Large scale analysis in von Hippel-Lindau disease

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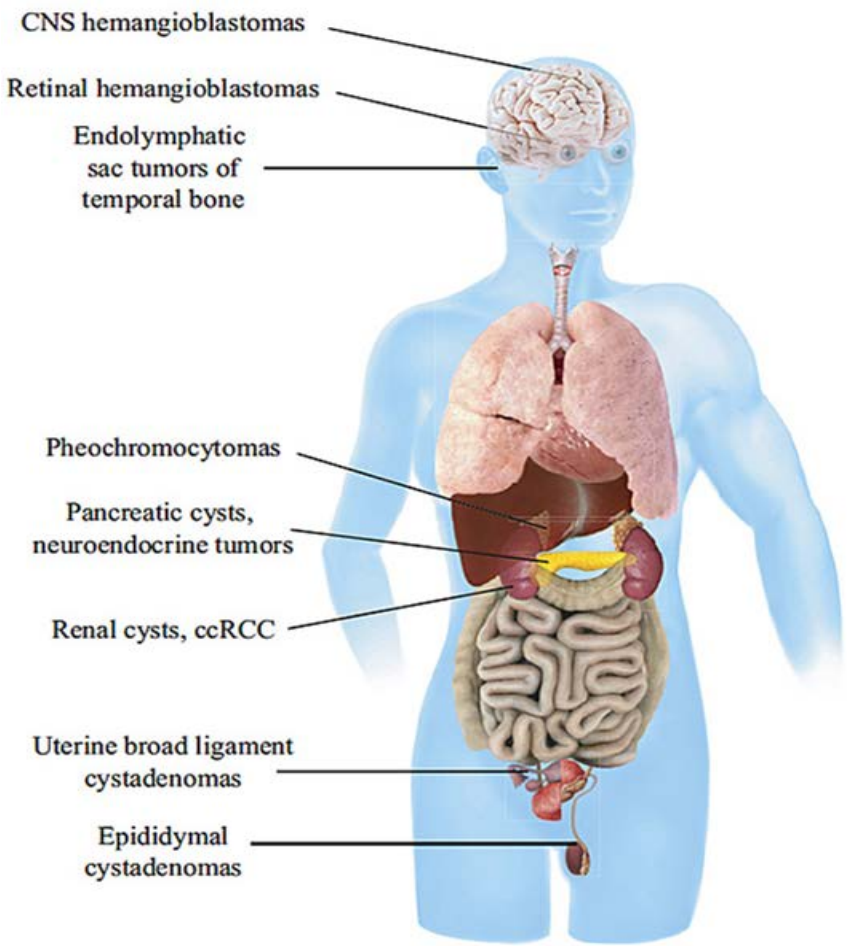
Conflict of Interests

- None to declare

Von Hippel Lindau

- Multi-system disorder
- Mutations in *VHL* gene responsible for degradation of hypoxia inducible factor 1-alpha (HIF1α)
- Results in hemangioblastomas
  - Eye
  - Brain
  - Spine
- Deafness (endolymphatic sac tumours)
- Pancreatic cysts
- variable expressivity = not all mutation carriers develop all manifestations
- Frameshift mutations result in risk of renal cell carcinoma “type 1”
- Missense mutation result in pheochromocytoma “type 2”
- Genetics is not straightforward



Adapted with permission from Ho & Jonasch (2014)

VHL Alliance

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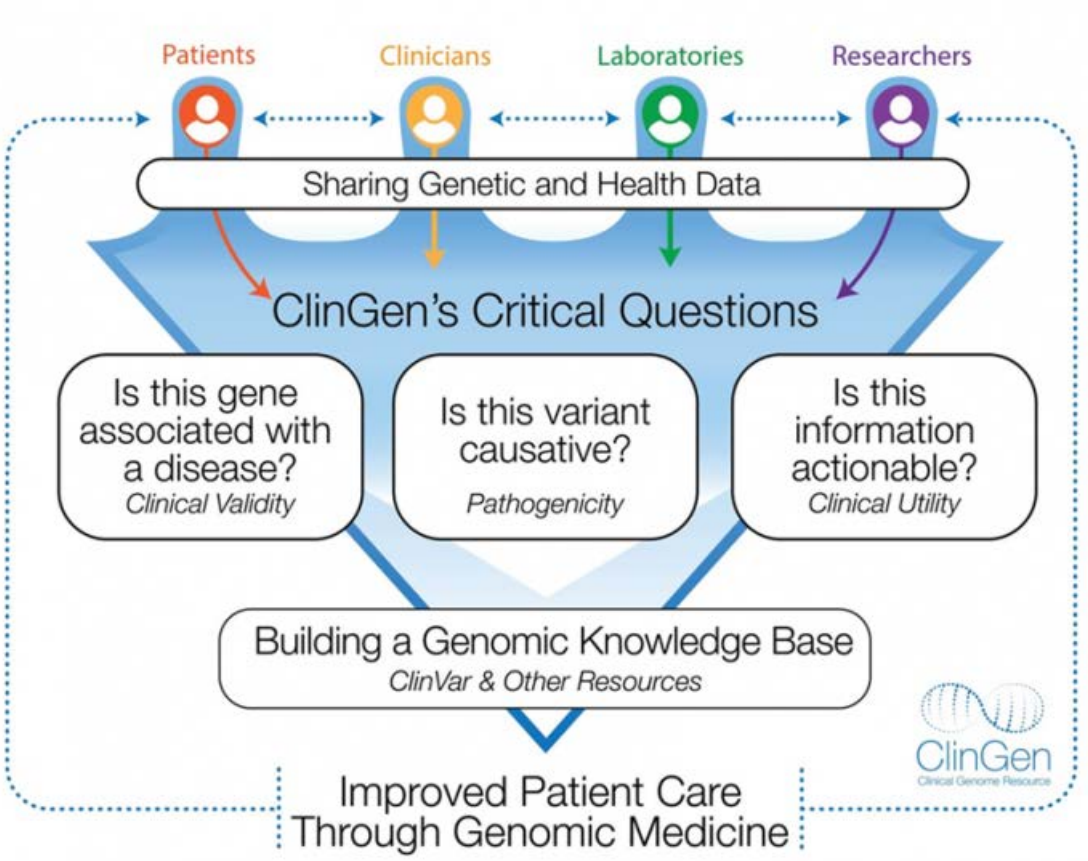
VHL vs other genes….

- Large gene-based consortium
- BRCA1/2 (ENIGMA)
- Cystic fibrosis
- Hereditary Colon Cancer (INSIGHT)



VHL Case Studies
Scenario 1: Clinical Case Study

- 23 year old patient with renal cell carcinoma
- 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?

Case study Patient Scenario: ClinVar gene database

- Assertion for (*VHL* c.345C>G) mutation is inconclusive on ClinVar, no phenotype described:

NM_000551.3(VHL):c.345C>G (p.His115Gln)

Interpretation

Go to:

Clinical significance:	Uncertain significance
Last evaluated:	Feb 5, 2016
Number of submission(s):	1

Assertion and evidence details

Go to:

Clinical assertions | Summary evidence | Supporting observations

Submitter	Allele origin	Individuals	Phenotypes (Affected status)	Ethnicity	Geographic origin	Citations	Description
Integrated Genetics/Laboratory Corporation of America	germline	not provided	not provided (unknown)	not provided	not provided	PubMed	not provided

VISION

VHL Information-Sharing International cONsortium

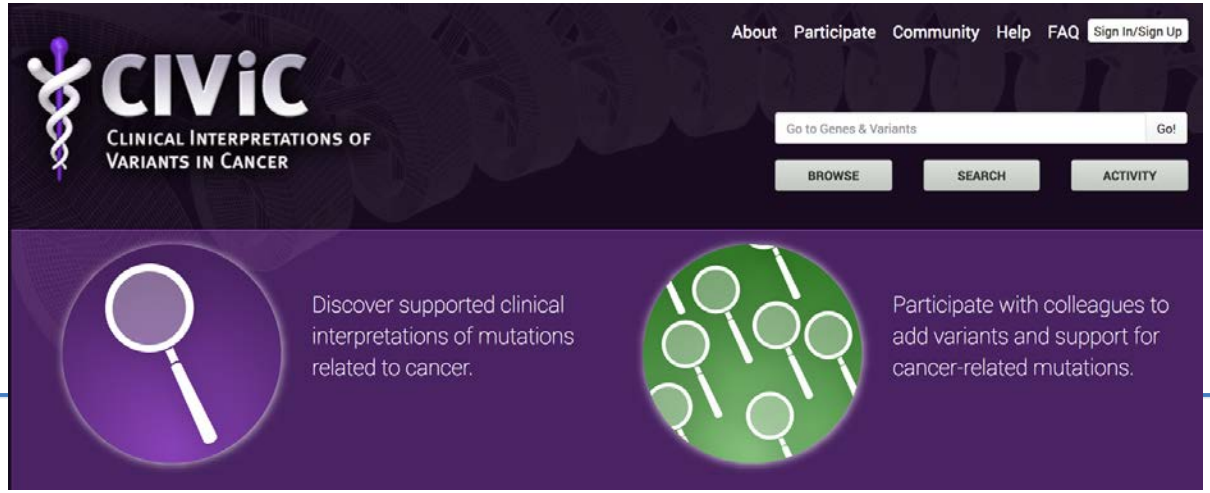
Mandate: Improve VHL disease understanding and treatment on a global scale by sharing genomic and clinical information.

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



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Assembling all VHL cases ever published

Unique papers from OVID Embase and OVID Medline
N = 4191 papers

Title & abstract review

343 papers Excluded
- Not English N = 333
- Not accessible N = 10

N = 3848 papers

Full-text review

3398 papers Excluded
- Not relevant to VHL N = 3186
- Only somatic data N = 212

N = 450 papers

Complete dataset

CIViC
Clinical Interpretations of Variants in Cancer

- Genotype-phenotype
- HPO terms
- HGVS nomenclature

N = 5127 cases

Preliminary analysis with complete patient information

N = 2705 patients

What does the data look like?

Confirmed De Novo?

Kindred Case?

What does the data look like?

Age Type?
- Evaluated
- Last known
- Death

Resolution?
- Patient
- Family
- Variant
- Tumor

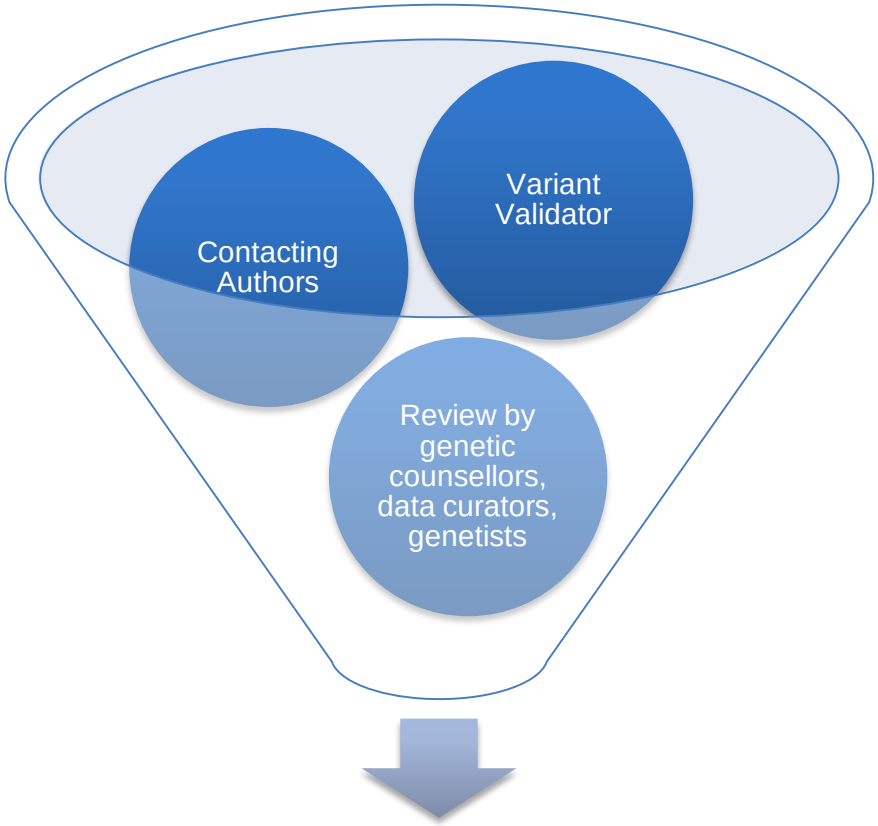
fo	Phenotype	Reference	Age	Sex	Notes	Evidence Stat	Resolution	Input	Warnings	HGVS_transcri	HGVS_intronic_
ry	HP:0009711	(Alegret et al, 2	E14Y0M; lk15Y	M	resulting in in-f	A case study o	Tumour	NM_000551.3:c.227_229del		NM_000551.3:c.227_229del	
sc	HP:0010797; H	(AlFadhli et al.,	unknown	F	index III-9	The germline V	Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	F	III-8		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	F	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	F	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	M	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	M	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	M	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	F	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	F	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	M	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	M	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	M	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
st	HP:0010797; H	(AlFadhli et al.,	unknown	F	I		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	
cy	HP:0002666; H	(Allen et al., 20	E11Y0M; lk22Y	unknown	patient #1 ; phe	Family history	Patient	NM_000551.3:c.292T>C		NM_000551.3:c.292T>C	
	none	(Allen et al., 20	lk24Y0M	unknown	patient #2; diagnosed at 24 w		Patient	NM_000551.3:c.292T>C		NM_000551.3:c.292T>C	
	none	(Allen et al., 20	lk39Y0M	unknown	patient #3; diagnosed at 39 w		Patient	NM_000551.3:c.292T>C		NM_000551.3:c.292T>C	

What does the data look like?

	Reference	Age	Sex	Notes	Evidence Stat	Resolution	Input	Warnings	HGVS_transcri	HGVS_intronic
	(Alegret et al, 2	E14Y0M; Ik15Y	M	resulting in in-fi	A case study o	Tumour	NM_000551.3:c.227_229del		NM_000551.3:c.227_229del	NM_000551.3:c.227_229del
; H	(AlFadhli et al.,	unknown	F	index III-9	The germline V	Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	F	III-8		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	F	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	F	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	M	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	M	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	M	III		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	F	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	F	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	M	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	M	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	M	II		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(AlFadhli et al.,	unknown	F	I		Patient	NM_000551.3:c.351G>T		NM_000551.3:c.351G>T	NM_000551.3:c.351G>T
; H	(Allen et al., 20	E11Y0M; Ik22Y	unknown	patient #1 ; phe	Family history	Patient	NM_000551.3:c.292T>C		NM_000551.3:c.292T>C	NM_000551.3:c.292T>C
	(Allen et al., 20	Ik24Y0M	unknown	patient #2; diagnosed at 24 w		Patient	NM_000551.3:c.292T>C		NM_000551.3:c.292T>C	NM_000551.3:c.292T>C
	(Allen et al., 20	Ik39Y0M	unknown	patient #3; diagnosed at 39 w		Patient	NM_000551.3:c.292T>C		NM_000551.3:c.292T>C	NM_000551.3:c.292T>C

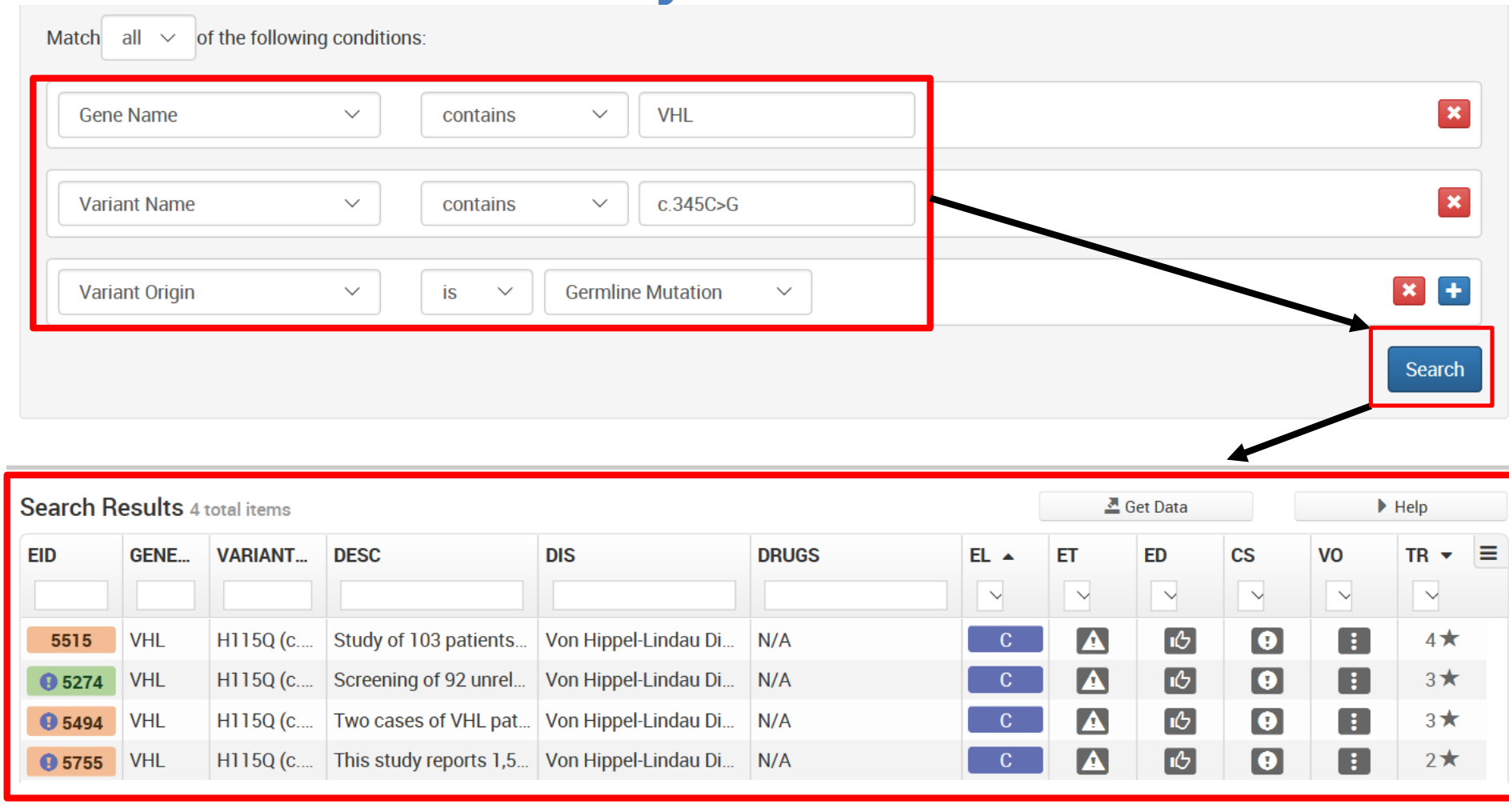
Wait, what's this section…?

Validating the data



High-quality variants

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



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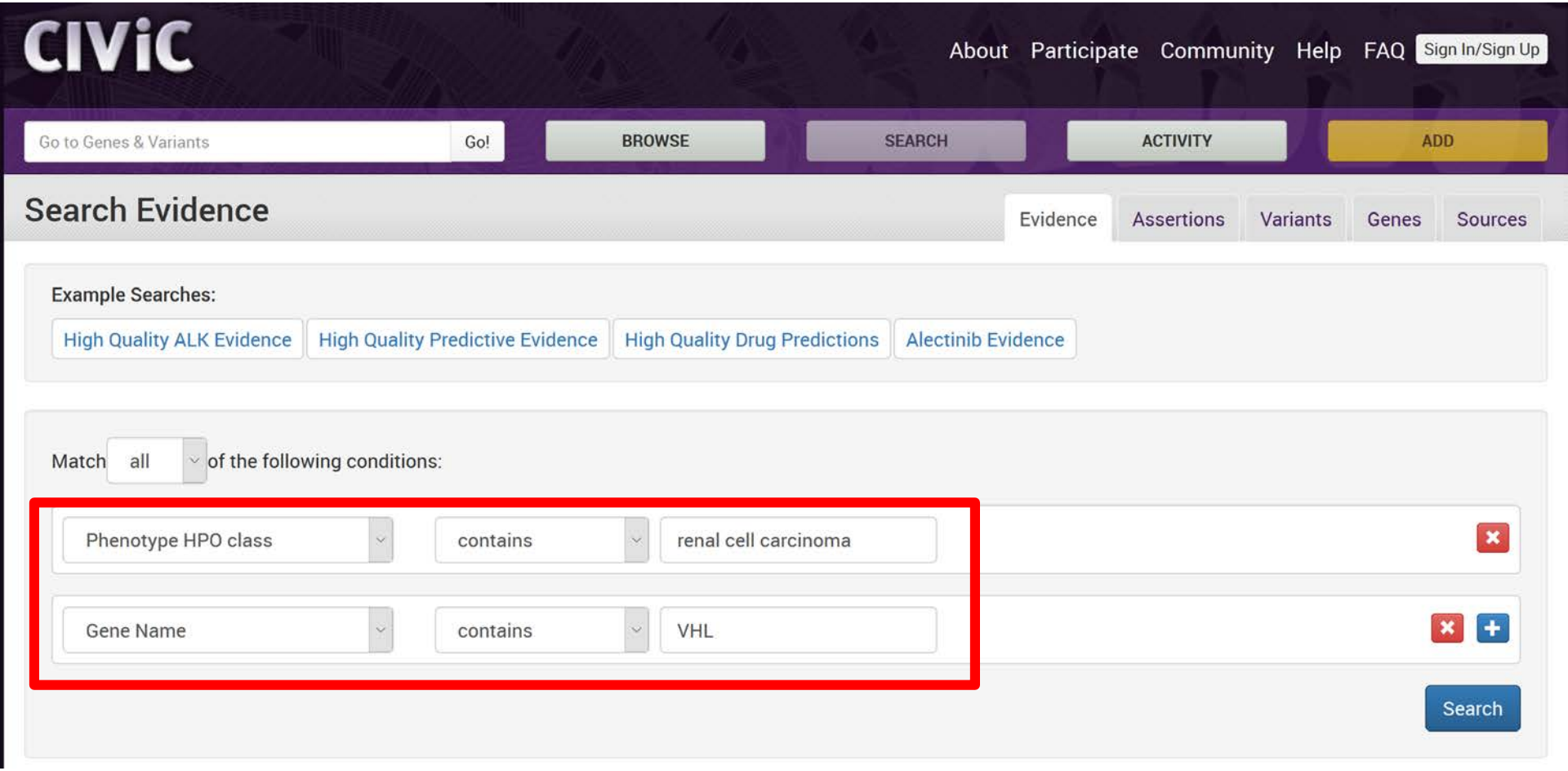
Case Study: Conclusion

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

Management decision: Patient should undergo surveillance and likely has VHL disease

CIViC vs Clinvar Search By Phenotype



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CIViC: Search By Phenotype

Search Results 421 total items

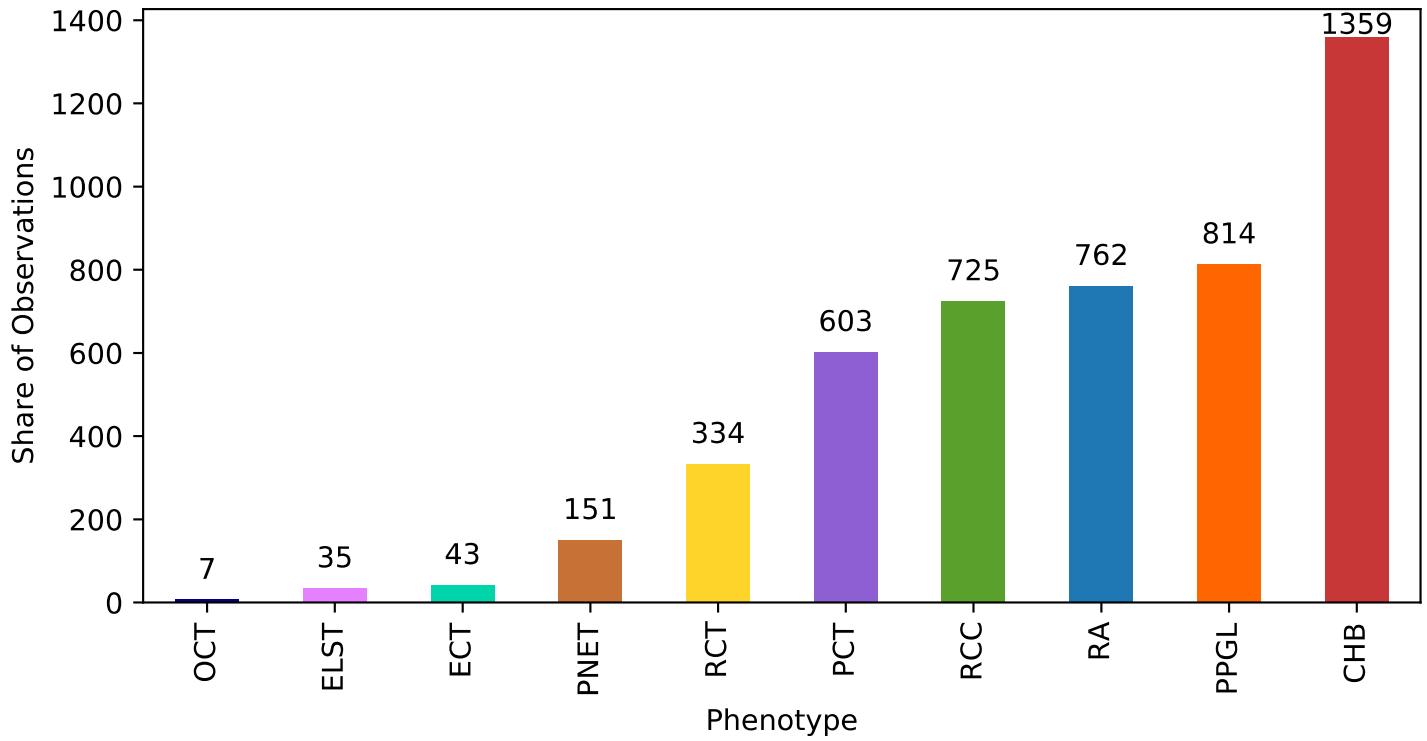
Get Data | Help

EID	GENE	VARIANT	DESC	DIS	DRUGS	EL	ET	ED	CS	VO	TR
5129	VHL	N131T (c....	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	B					4★
6061	VHL	L188Q (c....	In a study of 114 unre...	Von Hippel-Lindau Di...	N/A	C					4★
5169	VHL	W88* (c.2...	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5159	VHL	S65L (c.1...	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5152	VHL	F136S (c....	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5145	VHL	L153C (c....	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5131	VHL	Q132P (c....	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5130	VHL	N78H (c.2...	Genotype-phenotype ...	Renal Cell Carcinoma	N/A	C					4★
1942	VHL	EXON 1-3 ...	Mutation detected in ...	Von Hippel-Lindau Di...	N/A	C					4★
5866	VHL	Y112N (c....	This paper analyzes a...	Von Hippel-Lindau Di...	N/A	C					4★
6420	VHL	EXON 1 D...	Molecular analysis of...	Von Hippel-Lindau Di...	N/A	C					4★
4916	VHL	V62C (c.1...	In a study of 114 unre...	Von Hippel-Lindau Di...	N/A	C					4★
4918	VHL	Q73* (c.21...	In a study of 114 unre...	Von Hippel-Lindau Di...	N/A	C					4★
4919	VHL	F76del (c....	This deletion mutatio...	Von Hippel-Lindau Di...	N/A	C					4★

Variants Associated with RCC

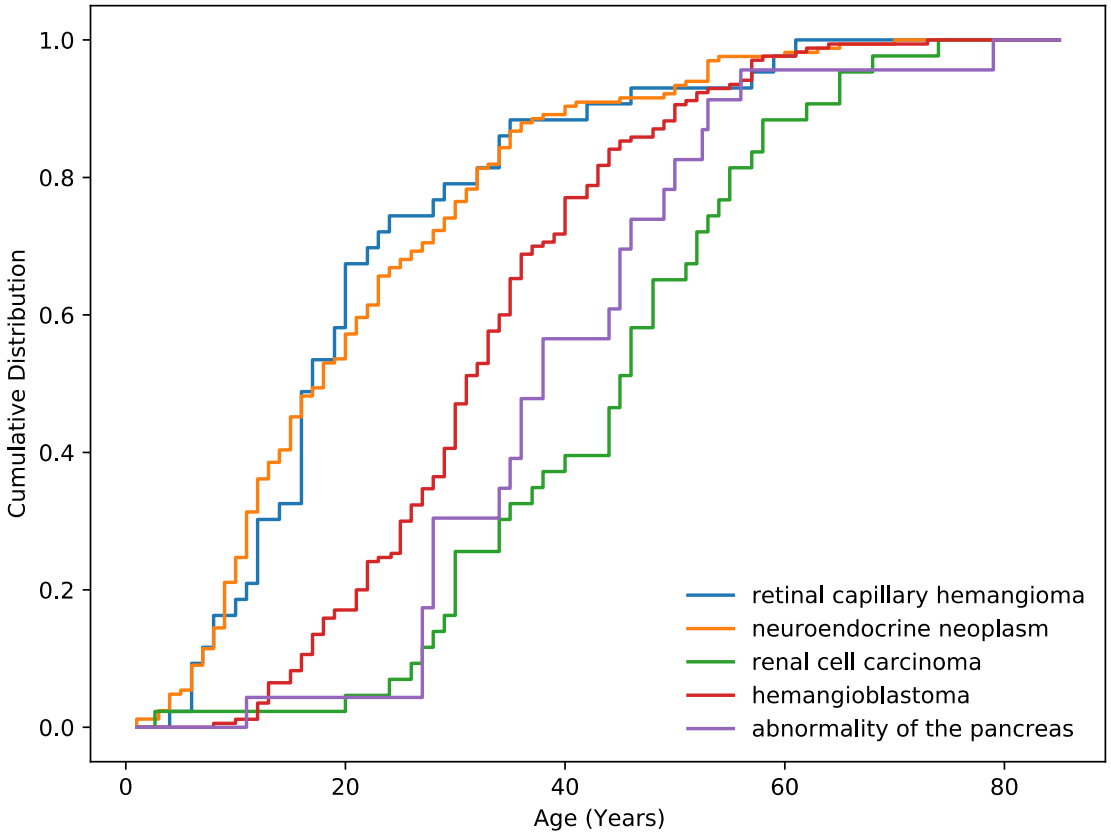
Analyses on aggregate VHL database…

Patient-level resolution: phenotype prevalence



Phenotype prevalence at patient-level data resolution showing highest reports of CNS hemangioblastoma.

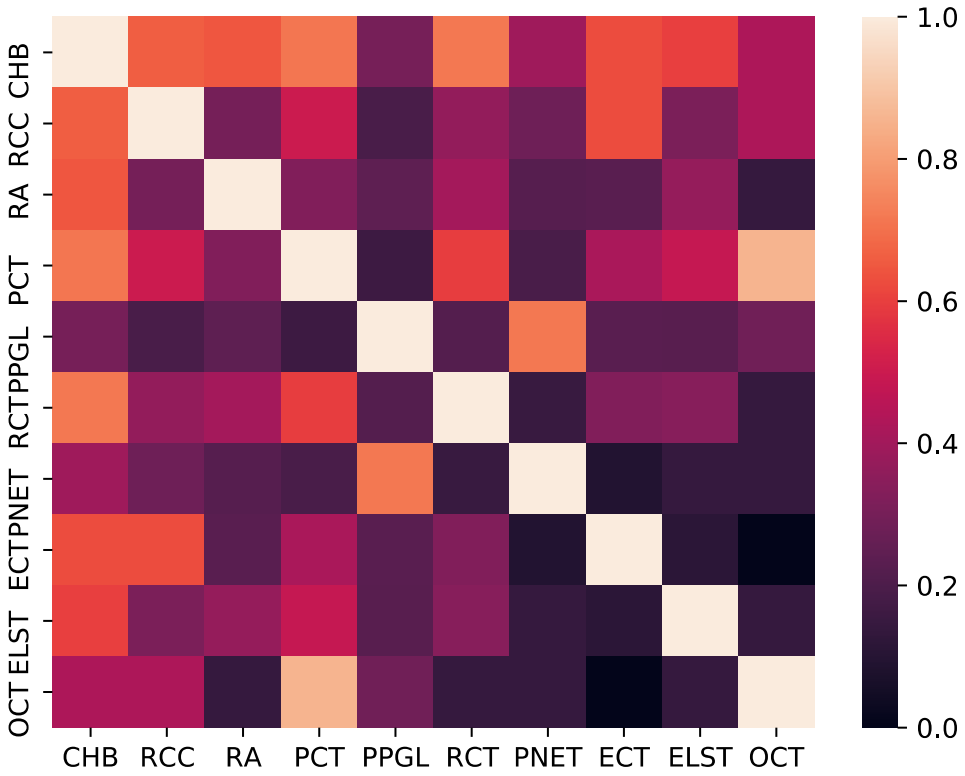
Patient-level resolution: age-related penetrance



Why is N = 458?

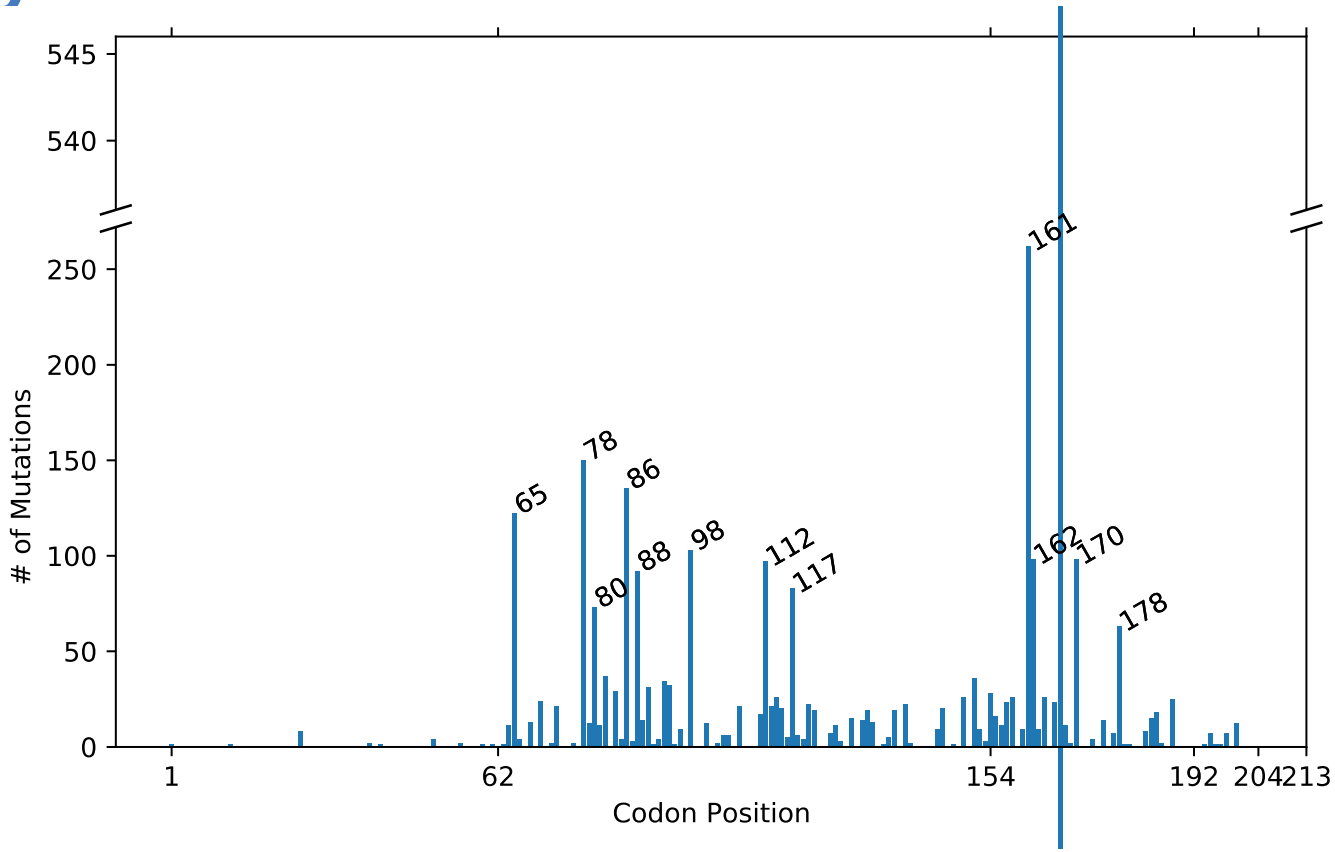
- Age of onset for patients with only one phenotype as a surrogate for age-related penetrance
- Suggests earlier onset with retinal angioma and pheochromocytoma/ paraganglioma.

Patient-level resolution: phenotype correlation ratios



High correlation between pheochromocytoma / paraganglioma and pancreatic neuroendocrine tumors.

Family-level resolution



Frequency of missense mutations in families supports potential hotspots at codon 167 and 161.

Next steps and what we learned

- Duplicated cohorts
- Challenges with aggregating different data types
- Release complete dataset for collaborative researchers
- Other genes?

Why was it not in ClinVar?

- ClinVar database quality

 Single submitter

 Expert Panel

NM_000551.3(VHL):c.345C>G (p.His115Gln)

Interpretation

Go to:

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Integrated Genetics/Laboratory Corporation of America	germline	not provided	not provided (unknown)	not provided	not provided	PubMed	not provided

VHL ClinGen Expert Panel

Creating Customized VHL-specific Rules


Eamonn Maher


Tina Pesaran


Carrie Horton


Jerry Machado

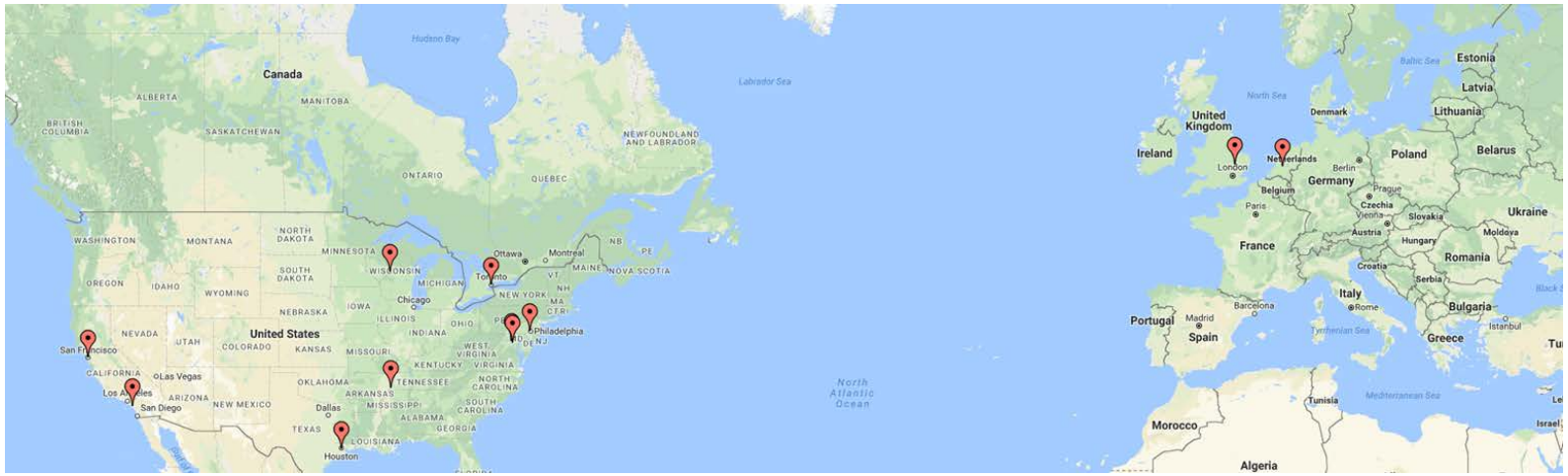

Deborah Ritter


Malachi Griffith


Raymond Kim


Minjie Luo


Chimene Kesserwan




Amit Tirosh

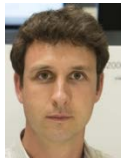

Sharon Plon


Kathleen Hruska


Hio Chung Kang

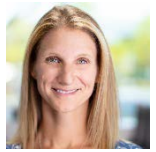

Ying Wang


Rachel Giles


Obi Griffith

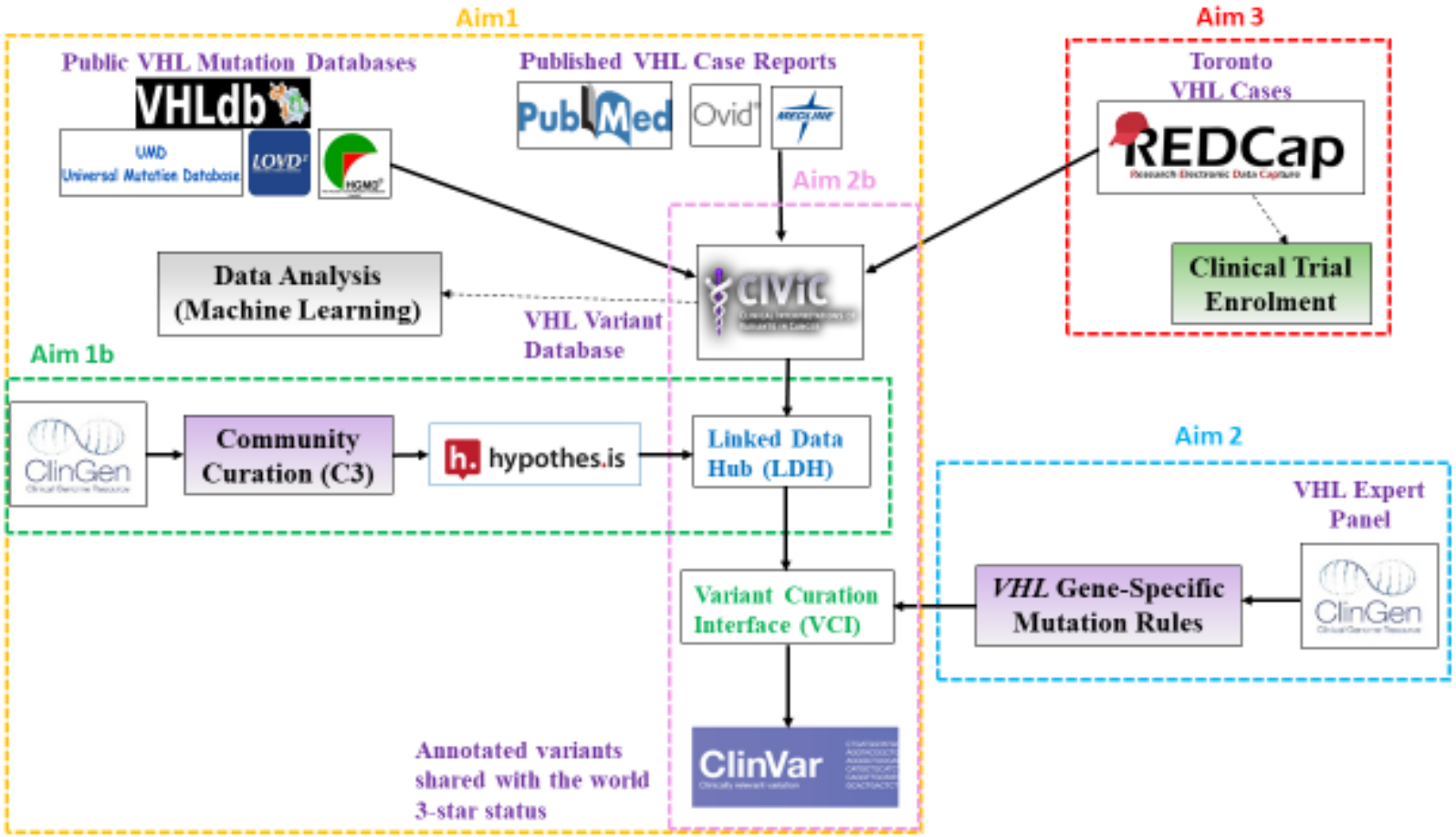

Kilannin Krysiak


Michael Anderson


Kelly McGoldrick

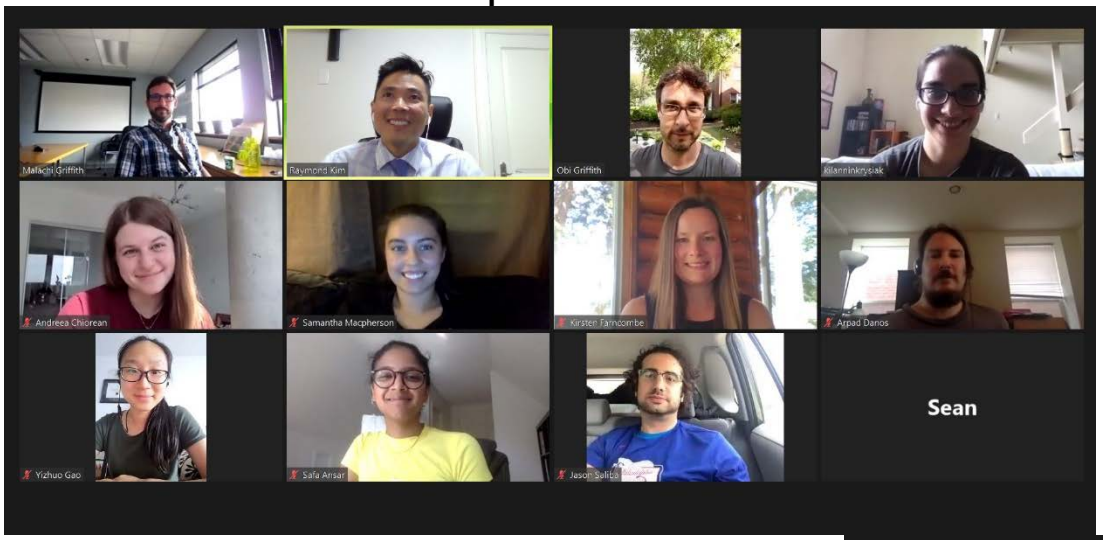
UHN Princess Margaret Cancer Centre

VISION Overview



Acknowledgements

This project has been supported by a VHL Alliance Research Grant. Funding contributions were also made through the Starbucks Clinical Genetics/Genomics Research Studentship Award.



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