Supplementary Materials: Ischemia Is Related to Tumour Genetics in Uveal Melanoma

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Table S1. Clinical characteristics of the TCGA study group ($n = 80$).

	Total	HIF1a		VHL	
CATEGORICAL	Cases (%)	Median	*p*-Value	Median	*p*-Value
Gender					
Male	45 (56)	9.95	0.72 [#]	8.05	0.95 [#]
Female	35 (44)	9.96		7.95	
Side					
Right eye (OD)	NA	NA	NA	NA	NA
Left eye (OS)	NA	NA		NA	
TNM cat. (8th)					
T1	0 (0)	NA	0.71 [*]	NA	0.80 [*]
T2	14 (18)	9.85		8.00	
T3	32 (40)	9.91		7.96	
T4	34 (43)	10.00		8.06	
Tumour pigmentation					
Light	39 (49)	10.30	0.012 [#]	8.34	<0.001 [#]
Dark	41 (51)	9.75		7.80	
Cell Type					
Spindle	43 (54)	9.75	0.048 [#]	7.95	0.87 [#]
Mixed + epithelioid	37 (46)	10.15		8.07	
Ciliary body involvement					
No	64 (80)	9.84	0.15 [#]	7.96	0.95 [#]
Yes	16 (20)	10.17		8.15	
Metastasis					
No	53 (66)	9.82	0.21 [#]	7.95	0.35 [#]
Yes	27 (34)	10.10		8.07	
Melanoma-Related Death					
No	60 (75)	9.89	0.25 [#]	8.00	0.12 [#]
Yes	20 (25)	10.10		8.01	
		Correlation		Correlation	
NUMERICAL	**Total**	**Spearman**	*p*-Value	**Spearman**	*p*-Value
Age – Median	61.5	0.048	0.67	−0.135	0.23
LBD – Median	16.0	−0.048	0.67	0.026	0.82
Prominence - Median	11.0	−0.062	0.59	−0.030	0.80

The *p*-values were calculated with the following: # Mann-Whitney *U* test, * Jonckheere test for trend.

Abbreviations: TNM, tumor node metastasis; LBD, largest basal diameter; Cat, category.

Table S2. Analysis of HIF1a and VHL mRNA expression in relation to chromosome status and BAP1 (based on the *n* = 80 cases from the TCGA data).

	Total	HIF1a		VHL	
CATEGORICAL	Cases (%)	Median	*p*-Value	Median	*p*-Value
All patients					
Chromosome 3					
D3	37 (46)	9.78	0.018 *	8.43	0.004 *
M3	37 (46)	10.19		7.95	
Chromosome 8q					
Normal	21 (26)	9.92	0.88	8.43	0.047 *
Gain	59 (74)	9.96		7.95	
BAP1 status					
Negative	40 (50)	10.27	0.002 *	7.91	0.023 *
Positive	40 (50)	9.69		8.27	
Sub group analysis					
Within D3 lesions					
D3/BAP1−	1	10.75	0.17	9.36	0.11
D3/BAP1+	35	9.78		8.43	
Within M3 lesions					
M3/BAP1−	34	10.35	0.014 *	7.95	0.29
M3/BAP1+	3	8.69		7.30	
Within D3/BAP1+ lesions					
D3/BAP1+/n8q	16	10.06	0.088	8.58	0.37
D3/BAP1+/8qgain	19	9.21		7.96	

The *p*-values were calculated with the Mann-Whitney *U* test; * indicates significant *p*-values. BAP1 status was based on mRNA expression data, dichotomized at the median into BAP1-positive and BAP1-negative. Abbreviations: BAP1+, BAP1-positive; BAP1-, BAP1-negative; n8q, normal chromosome 8q; 8qgain, gain of chromosome 8q; D3, disomy 3; M3, monosomy 3; IHC, immunohistochemistry.

Table S3. Univariate and multivariate regression analysis on HIF1a and VHL expression (based on the *n* = 80 cases from the TCGA data, with known chromosome 3 status in 74 cases).

	HIF1a		VHL	
Variables	B (95%CI)	*p*-Value	B (95%CI)	*p*-Value
Univariate regression				
Chr. 3 (M3 vs. D3)	0.53 (0.13; 0.92)	0.010 *	−0.47 (−0.80; −0.14)	0.005 *
BAP1 (BAP1− vs. BAP1+)	−0.64 (−1.01; −0.28)	0.001 *	0.32 (0.001; 0.64)	0.049 *
LBD (per mm increase)	−0.003 (−0.06; 0.05)	0.92	0.007 (−0.04; 0.05)	0.74
Multivariate regression				
Model 1				
Chr. 3	−0.55 (−1.39; 0.29)	0.20	−1.14 (−1.85; −0.43)	0.002 *
BAP1	−1.21 (−2.05; −0.36)	0.006 *	−0.75 (−1.46; −0.04)	0.039 *
Model 2				
LBD	−0.01 (−0.06; 0.04)	0.67	0.01 (−0.03; 0.05)	0.61
BAP1	−0.66 (−1.04; −0.28)	0.001 *	0.31 (−0.02; 0.64)	0.061
Model 3				
LBD	−0.04 (−0.09; 0.02)	0.21	0.02 (−0.03; 0.06)	0.48
Chr. 3	0.60 (0.18; 1.01)	0.006 *	−0.48 (−0.83; −0.14)	0.006 *
Univariate regression				
Within D3 (n = 37)				
LBD	−0.04 (−0.13; 0.04)	0.33	0.01 (−0.06; 0.08)	0.74
Within M3 (n = 37)				
LBD	−0.03 (−0.11; 0.05)	0.47	0.02 (−0.04; 0.09)	0.47

* indicates significant *p*-values. Abbreviations: CI, confidence interval; Chr. 3, chromosome 3; LBD, largest basal diameter; D3, disomy 3; M3, monosomy 3.

Table S4. Overview of hypoxia and angiogenesis-related genes.

mRNA	Name	Locus	EntrezID	Probe name	Probe number	Remarks
Ischemic markers						
HIF1A	Hypoxia Inducible Factor-1alpha	14q23.2	3091	HIF1A_p1	ILMN_2379788	
VHL	Von Hippel–Lindau	3p25.3	7428	VHL_p2	ILMN_1738579	
Vascular markers						
VEGF-A	Vascular Endothelial Growth Factor-A	6p21.1	7422	VEGFA_p1	ILMN_2375879	
VEGF-B	Vascular Endothelial Growth Factor -B	11q13.1	7423	VEGFB_p3	ILMN_1722855	
VEGF-C	Vascular Endothelial Growth Factor-C	4q34.3	7424	VEGFC_p1	ILMN_1701204	
PECAM1	Platelet Endothelial Cell Adhesion Molecule 1	17q23.3	5175	PECAM1_p1	ILMN_1689518	Also known as: CD31
CD34	Cluster of Differentiation 34	1q32.2	947	CD34_p1	ILMN_2341229	
VWF	Von Willebrand Factor	12p13.31	7450	VWF_p1	ILMN_1752755	
Immune infiltrate						
CD3D	Cluster of Differentiation 3D	11q23.3	915	CD3D_p1	ILMN_2261416	Lymphocyte marker
CD4	Cluster of Differentiation 4	12p13.31	920	CD4_p1	ILMN_1727284	Lymphocyte marker
CD8A	Cluster of Differentiation 8A	2p11.2	925	CD8A_p3	ILMN_2353732	Lymphocyte marker
CD68	Cluster of Differentiation 68	17p13.1	968	CD68_p1	ILMN_1714861	Macrophage marker
Other markers						
BAP1	*BRCA1* Associated Protein1	3p21.1	8314	BAP1_p1	ILMN_1768363	