



What's new in VHL Research



Speaker: Eric Jonasch, M.D.
Urologic Oncology
M.D. Anderson Cancer Center, Houston

Host: Joyce Graff
VHL Family Alliance, Boston

What's New In VHL Research

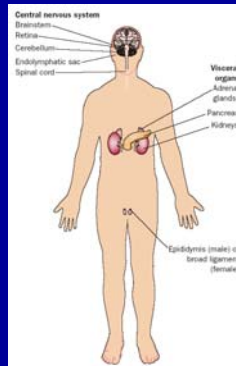
Eric Jonasch
November 8, 2008
UT MD Anderson Cancer Center

Von Hippel Lindau Disease

- Occurs in 1:32 000 to 1:40 000 births per year.
- Twenty percent are *de novo* mutations (no family members have it yet).
- Autosomal dominant transmission (means if you get the gene, you develop the disease).
- Genotype-phenotype correlation (means we can predict to some degree which organs will be affected).

VHL Is A Multisystem Disorder

1. Endolymphatic organs.
2. Eye.
3. Central nervous system.
4. Pancreas.
5. Kidney.
6. Adrenal.
7. Epididymis/broad ligament.



Lonser *et al*, Lancet 2003

Not All People With VHL Are Affected Equally

- Type 1: No pheochromocytomas large deletions
- Type 2a: Pheo, rare kidney & CNS Y98H
- Type 2b: Pheo, kidney & CNS R167W, R167Q
- Type 2c: Pheo only L188V, V84L
- Can begin to correlate some mutations to clinical manifestations,
- In addition, even within families with the same mutation, there can be varied expression of the phenotype (so what your other parent brings to the table can affect how the VHL gene is manifested).

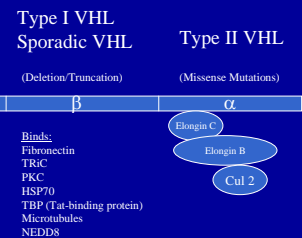
Frequency and Age of Onset of von Hippel Lindau Disease Lesions

	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%
Pheochromocytomas	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

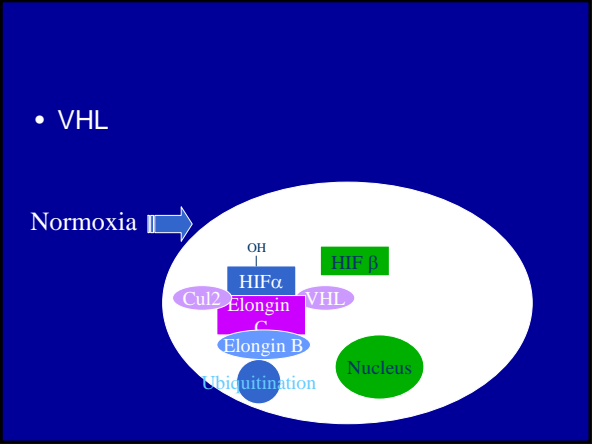
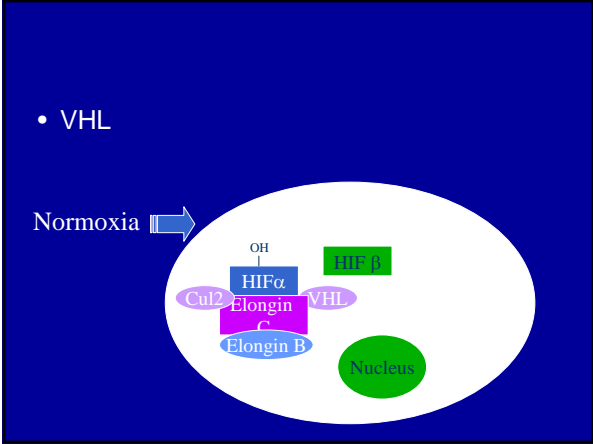
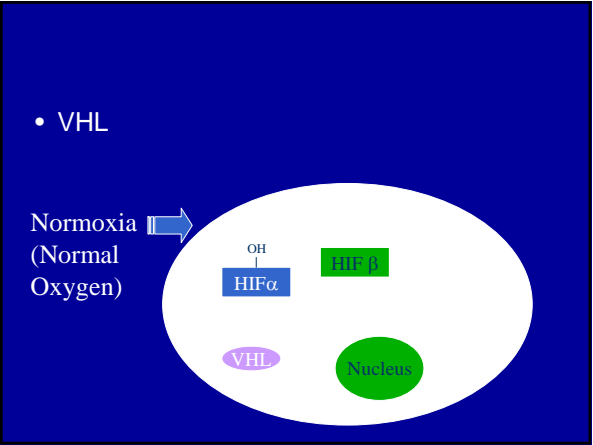
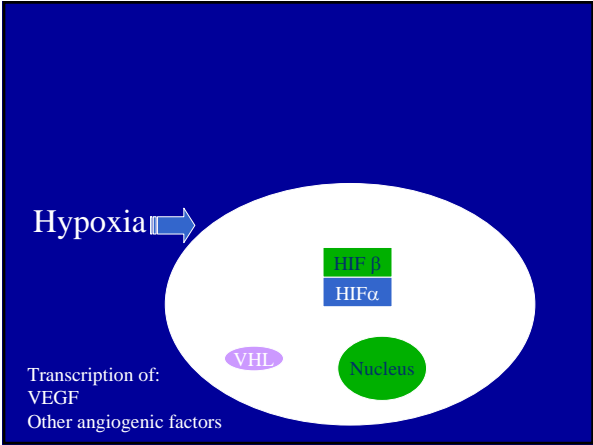
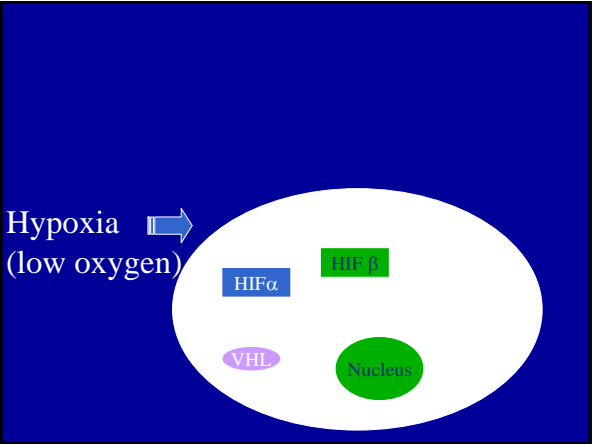
Lonser *et al*, Lancet 2003

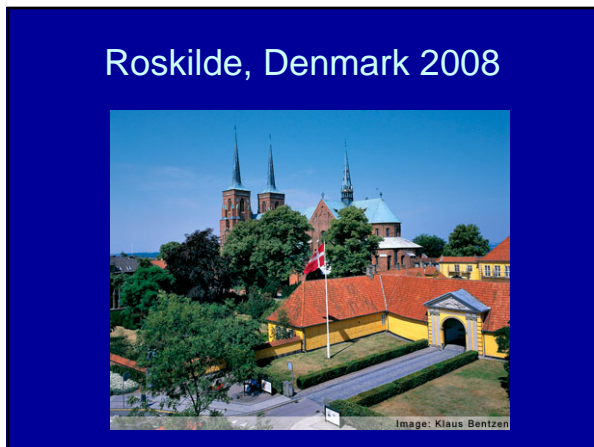
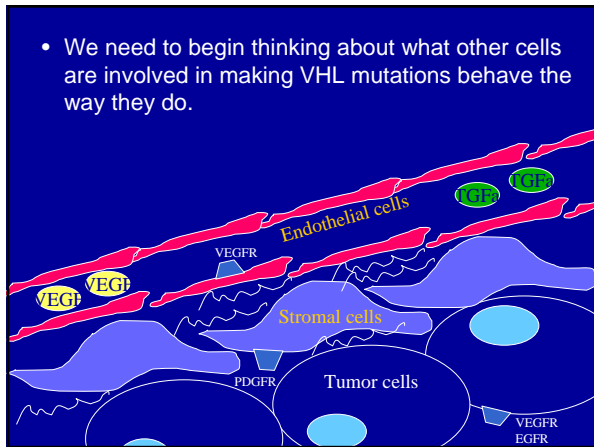
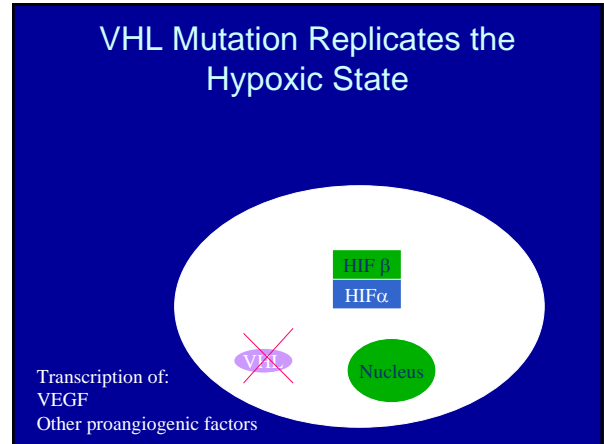
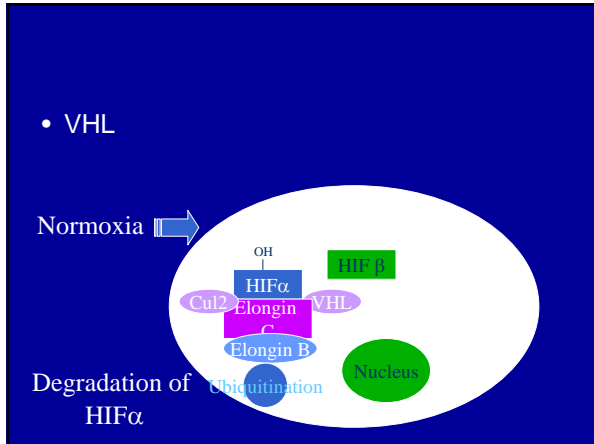
VHL Gene and Gene Product

- Located on 3p25
- 213 amino acid protein.

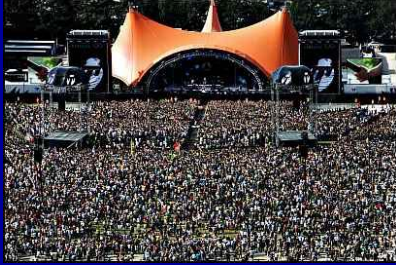


VHL as a HIF Regulator





Roskilde Music Festival



Highlights

1. For those people who present with VHL-like findings but do not have a mutation: Possibility of Succinate Dehydrogenase mutations.
2. For those who are working on understanding how to treat VHL affected organs: Receptor studies in kidney cancer and hemangioblastomas.

Succinate Dehydrogenase (SDH)

- Is an enzyme, important for cell nutrition.
- Different forms SDHA, B, C, D.
- Are associated with pheochromocytomas, paragangliomas, and kidney cancers.

Genetic Testing for SDH

- Is available!
- Blood test like for VHL.
- Results available in 6 weeks.

Receptor Testing in Hemangioblastomas and Kidney Tumors

- Are there differences in the receptors in the blood vessel cells in kidney cancer and hemangioblastomas?
- This information is important for us to figure out what the best treatments are going to be for each organ in VHL.

Materials and Methods

- 20 hemangioblastoma and 20 primary RCC cases acquired after laboratory protocol obtained IRB approved.

Results

	(Hemangioblastoma)			(RCC)			Wilcoxon test
	N	mean	SD	N	mean	SD	p-value
pVEGFR2	20	11.268	0.498	20	11.752	0.378	0.003
VEGFR.total	20	12.977	0.478	20	13.081	0.859	0.192
pPDGFR	20	10.952	0.654	20	10.805	0.839	0.82
PDGFR.total	20	13.078	0.659	20	12.842	0.851	0.947
VEGFR.ratio	20	0.206	0.122	20	0.372	0.431	0.043
PDGFR.ratio	20	0.145	0.067	20	0.157	0.077	0.602

What it means

- The VEGF receptor levels and the activation of the VEGF receptor are higher in kidney cancer.
- This may mean that drugs that block this receptor will be more effective in kidney tumors than hemangioblastomas.

What we need to do

- Continue this research to add strength to our findings.
- Figure out which receptors are increased in hemangioblastomas, pheochromocytomas and NETs of the pancreas to tailor our therapy.

Conclusions

- We have an ever-improving understanding of VHL biology.
- Those who have VHL-like syndromes may have testing available for diagnosis of SDH.
- Our ongoing work studying receptors in VHL related tissue will result in tailored therapy for patients with VHL.

With Thanks To:

- Ian McCutcheon
- Greg Fuller
- Apocell Inc
- The patients who made this possible.



For the handout . . .

- <http://vhl.org/support>
Click on "webinars"
- To contact Dr. Jonasch's and the VHL Clinical Care Center:
ccg@mdanderson.org or by phone
at +1 (713) 745-7391
- To contact VHLFA: info@vhl.org
1-800-767-4845 or +1-617-277-5667
<http://vhl.org>



Teamwork for Health

Families and Health Care Professionals
working together
to improve diagnosis, treatment, and
quality of life
for individuals and families
affected with von Hippel-Lindau

VHL Family Alliance