VISION: VHL Information Sharing cONsortium

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Challenges for VHL

1. VHL is a rare disease – few pathogenic mutations are known
   - Evidence to support interpretations is difficult to find (few databases exist).

2. 20% of VHL mutations are de novo
   - No family history available

3. ACMG rules are not gene-specific
   - VHL experts must adapt rules to VHL
   - This will increase the accuracy of interpretations

VHL Case Studies

Scenario 1: Clinical Case Study

- 23 year old patient with pheochromocytoma
- Gene panel testing reveals a germline VHL variant:
  - c.345C>G [p.H115Q missense mutation]
  - Lab classification: Variant of unknown significance
- Family history is negative for VHL disease
  - No VHL mutations in family members
- Does this patient have VHL disease?
- Should this patient receive life-long surveillance?

VHL Case Studies

Scenario 2: VHL Research

- Researcher wants to know what VHL variants are associated with hemangioblastoma
- Where to look?
  - PubMed
  - Google Scholar
  - Databases
**Case study: ClinVar**

- Assertion for (VHL c.345C>G) mutation is *inconclusive* on ClinVar, no phenotype described:
  
  NM_000061.3(VHL):c.345C>G [p.His115Gln]

**Classifying Genetic Variants**

- The American College of Medical Genetics and Genomics (ACMG) developed rules to determine the medical relevance of a genetic variant:
  - Requires certain info about the variant (e.g. population frequency, disease segregation, gene function etc.)
  - Severe (pathogenic) or benign (harmless)
  - 30% of panel testing results are uncertain, and difficult to make medical decisions on such "private variants"

**How to overcome this?**

- Large gene-based consortium
  - BRCA1/2 (ENIGMA)
  - Cystic fibrosis
  - Hereditary Colon Cancer (INSIGHT)
- Share information about gene variants
- Share information about families

**VISION**

**VHL Information-Sharing International Consortium**

**Mandate:** Improve VHL disease understanding and treatment on a global scale by sharing genomic and clinical information.

**Projects:**

- Curate a database of VHL variants
- Establish an Expert Panel to:
  1. Create rules for VHL variant interpretation
  2. Use VHL rules to identify pathogenic variants
- Freely share data with the VHL community around the world
Housing VHL Variants in CIViC

- VHL information is scattered and unorganized
- Open access, community-driven web resource for Clinical Interpretation of Variants in Cancer
- Standardized (Human Phenotype Ontology)
- Centralized, debated, and interpreted data of associations between specific mutations, phenotypes, and responses to a targeted therapy
- Search by variant, phenotype, disease, therapy

Assembling all VHL cases ever published

Information Specialist optimized search to identify VHL publications
- Remove duplicates & untranslated articles
- Remove articles that do not report VHL mutations
- Remove publications with identical patients ("double-counting")
- Remove non-human studies (e.g. canine/rodent studies)
- Record family history and age of disease onset
- Extract patient genotypes and manifestations
- Standardize mutation coordinates and nomenclature
- Convert phenotypes to standardized HPO terms

CIViC 1324 Evidence Statements

Back to the case, c.345C>G
CIViC: Search By Variant

Search Results: 4 total terms
- EID: 123
- GENE: VHL
- VARIANT: H1150c.345C>G
- BEISE: Study of ED patients. VHL variant detected. M/F
Case Study: Conclusion

- CIViC Evidence Supports c.345C>G Pathogenicity
- Ask lab to reclassify, pathogenic

Management decision: Patient should undergo surveillance and likely has VHL disease
CIViC: Search By Phenotype

Local VHL populations: REDCap

- CIViC Captures published patients
- VHL disease is a multisystem disease
  - Existing databases only focus on specific manifestations
- Our database captures highly detailed, head-to-toe clinical data
  - Input from Multiple VHL authorities from different organ systems
  - REDCap has 8000 fields!
- Free to use, shareable

REDcap Data - 88 Toronto pts

<table>
<thead>
<tr>
<th>N (%), Total number of patients 87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age 35</td>
</tr>
<tr>
<td>Mean Age of Genetic Diagnosis 24</td>
</tr>
<tr>
<td>Female 54 (62)</td>
</tr>
<tr>
<td>Male 33 (38)</td>
</tr>
<tr>
<td>Probands 40 (46)</td>
</tr>
<tr>
<td>de novo VHL 23 (26)</td>
</tr>
<tr>
<td>Genetic Testing 81 (93)</td>
</tr>
<tr>
<td>+ VHL a 77 (95)</td>
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<tr>
<td>Results unknown a 4 (5)</td>
</tr>
<tr>
<td>Mutation Type</td>
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<tr>
<td>Missense b 36 (47)</td>
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<tr>
<td>Nonsense b 5 (6)</td>
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<tr>
<td>Frameshift b 17 (22)</td>
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<tr>
<td>Large Deletion b 13 (17)</td>
</tr>
<tr>
<td>Intronic/Splice b 5 (6)</td>
</tr>
<tr>
<td>UTR b 1 (1)</td>
</tr>
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VISION Overview

- Public VHL Mutation Databases
  - UMD (Universal Mutation Database)
  - LOVD (Low Density Oligonucleotide Venn Diagram)
- Published VHL Case Reports
  - PubMed
- Toronto VHL Cases
  - REDCap

VHL Expert Panel

VHL Gene-Specific Mutation Rules

VHL Variant Database

Data Analysis (Machine Learning)

Clinical Trial Enrolment

Three-star variants shared with the world

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