VHL 101

Sarah Nielsen, MS, CGC
Genetic Counselor
The University of Chicago
Cancer Risk Clinic
von Hippel-Lindau (VHL) History

• Eugene von Hippel
  – German ophthalmologist
  – 1904 “angiomatosis retinae”

• Arvid Lindau
  – Swedish pathologist
  – 1927 “Angiomatosis of the central nervous system”

• 1964 Named “Von Hippel-Lindau disease”
Hatfield – McCoy Feud

- Hatfield: English
- McCoy: Irish
- Started in 1865 when a McCoy who joined the Union army was shot by a Hatfield upon his return home from the war
- 13 Murders in 25 years of feuding

Hatfield clan 1897
A Famous VHL Family – the MCC kindred

Pheochromocytoma in von Hippel-Lindau Disease: Clinical Presentation and Mutation Analysis in a Large, Multigenerational Kindred*

NUZHET O. ATUK, CATHERINE STOLLE, JOHN A. OWEN, JR., JOHNSON T. CARPENTER, AND MARY LEE VANCE

Nephrology and Endocrinology and Metabolism Divisions, Department of Internal Medicine, University of Virginia Health Sciences Center, Charlottesville, Virginia 22908; and Department of Genetics, University of Pennsylvania, Philadelphia, Pennsylvania

• Followed since 1964
• 2007 Associated Press story: The “Rage” Disease
VHL and Pheo go Prime Time

• Grey’s Anatomy story line about a VHL patient named Henry, played by Scott Foley, with a dangerous adrenal tumor

• Doctors know that the tumor needs to be removed, as it can cause sudden bursts of adrenaline at random intervals, leading to panic attacks, racing heart beats, high blood pressure, heart attack or stroke. But the patient has maxed out his insurance.

• Writers focused more on the emotional impact the disease causes than on the usual physical impact the disease has on the patient
VHL Overview

• U.S. incidence = 1/32,000 live births
  – 125 new cases per year in the United States (≈4 million births/year)
• Mean age of diagnosis is ~25 years old
  – Can present as early as age 5
• Symptoms can include:
  – Headaches
  – Problems with balance and walking
  – Dizziness
  – Weakness of the limbs
  – Vision problems
  – High blood pressure
• 90% penetrance by age 65
  – Variable presentation, even within the same family
Affected Organs
(Abnormal Blood Vessel Growth)

- CNS - hemangioblastoma
  - Brain
  - Spinal Cord
- Eyes - angioma
- Ears – endolymphatic sac tumor
- Liver - cyst
- Pancreas – cyst and neuroendocrine tumors
- Adrenal - pheochromocytoma
- Kidney – cyst and renal cell carcinoma (clear cell)
- Testis – bilateral epididymal cysts
- Ovary – bilateral cystadenoma of broad ligament
• **Tumor:** abnormal mass of tissue
  – Tumors develop when cells grow out of control
  – **Benign** tumors are non-cancerous
  – **Malignant** tumors are cancerous; they can invade nearby tissues and can spread to other parts of body

• **Hemangioblastomas (angiomas)** are types of tumors in the eyes, brain, spine made up of bundles of blood capillaries

• **Cysts** are not tumors, they are fluid-filled sacs
Diagnostic Criteria

• Isolated (Index) case:
  – ≥ 2 hemangioblastomas of retina or brain
  OR
  – 1 hemangioblastoma AND 1 of the following:
    • Cyst: kidney / pancreas
    • RCC
    • Pheochromocytoma
    • Endolymphatic sac tumor
    • Papillary cystadenoma

• Family history of VHL
  – any 1 of above clinical features
Genetics of VHL

- **VHL gene (chromosome 3p25-26)**
  - Tumor suppressor
  - Discovered in 1993
  - *Science* May 28;260(5112):1317-20

- ~100% mutation detection rate for patients who meet clinical diagnostic criteria
  - 72% point mutations
  - 28% deletions

- Genetic testing appropriate for children re: early age of onset
Autosomal Dominant Inheritance

- 80% familial/inherited
- 20% *de novo* mutations
VHL

No Pheochromocytoma

VHL Type I

VHL Type 2

Deletion, Insertion, Nonsense, Missense

Pheochromocytoma

Renal Cell Carcinoma

No Renal Cell Carcinoma

VHL Type 2A

Missense mutations

VHL Type 2B

Missense mutations

VHL Type 2C

Missense mutations
VHL Function and Types of Mutations

- > 500 VHL germline mutations identified
  - Deletions (15-20%)
  - Missense (27%)
  - Truncating (27%)
  - Splice site
VHL Controls HIF-1 Levels

- HIF is key in cellular responses to hypoxia
  - Activates genes involved in energy metabolism, angiogenesis and apoptosis
- pVHL regulates degradation of HIF-1 α subunits
  - Under normoxic conditions, HIF-1 subunits degraded
  - Abnormal pVHL stabilizes HIF-1 subunits, upregulation of angiogenesis genes \(\Rightarrow\) highly vascularized tumors
Hemangioblastomas

- Most common tumors in VHL (60-80% of patients)
- Overgrowth of blood vessels in the retina (40%), cerebellum (80%) and spine (20%)
  - Tumors tend to be multiple and occur at earlier ages (av. age diagnosis is 29 y/o)
- Retinal angiomas are usually asymptomatic early on; CNS hemangioblastomas may cause symptoms such as headaches, balance/walking problems, arm/leg weakness
Renal Lesions

- RCC/renal cysts: 60% of all VHL patients
- Renal cysts are typically asymptomatic and do not require treatment
- Renal cell carcinoma (RCC)
  - 25-45% of VHL patients
  - Clear-cell histology
  - Avg. age dx: 25-58 years
  - Often bilateral / multiple
Pheochromocytoma (Pheo)

- Neuroendocrine tumor of adrenal gland (medulla) that secretes hormones
- 10-20% patients overall (up to 60% in VHL Type 2)
- Early-onset (av. age dx. is 30 y/o)
- Bilateral (40%) and multiple (58%)
- May be extra-adrenal (head/neck, chest, abdomen), rarely malignant (<5%)
- Symptoms: heart rate/blood pressure elevations, episodic sweating, anxiety, headaches, weight loss
Other VHL Manifestations

• Pancreas
  – 75% pts have cysts, 12% have solid tumors
  – Cysts: usually asymptomatic but large cysts may require surgical drainage
  – “Cystadenomas” & islet cell tumors can cause problems if they are blocking ducts (diarrhea, constipation, fatty stools, digestive complaints, weight loss; diabetes; jaundice, pain, inflammation, infection)

• Inner ear- Endolymphatic Sac Tumors (ELSTs)
  – 15% of pts
  – Subtle changes in “texture” of hearing to profound hearing loss: tinnitus (ringing in ears), dizziness, fullness in ears, weakness in nerve that runs through cheek

• Reproductive organs- papillary cystadenomas of epididymis (men) and broad ligament (women)
  – Usually asymptomatic and do not require treatment unless interfering with fertility
## VHL Screening Recommendations

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<th>Age</th>
<th>Screening</th>
<th>Frequency</th>
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| 0-4 | • Eye/retinal exam with indirect ophthalmoscope  
     • PE w/ BP check & neurological assessment | Annually  
     Annually |
| 5-15 | Above plus:  
        • Test for plasma free metanephrines, or urinary metanephrines using 24-hour urine test  
        • Abdominal u/s from 8yrs or earlier if indicated; abdominal MRI or functional imaging scan only if biochemical abnormalities found  
        • Audiology assessment; in the case of repeated ear infections, MRI with contrast of the internal auditory canal | Annually  
     Annually  
     2-3 yrs (1 yr if tinnitus, hearing loss or vertigo) |
| 16+ | Above plus:  
       • Quality ultrasound of abdomen  
       • MRI of abdomen with/without contrast  
       • MRI of brain and cervical spine with/without contrast | Annually  
       Every 1-2 yrs.  
       Every 1-2 yrs |