A Comparison of Two Large Western PA VHL Type 2A Families

Sarah M. Nielsen, MS
Dept. of Human Genetics
Graduate School of Public Health
University of Pittsburgh

Von Hippel-Lindau Disease (VHL)

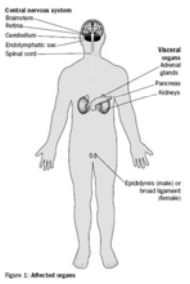


Figure 1: Affected organs

http://cancergenetics.wordpress.com/2009/05/09/today-von-hippel-lindau-disease-day/

- Autosomal dominant endocrine tumor syndrome
- Benign and malignant tumors:
  - Adrenal glands- *pheochromocytoma*
  - Pancreas- *neoplasms and/or cysts*
  - Kidneys- *renal cell carcinoma (RCC)*
  - Eyes- *retinal angioma*
  - Brain, Spine } *CNS hemangioblastoma*
- 90% penetrance by age 65
- U.S. incidence = 1/32,000

VHL Subtypes

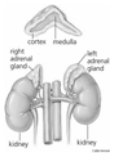
- Clinical and allelic heterogeneity are hallmarks of VHL
- 4 phenotypes described based on frequency of pheochromocytoma (pheo) and renal cell carcinoma (RCC)
  - Pheo risk: <5% type 1; >60% type 2

VHL subtype	VHL mutation	HB	RCC	Pheo
1	Deletion, Insertion, Nonsense, Missense	High risk	High risk	Low risk
2A	Missense	High risk	Low risk	High risk
2B	Missense	High risk	High risk	High risk
2C	Missense	Low risk	Low risk	High risk

HB, hemangioblastoma; RCC, renal cell carcinoma; Pheo, pheochromocytoma

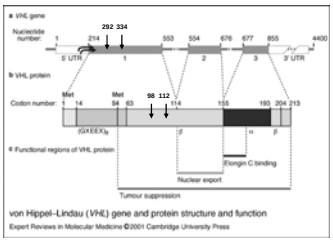
Adapted from [Bryant et al. 2003]

VHL Type 2A



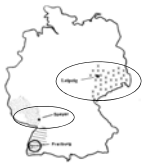
- Pheochromocytoma (pheo)
- CNS hemangioblastoma (HB)
- Retinal angioma (RA)
- Rarely renal cell carcinoma (RCC)

Genetics of VHL



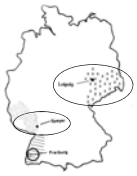
- Chromosome 3p25-26
- Tumor suppressor gene
- Y98H & Y112H mutations:
  - Exon 1 of *VHL* gene
  - Missense mutations
  - Tyrosine to Histidine

VHL Type 2A Families



- Family 1
  - Y112H
  - First described in 1962 by S.A.T. (complete phenotypic characterization in 1993)
  - Originate from east-central Germany (Leipzig)
  - Currently largest kindred with pheochromocytoma in literature (24 cases of pheo)

VHL Type 2A Families



- Family 2
  - Y98H
  - Black Forest founder mutation
  - Partially evaluated through NIH
  - Never described independently in literature
    - Large family, and even more cases of pheo than Family 1

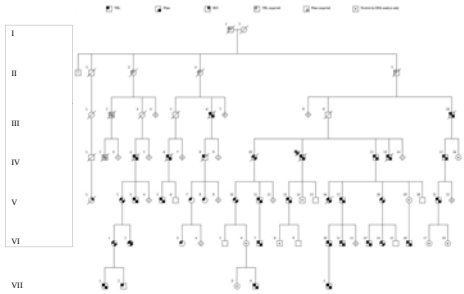
Hypothesis

- Genetic differences between 2 families may correlate with differences in disease expression
  - Particularly related to pheochromocytoma, the most frequent manifestation in both families

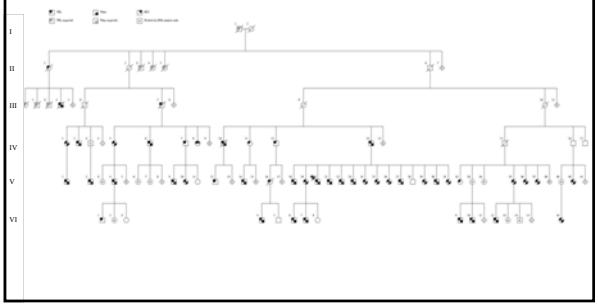
Methods

- 1) IRB to establish Inherited Endocrine Tumor Database
- 2) Pedigree construction
- 3) Patient contact
- 4) Tabulate all family members with VHL
- 5) Analyze pheo data
- 6) Statistical analysis

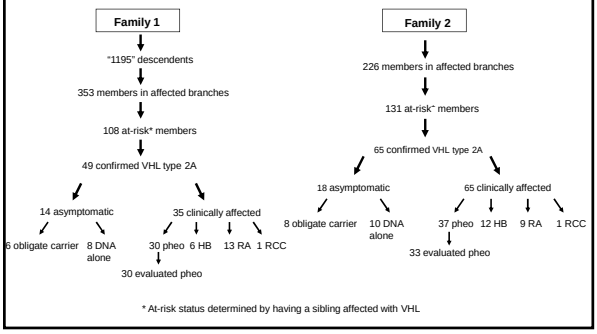
Family 1 pedigree



Family 2 pedigree



Pedigree Breakdown



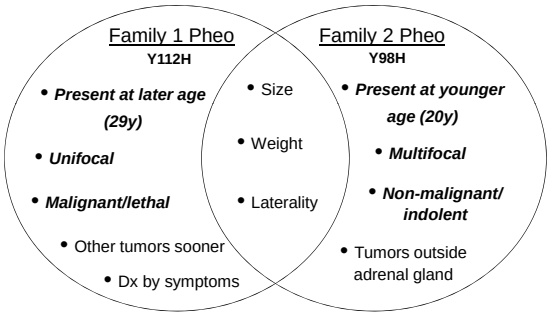
Summary of Findings

- Expression of VHL type 2A similar between 2 families
- High rate of pheo, low rate of RCC

Summary of Findings

- 2nd most common manifestation
  - RA in Family 1
  - HB in Family 2
- Compliance and delivery of medical care
- Genetic and *environmental* factors

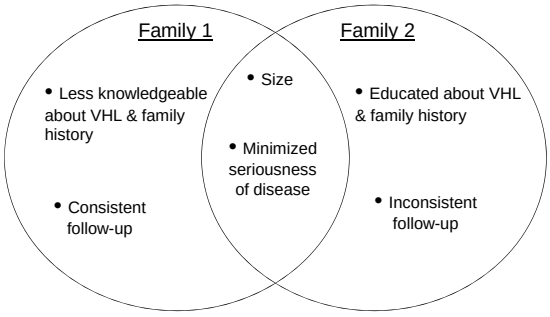
Summary of Findings



Clinical Take Home Points

- Importance of screening for pheo in childhood in pts genetically at-risk
- Children with pheo/paraganglioma should be tested for *VHL/SDHD* mutations
- Patients with Y98H mutation should have MIBG scan for tumor localization
- Lower threshold for converting from laparoscopic to open resection in individuals with Y112H mutations
- Screening for RCC is unnecessary in VHL type 2A pts
- Biochemical screening is the standard of care for **asymptomatic, normotensive** pts

Psychosocial Issues



Acknowledgments

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Thank you! Questions?