BMC Cancer

RESEARCH

Open Access

Factors that predict progression of von Hippel-Lindau disease-related malignancy: a longitudinal cohort study

Jae Ho Lee[1†], Hyun Young Lee[2†], Ji Eun Park[3*], Min-Ju Kim[4], Dae Wook Hwang[5], Sangjoon Chong[6], Moinay Kim[6], Joo Yong Lee[7], Cheryn Song[8] and Beom Hee Lee[9]

Abstract

Background Von Hippel-Lindau (vHL) disease encompasses various genetic subtypes with poorly defined progression patterns. This retrospective study of a longitudinal cohort aimed to characterize follow-up duration, treatment rates, and progression patterns according to genomic subtype, and to identify risk factors for progression.

Methods Between June 2003 and June 2020, the study enrolled 94 patients (mean age, 37.1 years; 49 females; 84 with missense mutations and 10 with truncating (i.e., insertion/deletion) mutations in the *VHL* tumor suppressor gene). MRI and CT imaging data were analyzed to compare tumor incidence between the two mutation groups. Cox regression analysis was used to assess predictors of hemangioblastoma (Hb) and renal cell carcinoma (RCC) progression based on genetic subtype, tumor volume, and clinical characteristics.

Results Patients with missense mutations were more often treated for RCC ($p = 0.013$) and adrenal pheochromocytoma ($p < 0.001$) than those with truncating mutations; however, genetic subtype was not a significant predictor of time-to-progression of Hb or RCC. Larger tumor volume at baseline was an independent predictor of Hb progression (HR, 1.029; 95% CI, 1.013–1.046; $p < 0.001$) and RCC (HR, 1.011; 95% CI, 1.005–1.017; $p < 0.001$). Male sex was also an independent predictor of RCC progression (HR, 3.368; 95% CI, 1.351–8.396; $p = 0.009$).

Conclusions Genetic subtype was not associated with progression of vHL disease, but missense mutations were associated with higher treatment rates for RCC and adrenal pheochromocytoma. The finding that progression of Hb and RCC is linked to larger baseline tumor volume and male sex may facilitate clinical management.

Keywords Von Hippel-Lindau (vHL) disease, Genetic subtypes, Tumor progression, Initial tumor volume, Male sex

[†]Jae Ho Lee and Hyun Young Lee are the co-first authors of this paper.

*Correspondence:
Ji Eun Park
jieunp@gmail.com
[1] Department of Radiology and Center for Imaging Science, Thyroid Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[2] Department of Urology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea
[3] Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-gil, Songpa-gu, Seoul, Korea
[4] Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, 86 Asanbyeongwon-Gil, Songpa-Gu, Seoul, Korea
[5] Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-Gil, Songpa-Gu, Seoul, Korea
[6] Department of Neurosurgery, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-Gil, Songpa-Gu, Seoul, Korea
[7] Department of Ophthalmology, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-Gil, Songpa-Gu, Seoul, Korea
[8] Department of Urology, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-gil, Songpa-gu, Seoul, Korea
[9] Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-Gil, Songpa-Gu, Seoul, Korea

Background

Von Hippel-Lindau (vHL) disease manifests as an autosomal dominant disorder characterized by high penetrance, which varies with age. The condition arises from germline mutations in the *VHL* gene, which is located on chromosome 3p25-26 and encodes the vHL protein (213 amino acids) [1]. The syndrome leads to significant morbidity and mortality and exhibits variable expression, manifesting as diverse phenotypes in terms of age at onset, type of manifestation, and tumor burden across various organs throughout life [1]. Recent molecular studies have shed light on the genetic subtypes of vHL syndrome; for example, patients with neuroendocrine tumors exhibit germinal mutations located mainly in exons 3 and 1, as well as a specific mutation (P86S), whereas patients with renal cell carcinoma (RCC) exhibit more truncating mutations than missense mutations [2–4]. Thus, treatment rates and progression trajectories according to genetic subtype remain poorly characterized.

Defining risk factors for vHL disease is important, and involves consultation with the patient and their family with respect to determining imaging surveillance and follow-up intervals. A recent guideline states that all patients with vHL disease should undergo imaging surveillance (MRI of the CNS, including both brain and spine), including use of contrast agents, as well as imaging of the abdomen, from 15 years old.

Nonetheless, there are no specific references to genomic variations of *VHL* [5]. The imaging surveillance and follow-up guidelines can be updated if risk factors for progression are identified, or differences in progression patterns according to particular genetic mutations can be found. The study hypothesis was as follows: do genetic alterations affect patterns of progression in terms of median TTP, as defined by an increase in tumor volume or development of a new lesion?

Therefore, we examined follow-up duration, treatment rates, and progression patterns (stratified by genomic subtype) in a longitudinal cohort of patients with vHL syndrome to identify risk factors for tumor progression.

Materials and methods

Patient population

This retrospective analysis was approved by the institutional review board (IRB number: 2020–1240) and adhered to the regulations of the Health Insurance Portability and Accountability Act. The need for written informed consent was waived by the IRB due to the retrospective nature of the study.

Initially, the study enrolled patients and family members suspected of having vHL syndrome based on imaging examinations or family history; subsequent genetic tests were requested between June 2003 and June 2020. The inclusion criteria were as follows: 1) subjects who completed gene testing for vHL; and 2) baseline imaging examinations of the CNS (brain and spine) and abdomen (kidney, pancreas, and adrenal gland), along with available follow-up images at least for 1-year. Patients were excluded when if baseline imaging was absent or follow up was inadequate.

Demographic (age, gender), imaging date, tumor characteristics (presence/absence of tumor, tumor location, and size), and germline genetic data (missense mutation/truncation mutation) were collected from each patient by a medical chart review conducted by two medical doctors (J.H.L., with 5 years of experience in neuroradiology and H.Y.L., with 5 years of experience in urology).

Genetic analysis

Assessment of *VHL* mutations and determination of germline genotype was conducted by analyzing peripheral blood samples obtained from either the study participant or a familial relative. *VHL* germline mutational status was determined by polymerase chain reaction (PCR) using previously documented *VHL* primers, followed by Sanger sequencing of the PCR products [6].

The *VHL* mutations comprised primarily missense mutations, small insertions or deletions, frame shifts, and splice site mutations. In cases involving large fragment deletions, multiplex ligation-dependent probe amplification (MLPA) analysis was conducted using MRC Holland's SALSA MLPA probe, according to standard protocols [7, 8]. All affected offspring of vHL patients were divided into two groups: those with missense mutations (all point mutations, excluding stop mutations) and those with a truncating mutation (stop mutations, nonsense mutation, small deletion/insertion, splice site mutation, or large fragment deletion) [9]. These *VHL* mutations were analyzed to identify prevalent variants, with subsequent analysis aimed at delineating their association with clinical phenotypes.

Imaging and analysis

Imaging of vHL disease after diagnosis was conducted in accordance with recently updated guidelines [5]. Below the age of 15 years, MRI images of the CNS (including both brain and spine), including the use of contrast agents, were obtained. Above the age of 15 years, MRI of the CNS (including both brain and spine), including use of contrast agents, and imaging of the abdomen (preferably by contrast-enhanced MRI) were obtained. MRI scans of the brain or spine were obtained either with 1.5 T or 3.0 T, using gadolinium-based contrast agents. For the abdomen, contrast-enhanced CT was the baseline examination, with follow-up imaging conducted by MRI

if renal cysts, RCC, or pancreatic neuroendocrine tumors (NET) were suspected.

Two radiologists (J.H.L and J.E.P, with 2 and 10 years, respectively, of experience in oncologic imaging) assessed all images (baseline and follow up) independently using a picture archiving and communication system. The readers recorded the presence of CNS (brain and spine) hemangioblastoma (Hb), RCCs, renal cysts, pheochromocytomas, pancreas serous cystadenomas, and pancreatic NETs on baseline CT, or on MRI scans taken at the baseline and follow up.

Detailed analyses of Hb and RCC included the following: 1) presence or absence of lesions, 2) number and location, 3) size (uni-dimensional, mm), 4) presence of a new lesion during follow up, 4) date of detection of the new lesion, and 5) the date of baseline and follow-up imaging, and the date of the final image. The number and volume of brain Hbs and RCCs at baseline was recorded. If a tumor was present at baseline but absent or decreased in size at the last follow-up, it was defined as "treated disease".

Definition of progression and death

Progression was defined as tumor growth of ≥ 5 mm, an increase in size ≥ 20%, or development of a new lesion or metastasis [10, 11]. Time-to-progression (TTP) was defined as the time between the initial image and the time of tumor removal or image confirming progression. Progression was determined by board-certified radiologists (J.E.P. and H.S.K. with 10 years and 25 years of experience, respectively, in oncologic imaging); any discrepancies were resolved by discussion. OS was calculated from the date of baseline imaging to the date of death from any cause. The date of death was obtained from the national health care data linked to our hospital, and the date of the last follow-up imaging was taken as the censored date.

Statistical analysis

Continuous variables are presented as the median (interquartile range) or as the mean and standard deviation, and categorical variables as numbers (percentages). Differences in clinicopathological factors between two groups were assessed using the Chi-square test for categorical variables, and Student's t-test for continuous variables.

Patients were divided into two groups: those with truncating mutations and those with missense mutations that lead to a single amino-acid change. Patterns of progression and TTP were analyzed and compared in the context of these genetic alterations.

Survival analysis was conducted using Kaplan–Meier plots, and data were analyzed using the log-rank test. A Cox proportional hazard regression model was used to assess the effects of genotype, age, sex, and initial tumor volume on the risk of the brain hemangioblastomas and RCC, and on risk of death in the different groups. A p value < 0.05 was considered statistically significant. Statistical analyses were performed by a biostatistician (M.J.K., with 15 years of experience) using R software version 4.1.2 (https://www.r-project.org).

Results

Patient characteristics

A total of 104 patients were initially enrolled in the study based on the inclusion criteria, and 7 patients without baseline imaging and 3 patients with inadequate follow-up were excluded based on the exclusion criteria. (Fig. 1).

Finally, a total of 94 patients with vHL (23 were related family members) were evaluated (84 patients with a missense mutation and 10 patients with a truncating mutation of insertion/deletion). The mean age at enrollment was 37.1 years [37.3 years for the missense mutation group and 35.6 years for the truncation mutation group]. The proportion of females and males among patients with missense mutations was approximately 52.4% ($n = 44$) and 47.6% ($n = 40$), respectively, and was similarly distributed among patients with truncating mutations at 5% (5 individuals each) without statistical difference. Patient sex and the follow-up duration for each subtype of tumor are summarized in Table 1.

Baseline imaging revealed no significant difference in the presence of Hb (brain or spine), RCC, renal cysts, pheochromocytoma, serous cystadenoma, or NETs between the two groups. The median follow-up duration was slightly longer for brain Hb patients with missense mutations group (median, 6.8 years; IQR, 3.35–10.58 years, $p = 0.032$) than for those with truncating mutations (median, 4.08 years; IQR, 2.29–4.59 years, $p = 0.032$). There were no significant differences between the groups in terms of age, sex, and median follow-up duration for the other diseases (RCC, renal cysts, pheochromocytoma, serous cystadenoma, or NETs).

Hb and RCC: paired comparison of tumor characteristics between baseline and follow up

At baseline, there was no significant difference in the median number or volume of brain Hbor RCC tumors between patients with missense mutations and truncating mutations.

The paired comparison between baseline and follow-up characteristics is shown in Table 2. Overall, adrenal pheochromocytoma was the most commonly identified and treated tumor during the study interval ($n = 21$ [25.61%]; $p < 0.001$). When comparing the two mutation groups, we found that patients in the missense mutation group received more treatments for RCC and

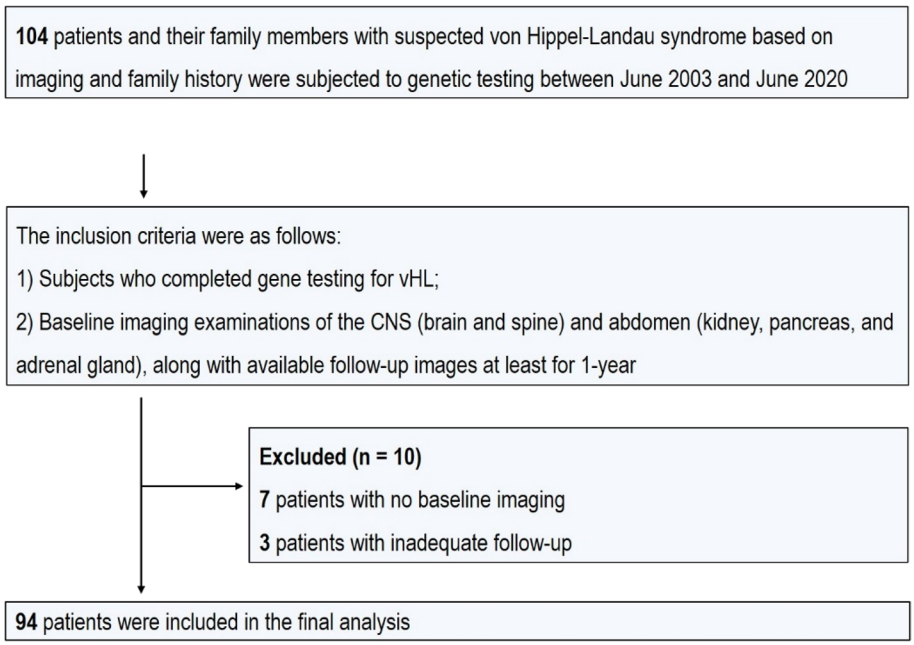

Fig. 1 Flow chart showing the study inclusion and exclusion criteria

Table 1 Clinical characteristics of patients with vHL syndrome

Characteristic	All	Missense mutation	Truncation mutation	*P* value (between two groups)
Number of patients	94	84	10	
Age (years)	37.12 ± 16.39	37.30 ± 16.34	35.60 ± 17.59	.759
Sex				
Female	49 (52.13%)	44 (52.38%)	5 (50.00%)	> .999
Male	45 (47.87%)	40 (47.62%)	5 (50.00%)	
Baseline				
Hemangioblastoma, brain	53 (61.63%)	47 (60.26%)	6 (75.00%)	.705
Median number	2 (1,5)	2 (1, 5)	3.5 (1, 5)	.660
Median volume (ml)	22 (8, 35)			
Renal cell carcinoma	27 (30.00%)	25 (31.25%)	2 (20.00%)	.717
Median number	2 (1, 4)	2(1, 3)	3 (1, 5)	.730
Median volume (ml)	40 (24, 102)	40 (25, 80)	89.5 (24, 155)	.746
Hemangioblastoma, spine	43 (55.13%)	40 (55.56%)	3 (50.00%)	> .999
Renal cysts (Kidney cysts)	47 (52.22%)	40 (50.00%)	7 (70.00%)	.320
Adrenal, pheochromocytoma	25 (27.47%)	22 (27.16%)	3 (30.00%)	> .999
Pancreas, serous cystadenoma	28 (31.11%)	23 (28.4%)	5 (55.56%)	.130
Pancreas, NET	15 (16.67%)	13 (16.05%)	2 (22.22%)	.642
Median FU duration (years)				
Hemangioblastoma, brain	6.32 (3.16, 9.89)	6.80 (3.35, 10.58)	4.08 (2.29, 4.59)	**.032**
Renal cell carcinoma	6.12 (2.61, 11.27)	6.18 (2.99, 11.33)	4.94 (1.24, 6.83)	.170

NET Neuroendocrine tumor, *FU* Follow up

Table 2 Paired comparison of data at baseline and at last follow up, according to the type of genetic alteration

Organ	ALL					Missense mutation					Truncation mutation				
	baseline	Last FU			*P*-value	baseline	Last FU			*P*-value	baseline	Last FU			*P*-value
		No	Yes	total			No	Yes	total			No	Yes	total	
Hemangioblastoma, brain	+	8 (10.13)	44 (55.7)	52 (65.82)	.132	+	6 (8.45)	40 (56.34)	46 (64.79)	.317	+	2 (25)	4 (50)	6 (75)	.157
Renal cell carcinoma	**total**	32 (40.51)	47 (59.49)	79 (100)	.090	total	28 (39.44)	43 (60.56)	71 (100)	**.013**	total	4 (50)	4 (50)	8 (100)	.317
	+	12 (14.63)	15 (18.29)	27 (32.93)		+	11 (15.07)	14 (19.18)	25 (34.25)		+	1 (11.11)	1 (11.11)	2 (22.22)	
Hemangioblastoma, spine	**total**	62 (75.61)	20 (24.39)	82 (100)	.739	total	57 (78.08)	16 (21.92)	73 (100)	.739	total	5 (55.56)	4 (44.44)	9 (100)	> .999
	+	5 (8.62)	31 (53.45)	36 (62.07)		+	5 (9.09)	29 (52.73)	34 (61.82)		+	0 (0)	2 (66.67)	2 (66.67)	
	total	23 (39.66)	35 (60.34)	58 (100)		total	22 (40)	33 (60)	55 (100)		total	1 (33.33)	2 (66.67)	3 (100)	
Renal cysts (Kidney cysts)	+	1 (1.24)	42 (52.5)	43 (53.75)	.180	+	1 (1.39)	36 (50)	37 (51.39)	.180	+	0 (0)	6 (75)	6 (75)	> .999
Adrenal,	**total**	34 (42.5)	46 (57.5)	80 (100)	**<.001**	total	32 (44.44)	40 (55.56)	72 (100)	**<.001**	total	2(25)	6 (75)	8 (100)	.317
	+	21 (25.61)	4 (4.88)	25 (30.49)		+	20 (27.03)	2 (2.7)	22 (29.73)		+	1 (12.5)	2 (25)	3 (37.5)	
Pheochromocytoma	**total**	76 (92.68)	6 (7.32)	82 (100)	.317	total	70 (94.59)	4 (5.41)	74 (100)	.564	total	6 (75)	2 (25)	8 (100)	.317
Pancreas, serous cystadenoma	+	3 (3.7)	24 (29.63)	27 (33.33)		+	2 (2.74)	20 (27.4)	22 (30.14)		+	1 (12.5)	4 (50)	5 (62.5)	
	total	56 (69.14)	25 (30.86))	81 (100)		total	52 (71.23)	21 (28.77)	73 (100)		total	4 (50)	4 (50)	8 (100)	
Pancreas, NET	+	7 (8.54)	8 (9.76)	15 (18.29)	.366	+	6 (8.11)	7 (9.46)	13 (17.57)	.317	+	1 (12.5)	1 (12.5)	2 (25)	> .999
	total	70 (85.37)	12 (14.63)	82 (100)		total	64 (86.49(	10 (13.51)	74 (100)		total	6 (75)	2 (25)	8 (100)	

adrenal pheochromocytoma ($p=0.013$ and $p<0.001$, respectively) than those in the truncation mutation group (Fig. 2).

Significantly more patients in the missense mutation group were treated for RCC ($n=11$ *vs.* 1; $p=0.013$). Likewise, significantly more patients in the missense mutation group were treated for adrenal pheochromocytoma ($n=20$ *vs.* 1; $p<0.001$).

Progression pattern of Hb and RCC according to genetic mutation group

Supplementary Table 1 depicts the progression patterns according to the type of genetic mutation. Overall, there were no significant differences in progression patterns between the missense and truncating mutation groups in terms of volume at the time of progression or development of a new Hb or RCC lesion.

Predictors of Hb and RCC progression and death

The results of Cox proportional hazard regression analysis are summarized in Table 3. Genetic alterations were not a significant predictor for TTP either for Hb ($p=0.438$) or RCC ($p=0.114$).

In patients with brain Hb, both univariable (HR, 1.028; 95% CI, 1.013–1.044; $p<0.001$) and multivariable Cox proportional regression analysis (HR, 1.029; 95% CI, 1.013–1.046; $p<0.001$) identified a larger tumor volume at baseline as being significantly associated with progression (Fig. 3).

Of the 27 patients with RCC on baseline imaging, metastasis was observed in 4 patients (14.5%, with 3 males, all carrying missense mutations) and 6 died. Of the 63 patients without RCC on baseline imaging, 9 developed RCC during follow-up, with no fatalities. Metastasis occurred in 2 (22.2%) of these patients, both of whom were male and carried missense mutations.

In univariable analysis in patients with RCC, both larger initial tumor volume (HR, 1.011; 95% CI, 1.005–1.017; $p<0.001$) and male sex (HR, 3.965; 95% CI, 1.651–9.522; $p=0.002$) were significantly associated with progression (Figs. 4). These data were confirmed by multivariable analysis (HR, 1.011; 95% CI, 1.005–1.017, $p<0.001$; and HR, 3.368; 95% CI, 1.351–8.396, $p=0.009$, respectively).

For OS, only initial larger volume of RCC was associated with shorter OS in univariable (HR, 1.011; 95% CI, 1.003–1.019; $p=0.005$) and multivariable analysis (HR, 1.022; 95% CI, 1.003–1.042; $p=0.021$).

Discussion

Here, we investigated differences in tumor incidence, treatment, and progression patterns during the follow up of patients with different genetic subtypes of vHL disease.

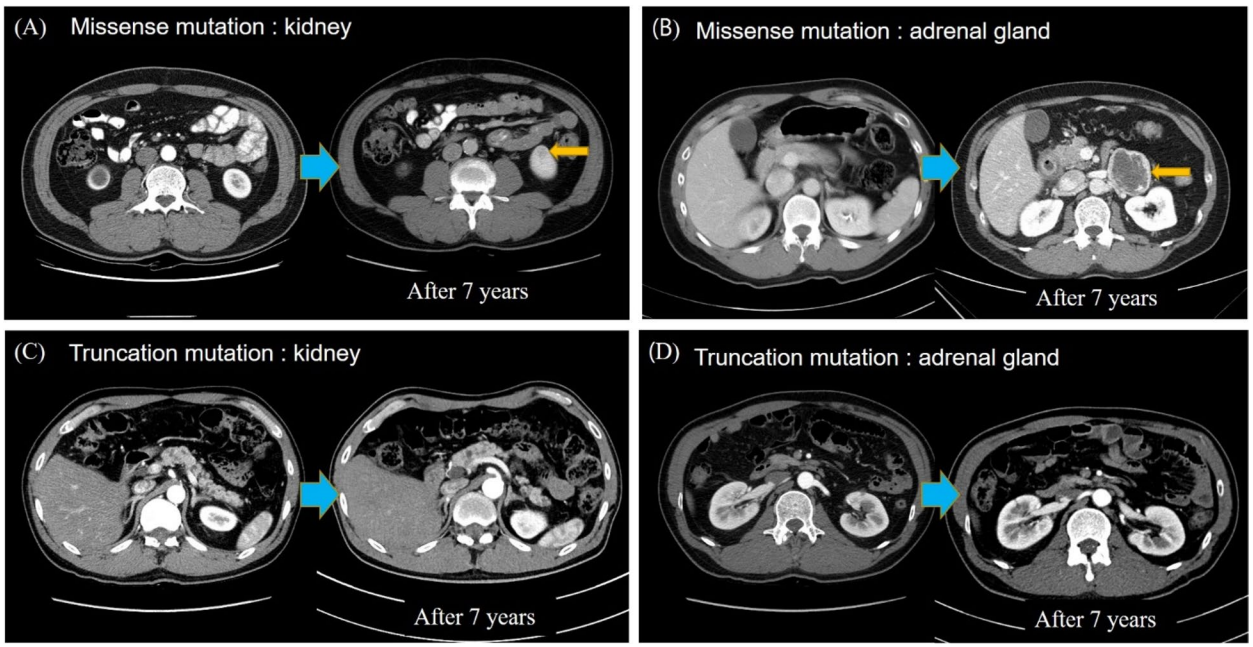

Fig. 2 Baseline and follow up (7-year) axial CT images from two patients of the same age and sex: one with a missense mutation and one with a truncation mutation. **A** A male patient in his early 50 s with a missense mutation and no RCC on baseline CT developed a small RCC (1.0 cm) in upper pole of the right kidney on follow-up CT scan. **B** He also developed a large pheochromocytoma (6.2 cm) in the left adrenal gland. (C & D) Another male patient of the same age with a truncation mutation had no RCC nor adrenal pheochromocytoma on a baseline CT scan. The patient had developed no new lesion at the time of follow-up CT

Table 3 Cox proportional hazard regression based on the type of genetic alteration, clinical variables, and tumor volume

	Univariable Analysis		Multivariable Analysis	
Variable	**Hazard Ratio**	***P* value**	**Hazard Ratio**	***P* value**
Hemangioblastoma, brain (*n* = 72)				
Genetic mutation groups	1.627 (0.475, 5.573)	.438	0.801 (0.206, 3.120)	.750
Age	1.001 (0.978, 1.024)	.952	0.999 (0.974, 1.024)	.922
Sex (male *vs.* female)	0.822 (0.400, 1.692)	.595	0.923 (0.423, 2.015)	.840
Initial volume	1.028 (1.013, 1.044)	**< .001**	1.029 (1.013, 1.046)	**< .001**
Renal cell carcinoma (*n* = 82)				
Genetic mutation groups	2.408 (0.811, 7.150)	.114	2.387 (0.771, 7.388)	.131
Age	0.980 (0.953, 1.007)	.145	0.978 (0.946, 1.011)	.191
Sex (male *vs.* female)	3.965 (1.651, 9.522)	**.002**	3.368 (1.351, 8.396)	**.009**
Initial volume	1.011 (1.005, 1.017)	**< .001**	1.011 (1.005, 1.017)	**< .001**

Genetic subtype groups are comparison between truncation mutation and missense mutation groups (reference: missense mutation)

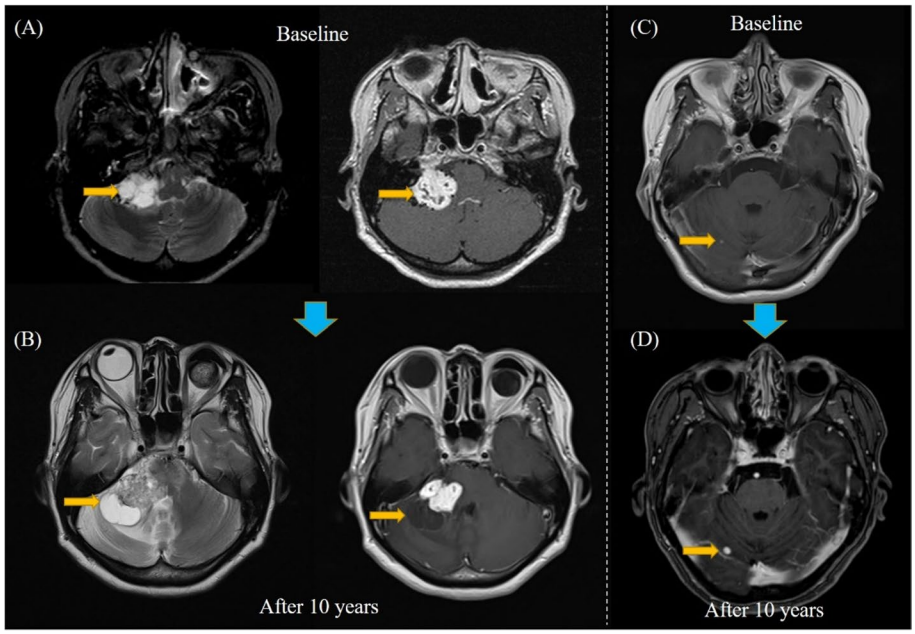

Fig. 3 Baseline and 10-year follow-up MRI images of the brains of two male patients in their late 40 s with missense mutations and brain hemangioblastomas with different volumes at baseline. **A** Axial T2-weighted and enhanced T1-weighted images reveal a relatively large hemangioblastoma (2.5 cm) in the right cerebellum of one patient. **B** The 10-year-follow-up MRI images show a marked increase in size (4.0 cm), with significant increase in the cystic portion. **C** Axial enhanced T1-weighted image reveals a tiny hemangioblastoma (0.2 cm) in the right cerebellum of another patient. **D** The 10-year-follow-up axial enhanced T1-weighted image shows a marginal increase in the size (0.5 cm) of the tumor

Patients with a missense mutation were treated more frequently for RCC and adrenal pheochromocytoma than those with a truncating mutation. Neither of these two genetic mutations were associated with progression of brain Hb or RCC. Rather, a larger tumor volume at baseline was associated with a greater risk of Hb and RCC progression, regardless of genetic group. In addition, male sex was associated with a higher risk of RCC progression. Thus, the data presented herein identified two major risk factors for progression within our longitudinal cohort of patients with vHL syndrome.

A greater proportion of patients in the missense mutation group than in the truncation group underwent treatment for RCC and adrenal pheochromocytoma. In the case of pheochromocytoma, prior studies indicate that missense mutations are frequently associated

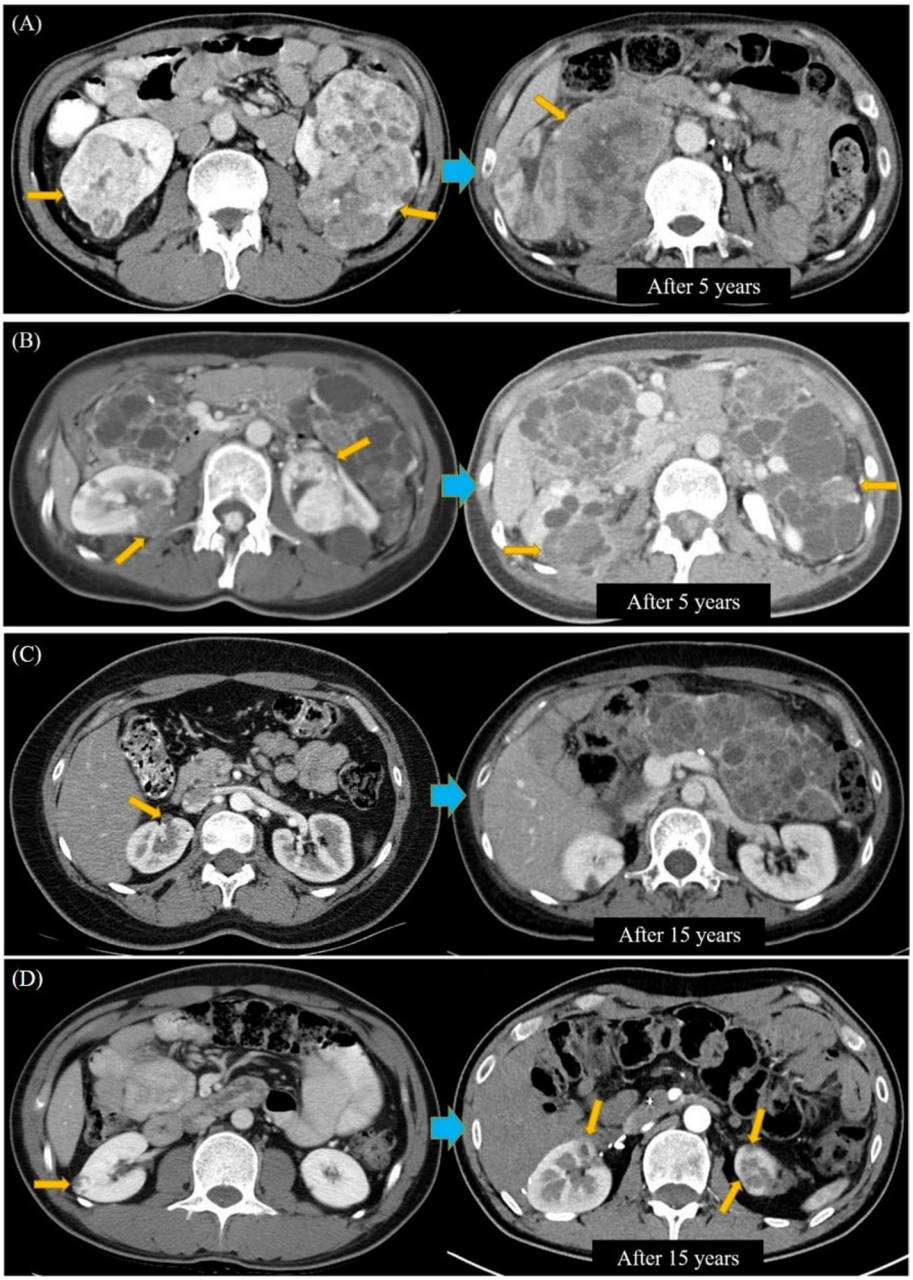

Fig. 4 Baseline and follow-up axial CT images of two patients of the same age and sex, both of whom had a missense mutation but different RCC volumes at baseline. **A** left A male patient in his early 40 s with large RCCs (~ 6.1 cm) in both kidneys. **A** right The patient underwent left radical nephrectomy and right partial nephrectomy, and the 5-year follow-up CT scan shows a large recurrent RCC (4.9 cm) in the mid pole of the right kidney. **B** left Another male patient of the same age with small RCCs (~ 2.0 cm) in both kidneys. **B** right A 5-year follow-up CT scan shows relatively small increase in the size of the RCCs (~ 3.8 cm) in both kidneys. **C** left. Baseline axial CT image of a female patient in her 40 s with a small RCC (0.5 cm) in the upper pole of the right kidney. She underwent tumorectomy and (**C**, right) a 15-year follow-up axial CT scan shows no recurrence. **D** left Baseline axial CT image of a male patient of the same age with a RCC in the mid pole of the right kidney. He underwent right and left partial nephrectomy, followed by radiofrequency ablation for bilateral RCC during the follow-up period. **D** right A 15-year follow-up axial CT scan shows multiple recurrent RCCs in both kidneys

with increased susceptibility to developing pheochromocytoma [12–15]. With respect to RCC, however, our findings contradict those of previous studies [3, 12, 16] showing that germline exon deletions and truncating mutations predispose individuals to RCC, and that mutations resulting in truncated proteins may increase the risk

of RCC in vHL patients. This may be because the median follow-up period (6.18 years) for the missense mutation group was longer than that for the truncation group (4.94 years), resulting in lead time bias. Another reason may be that the treatment rate is affected by decisions made by patients and doctors that more patients were treated for incidentally found early RCC in missense mutation group while they treated and followed-up with adjacent adrenal pheochromocytoma.

We also found that a larger tumor volume at baseline was significantly associated with progression among patients with hereditary brain Hb. By contrast, prior studies indicate that tumor size in those with sporadic CNS hemangioblastomas does not significantly impact survival [17], nor does it serve as a significant prognostic indicator [18]. This discrepancy may stem from differences in the nature of sporadic and hereditary Hbs. Notably, in vHL disease, enlargement of tumor cysts occurs at a much faster pace than in sporadic Hbs, leading to localized compression of adjacent tissue and an increased risk of hemorrhage and decompensation of the brain stem [19]. Moreover, hereditary Hbs may exhibit a more aggressive phenotype than sporadic cases, which is attributable to their rapid growth pattern or multifocal evolution [20–22].

In terms of progression patterns between the missense mutation and truncation groups, multivariable analyses revealed that a larger tumor volume at baseline was independently associated with progression of RCC and brain Hb. Peng et al. previously reported that in patients with VHL disease, RCC with larger initial tumor size (>4 cm) and missense mutations exhibited faster tumor growth [23]. In our study, missense mutations were not associated with a faster tumor growth rate. According to the findings of Liu et al., patients in the non-HIF-α binding site missense mutation group exhibited a lower risk of RCC compared to those in the combined HM and truncation group [14]. Our study may have had a high prevalence of HIF-α binding site missense mutations, which could have contributed to these findings. It is well known that in cases of sporadic RCC, baseline tumor size is associated with adverse survival outcomes, thereby serving as a prognostic indicator for poor recurrence-free survival and cancer-specific survival [24–26]. To the best of our knowledge, our study is the first to demonstrate an association between progression of hereditary RCC and tumor size at baseline.

Notably, multivariablee analysis also identified male sex as being independently associated with progression in patients with hereditary RCC. The prognostic significance of sex in patients with sporadic RCC remains controversial. Previous studies note a twofold higher incidence of sporadic RCC in men than in women [27], and that females present with less advanced tumor stage than males, and exhibit better cancer-specific survival outcomes [28]. By contrast, Majdoub et al. [24] concluded that sex had no influence on recurrence-free survival or cancer-specific survival in those with sporadic RCC. In addition, two large cohort studies demonstrated no disparities in cancer-specific survival rates between sexes, despite males being more frequently diagnosed at an advanced tumor stage [29, 30]. At present, evidence concerning the association between male sex and prognosis of hereditary RCC is lacking. Nonetheless, based on the outcomes of our investigation, male sex could potentially be linked to a poorer prognosis in individuals with hereditary RCC.

Of note, there was relatively small proportion of truncating mutations than missense mutations when compared with previous studies. Binderup et al. included 52 VHL mutation carriers in their study, reporting that patients with truncating mutations (57.7%) were more prevalent than those with missense mutations (42.3%) [15]. Additionally, in a study by van Houwelingen et al. conducted on patients with sporadic renal cell carcinoma, the majority of mutations were truncating mutations (47%) [31]. The lower proportion of truncating mutations compared to missense mutations in our study may be attributed to the fact that our cohort was based on genotype identified through genetic testing and missense mutations can exhibit variable phenotypic expression. Previous studies often selected cohorts based on phenotype, potentially leading to a higher proportion of truncating mutations. This is because truncating mutations, compared to missense mutations, involve more significant nucleotide changes and are more likely to manifest phenotypically.

Consequently, the proportion of truncating mutations in our genotype-based cohort may be lower than in phenotype-based cohorts from previous studies. Notably, a study by Hwang et al., which included 77 genetically confirmed VHL disease patients, also demonstrated a higher proportion of missense mutations (62.3%) compared to truncating mutations (33.8%), consistent with our findings [32]. Furthermore, our study included a larger cohort of over 100 genetically confirmed VHL disease patients. Nevertheless, a larger cohort study would be necessary to further investigate this aspect.

This study has several limitations. First, the number of patients was small and restricted to a single ethnic group, limiting the generalizability of the study results. Second, although genetic subgroups are diverse, we simplified them into two groups: missense mutations and truncating mutations and subgroup analysis was not feasible due to the small number of patients in each group. A multi-national study of a large cohort is

needed to examine genotype–phenotype correlations. Third, the imaging interval was not standardized, and the follow-up interval was not regular, which led to lead time bias, particularly with respect to RCC treatment rates in the missense mutation group.

In conclusion, our data show that genetic subtype is not associated with progression; however, patients with missense mutation have a higher incidence of RCC and adrenal pheochromocytoma than those with a truncating mutation. Progression of Hb and RCC is associated with a larger tumor volume at baseline and with male sex. When vHL patients hold these two risk factors, close monitoring is warranted. Defining risk factors for vHL disease will facilitate meaningful consultation with patients and their families, as well as future imaging surveillance.

Abbreviations

CNS	Central nervous system
CT	Computed tomography
Hbll	Hemangioblastoma
HR	Hazard ratio
MLPA	Multiplex ligation-dependent probe amplification
MRI	Magnetic resonance imaging
NET	Neuroendocrine tumors
PACS	Picture archiving and communication system
PCR	Polymerase chain reaction
RCC	Renal cell carcinoma
TTP	Time to progression
Vhl	Von Hippel-Lindau

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13985-5.

Supplementary Material 1.

Acknowledgements
None.

Authors' contributions
JH Lee determined the study concepts/design and acquired, analyzed, and interpreted the patient data regarding the vHL disease and the genetic subtypes. JH Lee also carried out the literature research, statistical analysis, and manuscript editing, and was a major contributor in writing the manuscript. HY Lee took part in literature research and interpreting the patient data on the genitourinary diseases related to vHL disease, statistical analysis, and manuscript editing. JE Park was the guarantor of the integrity of the entire study and was involved in determining the study concepts/design, data acquisition /analysis/interpretation, literature research, and manuscript editing. MJ Kim had a major role in the data analysis and statistical analysis of the patient data. C Song and DW Hang contributed to the literature research on the genitourinary and pancreatic manifestations of the vHL disease respectively, and manuscript editing. SJ Chong and M Kim were involved in the literature research on the brain and spine Hbll of the vHL disease and manuscript editing. JY Lee provided the clinical experiences and insight from the literature research on the retinal and brain Hbll of the vHL disease. BH Lee was a major contributor in the literature research on the genetics of the vHL disease and manuscript editing. Lastly, all authors were involved in manuscript drafting/revision for important intellectual content, approved the final version of the submitted manuscript, and agreed to ensure any questions related to the work were appropriately resolved.

Funding
This research received funding from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, Information and Communication Technologies & Future Planning (RS-2023–00305153); and the Ministry of Health & Welfare, Republic of Korea (HI22C0471 and HI22C1723).

Data availability
Data used in this study can be obtained from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Asan Medical Center Institutional Review Board (IRB number: 2020–1240) which waived the requirement for informed consent because the patient images were collected retrospectively, and identification information was removed for Health Insurance Portability and Accountability Act (HIPAA) compliance. This study was conducted in accordance with the declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 16 October 2024 Accepted: 20 March 2025
Published online: 28 March 2025

References

1. Latif F, Tory K, Gnarra J, Yao M, Duh FM, Orcutt ML, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science. 1993;260(5112):1317–20.
2. Bukavina L, Bensalah K, Bray F, Carlo M, Challacombe B, Karam JA, et al. Epidemiology of renal cell carcinoma: 2022 update. Eur Urol. 2022;82(5):529–42.
3. Gallou C, Joly D, Mejean A, Staroz F, Martin N, Tarlet G, et al. Mutations of the VHL gene in sporadic renal cell carcinoma: definition of a risk factor for VHL patients to develop an RCC. Hum Mutat. 1999;13(6):464–75.
4. Corcos O, Couvelard A, Giraud S, Vullierme MP, O'Toole D, Rebours V, et al. Endocrine pancreatic tumors in von Hippel-Lindau disease: clinical, histological, and genetic features. Pancreas. 2008;37(1):85–93.
5. Louise MBM, Smerdel M, Borgwadt L, Beck Nielsen SS, Madsen MG, Moller HU, et al. von Hippel-Lindau disease: updated guideline for diagnosis and surveillance. Eur J Med Genet. 2022;65(8):104538.
6. Wang X, Zhang N, Ning X, Li T, Wu P, Peng S, et al. Higher prevalence of novel mutations in VHL gene in Chinese Von Hippel-Lindau disease patients. Urology. 2014;83(3):675.e1-5.
7. Wang JY, Peng SH, Li T, Ning XH, Liu SJ, Hong BA, et al. Risk factors for survival in patients with von Hippel-Lindau disease. J Med Genet. 2018;55(5):322–8.
8. Peng S, Shepard MJ, Wang J, Li T, Ning X, Cai L, et al. Genotype-phenotype correlations in Chinese von Hippel-Lindau disease patients. Oncotarget. 2017;8(24):38456–65.
9. Nordstrom-O'Brien M, van der Luijt RB, van Rooijen E, van den Ouweland AM, Majoor-Krakauer DF, Lolkema MP, et al. Genetic analysis of von Hippel-Lindau disease. Hum Mutat. 2010;31(5):521–37.
10. Tirosh A, Sadowski SM, Linehan WM, Libutti SK, Patel D, Nilubol N, et al. Association of VHL genotype with pancreatic neuroendocrine tumor phenotype in patients with von Hippel-Lindau Disease. JAMA Oncol. 2018;4(1):124–6.
11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.

12. McNeill A, Rattenberry E, Barber R, Killick P, MacDonald F, Maher ER. Genotype-phenotype correlations in VHL exon deletions. Am J Med Genet A. 2009;149A(10):2147–51.
13. Dhanda M, Agarwal A, Mandal K, Gupta S, Sabaretnam M, Chand G, et al. Clinical, biochemical, tumoural and mutation profile of VHL- and MEN2A-associated pheochromocytoma: a comparative study. World J Surg. 2022;46(3):591–9.
14. Liu SJ, Wang JY, Peng SH, Li T, Ning XH, Hong BA, et al. Genotype and phenotype correlation in von Hippel-Lindau disease based on alteration of the HIF-alpha binding site in VHL protein. Genet Med. 2018;20(10):1266–73.
15. Binderup ML, Budtz-Jørgensen E, Bisgaard ML. Risk of new tumors in von Hippel-Lindau patients depends on age and genotype. Genet Med. 2016;18(1):89–97.
16. Ong KR, Woodward ER, Killick P, Lim C, Macdonald F, Maher ER. Genotype-phenotype correlations in von Hippel-Lindau disease. Hum Mutat. 2007;28(2):143–9.
17. Yin X, Duan H, Yi Z, Li C, Lu R, Li L. Incidence, prognostic factors and survival for hemangioblastoma of the central nervous system: analysis based on the surveillance, epidemiology, and end results database. Front Oncol. 2020;10:570103.
18. Wang Q, Meng S, Cheng J, Zhang S, Ju Y, Fang Y, et al. Central nervous system hemangioblastomas: an age-stratified analysis. Clin Neurol Neurosurg. 2020;199:106281.
19. Mazzapicchi E, Restelli F, Falco J, Broggi M, Gatti L, Alongi P, et al. Sporadic and von Hippel-Lindau related hemangioblastomas of brain and spinal cord: multimodal imaging for intraoperative strategy. Cancers (Basel). 2022;14(22).
20. Peyre M, David P, Van Effenterre R, François P, Thys M, Emery E, et al. Natural history of supratentorial hemangioblastomas in von Hippel-Lindau disease. Neurosurgery. 2010;67(3):577–87; discussion 587.
21. Resche F, Moisan JP, Mantoura J, de Kersaint-Gilly A, Andre MJ, Perrin-Resche I, et al. Haemangioblastoma, haemangioblastomatosis, and von Hippel-Lindau disease. Adv Tech Stand Neurosurg. 1993;20:197–304.
22. Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. J Neurosurg. 2003;98(1):82–94.
23. Peng X, Chen J, Wang J, Peng S, Liu S, Ma K, et al. Natural history of renal tumours in von Hippel-Lindau disease: a large retrospective study of Chinese patients. J Med Genet. 2019;56(6):380–7.
24. Majdoub M, Yanagisawa T, Quhal F, Laukhtina E, von Deimling M, Kawada T, et al. Role of clinicopathological variables in predicting recurrence and survival outcomes after surgery for non-metastatic renal cell carcinoma: Systematic review and meta-analysis. Int J Cancer. 2024;154(7):1309–23.
25. Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, et al. Epidemiology of renal cell carcinoma. World J Oncol. 2020;11(3):79–87.
26. Zequi SdC, Mourão TC, de Oliveira MM, Curado MP, Gueglio G, da Costa WH, et al. Predictors of survival outcomes in non-metastatic renal cell carcinoma in Latin America and Spain: a multicentric analysis. Kidney Cancer. 2019;3(4):253–61.
27. Scelo G, Li P, Chanudet E, Muller DC. Variability of sex disparities in cancer incidence over 30 years: the striking case of kidney cancer. Eur Urol Focus. 2018;4(4):586–90.
28. Beisland C, Medby PC, Beisland HO. Renal cell carcinoma: gender difference in incidental detection and cancer-specific survival. Scand J Urol Nephrol. 2002;36(6):414–8.
29. Aron M, Nguyen MM, Stein RJ, Gill IS. Impact of gender in renal cell carcinoma: an analysis of the SEER database. Eur Urol. 2008;54(1):133–40.
30. Woldrich JM, Mallin K, Ritchey J, Carroll PR, Kane CJ. Sex differences in renal cell cancer presentation and survival: an analysis of the National Cancer Database, 1993–2004. J Urol. 2008;179(5):1709–13 discussion 13.
31. van Houwelingen KP, van Dijk BA, Hulsbergen-van de Kaa CA, Schouten LJ, Gorissen HJ, Schalken JA, et al. Prevalence of von Hippel-Lindau gene mutations in sporadic renal cell carcinoma: results from The Netherlands cohort study. BMC Cancer. 2005;5:57.
32. Hwang S, Kang SW, Kim JW, Kim SJ. Genotype-phenotype correlation of ocular von Hippel-Lindau disease in Koreans. PLoS ONE. 2024;19(10):e0311665.

Publisher's Note