Hereditary Renal Masses: A Comprehensive Approach to Education & Treatment

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Department of Urology

13th Annual Floyd A. Fried Symposium
June 20, 2015
Hereditary Renal Masses

• UNC Comprehensive Clinical Care Center
• History
• Overview of conditions
• Collaboration
Hereditary Renal Masses

UNC Lineberger is a von Hippel-Lindau Comprehensive Clinical Care Center
History

• 2012: Submitted application to VHLA become a VHL CCC
• 2012: Accepted as one of 8 CCC across the country

• 2014: Submitted application to become a VHL CCCC, which added specialists & communication plan
• 2014: Accepted as one of 9 CCCC across the country

• Currently, 9 CCCC, 19 CCC, 16 International Centers
History

• Why?
  – Physician scientists who are experts in VHL
  – We are seeing these patients in our clinics
  – We have the experts
VHL CCCC

• Goals
  – To improve diagnosis and treatment of VHL
  – To provide coordination of care across medical specialties
  – To provide resource centers for patients and physicians who are new to VHL
  – To provide a ready channel for communicating advances to these centers of expertise
  – To provide a model that can be replicated elsewhere
VHL CCCC

- **Criteria**
  - Sponsoring MD, point of contact, screening protocol
  - Specialists
    - Geneticist, Genetic Counselor, Ophthalmologist, Urologist, Endocrinologist, Radiologist, Neurosurgeon, **Nephrologist, Oncologist**
    - Neurology, Neurooncology, Neurootology, Gynecology, MFM, Dermatology, Pulmonology, Social Work, Psychiatry, Nutrition

- **Screening Services**
  - MRI, CT, MIBG, Audiology, Genetic Testing, Eye/Retinal Exam, Fluorescein Angiography, Psychosocial
  - PET, PET/CT, Ultrasound
VHL CCCC

• Criteria
  – Treatments
    • Stereotactic Radiosurgery, RFA, Cryoablation, Open & lap partial nephrectomy, open & lap partial adrenalectomy, retinal laser surgery
    • Robotic partial nephrectomy/adrenalectomy
Conditions

- Von Hippel-Lindau (VHL)
- Birt-Hoggé-Dube (BHD)
- Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)
- Tuberous Sclerosis Complex (TSC)
- Hereditary Papillary Renal Cell Carcinoma (HPRCC)
VHL: Basic Science

• Autosomal-dominant germline mutation with a deletion in the VHL tumor suppressor gene on short arm of chromosome 3
  – leading to abnormal growth of blood vessels
• VHL gene is the primary regulator of cellular hypoxia signaling
• If VHL complex is malfunctioning, levels of Hypoxia Inducible Factor (HIF) rise
  – Overproduction of VEGF and PDGF → signal target cells to stimulate growth & reproduction
VHL: Renal Cell

• HIF-1α inhibits cell growth
• HIF-2α drives tumor progression
• ccRCC cell lines show increase in hypoxia associated factor (HAF)
• HAF drives increased levels of HIF-2α

Clear cell RCC, sometimes bilateral
VHL

- 1 in 32,000, 20% de novo
- Clinical symptoms usually present in 20’s
## VHL: Manifestations

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Most cmn age (years)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal hemangioblastomas</td>
<td>12-25</td>
<td>20-60%</td>
</tr>
<tr>
<td>Endolymphatic sac</td>
<td>16-28</td>
<td>11-16%</td>
</tr>
<tr>
<td>Cerebellar hemangioblastomas</td>
<td>18-25</td>
<td>44-72%</td>
</tr>
<tr>
<td>Brainstem hemangioblastomas</td>
<td>24-35</td>
<td>10-25%</td>
</tr>
<tr>
<td>Spinal cord hemangioblastomas</td>
<td>24-35</td>
<td>13-50%</td>
</tr>
<tr>
<td>RCC</td>
<td>25-50</td>
<td>50%</td>
</tr>
<tr>
<td>Pheo</td>
<td>12-25</td>
<td>10-20%</td>
</tr>
<tr>
<td>Pancreatic lesions</td>
<td>24-35</td>
<td>Cysts (70%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serous Cystadenoma (9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroendocrine tumor (9%)</td>
</tr>
</tbody>
</table>
VHL: Collaboration

Urology
Oncology
Neurosurgery
Ophthalmology
GI Surgery
Neuro-otology
Endocrinology
Genetics
Birt-Hogg-Dubé

- Autosomal dominant mutation in folliculin (FLCN) gene
- Very rare, ~ 500 families worldwide

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrofolliculomas of face, ears, neck, upper body</td>
<td>90%</td>
</tr>
<tr>
<td>Pulmonary Cysts</td>
<td>90% (25% will have pneumothorax)</td>
</tr>
<tr>
<td>Kidney Cancer</td>
<td>25%</td>
</tr>
</tbody>
</table>
BHD: Collaboration

Urology
Pulmonology
Dermatology
Genetics
Hereditary Leiomyomatosis and Renal Cell Carcinoma

- Autosomal Dominant genetic alteration of fumarate hydratase (FH) gene
- Very rare, ~1,500 patients worldwide

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine fibroids</td>
<td>High</td>
</tr>
<tr>
<td>Skin leiomyomas</td>
<td>High</td>
</tr>
<tr>
<td>Renal Cell Carcinoma (Papillary Type 2 or Collecting Duct)</td>
<td>Low</td>
</tr>
</tbody>
</table>

Suspicious renal mass should be acted upon quickly given aggressive subtypes
HL RCC: Collaboration

Urology
Oncology
Gynecology
Dermatology
Genetics
# Tuberous Sclerosis Complex

- Autosomal dominant mutation in TSC 1 or TSC 2
- 1 in 6,000 live births

## Manifestation & Frequency

<table>
<thead>
<tr>
<th>Neurological</th>
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<tbody>
<tr>
<td>Cortical Tubers</td>
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<tr>
<td>Cortical Tubers</td>
<td></td>
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<tr>
<td>Subependymal Nodules</td>
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<tr>
<td>SEGA</td>
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<tr>
<td>Epilepsy (5-15%)</td>
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<tr>
<td>Intellectual Dysfunction (85%)</td>
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<tr>
<td>TSC-Assoc Neuropsychiatric Disorders (45-60%)</td>
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<thead>
<tr>
<th>Skin</th>
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<tbody>
<tr>
<td>Facial angiofibromas</td>
<td></td>
</tr>
<tr>
<td>Shagreen patch</td>
<td></td>
</tr>
<tr>
<td>Hypomelanotic macules</td>
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<tr>
<td>Fibrous cephalic plaque</td>
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<table>
<thead>
<tr>
<th>Renal</th>
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<tbody>
<tr>
<td>Angiomyolipomas (70-80%)</td>
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<thead>
<tr>
<th>Cardiac</th>
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<tr>
<td>Rhabdomyomas (47-67%)</td>
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<tr>
<th>Ophto</th>
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<tr>
<td>Depigmented patches</td>
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<table>
<thead>
<tr>
<th>Pulmonary</th>
<th></th>
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<tbody>
<tr>
<td>LAM</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Oral</th>
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</thead>
<tbody>
<tr>
<td>Gum fibromas</td>
<td></td>
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<tr>
<td>Dental pits (90%)</td>
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</table>
TSC: Collaboration

Urology
Neurology
Neurosurgery
Psychiatry
Dermatology
Cardiology
Ophthalmology
Interventional Radiology
Pulmonology
Dentistry
Hereditary Papillary RCC

- Autosomal dominant mutation in c-met gene
- Type 1 papillary
- Multiple bilateral tumors
- Suspect if multiple family members have type 1 papillary RCC
Algorithm

Referral through new patient coordinator
*Genetics, Urology, Self referrals*

Pre-visit diagnostics (if applicable)

Consult with Dr Kim or Mary Dunn

Referrals to specialists

Follow up with Mary Dunn for Care Plan and coordination of future care
2nd Friday of each month in the NC Cancer Hospital
Care Plan

Components

• Personal history
• Family history
• Names of care team providers
• Follow up guidelines & schedule
• Contact info

Patient & providers receive a copy
Updated at each visit & PRN
UNC VHL Comprehensive Clinical Care Center

Patient:

VHL Treatment Summary and Care Plan

VHL History:

VHL Family History:

Manifestations:

- Neurologic
  - Hemangioblastomas
    - Brain:
    - Spine:
  - Urologic
    - Renal cell carcinoma:
    - Renal cysts:
  - Ophthalmic
    - Hemangioblastomas:
    - Vision loss:
  - Gastrointestinal:
    - Pancreatic cystadenomas:
    - Inner ear:
    - Endolymphatic Sac Tumor:
    - Hearing loss:

VHL Care Team:
Oncology/VHL Care Center: Mary Dunn, NP and Billy Kim, MD
Neurosurgery:
ENT:
Ophtha:
Other:

VHL Care Plan:
- Brain imaging: Every 12 months, last due
- Spine imaging: Every 12 months, last due
- Abdominal imaging: Every 12 months, last due
- Audiometry: Every 12 months, last due
- Ophthalmology: Every 12 months, last due
- Urine markers: NA
- Genetic testing: Complete

Current Recommendations:
As above, except for the following: NA

VHL Disease management plan:
1. Coordinated Health: Annual evaluation at VHL Comprehensive Clinical Care Center to review abdominal imaging, audiometry, and ophthalmology and discuss any needed revisions to the plan.

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Coordinator, UNC VHL Comprehensive Clinical Care Center
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Mw Dunn@med.unc.edu
Von Hippel-Lindau Clinical Care Center

UNC Healthcare has a long standing tradition and culture of engaging in a multidisciplinary approach to managing complex medical problems. This approach is what is needed for evaluating and treating von Hippel-Lindau syndrome, a condition that can affect multiple organ systems.

UNC was selected by the VHL Family Alliance as a VHL Clinical Care Center in January 2012, and joined the ranks of over 20 other Clinical Care Centers across the United States.

Kidney cancer (renal cell carcinoma) sometimes occurs as a part of familial syndromes in which multiple members of a family can be affected with kidney cancers and often other growths. There are several syndromes which are known to be associated with this type of kidney cancer: von Hippel-Lindau, neurofibromatosis type 1 (NF1), Beckwith-Wiedemann syndrome, Sturge-Weber syndrome, Ondine's curse and familial adenomatous polyposis (FAP).
Cancer in our Genes International Patient Database (CGIP)

Database for VHL, HLRCC, BHD & SDH

- Create a single source of info for researchers & patients
- Include large # of patients to allow for more accurate research
- Learn about natural history of these conditions
- Find links
- Discover treatments
- Match patients to clinical trials
Resources

• VHL Alliance
• BHD Foundation
• HLRCC Family Alliance
• TSC Alliance
<table>
<thead>
<tr>
<th>Provider</th>
<th>Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billy Kim, MD</td>
<td>Sponsor, Oncology</td>
</tr>
<tr>
<td>Mary Dunn, NP</td>
<td>Coordinator, Urology, Oncology</td>
</tr>
<tr>
<td>Ofri Leitner, CGC &amp; Catherine Fine, CGC</td>
<td>Clinical Genetics</td>
</tr>
<tr>
<td>James Evans, MD, PhD</td>
<td>Medical Genetics</td>
</tr>
<tr>
<td>Seema Garg, MD, PhD</td>
<td>Ophthalmology</td>
</tr>
<tr>
<td>Timothy Gershon, MD, PhD</td>
<td>Neurology</td>
</tr>
<tr>
<td>Matt Ewend, MD &amp; Deanna Sasaki-Adams, MD</td>
<td>Neurosurgery</td>
</tr>
<tr>
<td>Jing Wu, MD, PhD</td>
<td>Neuro-oncology</td>
</tr>
<tr>
<td>Will Pendergraft, MD, PhD &amp; Keisha Gibson, MD, MPH</td>
<td>Nephrology (Adult &amp; Peds)</td>
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<tr>
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<tr>
<td>Julie Sharpless, MD</td>
<td>Endocrinology</td>
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<tr>
<td>Craig Buchman, MD</td>
<td>Neurotology</td>
</tr>
<tr>
<td>Keith Smith, MD, PhD</td>
<td>Radiology</td>
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<tr>
<td>Edward Pickens, MD</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>Paola Gehrig, MD</td>
<td>Gynecology</td>
</tr>
<tr>
<td>Kathryn Menard, MD, MPH</td>
<td>Maternal-Fetal Medicine</td>
</tr>
<tr>
<td>Dean Morrell, MD</td>
<td>Dermatology</td>
</tr>
<tr>
<td>Pamela Durham, LCSW</td>
<td>Social Work</td>
</tr>
<tr>
<td>Don Rosenstein, MD</td>
<td>Psychiatry</td>
</tr>
<tr>
<td>Matt Nielsen, MD, MS &amp; Mike Woods, MD</td>
<td>Urology</td>
</tr>
</tbody>
</table>
Referral Sources
Conclusion

• Complexity
  – Manifestations + co morbidities
• Collaboration
  – Group of experts
• Coordinated Care
  – Care Plans
• Communication
  – Patient, care team, outside providers

Please contact me if you would like to discuss and/or refer a patient to our program
Thank you!