## Outline

- How does VHL disease manifest in the eye?
- What is the nature and appearance of VHL eye tumors and how do they affect eye health?
- How do eye doctors detect and monitor VHL tumors?
- What treatments exist for VHL eye tumors?
- Some common questions regarding VHL eye tumors
VHL: a multisystemic cancer syndrome

Lonser et al., 2003
Definition of VHL disease in the eye

- Hallmark lesion of ocular VHL disease
  - Retinal capillary hemangioblastoma
- Early Descriptions
  - 1870’s – 1890’s: First descriptions of large “aneurysmal dilatations of retinal vessels”; “associated with exudation”
  - 1904: Described by Eugene von Hippel as “angiomatosis retinae”
  - 1926-27: Association of cerebellar and retinal hemangioblastomas by Arvid Lindau
A Little Eye Anatomy....... 

- Structure of the eye and retina
  - The eye as a “camera”
  - Retina = “film” of the eye
A Little Eye Anatomy...

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A Little Eye Anatomy....... 

- Parts of the retina 
  - Central vs. Peripheral retina 
  - Optic nerve
Retinal capillary hemangioblastoma (RCH)

- Features of ocular VHL lesion
  - Slow growth of lesion within blood vessels of the retina
  - Circumscribed, orange-red lesion, round in shape
  - Supplied by dilated, tortuous feeding and draining retinal vessels
Retinal capillary hemangioblastoma (RCH)

- Distribution
  - Peripheral
  - Juxtapapillary RCHs
    - Located adjacent to the optic nerve
    - Variable size and prominence
    - No obvious feeding and draining vessels
Secondary structural effects of RCHs

- **Exudation**
  - Disruption in retinal structure and function due to:
    - Retinal edema and serous detachment
    - Deposition of intraretinal lipid
Secondary structural effects of RCHs
Secondary structural effects of RCHs

- **Fibrosis**
  - Arises from secondary preretinal glial proliferation
  - Distortion of the retina (macular pucker)
  - Tractional retinal detachment
End-stage effects of RCHs

- Massive exudation and retinal detachment
- Uveitis, glaucoma, phthisis, loss of eye
Unusual variant of ocular VHL – retinal vascular proliferation

- Fine superficial vessels in juxtapapillary position
- Association with epiretinal fibrosis

Wong et al., Arch Ophthalmol, 2008
Diagnostic imaging of RCHs

- Fluorescein angiography
  - To highlight the presence of RCHs
  - To characterize the extent of exudation
Diagnostic imaging of RCHs

- **Optical Coherence Tomography (OCT)**
  - To monitor lesion growth
  - To monitor lesion exudation and response to treatment
Treatments for Ocular VHL Disease

• **Observation**
  - Decision to treat small, non-exudative peripheral lesions
    - Early intervention vs. careful monitoring

• **Ablative Laser photocoagulation**
  - Mainstay of treatment for small peripheral lesions
  - Goal: to induce
    - Growth cessation
    - Decreased exudation
Treatments for Ocular VHL Disease

• Cryotherapy
  o Considered for lesions that are
    ➢ Anterior
    ➢ Larger (>3mm)
    ➢ Associated with extensive fluid

• Radiotherapy
  o Plaque radiotherapy
  o External beam radiotherapy

• Vitrectomy
  o Indications: Fibrosis, retinal detachment, extensive hemorrhage
Juxtapapillary RCHs: A Treatment Dilemma

- **Difficulty in treatment**
  - Difficulty with access (posterior position)
  - Ablative treatments:
    - Damage the optic nerve, nerve-fiber layer, retinal blood supply
    - May induce increased fibrosis, subretinal hemorrhage
Take Home Points

• Ocular VHL consists of the emergence of tumors in blood vessels of the retina
• Leakage from retinal tumors can disrupt the structure of the retina resulting in vision loss
• VHL retinal tumors may be treated by a variety of treatments
• Early detection and treatment can be associated with better vision outcomes
Some common questions on ocular VHL

- How can I tell if I have ocular VHL?
Some common questions on ocular VHL

- How often should a patient with VHL consult their eye doctor?
Some common questions on ocular VHL

- Will everyone with VHL disease develop ocular VHL?

- Prevalence of RCHs in patients with clinical diagnosis of VHL
  
  - Cross-sectional analysis of 890 patients with diagnosis of VHL disease (872 with characterized mutations in VHL gene)
  
  - Overall prevalence: 37.6%
Some common questions on ocular VHL

• I have been diagnosed with VHL and am concerned about my vision. Am I likely to go blind?
  
  • Distribution of visual acuities in better and worse-seeing eye
    • Visual impairment is usually monocular in nature
    • Low prevalence of binocular impairment (1 in 19 or 5.7% of patients have Va <20/160 in both eyes)
Some common questions on ocular VHL

- I have been diagnosed with VHL and am concerned about my vision. Am I likely to go blind?
Clinical trials for new treatment modalities

- **Anti-VEGF treatments**
  - **Systemic** anti-VEGF treatments: limited success in case studies
    - **SU5416** (Aiello et al. 2002, Girmens et al., 2003, Madhusudan, 2004),
    - **Bevacizumab** (von Buelow et al., 2007)
  - **Local** anti-VEGF treatments:
    - **Pegaptanib** (aptamer that inhibits VEGF isoform 165) (Dahr et al., 2007)
      - 5-patient open label trial
      - Intravitreal injections every 6 weeks for >6 injections
      - no vision improvement, minimal anatomical improvement
Clinical trials for new treatment modalities

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Clinical trials for new treatment modalities

• **Anti-VEGF treatments**
  
  o **Local anti-VEGF treatments:**
    
    ➢ *Ranibizumab* (Wong et al., 2008)
    
    ➢ 5-patient open label trial
    
    ➢ Intravitreal injections every 4 weeks for 1 year
    
    ➢ minimal beneficial anatomical or functional improvement
  
  o **Viable target for intervention?**
    
    o Delivery of therapeutic dose to RCH: systemic vs. intravitreal approaches
    
    o Relationship between VEGF signaling and RCH characteristics (growth, exudation, fibrosis)
    
    o Combination treatment: Inhibition of PDGF signaling

(Wong et al., 2008)
Phenotype of Ocular VHL

- Impact of ocular VHL disease on eye health
  - Cross-sectional analysis of 335 patients with ocular VHL disease
  - Demographics

| Number of patients | • 335 patients from 220 families.
  • 1.5±1.2 patients per family (range 1-13) |
<table>
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<tbody>
<tr>
<td>Gender</td>
<td>45% male : 55% female</td>
</tr>
</tbody>
</table>
| Age                | 36.9±13.7 years
  (range 8.6 – 84.3) |
| Race               | 91% white: 4.8%
  Hispanic: 2.4%
  Asian: 1.8%
  Black |

(Wong et al., 2008)
Phenotype of Ocular VHL

- Laterality
  - Unilateral = 42%, Bilateral = 58%
    - Not associated with age or gender
Phenotype of Ocular VHL

- Severely Affected eyes
  - 1 in 5 patients had at least one eye enucleated or structurally disrupted
  - Risk of severe involvement increased with age and bilateral involvement

- All eyes (n=670 of 335 patients)
  - Eyes with RCHs (n=529, 79%)
    - Severe involvement, RCHs cannot be visualized (n=71, 13%)
      - Enucleations (n=42)
      - Structural disruptions (n=29)
    - RCHs can be individually evaluated (n=458, 87%)
  - Eyes without RCH (n=141, 21%)
    - In juxtapapillary location only (n=37, 8.1%)
    - In peripheral location only (n=388, 84.7%)
    - Both juxtapapillary and peripheral locations (n=33, 7.2%)
Phenotype of Ocular VHL

- Ocular phenotype of RCH
  - Majority of RCHs located in peripheral retina

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 Phenotype of Ocular VHL

- Number of peripheral RCHs
  - Average no. of peripheral RCHs = **2.5 ± 1.8** (range 1 – 11)
  - **25%** extended > 1 quadrant of peripheral retina
  - No association between RCH number and age (p=0.60) or extent of peripheral retinal involvement (p=0.70)
Impact of Ocular VHL on Vision

- Distribution of visual acuities in better and worse-seeing eye
  - Visual impairment is usually **monocular** in nature
  - Low prevalence of binocular impairment (1 in 19 or 5.7% of patients have Va <20/160 in both eyes)
- However, impact of RCH on vision is significant
  - OR in eyes with RCHs (versus eyes without RCHs)
    - Moderate vision loss (< 20/40) = 9.1 (4.1–20.2)
    - Severe vision loss (< 20/160) = 12.8 (4.4–37.7).
Impact of Ocular VHL on Vision

- **Location of tumor**
  - Juxtapapillary tumors associated with worse vision
- **Number of peripheral tumors**
- **Extent of peripheral retina involved**

<table>
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<tr>
<th>Eyes with RCHs in:</th>
<th>Mean Va ± std dev.</th>
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<tbody>
<tr>
<td>Peripheral RCH only</td>
<td>75.9 letters (≥ 20/32)</td>
</tr>
<tr>
<td>Optic disk RCH only</td>
<td>67.1 letters (≥ 20/50)</td>
</tr>
<tr>
<td>Both Optic disk and periphery RCH</td>
<td>58.8 letters (≥ 20/62)</td>
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</tbody>
</table>
Genotype-Phenotype Correlation in von Hippel-Lindau Disease With Retinal Angiomatosis

Wai T. Wong, MD, PhD; Elvira Agrón, MS; Hanna R. Coleman, MD; George F. Reed, PhD; Karl Csaky, MD, PhD; James Peterson, PhD; Gladys Glenn, MD, PhD; W. Marston Linehan, MD; Paul Albert, PhD; Emily Y. Chew, MD
Genotype-Phenotype Correlations in Ocular VHL Disease

- Genotype and the prevalence of ocular VHL disease

<table>
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<tr>
<th>Type of Mutational Class</th>
<th>Prevalence of RCHs</th>
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<tbody>
<tr>
<td>Amino-acid Substitution</td>
<td>37.8%</td>
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<tr>
<td>Protein Truncation</td>
<td>40.2%</td>
</tr>
<tr>
<td>Complete Deletion</td>
<td>14.5%*</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>37.1%</strong></td>
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(n = 839 patients with mutations in VHL gene)

Patients with complete deletions have the lowest rate of RCH ocular involvement
Genotype-Phenotype Correlations in Ocular VHL Disease

- Genotype and the phenotype of ocular VHL disease
Genotype-Phenotype Correlations in Ocular VHL Disease

- Genotype and visual acuity
Genotype-Phenotype Correlations in Ocular VHL Disease

- Genotype-phenotype correlations
  - Genotype category had no impact on:
    - Whether one or both eyes are affected
    - Whether an eye becomes phthisical or enucleated
    - How many tumors form
  - Genotype category influenced:
    - How likely ocular involvement occurs
    - Where tumors were located
    - Visual acuity outcome
- Complete deletion of VHL protein:
  - Lower incidence of ocular disease (1 in 6, compared to 1 in 3)
  - Better visual acuity outcome
Genotype-Phenotype Correlations in Ocular VHL Disease

- Significance of the position of missense mutations (n = 412 patients)
  - Prevalence of ocular VHL disease
  - $\alpha$-domain vs $\beta$-domain: 46% vs 34% ($p = 0.016$)
- Phenotype of ocular VHL disease

<table>
<thead>
<tr>
<th>Ocular Phenotype</th>
<th>Mutations in the $\alpha$-Domain</th>
<th>Mutations in the $\beta$-Domain</th>
<th>OR (95% CI) $\alpha$-Domain vs. $\beta$-Domain</th>
<th>$P$</th>
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<tr>
<td>All Participants with RCHs (n = 157)</td>
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<tr>
<td>Bilateral RCHs</td>
<td>38/71 (53.5)</td>
<td>55/86 (64.0)</td>
<td>0.71 (0.33–1.50)</td>
<td>0.3661</td>
</tr>
<tr>
<td>Severe structural involvement in at least 1 eye</td>
<td>16/71 (22.5)</td>
<td>14/86 (16.3)</td>
<td>1.71 (0.66–4.40)</td>
<td>0.2673</td>
</tr>
<tr>
<td>Juxtapapillary RCH in at least 1 eye</td>
<td>13/86 (15.1)</td>
<td>26/71 (36.6)</td>
<td>4.56 (1.77–11.76)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Peripheral RCH in at least 1 eye</td>
<td>78/86 (90.7)</td>
<td>55/71 (77.4)</td>
<td>0.24 (0.08–0.71)</td>
<td>0.0104</td>
</tr>
<tr>
<td>All Participants with RCHs in the Peripheral Retina (n = 133)</td>
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<tr>
<td>At least 1 eye with $\geq$3 peripheral RCH</td>
<td>22/55 (40.0)</td>
<td>38/78 (48.7)</td>
<td>0.72 (0.32–1.62)</td>
<td>0.4244</td>
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<tr>
<td>At least 1 eye with $\geq$5 peripheral RCH</td>
<td>13/55 (23.6)</td>
<td>17/78 (21.8)</td>
<td>1.28 (0.51–3.21)</td>
<td>0.5959</td>
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<td>$&gt;1$ Quadrant involved in periphery</td>
<td>22/55 (40.0)</td>
<td>20/78 (25.6)</td>
<td>1.45 (0.62–3.42)</td>
<td>0.3921</td>
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Summary

• Clinical characterization of a large population of VHL patients with ocular VHL disease
  ➢ Quantitative characterization of phenotypic features
  ➢ Assessment of visual impact of ocular VHL disease
  ➢ Assessment of natural history of disease
  ➢ Identification of phenotypes that lead to vision loss

• Genotype-phenotype correlations
  ➢ Profile the influence of genotype of VHL mutations on prevalence and functional outcome of ocular disease

• Therapeutic challenges
  ➢ Predictive models for ocular follow-up and treatment
  ➢ New modalities for exudative juxtapapillary lesions
Retinal capillary hemangioblastoma (RCH)

- Optic nerve VHL lesion