Interhospital Endocrine Conference 2/2566

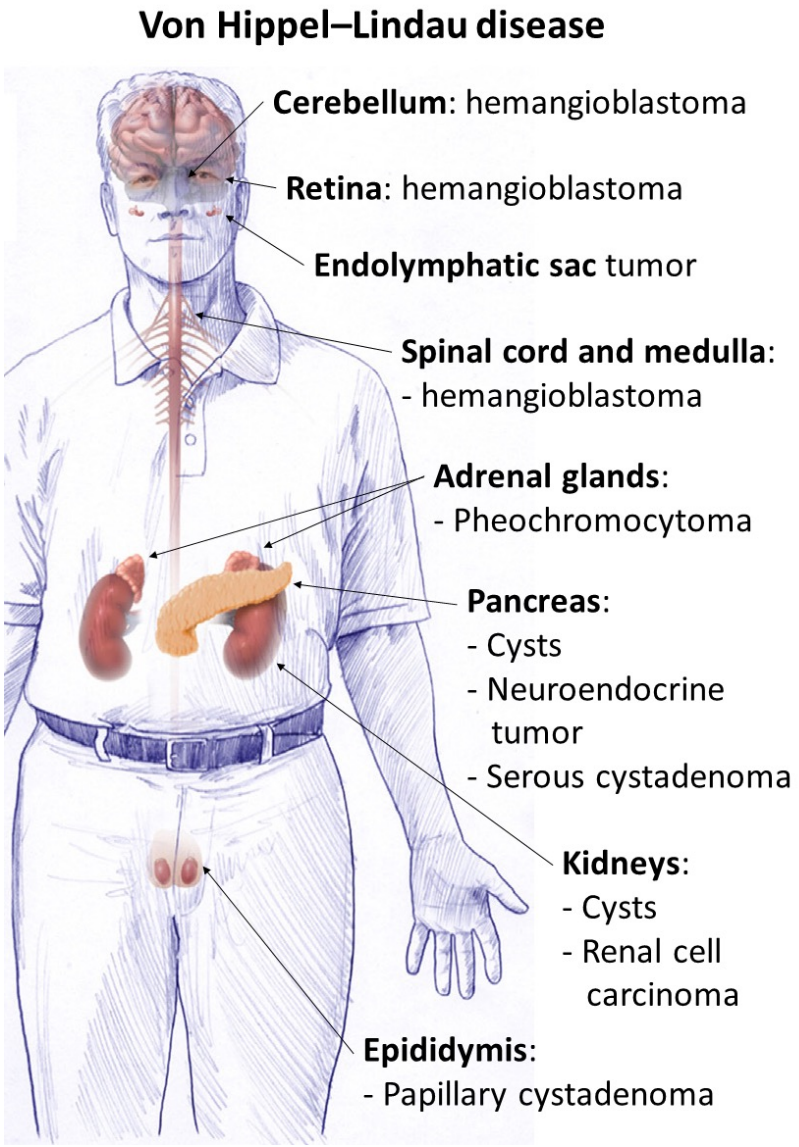
Case 1

Von Hipple Lindau (VHL) syndrome

- Clinical manifestation
- Diagnostic criteria
- Surveillance
- Molecular aspect & treatment

VHL disease/syndrome

- Visceral cysts and benign tumors with potential for subsequent malignant transformation.
- Resulted from a mutation in the VHL tumor suppressor gene on chromosome 3p25.3
- Incidence: 1 in 36,000 births
- Autosominal dominant, however, 20% of all patients are first-in-family or *de novo* cases

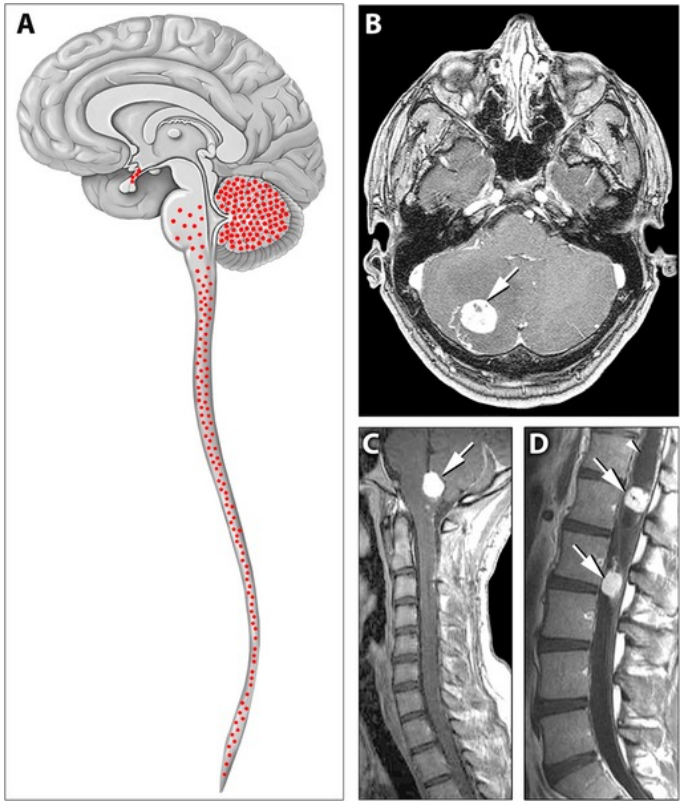


	Mean (range) age of onset (years)	Frequency in patients (%)
CNS		
Retinal haemangioblastomas	25 (1–67)	25–60%
Endolymphatic sac tumours	22 (12–50)	10%
Craniospinal haemangioblastomas		
Cerebellum	33 (9–78)	44–72%
Brainstem	32 (12–46)	10–25%
Spinal cord	33 (12–66)	13–50%
Lumbosacral nerve roots	Unknown (..)	<1%
Supratentorial	Unknown (..)	<1%
Visceral		
Renal cell carcinoma or cysts	39 (16–67)	25–60%
Phaeochromocytomas	30 (5–58)	10–20%
Pancreatic tumour or cyst	36 (5–70)	35–70%
Epididymal cystadenoma	Unknown (..)	25–60%
Broad ligament cystadenoma	Unknown (16–46)	Unknown

Lancet. 2003 Jun 14;361(9374):2059-67. doi: 10.1016/S0140-6736(03)13643-4.

CNS hemangioblastoma (CNS HB)

- **The cardinal feature of VHL disease**
- The presenting feature in 40% of cases
- Occurred in 60–80% of VHL patients and most commonly occur in the cerebellum, spinal cord and brain stem with supratentorial lesions being rare.
- **Symptoms:** ↑ICP, limb or truncal ataxia (depending on the tumor location)
- Hemangioblastomas with an associated cyst tend to become symptomatic sooner.



1 European Journal of Human Genetics (2011) 19, 617–623
2 https://doi.org/10.1371/journal.pmed.0040060

CNS hemangioblastoma (CNS HB)

- Benign tumor and the growth rate is variable so that some tumors may be static for a number of years
    - Removal of asymptomatic lesions is not usually indicated

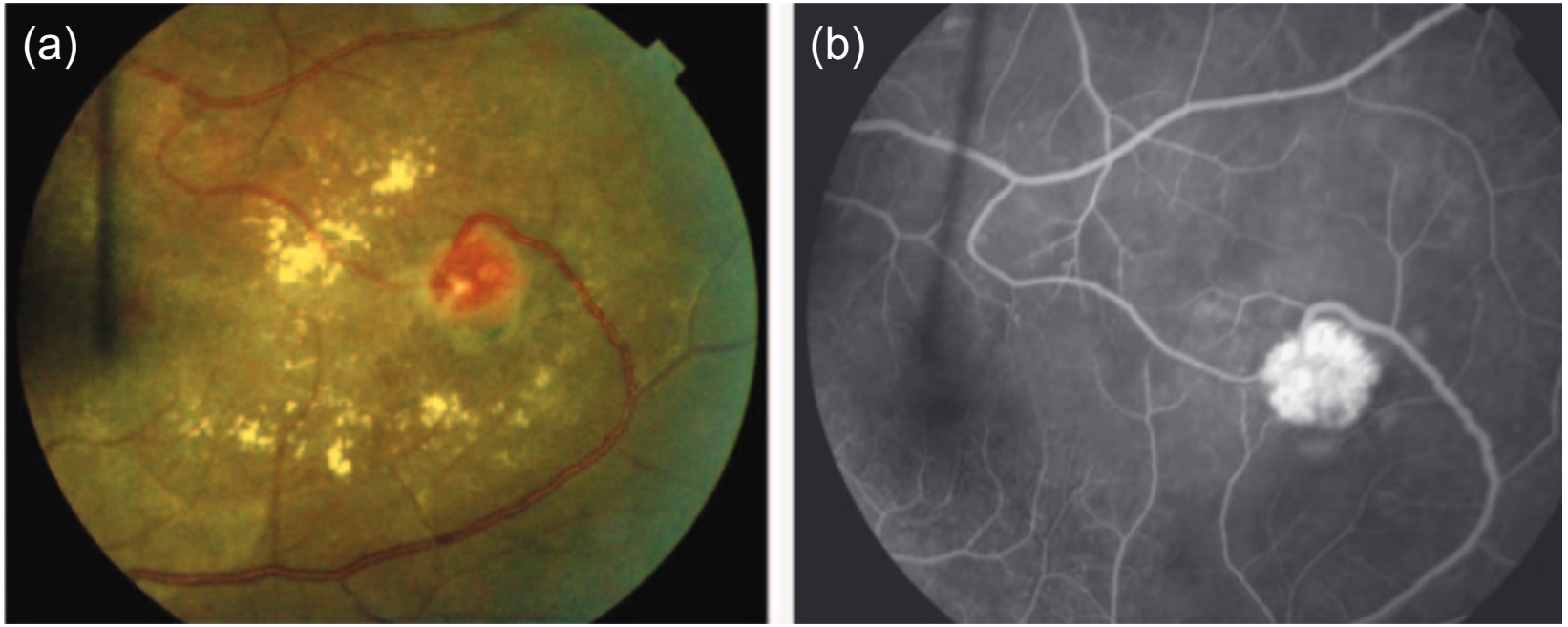
- Surgery is indicated in symptomatic patient
- Stereotactic RT may be an alternative to conventional neurosurgery for non-cystic small HB.

Retinal hemangioblastoma (Retinal HB)

- **Retinal angiomas are usually multiple and bilateral in about one half of cases.**
- The cumulative risk of visual loss from retinal angiomas
  - 35% in all gene carriers
  - 55% in patients with retinal angiomas at age 50 years
- On average, potentially sight-threatening complications such as exudation, retinal traction or hemorrhage tend to be associated with larger angiomas.
- Management is identifying asymptomatic angiomas to prevent further complications.

European Journal of Human Genetics (2011) 19, 617–623

Retinal hemangioblastoma (Retinal HB)

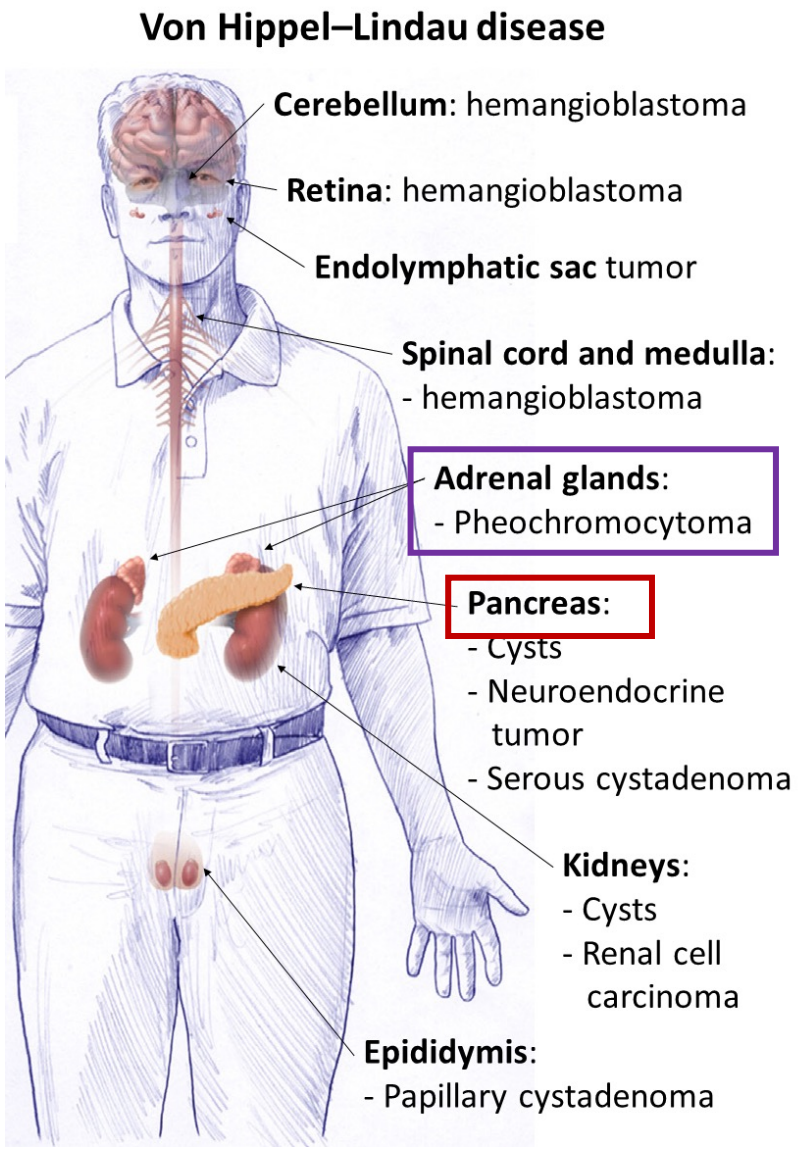


(a) Ophthalmoscopic image shows a well-defined, orange-red mass associated with a prominent feeding artery and a draining vein.
(b) Fluorescein angiogram of this retinal angioma shows its hyper-fluorescence.

doi: 10.1148/rg.281075052.

Renal cell carcinoma (RCC)

- **An important cause of death in VHL disease.** The lifetime risk is about 70%.
- Mean age at clinical diagnosis is 40 years
- Multiple renal cysts are common in VHL disease and rarely compromise renal function.
- Regular surveillance is recommended in VHL patients to early detection asymptomatic RCC.
- **Partial nephrectomy is performed when size reached 3 cm diameter.**



Pheochromocytoma (PC)

- Mean age at diagnosis is 30 years.
- Risk of malignancy for PC in VHL is less than 5%

Pancreas

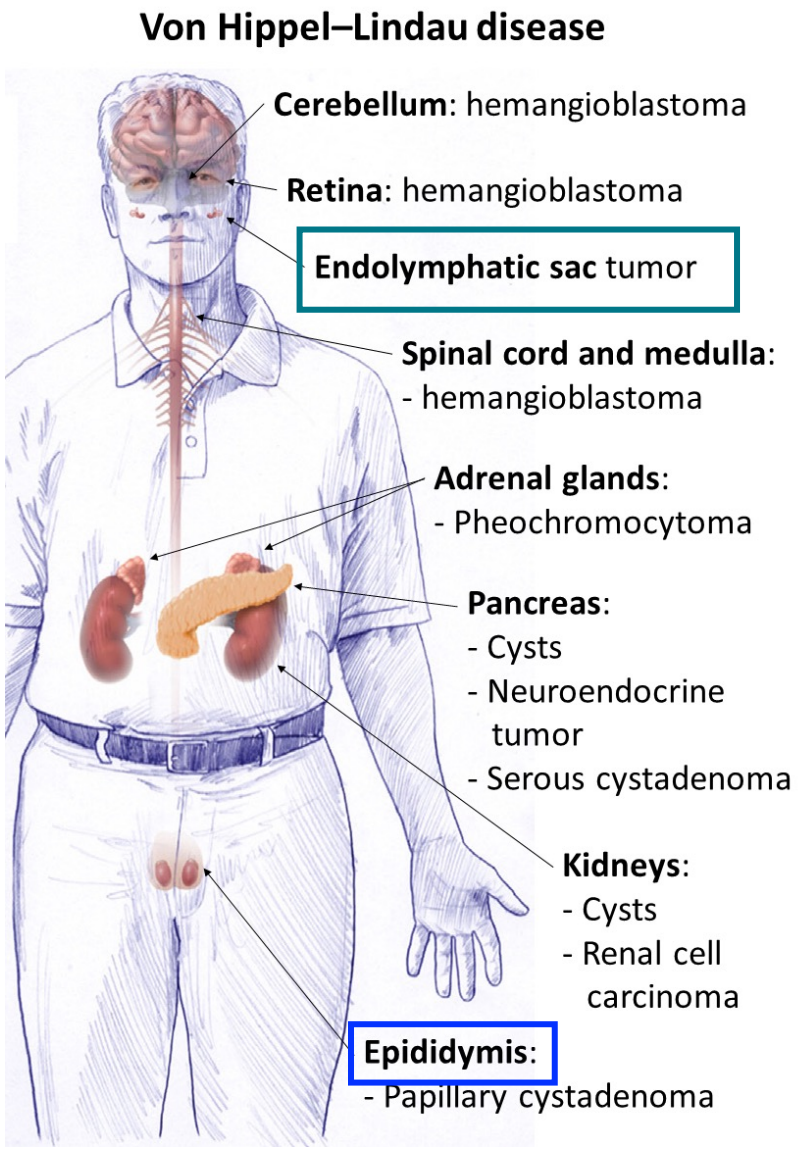
Cysts

- Multiple cysts are the most frequent pancreatic manifestation and are present in most older patients
- Rarely imparied pancreatic function

Tumors (5-10% of cases)

- Solid non-secretory islet cell tumors
- Best detected by contrast enhanced MRI with early arterial phase imaging

European Journal of Human Genetics (2011) 19, 617–623



Head and neck paragangliomas

- 0.5% of VHL patients
- mostly as carotid body tumors

Endolymphatic sac tumor

- Found in 11% of patients
- Detected by CT, MRI
- **Bilateral ELSTs are considered pathognomonic for VHL disease.**
- Asymptomatic > Symptomatic (hearing loss)

Epididymal cystadenomas

- 60% of males with VHL disease and are often bilateral
- usually asymptomatic and do not require treatment

Broad ligament cystadenomas (rare)

Panel 2: **Genotype-phenotype classifications in families with von Hippel-Lindau disease***

	Clinical characteristics
Type 1	Retinal haemangioblastomas
	CNS haemangioblastomas
	Renal cell carcinoma
	Pancreatic neoplasms and cysts
Type 2A	Phaeochromocytomas
	Retinal haemangioblastomas
	CNS haemangioblastomas
Type 2B	Phaeochromocytomas
	Retinal haemangioblastomas
	CNS haemangioblastomas
	Renal cell carcinomas
	Pancreatic neoplasms and cysts
Type 2C	Phaeochromocytoma only

*Endolymphatic sac tumours and cystadenomas of the epididymis and broad ligament have not been assigned to specific von Hippel-Lindau types.

Lancet. 2003 Jun 14;361(9374):2059-67. doi: 10.1016/S0140-6736(03)13643-4.

Von Hipple Lindau (VHL) syndrome

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Diagnosis

Von Hippel Lindau syndrome

WWW.VHL.ORG

International criteria

Any item of the followings:

- Multiple CNS or retinal hemangioblastomas (HB)
- CNS or retinal HB and one visceral lesion (clear-cell renal cell carcinoma (RCC), pheochromocytoma (PC) or paraganglioma (PPGL), or pNET)
- Positive family history or a pathogenic variant in the VHL gene and one CNS or retinal HB or visceral lesion

Danish criteria

Any item of the followings:

- Any two VHL-related manifestations (CNS HB, retinal HB, endolymphatic sac tumor, RCC, PC, PPGL or glomus tumor, pNET and/or multiple cysts)
- Pathogenic variant in the VHL gene and any clinical manifestation
- At least one first-degree relative with VHL and any one clinical manifestation

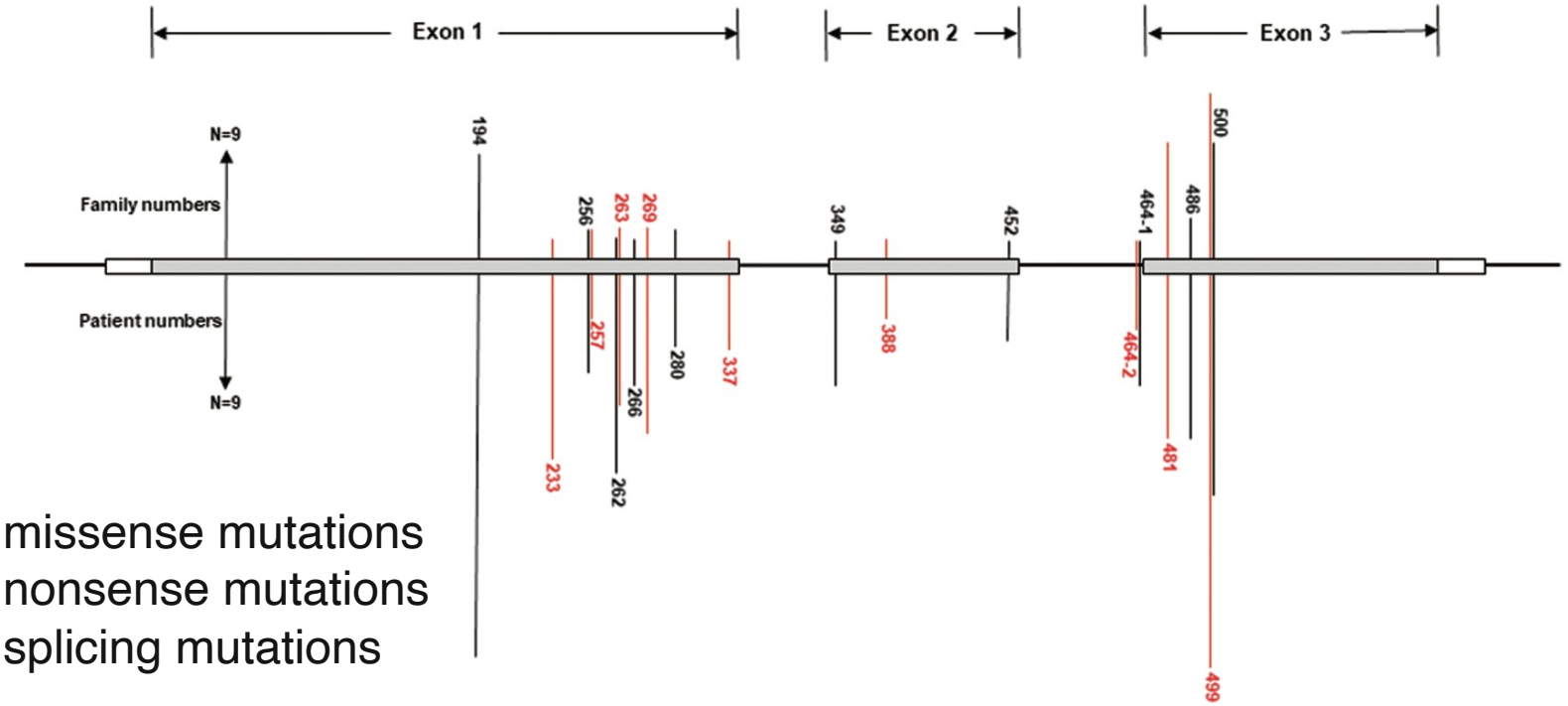
Cancers 2023, 15, 1657. https://doi.org/10.3390/cancers15061657

Genetics testing

Heterozygous **nonsense mutation** of **c.263G>A** (p.Trp88Stop) in **exon 1** of VHL gene was found.

Distribution of the frequent germline mutation sites in VHL gene (N = 258)

Of the 19 frequent germline mutations, 10 were located in exon 1, 3 were located in exon 2, 4 were located in exon 3, and 2 were located in intron 2. Notably, there were 4 hotspot mutation sites (194, 481, 499, and 500).



70% missense mutations
20% nonsense mutations
10% splicing mutations

Front. Genet. 10:867.
https://doi.org/10.3389/fgene.2019.00867

Group	NC	CNS hemangioblastoma		Retinal angioma		renal clear cell carcinoma		pancreatic tumor or cyst		pheochromocytoma		genital system (epididymis or board ligament)	
		Ratio (%)	OA (Mean ± SD)	Ratio (%)	OA (Mean ± SD)	Ratio (%)	OA (Mean ± SD)	Ratio (%)	OA (Mean ± SD)	Ratio (%)	OA (Mean ± SD)	Ratio (%)	OA (Mean ± SD)
1*	c.194C > T	62.5	34.1 ± 13.8	8.3	(30, 53)	37.5	45.4 ± 12.5	45.8	43.5 ± 13.5	4.2	(34)	16.7	25.0 ± 8.3
	p.Ser65Leu	(15/24)	(15–59)	(2/24)		(9/24)	(25–60)	(11/24)	(25–65)	(1/24)		(4/24)	(17–34)
	c.194C > G	71.4	30.2 ± 18.3	—	—	57.1	36.3 ± 13.6	42.9	32.3 ± 13.6	—	—	—	—
	p.Ser65Trp	(5/7)	(17–61)			(4/7)	(24–48)	(3/7)	(24–48)				
2	c.233A > G	21.1	41.8 ± 10.4	—	—	15.8	38.3 ± 2.5	36.8	27.4 ± 6.9	10.5	(28, 36)	—	—
	p.Asn78Ser	(4/19)	(30–51)			(3/19)	(36–41)	(7/19)	(20–40)	(2/19)			
3	c.256C > T	33.3	34.0 ± 2.6	22.2	(11,12)	55.6	34.0 ± 4.1	33.3	33.3 ± 2.5	11.1	(31)	—	—
	p.Pro86Ser	(3/9)	(31–36)	(2/9)		(5/9)	(30–40)	(3/9)	(31–36)	(1/9)			
4	c.257C > T	75.0	26.3 ± 8.0	50.0	(26, 32)	75.0	28.0 ± 9.2	75.0	27.0 ± 10.5	—	—	25.0	(26)
	p.Pro86Leu	(3/4)	(18–34)	(2/4)		(3/4)	(20–38)	(3/4)	(17–38)			(1/4)	
5	c.262T > C	52.4	41.1 ± 9.1	—	—	38.1	37.4 ± 12.9	4.8	(30)	4.8	(50)	—	—
	p.Trp88Arg	(11/21)	(29–62)			(8/21)	(23–65)	(1/21)		(1/21)			
6*	c.263G > A	75.0	25.0 ± 12.3	—	—	50.0	(28, 34)	50.0	(28, 38)	25.0	(39)	50.0	(11,32)
	p.Trp88Stop	(3/4)	(11–34)			(2/4)		(2/4)		(1/4)		(2/4)	
	c.263G > C	77.8	29.9 ± 8.4	22.2	(25, 35)	11.1	(30)	22.2	(30, 31)	—	—	11.1	(24)
	p.Trp88Ser	(7/9)	(20–44)	(2/9)		(1/9)		(2/9)				(1/9)	
7	c.266T > C	54.5	27.7 ± 7.5	45.5	29.6 ± 13.1	54.5	39.5 ± 9.3	36.4	25.8 ± 2.2	9.1	(45)	—	—
	p.Leu89Pro	(6/11)	(20–40)	(5/11)	(15–42)	(6/11)	(24–52)	(4/11)	(24–29)	(1/11)			
8	c.269A > T	66.7	29.9 ± 13.4	13.3	(23, 30)	26.7	41.5 ± 15.5	33.3	41.4 ± 17.0	6.7	(38)	—	—
	p.Asn90Ile	(10/15)	(16–63)	(2/15)		(4/15)	(26–63)	(5/15)	(17–63)	(1/15)			
9	c.280G > T	66.7	34.5 ± 13.5	33.3	(17, 29)	50.0	35.0 ± 15.9	33.3	(29, 53)	16.7	(35)	33.3	(14, 20)
	p.Glu94Stop	(4/6)	(23–54)	(2/6)		(3/6)	(23–53)	(2/6)		(1/6)		(2/6)	
10	c.337C > T	50.0	40.0 ± 22.5	50.0	23.0 ± 7.2	50.0	35.3 ± 11.3	33.3	(26, 27)	—	—	16.7	(18)
	p.Arg113Stop	(3/6)	(28–66)	(3/6)	(17–31)	(3/6)	(26–48)	(2/6)				(1/6)	
11	c. 349T > G	72.7	30.0 ± 14.6	45.4	23.8 ± 18.2	54.5	45.8 ± 8.1	72.7	43.4 ± 14.3	9.1	(18)	9.1	(44)
	p.Trp117Gly	(8/11)	(12–47)	(5/11)	(7–44)	(6/11)	(37–61)	(8/11)	(21–59)	(1/11)		(1/11)	
12	c.388G > C	50.0	(30, 30)	—	—	25.0	(31)	25.0	(31)	25.0	(30)	—	—
	p.Val130Leu	(2/4)				(1/4)		(1/4)		(1/4)			
13	c.452T > G	71.4	34.2 ± 18.1	14.3	(26)	42.9	36.7 ± 11.7	28.6	(32, 38)	—	—	—	—
	p.Ile151Ser	(5/7)	(14–60)	(1/7)		(3/7)	(28–50)	(2/7)					
14	Intron 2 #	54.5	33.0 ± 18.4	—	—	36.4	42.3 ± 16.5	36.4	42.3 ± 16.5	—	—	9.1	(10)
	c.464–1 G > C	(6/11)	(16–66)			(4/11)	(28–66)	(4/11)	(28–66)			(1/11)	
15	Intron 2 #	40.0	(24, 57)	20.0	(57)	60.0	40.3 ± 16.8	60.0	40.3 ± 16.8	20.0	(58)	—	—
	c.464-2 A > G	(2/5)		(1/5)		(3/5)	(21–51)	(3/5)	(21–51)	(1/5)			
16	c.481C > T	80.0	27.4 ± 9.4	6.7	(28)	66.7	36.6 ± 8.2	60.0	32.3 ± 9.7	6.7	(41)	13.3	(30, 36)
	p.Arg161Stop	(12/15)	(14–40)	(1/15)		(10/15)	(23–47)	(9/15)	(14–46)	(1/15)		(2/15)	
17	c.486C > G	80.0	31.4 ± 10.0	26.7	36.5 ± 16.3	53.3	41.8 ± 10.3	40.0	33.0 ± 12.9	6.7	(29)	6.7	(23)
	p.Cys162Trp	(12/15)	(12–49)	(4/15)	(17–54)	(8/15)	(29–56)	(6/15)	(17–56)	(1/15)		(1/15)	
18	c.499C > T	35.5	30.9 ± 13.8	12.9	23.5 ± 8.7	22.6	35.4 ± 11.8	29.0	36.9 ± 14.5	32.3	33.3 ± 14.3	3.2	(31)
	p.Arg167Trp	(11/31)	(16–65)	(4/31)	(13–34)	(7/31)	(18–54)	(9/31)	(19–67)	(10/31)	(12–58)	(1/31)	
19	c.500G > A	62.5	35.6 ± 12.6	16.7	23.0 ± 6.8	41.7	38.3 ± 13.6	20.8	37.2 ± 14.5	37.5	36.3 ± 11.9	—	—
	p.Arg167Gln	(15/24)	(15–52)	(4/24)	(14–30)	(10/24)	(22–54)	(5/24)	(22–53)	(9/24)	(14–52)		

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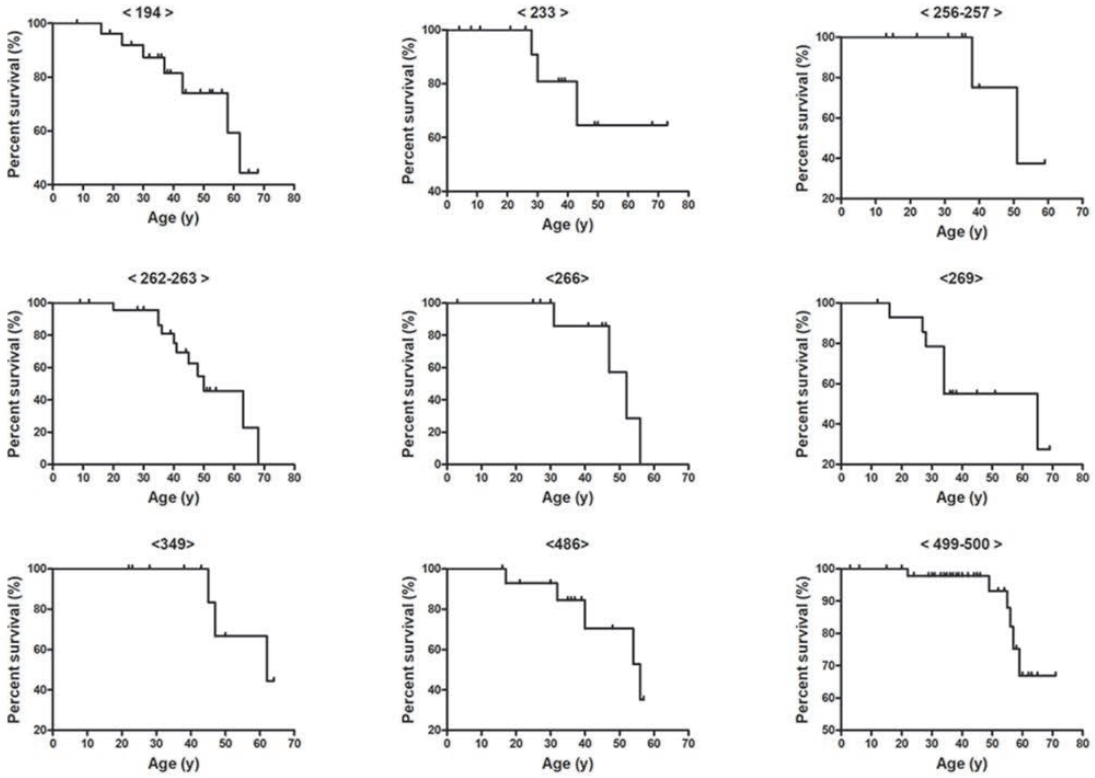
VHL frequent germline mutations and survival



The mean age at death for the patients in this cohort was 42.4 ± 13.5 years

Front. Genet. 10:867.
https://doi.org/10.3389/fgene.2019.00867

Case report: VHL syndrome with pathogenic variant c.263G>A (p.Trp88 *) described in the Human Gene Mutation Database

References	Type of genetic variant	Phenotype
Gallou[1, 2]	Transition/nonsense	Clear cell renal carcinoma
Mattocks[3]	Transition/nonsense	Not described
Sandra[4]	Non sense	Clear cell renal carcinoma, optic nerve hemangioblastoma, cystic pancreatic neoplasm

1 Hum Mutat. (2000) 16:437–43
2 Hum Mutat. (1999) 13:464–75
3 Pharmacogenetics. (2001) 11:521–35
4 Front. Oncol. (2020) Vol 10
doi: 10.3389/fonc.2020.00139

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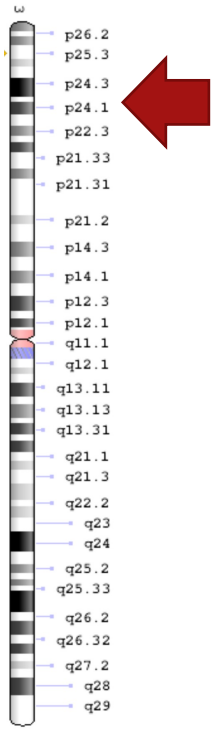
Surveillance protocal for VHL

Modality (Tumor being screened)	Starting age			
	5 y	11 y	15 y or older	65 y or older
Blood pressure & pulse	annual	annual	annual	annual
Metanephrines (Pheochromocytoma)	annual	annual	annual	If indicated
Dilated eye exam (Retinal hemangioblastoma)	annual	annual	annual	annual
MRI brain & Spine (CNS hemangioblastoma)	-	biannual	biannual	If indicated
Audiogram (Endolymphatic Sac Tumor)	-	biannual	bianuual (MRI IAC once at beginning)	If indicated
MRI abdomen (RCC, Pheo, PNET/cysts)	-	-	biannual	If indicated

IAC, internal audiotory canal

Adapted from VHL active surveillance guideline
https://www.vhl.org/care-treatment/resources/

Molecular aspect of VHL



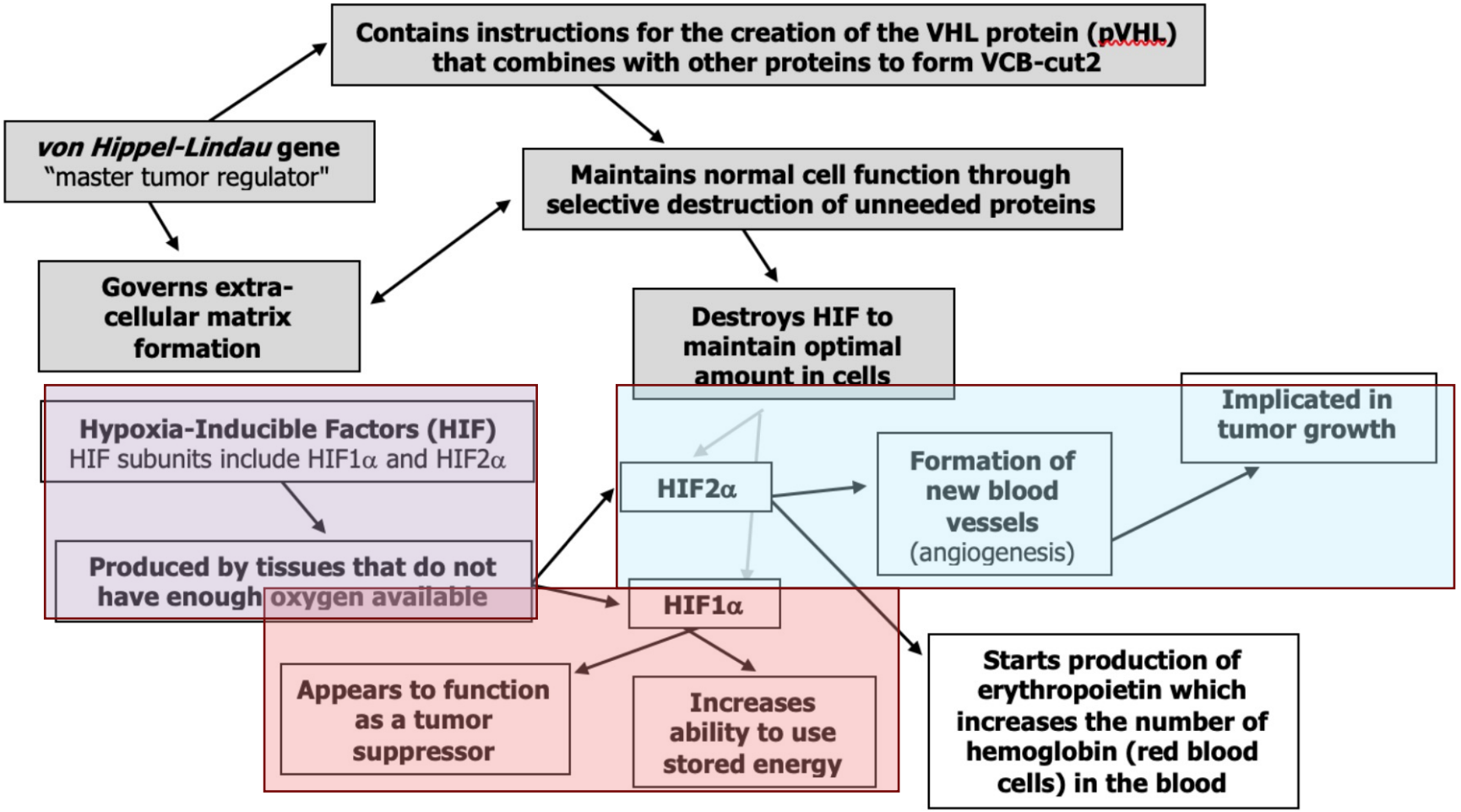
VHL gene

- **VHL gene locates in chromosome 3p25-p26 and encodes VHL proteins (pVHL), acting as tumor-suppressing proteins.**
- The **majority of VHL mutations** are **deletion and missense.**
- **VHL protein contains α and β-domain**
  - α-domain: maintaining VHL protein stability by binding to translational elongation factor C
  - β-domain:
    - substrate recognizer for pVHL.
    - binds with HIF subunit and controls HIF subunit degradation.
- **VHL mediates tumor invasion and metastasis by regulating HIFs protein expression.**

HIF, hypoxia-inducible factor

Interaction of the Von Hippel-Lindau (VHL) Protein and Hypoxia Inducible Factor (HIF) Subunits

Gray box pertains to VHL protein function; White box pertains to effects of HIF

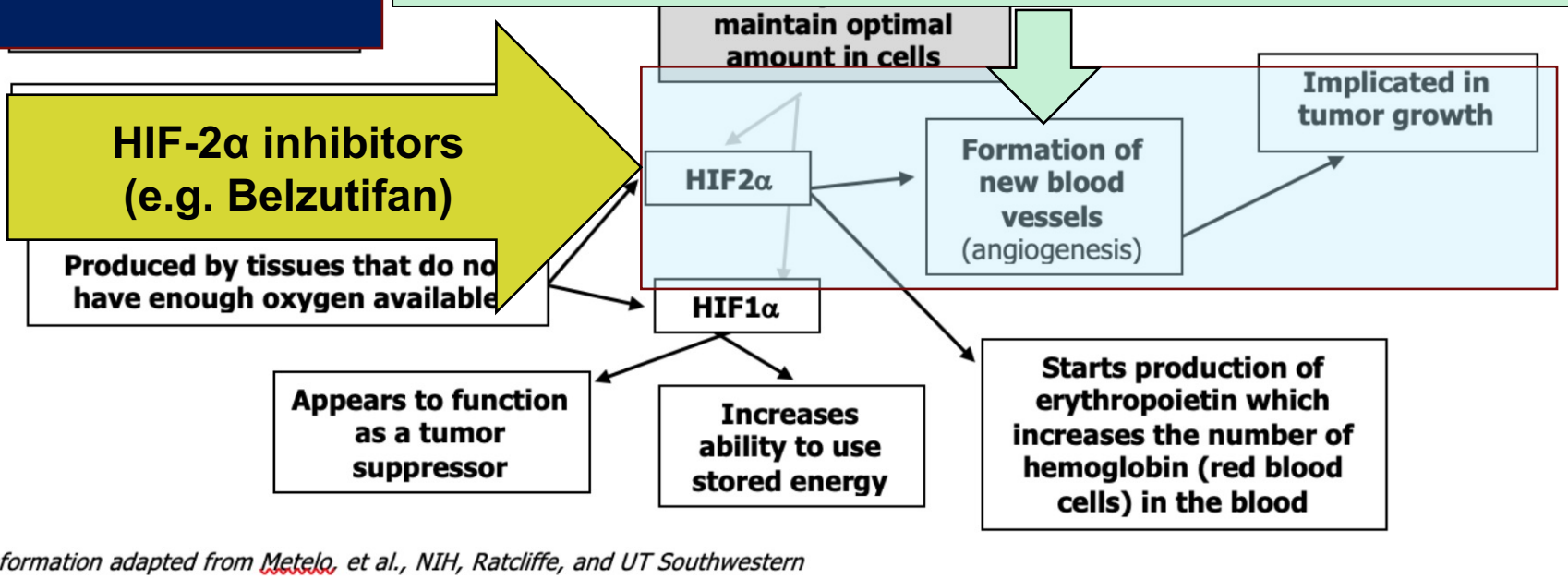


Information adapted from Metelo, et al., NIH, Ratcliffe, and UT Southwestern

Treatments

Angiogenesis inhibitors

- None of the drugs have been approved for treating VHL.
- **Sunitinib**: 33% response for RCC w/o impact on hemangioblastoma
- **Pazopanib**: 42% overall response rate, 50% for kidney. Small response in hemangioblastoma



Information adapted from Metelo, et al., NIH, Ratcliffe, and UT Southwestern

Belzutifan NEJM 2021; 385:2036-2046