Figure S1. Distribution of PBRM1 expression according to *PBRM1* mutational status. PBRM1, polybromo 1; wt, wild-type.

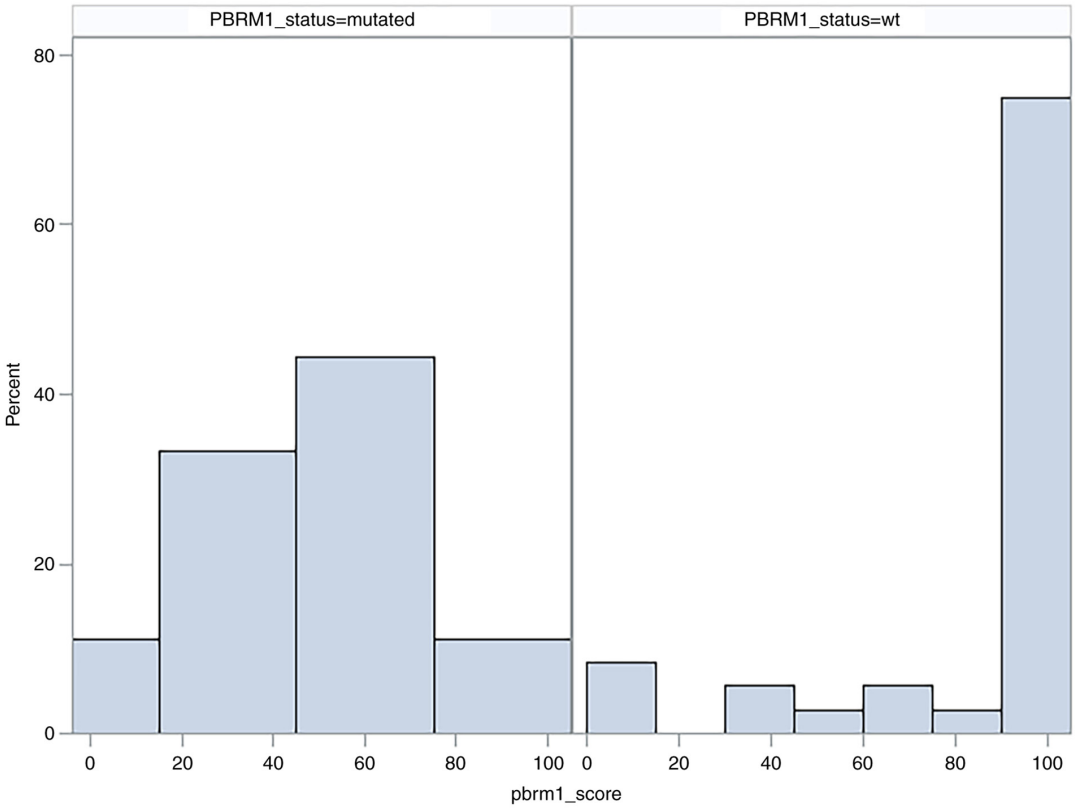

Table SI. *PBRM1* mutational status in VHL-associated and sporadic ccRCC.

Tumor number	Sex	Age, years	Type of RCC	Size, cm	ISUP grade	Stage	VHL status	CGH array results on 3p	*PBRM1* mutation	*PBRM1* exon	Mutation type	COSMIC[a]
50201	M	31	VHL-ccRCC	8.5	3, high	3a, high	Mutated	Loss	c.1248delA, p.Lys416fs	11	Frameshift	1 description
5953	F	34	VHL-ccRCC	3.8	4, high	3b, high	Mutated	*nd*	c.A2258C, p.His753Pro	16	Missense	1 frameshift
2203	M	61	VHL-ccRCC	6.6	3, high	3a, high	Mutated	*nd*	c.T4672G, p.Tyr1557X	28	Nonsense	No description
4667	F	70	sporadic ccRCC	9	3, high	3b, high	Mutated	Loss	c.A1129T, p.Thr377Ser; c.G1765A, p.Asp589Asn	11 14	Missense	No description/1 description
5887	M	85	sporadic ccRCC	12	2, low	3a, high	Mutated	Loss	c.T1674G, p.Tyr558X	14	Nonsense	1 missense
8527	F	77	sporadic ccRCC	5.5	2, low	3b, high	Mutated	*nd*	c.C3129G, p.Tyr1043X	20	Nonsense	1 description
1919	F	75	sporadic ccRCC	6	2, low	3b, high	Wild-type	Loss	c.C3441G, p.Tyr1147X	21	Nonsense	No description
7294	F	65	sporadic ccRCC	6	4, high	3b, high	Mutated	Loss	c.4022delCTCT, p.Ser1341fs	24	Frameshift	No description
5835	M	60	sporadic ccRCC	5	2, low	1b, low	Mutated	Loss	c.G4279T, p.Glu1427X	25	Nonsense	No description

[a]COSMIC (https://cancer.sanger.ac.uk/cosmic), the description represents the number of somatic mutations already reported in this database. At the same amino-acid position, some different mutations were described (frameshift or missense). COSMIC, The Catalogue Of Somatic Mutations in Cancer; PBRM1, polybromo 1; VHL, Von Hippel-Lindau; ccRCC, clear-cell renal cell carcinoma; ISUP, International Society of Urological Pathology; M, male patients; F, female patients; CGH, comparative genomic hybridization; nd, not determined.

Table SII. PBRM1 expression by IHC according to *PBRM1* mutational status.

PBRM1 expression by IHC	*PBRM1* wild-type (n=36)	*PBRM1* mutated (n=9)
Intensity, median (interquartile range)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Percentage, median (interquartile range)	100.0 (85.0-100.0)	50.0 (30.0-50.0)
Continuous score[a], median (interquartile range)	100.0 (85.0-100.0)	50.0 (30.0-50.0)
Qualitative score by IHC[b]		
Negative staining, % (n)	16.7 (6)	88.9 (8)
Positive staining, % (n)	83.3 (30)	11.1 (1)

[a]Score was calculated as the product between intensity and percentage; [b]qualitative score was derived from continuous score using a cut-off of 50% where negative staining was ≤50% and positive staining was >50%. In terms of *PBRM1* mutation, 57.1% (8/14) mutations were observed in PBRM1-negative tumors compared with 3.2% (1/31) in PBRM1-positive tumors. IHC, immunohistochemistry; PBRM1, polybromo 1.

Table SIII. Association between *PBRM1* mutational status and pathological data according to VHL-associated and sporadic ccRCC series.

A, Tumor stage

	VHL-ccRCC, % (n)			Sporadic ccRCC, % (n)			Overall, % (n)		
PBRM1 mutational status	Low	High	P-value	Low	High	P-value	Low	High	P-value
Wild-type	75.0 (15)	25.0 (5)	P=0.03	56.3 (9)	43.8 (7)	P=0.16	66.7 (24)	33.3 (12)	P<0.01
Mutated	0.0 (0)	100.0 (3)		16.7 (1)	83.3 (5)		11.1 (1)	88.9 (8)	

B, ISUP grade

	VHL-ccRCC, % (n)			Sporadic ccRCC, % (n)			Overall, % (n)		
PBRM1 mutational status	Low	High	P-value	Low	High	P-value	Low	High	P-value
Wild-type	55.0 (11)	45.0 (9)	P=0.22	43.8 (7)	56.3 (9)	P=0.64	50.0 (18)	50.0 (18)	P=1.00
Mutated	0.0 (0)	100.0 (3)		66.7 (4)	33.3 (2)		44.4 (4)	55.6 (5)	

P-values were obtained by comparing PBRM1 wild-type with PBRM1 mutated results. P=0.005 was obtained after controlling for series (VHL and sporadic ccRCC; Cochran-Mantel-Haenszel) in the tumor grade assessment. P=0.75 was obtained after controlling for series (VHL and sporadic ccRCC; Cochran-Mantel-Haenszel) in the ISUP grade assessment. PBRM1, polybromo 1; VHL, Von Hippel-Lindau; ccRCC, clear-cell renal cell carcinoma; ISUP, International Society of Urological Pathology.

Table SIV. Distribution of HIF subtypes according to *PBRM1* mutational status in VHL-associated and sporadic ccRCC series.

A, VHL-ccRCC

	HIF subtypes				P-values		
PBRM1 mutational status	Double Negative, % (n)	HIF1$^+$, % (n)	HIF1$^+$/HIF2$^+$, % (n)	HIF2$^+$, % (n)	PBRM1 vs. all HIF staining	PBRM1 vs. HIF1$^+$ and HIF1$^+$/HIF2$^+$	PBRM1 vs. HIF2$^+$ and HIF1$^+$/HIF2$^+$
Wild-type (n=20)	0.0 (0)	50.0 (10)	35.0 (7)	15.0 (3)	P=1.00	P=1.00	P=1.00
Mutated (n=3)	0.0 (0)	66.7 (2)	33.3 (1)	0.0 (0)			
All (n=23)[a]	0.0 (0)	52.2 (12)	34.8 (8)	13.0 (3)			

B, Sporadic ccRCC

	HIF subtypes				P-values		
PBRM1 mutational status	Double Negative, % (n)	HIF1$^+$, % (n)	HIF1$^+$/HIF2$^+$, % (n)	HIF2$^+$, % (n)	PBRM1 vs. all HIF staining	PBRM1 vs. HIF1$^+$ and HIF1$^+$/HIF2$^+$	PBRM1 vs. HIF2$^+$ and HIF1$^+$/HIF2$^+$
Wild-type (n=16)	0.0 (0)	37.5 (6)	18.8 (3)	43.8 (7)	P=0.34	P=0.40	P=0.20
Mutated (n=6)	16.7 (1)	50.0 (3)	0.0 (0)	33.3 (2)			
All (n=22)[a]	4.6 (1)	40.9 (9)	13.6 (3)	40.9 (9)			

C, Overall

	HIF subtypes				P-values		
PBRM1 mutational status	Double Negative, % (n)	HIF1$^+$, % (n)	HIF1$^+$/HIF2$^+$, % (n)	HIF2$^+$, % (n)	PBRM1 vs. all HIF staining	PBRM1 vs. HIF1$^+$ and HIF1$^+$/HIF2$^+$	PBRM1 vs. HIF2$^+$ and HIF1$^+$/HIF2$^+$
Wild-type (n=36)	0.0 (0)	44.4 (16)	27.8 (10)	27.8 (10)	P=0.28	P=0.27	P=0.14
Mutated (n=9)	11.1 (1)	55.6 (5)	11.1 (1)	22.2 (2)			
All (n=45)	2.0 (1)	47.0 (21)	24.0 (11)	27.0 (12)			

P-values were obtained by comparing HIF subtypes with PBRM1 mutational status. P=0.29 was obtained after controlling for series (VHL and sporadic ccRCC; Cochran-Mantel-Haenszel) in the overall group. When regrouping HIF1$^+$ with HIF1$^+$/HIF2$^+$, P=0.24 was obtained, which was not significant. When regrouping HIF2$^+$ with HIF1$^+$/HIF2$^+$, P=0.16 was obtained, which was not significant. [a]P-value comparing HIF distribution between VHL-ccRCC and sporadic ccRCC was 0.06. PBRM1, polybromo 1; VHL, Von Hippel-Lindau; ccRCC, clear-cell renal cell carcinoma; HIF, hypoxia inducible factor.