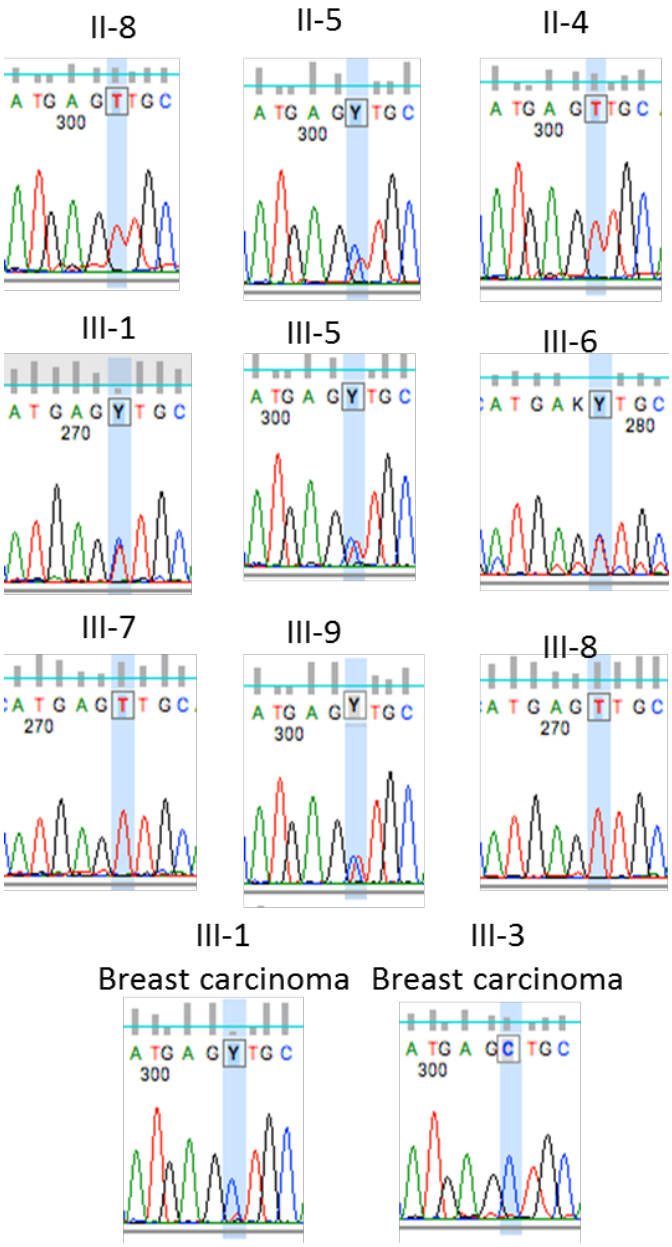

Figure S2. *BAP1* mutation analysis in family A

Sanger sequencing electropherograms showing the segregation of the *BAP1* mutation in family A c.277A>G (reverse sequences) and the loss of the wild type allele in 2 breast tumors arisen in this family.

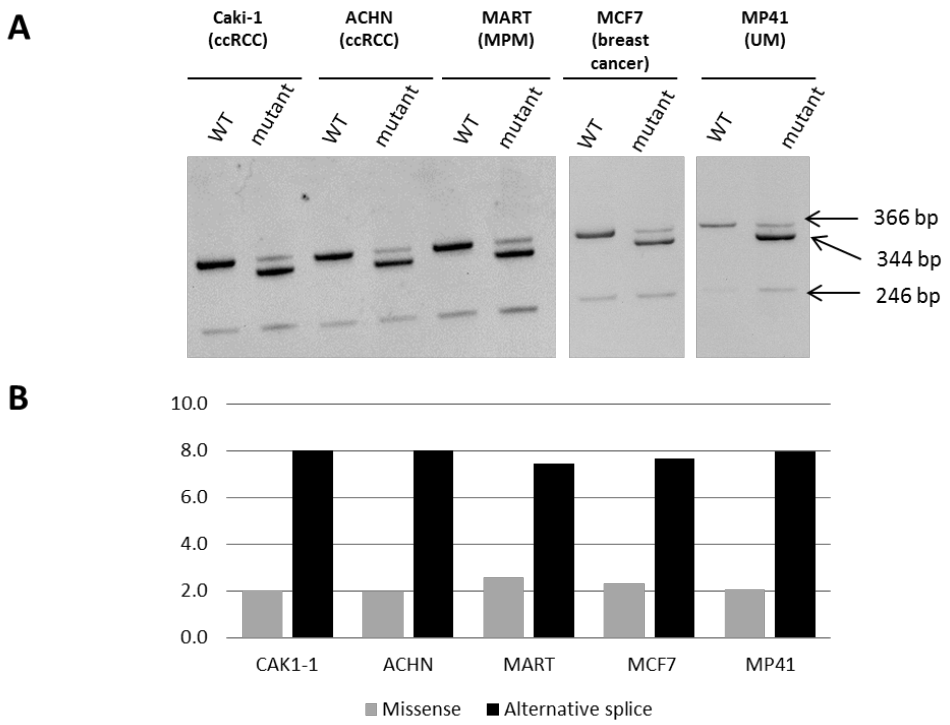

Figure S3. Splicing effect of *BAP1* mutation by minigene transcript analysis

The ExonTrap pET01 plasmid (Mo Bi Tec GmbH, Gottingen,Germany) containing *BAP1*exon 5 with or without the family A c.277A>G mutation was constructed. The plasmids were transfected in CAKi-1 and ACHN clear-cell renal cell carcinoma (ccRCC; ATCC HTB-46 and CRL-1611), MART malignant pleural mesothelioma (MPM), MCF7 luminal breast cancer (ATCC HTB-22) and MP41 uveal melanoma (UM) (Némati F, 2010); cell lines and RNA was extracted 48 hours after transfection.

A. Transcript analysis was done after reverse transcription, amplification, and migration on 8% acrylamide gel. Four transcripts are visible: the wild type and the c.277A>G mutation transcripts corresponding to the 366bp bands, the alternatively spliced, and pET01 basal splicing corresponding to 344 and 246bp bands, respectively.

B. Proportion of transcripts with the missense mutation versus proportion of transcripts with alternative splicing after quantification by ImageJ.

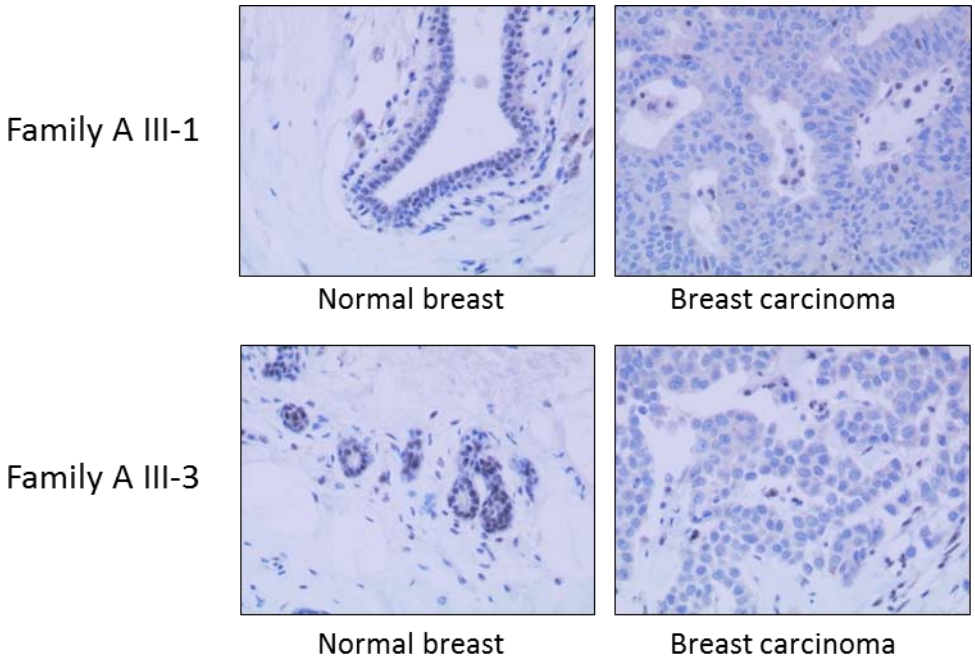

Figure S4. Immunohistochemistry for BAP1 expression in breast tumors from family A

The left panel shows adjacent normal breast tissues, right panel the tumor tissues. The purple staining illustrates a nuclear immune-labeling of BAP1 protein. The right panel shows tumor cells with a blue counter-staining indicating a lack of BAP1 expression in these tumors.

Table S1. Summary of whole exome sequencing in family A

			Unknown SNVs* (dbSNP137)		
	III-1	**III-5**	**III-1**	**III-5**	**Common/ Shared**
Tags	178556178	174674938			
Mapped	123551476	141039044			
Unique	105445816	120675946			
SNVs	78490	81228			
Not in self-homology			10712	12113	**83**
Intergenic			2300	2680	**7**
Intronic			7652	8601	**63**
Exonic			748	822	**9**
Non-synonymous			497	546	**7**
In IBD regions			106	117	**4**
Probably damaging			97	98	**5**

*The resulting list of unknown SNVs was obtained after filtering by (i) minimal coverage for each of the two exomic sequencing runs (>4 reads/run); (ii) frequency of altered allele (<90%, e.g. heterozygous status of the SNV); (iii) absence of self-homology of the locus in the genome (self-homologous regions were obtained from UCSC table browser by extracting "self-chain" feature for the human genome); (iv) not present in dbSNP137 database.

SNV: single nucleotide variant; IBD: identical by descent.

Table S2. Unknown non-synonymous single nucleotide variants (SNVs) common for family A III-1 and III-5 relatives

N	Chromosome	Position	Ref/Alt	Gene	Accession NCBI	Variant RNA	Variant protein	Prediction*	IBD III-1 / III-5	IBD RCC III-1 / III-5	Coverage Ref	Coverage Alt	Alt/Coverage
1	3	52442072	A/G	*BAP1*[a]	NM_004656.2	c.A277G	p.Thr93Ala	h	1	1	22	8	0.27
2	3	124397063	G/A	*KALRN*[a]	NM_001024660.3 NM_007064.3	c.G7220A c.G2129A	p.Arg2407His p.Arg710His	h	1	1	21	14	0.4
3	7	43484869	G/T	*HECW1*[c]	NM_015052.3	c.G2098T	p.Arg700S	m	0	0	38	8	0.21
4	8	145668066	T/C	*TONSL*[b]	NM_013432.4	c.T572C	p.Leu191Pro	h	0	0	7	6	0.53
5	13	103519045	G/A	*ERCC5*[a]*;* *BIVM-ERCC5*	NM_000123.3 NM_001204425.1	c.G2383A c.G3745A	p.Arg795Thr p.Arg1249Thr	h	1	1	25	21	0.48
6	13	107187273	G/A	*EFNB2*[c]	NM_004093.3	c.G40A	p.Glu14Ser	m	1	1	26	17	0.4
7	14	39647068	T/A	*PNN*[b]	NM_002687.3	c.T446A	p.Leu149X	h	0	0	18	7	0.44

*m – medium and h – high predicted effect on the protein function by PolyPhen.

Ref/Alt: reference allele/alternative allele; IBD: identical by descent; IBD RCC: allelic variant in IBD region retained in the RCC from III-1.

a, b and c: validated, not validated and not tested by Sanger sequencing, respectively.

Table S3. Unknown indel leading to frameshift in coding regions in family A

N	Chromosome	Position	InDel*	Gene	Accession NCBI	Variant RNA	IBD III-1/III-5	Coverage Ref	Coverage Alt	Alt/Coverage
1	20	58587784	I 1	*CDH26*	NM_021810.4 NM_177980.2	c.497delA c.2498delA	0	39	5	0.13

*Short insertions and deletions (InDel) were searched by two different approaches: (i) using Bioscope pipeline (Applied Biosystems) for InDels detection; and (ii) aligning non mapped reads with BWA aligner (with 10 mismatches, 2 gap openings and maximal gap extension of 10 bp) and calling InDels by the SAMtools pileup (Li H, 2009). Short insertions and deletions annotated with SeattleSeq Annotation tool (http://snp.gs.washington.edu/SeattleSeqAnnotation137).
Ref/Alt: reference allele/alternative allele; IBD: identical by descent

Table S4. Identical by descent (IBD) regions and cancers in family A

chr	position	size	Nb SNPs	III-1 kidney breast[a]	III-3 breast	III-5 kidney	III-6 healthy	III-7 lung	III-8 breast	III-9 ACUP	II-8 healthy
3p	47.4-71.7	20.1	8072	1[b]	1	1	1	0	0	1	0
3q	162.9-197.9	7.1	1870	1	1	1	1	1	0	1	1
4p	9.9-28.3	17.5	6713	1	1	1	1	0	0	1	0
4q	139.4-146.2	6.7	1809	1	1	1	0	1	0	0	1
7p	0.1-13.9	6.2	2790	1	1	1	0	1	0	1	0
7q	61.1-71.9	5.2	1689	1	1	1	0	1	1	1	0
7q	155.5-159.0	3.5	980	1	1	1	0	1	0	0	1
13q	99.5-112.0	3.1	1659	1	1	1	1	0	0	1	0
18p	1.6-8.5	6.9	2900	1	1	1	1	1	1	1	0
19p	6.9-24.5	11.1	2126	1	1	1	1	1	1	1	0
20p	13.8-26.3	12.5	5133	1	1	1	0	1	1	1	0

[a] : Segregation analysis was performed based on identical by descend (IBD) regions inferred from the SNP-array genotyping of constitutional DNA (available for 10 individuals). IBD segments for any two individuals were inferred by calculating number of contradictory calls (AA/BB and BB/AA pairs) in a 400 SNPs sliding window; less than 5 contradictory SNP calls per sliding window were taken as compatible with allele sharing; 40 SNPs window was used to narrow down the IBD boundary; minimal region of IBD was set at 3Mb. Segments with haplotype shared between III-1, III-3 and III-5 individuals were compared to other genotyped individuals from the generation III and individual II-8. [b] : "1" indicated IBD and "0", the absence of IBD in this given region. Chr: chromosome; position is given in megabases; size: size of the IBD segment in megabases; Nb SNPs: number of contiguous SNPs in Affymetrix SNP6.0 included in the IBD segment. ACUP: adenocarcinoma of unknown primary origin. Heathy: no reported malignancy.

Table S5. Rare non-synonymous single nucleotide polymorphisms (SNPs) common for family A III-1 and III-5 relatives

N	Chromosome	Position	Ref/Alt	Gene	rsID	MAF	Prediction*	IBD III-1 / III-5	LOH RCC III-1	Coverage Ref	Coverage Alt	Alt/Coverage
1	3	121388135	C/T	*GOLGB1*	rs114155768	0.165	h	1	0	36	13	0.27
2	11	47647238	A/G	*MTCH2*	rs78071782	NA	h	1	0	49	29	0.37
3	11	47647265	A/G	*MTCH2*	rs76666113	0.044	h	1	0	49	25	0.34
4	19	10334725	A/G	*S1PR2*	rs117064827	0.815	h	1	0	7	7	0.50
5	20	13846148	C/T	*SEL1L2*	rs146654307	0.151	h	1	0	20	21	0.51
6	20	42341646	G/A	*MYBL2*	rs138907287	0.055	h	1	0	20	7	0.26

* h – high predicted effect on the protein function by PolyPhen.

Ref/Alt: reference allele/alternative allele; rsID: nomenclature of the single nucleotide polymorphism in dbSNPv137; MAF: minor allele frequency in dbSNPv137; NA: non available; IBD: identical by descent; LOH RCC: loss of heterozygosity of the SNP locus in the RCC from III-1. The gray colomn points out the absence of LOH in family A RCC for all loci, excluding them as gene candidates.

Table S6. Clinical characteristics of the familial renal cell carcinoma (RCC) cohort

ID	Index Case		RCC in the family			Other cancers in the family
	RCC	Age at onset	Relatives	Cancer	Age at onset	
c2_01	ccRCC	39	sister	ccRCC	43	prostate
			father	renal cyst	NA	
c2_02	ccRCC	66	brother	RCC	34	
c2_03	ccRCC	43	aunt	RCC	70	pancreas, breast
			cousin	RCC	50	
c2_04	atypical papillary RCC	65	father	RCC	NA	prostate
			grandfather	RCC	NA	
c2_05	bilateral ccRCC polycystic syndrome	33 NA				
c2_06	ccRCC	30	father	ccRCC	42	
c2_07	ccRCC	53	twin brother	ccRCC	53	
			mother	RCC	58	
c2_08	VHL-like*					
c2_09	ccRCC renal cysts	43 NA	father	RCC	73	
c2_10	ccRCC renal cysts	44 NA	father	ccRCC	44	
			uncle	ccRCC	62	
c2_11	ccRCC renal cysts	42 NA	mother	RCC	54	
			aunt	RCC	NA	
c2_12	ccRCC	40	mother	ccRCC	69	breast
c2_13	RCC	45	brother	RCC	34	naevi, pancreas, breast, lung, prostate
c2_14	bilateral papillary RCC	53	grandfather	bilateral RCC	66	naevi
c2_15	ccRCC	33	mother	RCC	56	
c2_16	ccRCC	62	father	RCC	53	testis
c2_17	ccRCC	58	father	RCC	68	
c2_18	ccRCC	70	son	ccRCC	41	naevi
			daughter	ccRCC	40	
c2_19	ccRCC	38	father	RCC	68	
c2_20	ccRCC	31	father	ccRCC	52	
c2_21	ccRCC	34	brother	ccRCC	54	lung, B-cell lymphoma
c2_22	ccRCC	62	father	RCC	84	
c2_23	angiomyolipoma	45	mother	ccRCC	60	
			brother	RCC	57	

c2_24	ccRCC	48	father	RCC	74	
c2_25	ccRCC	63	brother	bilateral ccRCC	57	
			cousin	RCC	60	
c2_26	ccRCC	45	mother	RCC	NA	
c2_27	bilateral ccRCC	54 & 58	mother	bilateral ccRCC	81 & 84	
c2_28	ccRCC	49	brother	RCC	73	
c2_29	ccRCC	46	cousin	RCC	NA	
c2_30	ccRCC	38	cousin	RCC	55	
c2_31	ccRCC	53	brother	RCC	52	
c2_32	ccRCC	48	father	RCC	46	
c2_33	ccRCC	54	mother	RCC	77	

RCC: renal cell carcinoma, ccRCC clear-cell RCC, NA: non available;
VHL-like*: family with typical Von Hippel Lindau (VHL) syndrome without VHL gene mutation identified. This family was therefore discarded from the study. Age of onset is given in years. This series of individuals was provided by the Centre Expert National Cancers Rares PREDIR, Le Kremlin-Bicêtre, France.

Table S7. Primers used for *BAP1* screening and sequencing

Primer Sequence	Forward (F) or Reverse (R)	Exons covered	Multiplex PCR for EMMA screen[a]
TTGTCTGTGTGTGGGACTGA	F	1 - 2	Mix 1
CTGCGATGAGGAAAGGAAAG	R	1 - 2	Mix 1
TCGGTAAGAGCCTTTTCTCC	F	3	Mix 4
GGCTGCTACAAAAAGGGAAG	R	3	Mix 4
ATCACAGCAAGGACACCTGA	F	4	Mix 3
CCCTTCTCAGCTCCTTTCAT	R	4	Mix 3
GCAAAGATGAAAGGAGCTGA	F	5	Mix 4
CCGCAACTGCATCTAAAAAC	R	5	Mix 4
CCCACCAGCCTTTTAAGAAA	F	6 -7	Mix 1
GGCAATATGGTGTAGGGTGA	R	6 -7	Mix 1
GGGTTTCACCCTACACCATATT	F	8	Mix 2
TGGTACCTTCCAACAAGCTG	R	8	Mix 2
TTCCAGATAGGCCCCTCATA	F	9	Mix 3
GGGCAAAGAAAAGATGTGGT	R	9	Mix 3
TCCCTGTGAGTGAATGGGTA	F	10	Mix 1
ACAGGTGCCTTTCTTTAGGG	R	10	Mix 1
AGAGCTTGCTGACTCCCATT	F	11	Mix 3
AGGATGAACACCAAGGAACC	R	11	Mix 3
CCATGTTGGCTTTCTCTCTGG	F	12	Mix 2
TCAACATTATCTGCTGCAGGG	R	12	Mix 2
GGCTTAGCATGGCTAGTTCA	F	13A	Mix 4
TCCTCTCCAAAAAGCACCTT	R	13A	Mix 4
TCCCAGAAGGACCTCTCAAT	F	13B	Mix 1
TGGGAAGAGAGGTCACAAGA	R	13B	Mix 1
AAGGTGCTTTTTGGAGAGGA	F	14	Mix 2
GAAAGTCTTCTGGCACATGG	R	14	Mix 2
AAGAGGTAGAGACCCTTGAGCA	F	15 -16	Mix 4
CTGAGCCAGCATGGAGATAA	R	15 -16	Mix 4
CGCTGCTGTCTTAACTGGAA	F	17	Mix 2
TCTCCAGCTGGGACTATTCA	R	17	Mix 2

[a]Screening for *BAP1* mutations was performed using Enhanced Mismatch Mutation Analysis (EMMA, Fluigent (Houdayer C, 2010)). 4 multiplex PCR were used to screen *BAP1* exons. *BAP1* coding regions were divided into amplicons of 450 bp or less. Raw data were analyzed using the dedicated Emmalys software (Fluigent, P/N: 5331254102). Heteroduplexes were detected by PCR fragments migration on ABI PRISM® 3100 Genetic Analyser (Applied Biosystems). For abnormal EMMA profiles, *BAP1* exons were amplified with the same set of primers and sequenced with BigDye Terminator V1.1, and analyzed using Seqscape V2.5 software (Applied Biosystems) according to the standard protocols.

Table S8. Clinical characteristics of familial cases with UM, MPM or CM

ID	Center for diagnosis	Index Case			BAP1 associated cancers in relatives				Other cancers in the family	BAP1 status
		sex	Cancer	Age at onset	Relative	sex	Cancer	Age at onset		
c1_01	IC	F	UM	69	cousin	M	UM	58	lung, pancreas, breast	wt
c1_02	IC	M	UM	33	cousin	M	UM	55		wt
c1_03	IC	M	UM	55	father	M	UM	77	prostate, breast	wt
c1_04	IC	M	UM	70	sister	F	UM	70		wt
c1_05	IC	M	UM	73	niece	F	UM	55	esophagus	wt
					sister	F	CM	NA		
c1_06	IC	M	UM	68	sister	F	UM	NA	histiocytoma, ovary, blood, prostate, lung, colon	wt
c1_07	IC	F	UM	70	sister	F	UM	43	myeloma, pituitary, brain	wt
					sister	F	CM	62		
c1_08	IC	F	UM	47	aunt	F	UM	49		wt
c1_09	IC	F	UM	69	cousin	M	UM	67	lung	wt
c1_10	IC	F	UM	47	mother	F	CM	64	colon	wt
c1_11	IC	F	UM	53	brother	M	2XCM	63	breast	wt
c1_12	IC	F	UM	30	uncle	M	CM	34	lung	wt
					aunt	F	CM	NA		
c1_13	IC	M	UM	68	daughter	F	CM	51	lymphoma, breast, prostate	wt
c1_14	IC	F	UM	63	niece	F	CM	43	breast, colon	wt
					niece	F	RCC	43		
c1_15	IC	F	UM	60	sister	F	CM	NA	colon, stomach	wt
					niece	F	CM	NA		
c1_16	IC	M	UM	38	mother	F	CM	27	prostate	wt
c1_17	IC	M	UM	66	brother	M	CM	39	breast, colon	wt
c1_18	IC	F	UM	43	father	M	CM	54	stomach, uterus, liver, bladder	wt
c1_19	IC	M	UM	24	uncle	M	CM	50	head-and-neck	wt
c1_20	IC	F	UM	22	grandmother	F	CM	65	breast	wt
c1_21	IC	F	UM	65	mother	F	CM	74	colon, liver	wt
c1_22	IC	M	UM CM	37 38	grandfather	M	CM	69		wt
c1_23	IC	F	UM	65	father	M	CM	85	pancreas, colon, breast	wt
c1_24	IC	M	UM	71	mother	F	CM	90	stomach, pancreas	wt
					grandfather	M	CM	75		

c1_25	IC	M	UM RCC	55, 58 56	aunt	F	CM	NA	cervix	wt
					aunt	F	RCC	NA		
c1_26	IC	F	UM	12	grandaunt	F	CM	50	testis	wt
c1_27	IC	F	UM	36	uncle	M	CM	55	breast	wt
					uncle	M	RCC	39		
					grandfather	M	RCC	NA		
c1_28	IC	F	MPM	60	father	M	MPM	60	leukemia	wt
					uncle_1	M	MPM	60		
					uncle_2	M	MPM	48		
c1_29	IC	F	MPM	49	cousin	M	MPM	49	prostate, lung	wt
c1_30	IC	F	UM	65	sister	F	CM	71	breast, lung, colon, prostate, uterus	wt
c1_31	IGR	F	UM	43	father	M	CM	70		wt
					cousin	M	CM	44		
c1_32	IGR	M	CM	58	sister	F	UM	48	NA	wt
c1_33	IC/IGR	F	MPM	62	brother	M	MPM	50	liver, thyroid	wt
					brother	M	RCC	50		
c1_34	IGR	M	CM	62	father	M	UM	50	NA	wt
c1_35	HB	F	CM	90	son	M	UM	NA	endometrium	wt
c1_36	HB	M	UM	24	father	M	CM	60	pancreas	wt
c1_37	HB	F	CM	40	uncle	M	UM	NA	CNS	wt
					grandfather	M	UM	NA		
					granduncle	M	UM	NA		
c1_38	HB	F	CM	NA	brother	M	CM	NA	prostate	wt
					father	M	UM	NA		
c1_39	HB	M	CM	76	brother	M	UM	NA	prostate	wt
c1_40	HB	M	CM	49	mother	F	UM	NA	NA	wt
c1_41	HB	F	CM	58	cousin	M	UM	NA	breast	wt
c1_42	HB	M	CM	60	mother	F	UM	NA	NA	wt
c1_43	HB	F	UM	51	nephew_1	M	CM	NA	NA	wt
					nephew_2	M	CM	NA		
c1_44	HB	F	CM	44	mother	F	UM	NA	NA	wt
c1_45	HB	F	CM	49	mother	F	UM	NA		wt
c1_46	HB	M	CM	63	maternal cousin	F	UM	NA	breast	wt
					uncle	M	CM	NA		
c1_47	HB	F	CM	49	brother	M	UM	NA	basal cell carcinoma, breast, colon	wt
					cousin	M	CM	NA		
c1_48	HB	M	UM CM	40 40						wt
c1_49	HB	F	UM CM	43 43					NA	wt

c1_50 family B	NHCS	M	UM RCC	35 36	brother	M	UM	49		mut
					uncle	M	UM	NA		
					sister	F	RCC	54		
					mother	F	RCC	57		
c1_51 family C	IC	M	UM MPM	52 59	twin brother	M	UM	53	bladder, colon	mut
					twin brother	M	MPM	59		
					cousin	F	MPM	41		
					aunt	F	RCC	50		
c1_52 family E	IC	F	UM	44	father	M	MPM		thyroid, bladder	mut
					grandfather	M	MPM			
c1_53 family F	CHHG	M	MPM	41	father	M	MPM	64		mut
c1_54 family G	HC	F	CM RCC	29,31,34 NA	father	M	MPM	59		mut
					brother	M	CM	49		
					sister	F	UM	57		
c1_55 family I	IJG	F	UM	44	father	M	CM	66		mut
c1_56 family J	HB	F	UM	53	brother_1	M	MPM	51	uterus, lung	mut
					brother_2	M	CM	45		
					brother_2	M	RCC	53		
					sister	F	RCC	33		
					nephew	M	UM	18		
c1_57 family K	HB	F	CM	47, 52	mother	F	CM	58	breast, lung	mut
					brother_1	M	CM	55		
					brother_2	M	MPM	38		
					brother_3	M	RCC	34		
					sister	F	UM	42		
c1_58 family D	IC	M	UM CM	48 34	mother	F	UM	70	breast, lung	mut
					grandfather	M	RCC	55		
c1_59 Family H	HC	M	MPM	62	brother	M	MPM	59	breast	mut
c1_60 family L	HB	M	CM	47	mother	F	UM	71	colon, prostate	mut

UM, uveal melanoma; CM, cutaneous melanoma; RCC, renal cell carcinoma; MPM, malignant pleural mesothelioma; CNS, tumor of the central nervous system; NA, not available. Age of onset is indicated in years. *BAP1* status: *BAP1* gene mutational status of the index case is indicated. mut: deleterious mutation; wt: wild-type. Center of diagnosis: IC: Institut Curie, Paris, France; HC: Hopital Cochin, Paris, France; IGR: Institut Gustave Roussy, Villejuif, France; HB: Hopital Bichat – Claude Bernard, Paris, France; NHCS: Nouvel Hopital Civil de Strasbourg , Strasbourg, France; CHHG: Centre Hospitalier Georges Renon, Niort, France; IJG: Institut Jean Godinot, Reims, France.

Table S9. Clinical characteristics of families carrying a *BAP1* deleterious mutation

Family	Individual	Cancers	Age at onset	BAP1 status	Gender	status
family B	I-1	RCC	57		F	deceased
	I-2	no			F	deceased
	I-3	UM	NA		M	deceased
	II-1	UM; RCC	49; 36	mut	M	alive
	II-2	RCC	54		F	deceased
	II-3	UM	35		NA	alive
	III-1	Spinal tumor	NA		M	alive
	III-2	no			F	alive
	III-3	no			F	alive
	III-4	no			M	alive
	III-5	no			M	deceased
	III-6	no			F	alive
	III-7	no			F	alive
	III-8	no			F	alive
family C	I-1	RCC	50		F	deceased
	I-2	no			F	unknown
	I-3	Digestive tract cancer	45		M	deceased
	I-4	MPM	54		M	deceased
	II-1	no			F	alive
	II-2	no			M	alive
	II-3	Unknown origin	NA	wt	M	deceased
	II-4	MPM	41	mut	F	alive
	II-5	MPM; UM	59; 52	mut	M	alive
	II-6	UM	54	mut	M	deceased
family D	I-1	RCC	55		M	deceased
	I-1	Lung	NA		NA	unknown
	II-1	UM	70		F	deceased
	II-2	no			M	deceased
	II-3	no			F	alive
	III-1	no			M	alive
	III-2	CM; UM; Basal-cell carcinoma	34; 48; 51	mut	M	alive
	III-3	no			M	alive
	III-4	no			M	alive
	III-5	no			F	alive
	III-6	no			M	alive
	III-7	UM	44		M	alive
family E	I-1	MPM	60		M	deceased
	II-1	MPM; Thyroid; Bladder	60; 55; 58		M	deceased
	III-1	UM; Thyroid	44; 34	mut	F	deceased
	III-2	no			F	alive
	III-3	no			M	deceased

family F	I-1	MPM	64		M	deceased
	II-1	MPM	41	mut	M	deceased
	II-2	NA	NA		M	alive
family G	I-1	MPM	59		M	deceased
	II-1	CM; Lung	49; 50	mut	M	deceased
	II-2	UM	57	mut	F	alive
	II-3	CM; RCC	29; 36	mut	F	alive
	II-4	no		wt	M	alive
	II-5	no		wt	M	alive
	II-6	no		wt	F	alive
family H	I-1	MPM	NA		M	deceased
	I-2	no			F	alive
	I-3	MPM	62	mut	M	alive
	II-1	no			F	alive
	II-2	no			F	alive
	II-3	no			M	alive
	II-4	no			F	alive
	II-5	no			F	alive
family I	I-1	CM	66		M	deceased
	II-1	UM	44	mut	F	deceased
family J	I-1	UM; Lung	53; 53	mut	F	alive
	I-2	CM; RCC	45; 53	mut	M	alive
	I-3	RCC	33		F	alive
	I-4	MPM	NA		M	alive
	I-5	no			M	alive
	I-6	no			M	alive
	I-7	no			F	alive
	I-8	no			M	alive
family K	I-1	CM	58		F	deceased
	II-1	CM	47; 52	mut	F	alive
	II-2	MPM	38		M	alive
	II-3	RCC	34		M	deceased
	II-4	UM	42		F	deceased
	II-5	no			F	alive
	II-6	CM	55		M	alive
	II-7	no			M	alive
	II-8	no			F	alive
	II-9	no			F	alive
family L	I-1	UM	39		F	deceased
	I-2	Prostate	63		M	alive
	II-1	CM	47	mut	M	alive
	II-2	no			M	alive

UM, uveal melanoma; CM, cutaneous melanoma; RCC, renal cell carcinoma; MPM, malignant pleural mesothelioma; no, no cancer reported; NA, not available. Age of onset is indicated in years. *BAP1* status: *BAP1* gene mutational status is indicated when biological sample available. mut: deleterious mutation; wt: wild-type.

Table S10. Estimation of lifetime risk for RCC in *BAP1* mutated families

	Number of individuals in the cohort	RCC in BAP1 mutated families	Lifetime risk of RCC[a]	P value binomial test[b]	95% CI	Risk	Relative risk
Male	36	5	0.0056	$<10^{-4}$	0.023-0.2	0.085	~15
Female	45	4	0.0021	$<10^{-7}$	0.04-0.28	0.13	~59
Unknown	2	0					

[a]Lifetime risk of renal cell carcinoma (RCC) in the French population estimated for women and men from (Belot A, 2008)

[b]Probability to have 5 and 4 RCCs by the age of 90 in the male and female cohorts, respectively.

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