The Genetic Subtyping of VHL

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Overview

1. Review Genetics Principles
2. Discuss the Subtyping of VHL
3. Questions

Genetics Background

Von Hippel Lindau

- 1:36,000 people has Von Hippel Lindau (VHL) syndrome
- Almost all will have symptoms by age 75
  - Most will have at least 1 symptom by the 2nd-3rd decade of life
  - Symptoms can be variable, even among members of the same family
- Most cases are inherited, but ~20% are new in an individual
- VHL is a "tumor suppressor" gene involved in cell communication pathways and in blood vessel formation
  - Harmful changes, or "mutations" in the VHL gene can lead to accumulation of proteins that are typically degraded
  - Proteins tell cells to continue dividing at a rapid pace - if tumors form
  - Tumors are typically "benign" but can cause problems due to location and size

Genetics Background
VHL Genetics

Rapid cell growth
Tumors Associated with VHL

- Hemangioblastomas
  - Brain, spinal cord, retina
- Clear cell renal cell carcinoma (RCC)
- Pheochromocytoma and paraganglioma
- Pancreatic neuroendocrine tumors (PNETs)
- Endolymphatic sac tumors (ELSTs)
- Papillary cystadenomas of the epididymis and broad ligament

VHL Mutation Classification

- Mutations can be caused by spelling mistakes in the genetic code or missing/extra genetic information
- VHL is classified into 5 different subtypes based on how a mutation affects the protein
  - Different mutations can lead to different symptoms of VHL (genotype/phenotype correlations)
  - Primarily associated with presence/absence of pheochromocytoma and then risk for renal cell carcinoma

How is Subtype Determined?

Subtype is based on 3 unique categories of mutation:

- Truncating variants/Exon deletions → cause protein to be only partially made
  - May also be called "nonsense" variants
- Total gene deletions → no protein is made
- Missense variants → A full protein is made, but its composition is altered

May also use clinical/family history correlations
### Subtypes and Associated Risks

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
<th>Type V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical manifestations</td>
<td>Pheochromocytoma</td>
<td>Cerebellar hemangioblastoma</td>
<td>Retinal angiomatosus hamartoma</td>
<td>Spinal angiomatosus hamartoma</td>
<td>Renal angiomatosus hamartoma</td>
</tr>
</tbody>
</table>

**Most common errors:**
- Translating words into numbers: Incorrect genetic changes are listed.
- Gene deletions are mentioned in lowercase, while the protein changes are in uppercase.

### Determining your Subtype

- Your doctor or genetic counselor can help you determine your VHL subtype based on your genetic test report.
- If you haven't had genetic testing, you can hypothesize your subtype based on personal and family history.
- Genetic test reports have two “values” that are designated:
  - "coding" change: c.1234A>T or c.1234delA
  - "protein" change: p.Arg41Cys or p.Arg41*

The "p" or protein value correlates most with VHL subtype.

### Purpose of Subtyping

- **Clinical risks and suspicion**
- **Research potential**
- Management is not currently based on subtyping.
  - Patients may more rarely develop symptoms outside their subtype.
  - Your genotype is a unique identifier for you and your family!