Melbourne Genomics
Health Alliance

Variant interpretation: from the clinic to the lab… and back again

Australian BioCommons webinar
7 December 2022

Alliance members

The Royal Melbourne Hospital
The Royal Children's Hospital Melbourne
The University of Melbourne
WEHI brighter together
murdoch children's research institute
CSIRO
agrf
Peter Mac Peter MacCallum Cancer Centre Victoria Australia
Austin Health
Monash Health

Supported by

Victoria State Government

Variant interpretation in a diagnostic setting

Naomi Baker
Medical Scientist
Victorian Clinical Genetics Services

Variant interpretation in a research setting

Joep Vissers
Curation Team Leader,
University of Melbourne
Centre for Cancer Research

Variant interpretation training

Amy Nisselle
Genomics Workforce Lead
Melbourne Genomics

Melbourne Genomics
Health Alliance

Poll

How much experience do you have with variant interpretation?

- Never heard of it!
- I know the term but that's about it
- I've dabbled but don't know much about the underlying concepts or processes
- I've been doing it for a while in a research setting
- I’ve been doing it for a while in a clinical setting
- I supervise others to do it

Variant interpretation in a diagnostic setting

Dr. Naomi Baker

Medical Scientist, Clinical Genomics, VCGS

Victorian Clinical Genetics Services
Murdoch Children's Research Institute

VCGS
leaders in genetic health

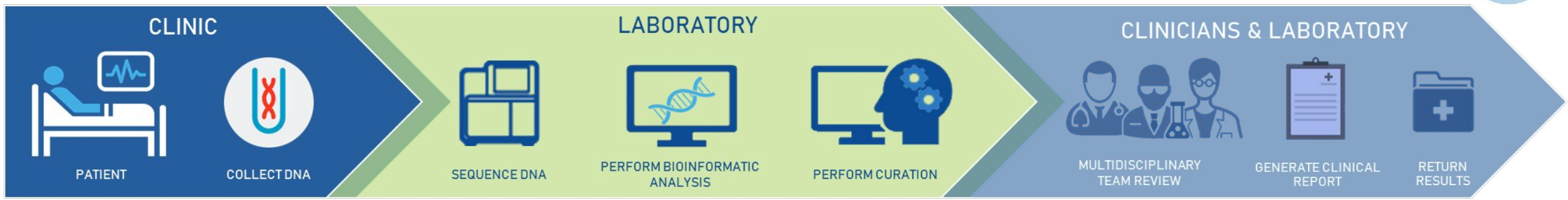
The genomic testing process

Our lab's role

My role

Genomic Testing processes, pipelines and people

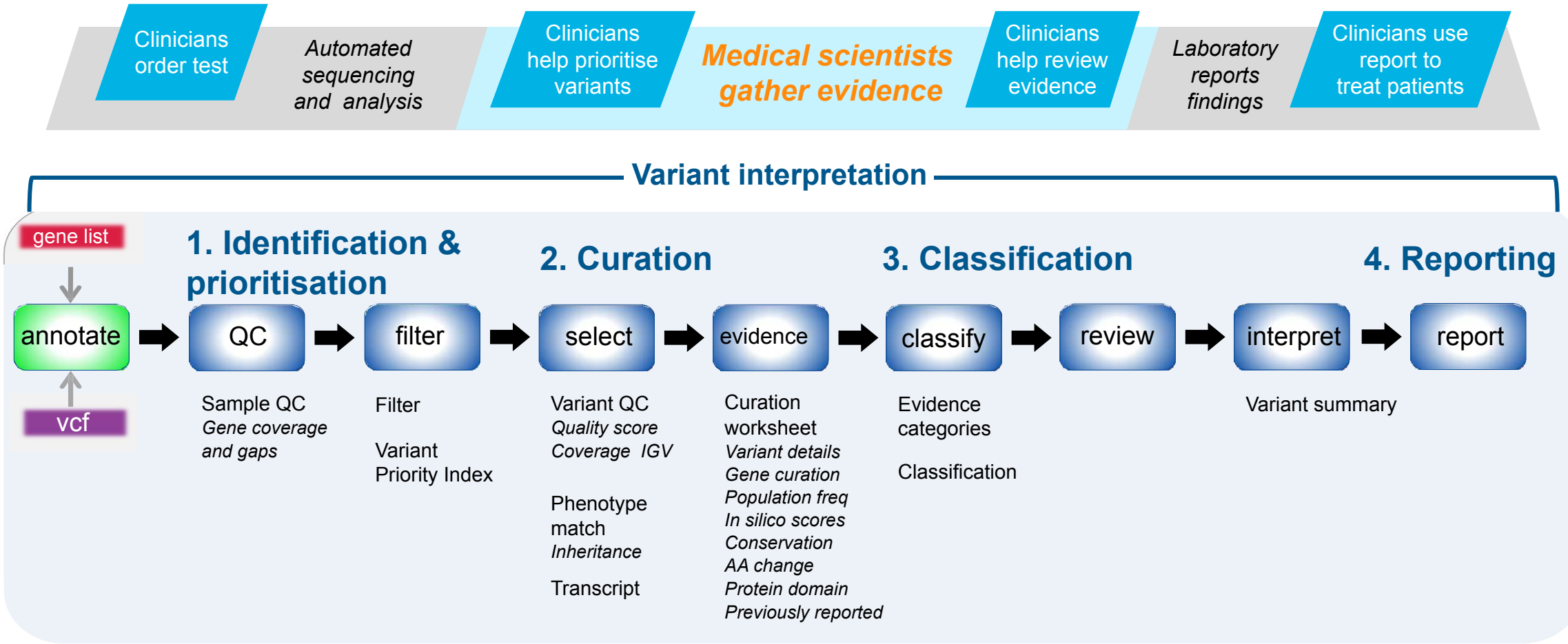
Primary Care / Hospital | Genomic Diagnostics | Genomic Diagnostics



Victorian Clinical Genetics Services
Murdoch Children's Research Institute

VCGS
leaders in genetic health

Variant interpretation is clinically integrated



PMID: 26217397; Sadedin, S. et al. (2015) Genome Med. 7(1):68. “Cpipe: a shared variant detection pipeline designed for diagnostic settings.”

PanelApp Australia: https://panelapp.agha.umccr.org/

PanelApp Australia

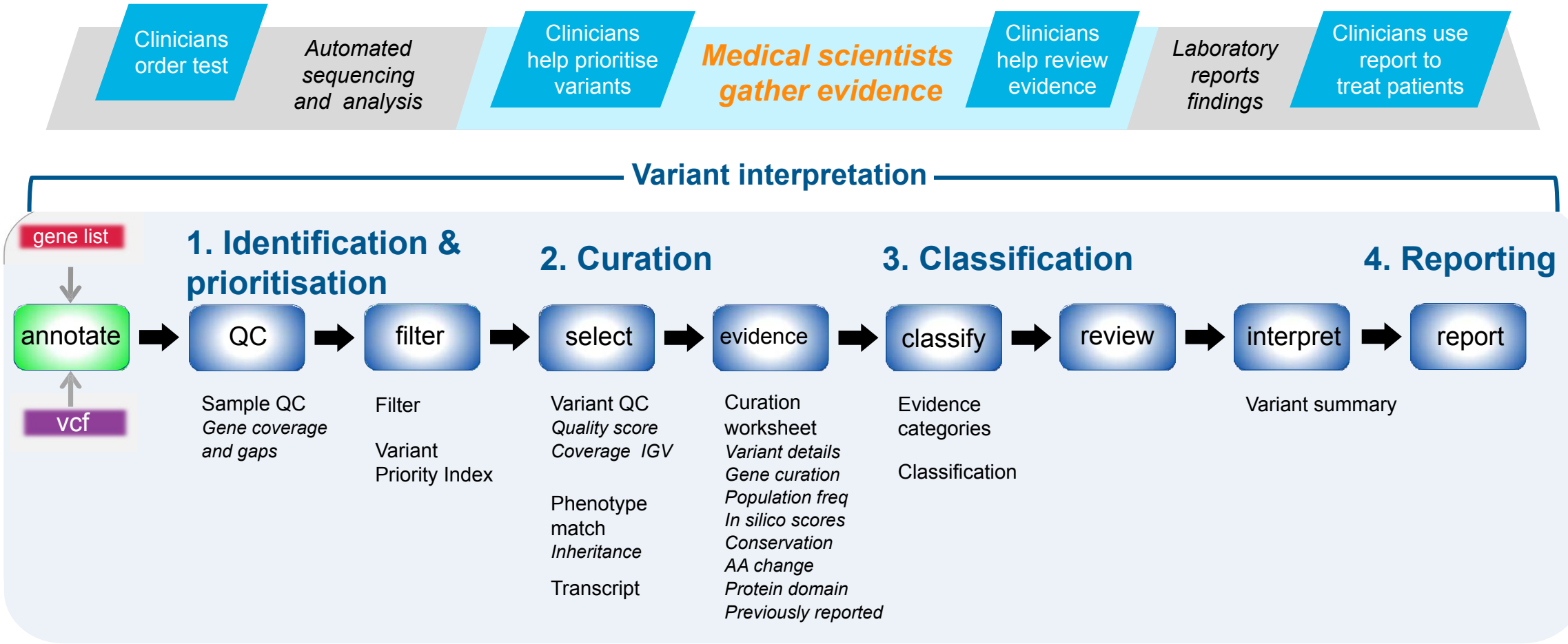
Malignant Hyperthermia Susceptibility (Version 1.6)

Green	CACNA1S	1 review Add review 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	**Sources** • Expert list • Expert Review Green **Phenotypes** • {Malignant hyperthermia susceptibility 5} MIM#601887 **Tags**
Green	RYR1	1 review Add review 1 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	**Sources** • Expert list • Expert Review Green **Phenotypes** • {Malignant hyperthermia susceptibility 1} MIM#145600 **Tags**
Green	STAC3	1 review Add review 1 green	BIALLELIC, autosomal or pseudoautosomal	**Sources** • Expert list • Expert Review Green **Phenotypes** • Myopathy, congenital, Baily-Bloch MIM#255995 **Tags**
Amber	ASPH	1 review Add review	MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown	**Sources** • Expert Review Amber • Literature **Phenotypes** • Exertional heat illness • malignant hyperthermia susceptibility, MONDO:0018493, ASPH-related **Tags**
Amber	ATP2A1	1 review Add review	BIALLELIC, autosomal or pseudoautosomal	**Sources** • Expert Review Amber • Literature **Phenotypes** • Brody myopathy MIM#601003 **Tags**
Amber	TRPV1	2 reviews Add review 1 red	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	**Sources** • Expert Review Amber • Literature **Phenotypes** • Malignant hyperthermia susceptibility **Tags**
Red	CACNB1	2 reviews Add review 1 red	Unknown	**Sources** • Expert list • Expert Review Red • Other • Royal Melbourne Hospital **Phenotypes** • Malignant hyperthermia susceptibility

Victorian Clinical Genetics Services
Murdoch Children's Research Institute

VCGS
leaders in genetic health

Variant interpretation is clinically integrated

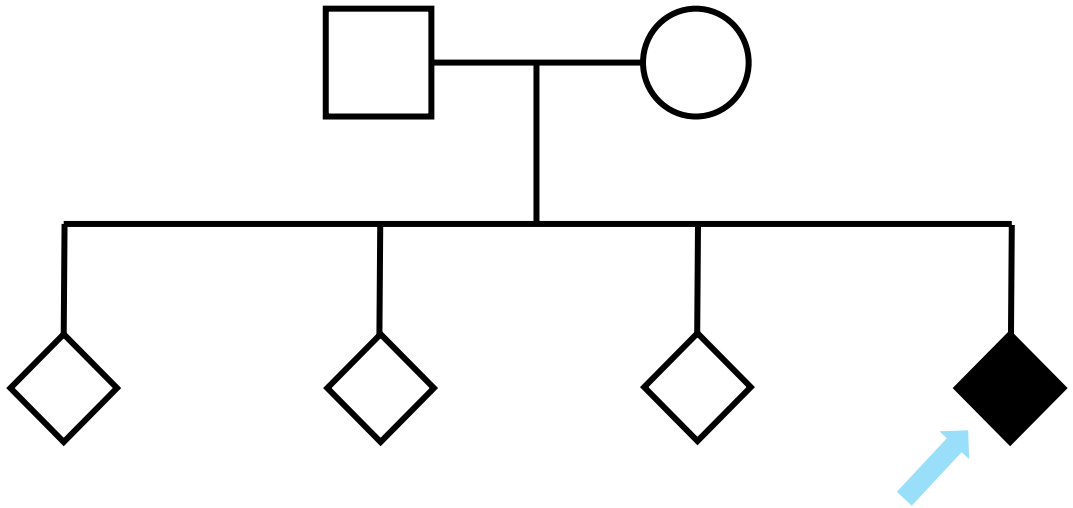


PMID: 26217397; Sadedin, S. et al. (2015) Genome Med. 7(1):68. “Cpipe: a shared variant detection pipeline designed for diagnostic settings.”

PanelApp Australia: https://panelapp.agha.umccr.org/

Case Study

- Paediatrician referral
- 2 yo with severe global developmental delay and hypotonia
- Trio WES analysis
  - Intellectual disability syndromic and non-syndromic
  - Autism
  - Mendeliome



de novo / recessive filter

gene panels

28 variants

phenotype match?

1 variant

TCF4 nonsense variant

pathogenic

diagnosis of Pitt-Hopkins syndrome

MUSCLE, SOFT TISSUES
- Hypotonia

NEUROLOGIC

Central Nervous System
- Mental retardation, severe
- Poor or absent speech development
- Delayed motor development
- Limited walking abilities
- Unstable, ataxic gait
- Incoordination
- Seizures
- Bulging of the caudate nuclei
- Ventricular asymmetry
- Agenesis or hypoplasia of the corpus callosum
- Atrophy of the frontal and parietal cortex
- Hypotonia

Behavioral Psychiatric Manifestations
- Happy personality
- Aggression
- Stereotypic movements

CFTR variant

pathogenic

incidental carrier finding

Victorian Clinical Genetics Services
Murdoch Children's Research Institute

VCGS
leaders in genetic health

OMIM (An Online Catalog of Human Genes and Genetic Disorders); https://www.omim.org/

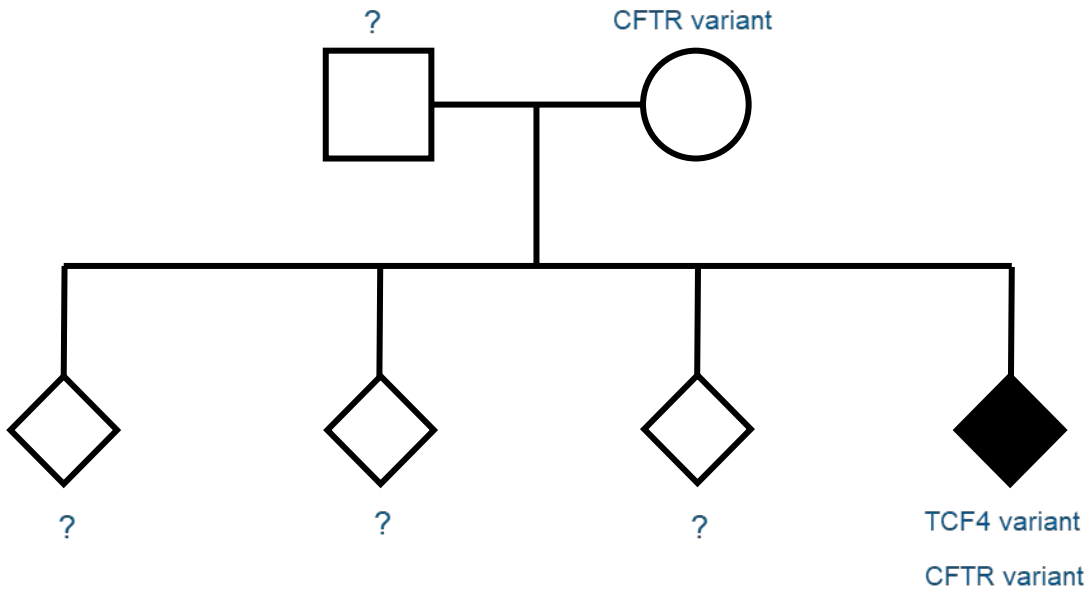
Case Study

- Paediatrician referral; Genetic counsellor provided additional support
  - Contact details for support groups, referral pathways, counselling tips

- CF panel testing for father
  - Clarify reproductive risk
  - Risk for siblings

- Referral for formal genetic counselling

- May eventually provide testing for extended family




B App Sci (MLS)
Honours / PhD
PostDoc
Medical Scientist
My Career Path

Variant interpretation in a diagnostic setting

- Provide answers for patients and families
- Interaction with clinicians (Clinical Geneticists, Genetic Counsellors, other referrers) and scientists
- Team effort
- Use and continuous development of scientific knowledge

Acknowledgments

- Genetics and Genomics Division
  - Sebastian Lunke (Head)
- Clinical Genomics – Clinical Geneticists
  - Zornitza Stark
  - Alison Yeung
- Clinical Genomics – Genetic Counsellors
  - Manny Jacobs
  - Sam Ayres
- Clinical Genomics – Scientists
  - Belinda Chong (Head)
  - Dean Phelan
  - Sarah-Jane Pantaleo
  - Ain Roesley
  - Anna Ritchie
  - Sze Chern Lim
  - Daniel Flanagan
  - Ee Ming Wong
  - Elena Savva
  - Hazel Phillimore
  - Karina Sandoval
  - Lucy Spencer
  - Michelle da Cunha Torres
  - Paul De Fazio
  - Shannon Cowie
  - Suliman Khan
  - Teresa Zhao

Variant interpretation in a research setting

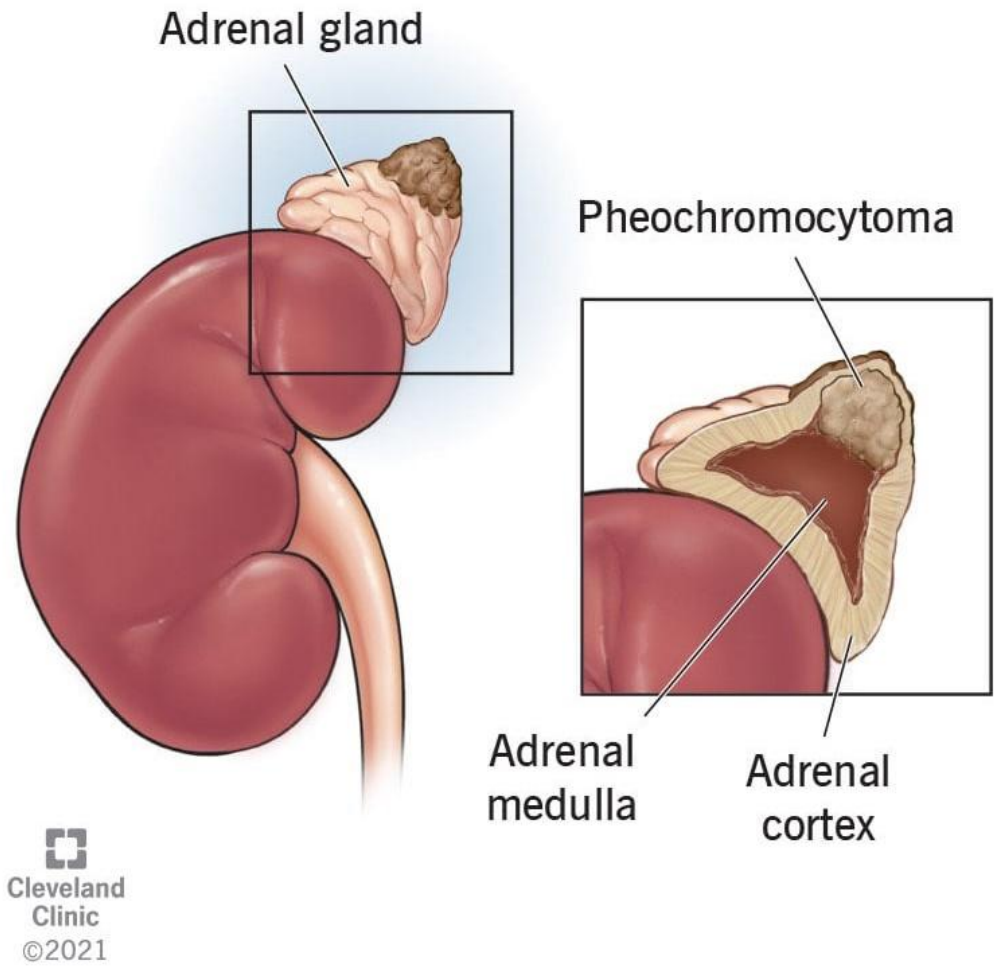
Joep Vissers
Curation Team Leader,
University of Melbourne
Centre for Cancer Research

Curation in the Research setting

Joep Vissers

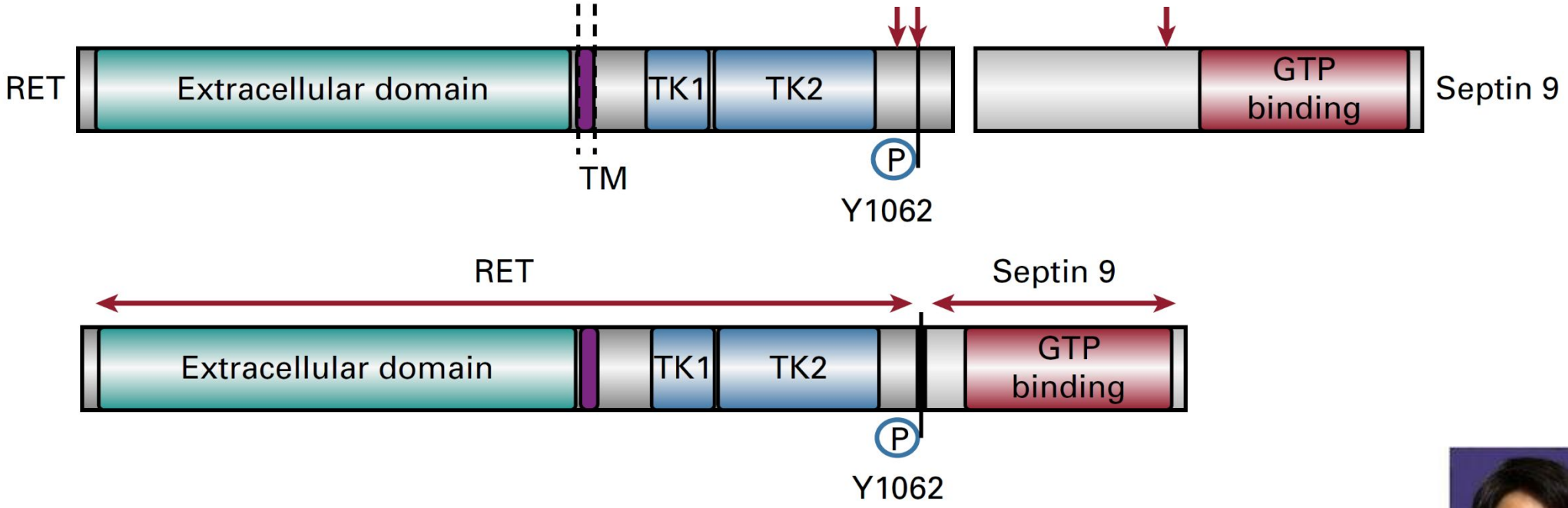
University of Melbourne Centre for Cancer Research (UMCCR)

Pheochromocytoma



From: my.clevelandclinic.org/health/diseases/23373-pheochromocytoma

RET::SEPTIN9 fusion gene

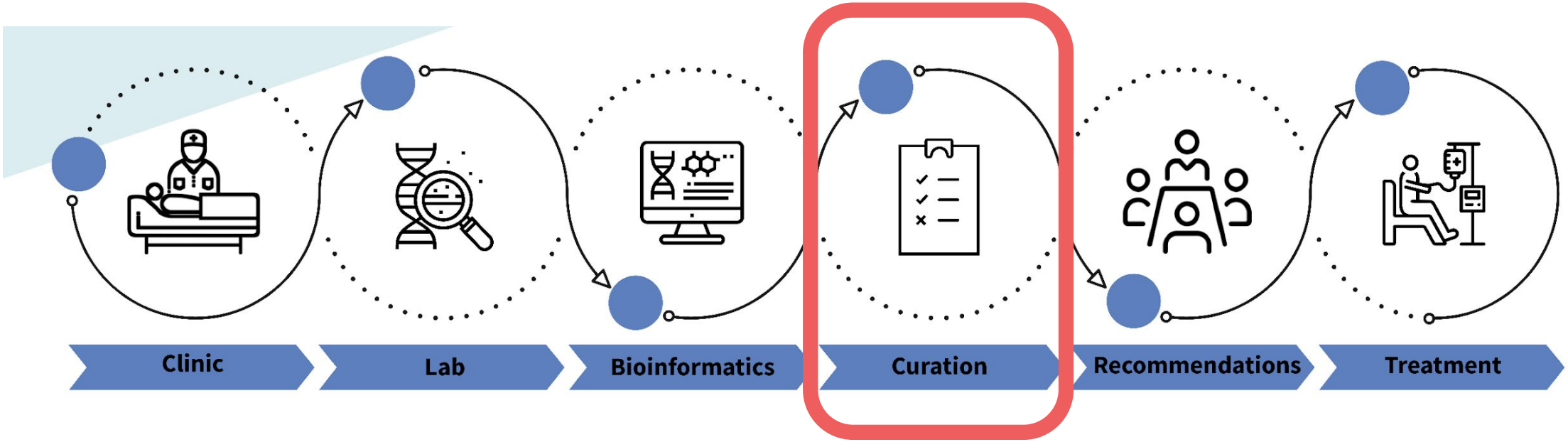


Huiling Xu, Peter Mac

Mweempwa et al, JCO Precis Oncol 2021

University of Melbourne Centre for Cancer Research

Precision oncology at UMCCR



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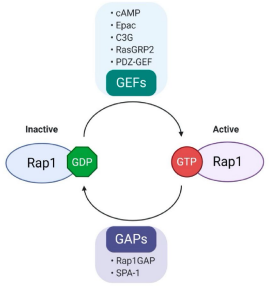
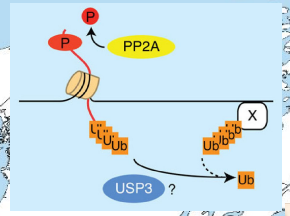
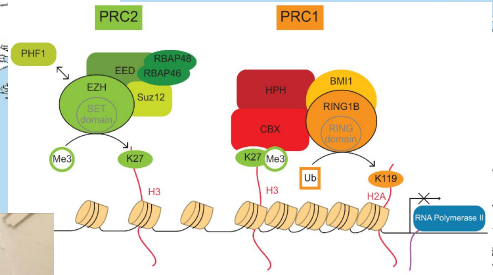
ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

Utrecht University







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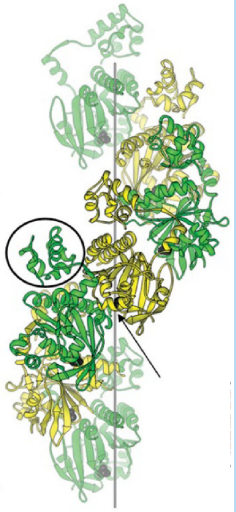


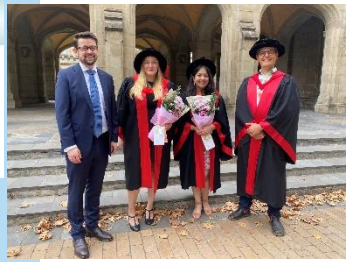
THE UNIVERSITY OF MELBOURNE

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

nature COMMUNICATIONS

ARTICLE

A *Drosophila* RNAi library modulates Hippo pathway-dependent tissue growth

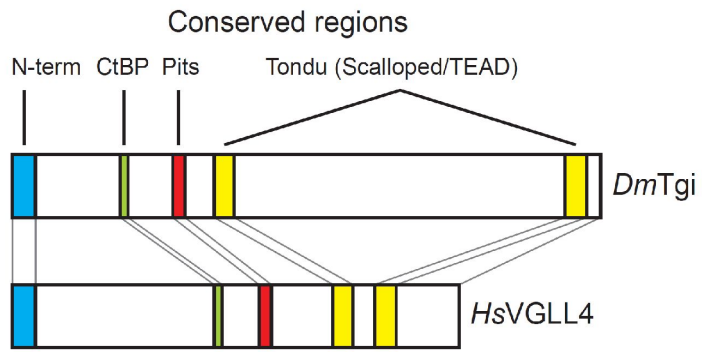


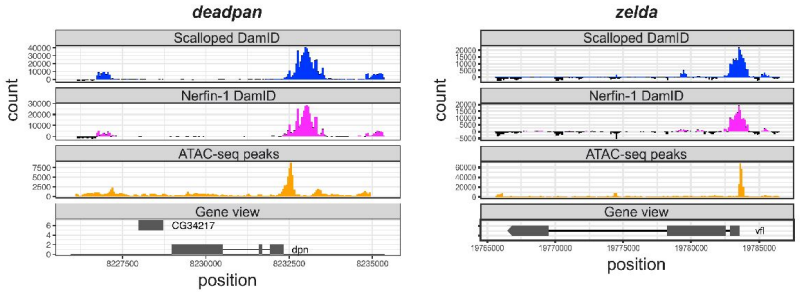
VICTORIAN CANCER AGENCY

VICTORIA State Government

Skills and expertise

Family	Member	Database	Accession	Score	Mass	Num. of r	Num. of si	Num. of si	Num. of si	emPAI	Description
1	1	UNIPROT	Q8IQJ9_D	13144	41114	308	296	33	33	152.38	SubName: Full=CG10741, isoform B; SubName: Full=RE45537p; - OS=Drosophila melanogaster (Fruit fly).
1	2	UNIPROT	B4H6V1_D	1889	43089	53	51	11	11	2.26	SubName: Full=GL22083; - OS=Drosophila persimilis (Fruit fly).
2	1	UNIPROT	A4V2S3_D	11958	42738	421	356	29	28	34.69	SubName: Full=C-terminal binding protein, isoform B; EC=1.1.1.-; SubName: Full=C-terminal binding protein, isoform C; EC=1.1
2	2	UNIPROT	B3P196_D	10585	51043	375	311	27	26	14.67	SubName: Full=GG19357; - OS=Drosophila erecta (Fruit fly).
2	3	UNIPROT	E8NH65_D	3819	20954	120	100	12	11	15.8	SubName: Full=LD15041p; Flags: Fragment; - OS=Drosophila melanogaster (Fruit fly).
3	1	UNIPROT	Q7JR58_D	8972	31961	301	286	22	22	84.53	SubName: Full=CG6543, isoform A; EC=4.2.1.17; SubName: Full=CG6543, isoform B; EC=4.2.1.17; SubName: Full=LD24265p; - O
3	2	UNIPROT	B4P459_D	7457	31802	241	229	19	19	51.87	SubName: Full=GE13337; - OS=Drosophila yakuba (Fruit fly).
3	3	UNIPROT	B3NRG4_D	6595	31758	215	198	15	15	31.58	SubName: Full=GG22466; - OS=Drosophila erecta (Fruit fly).
3	4	UNIPROT	B4N5T9_D	4620	32190	185	152	16	13	7.67	SubName: Full=GK17937; - OS=Drosophila willistoni (Fruit fly).
4	1	UNIPROT	B4L1X2_D	2800	72387	93	86	32	32	4.4	SubName: Full=GI14717; - OS=Drosophila mojavensis (Fruit fly).
4	2	UNIPROT	B3P0S6_D	2324	71286	77	75	25	24	2.86	SubName: Full=GG16900; - OS=Drosophila erecta (Fruit fly).
4	3	UNIPROT	Q6XIY7_D	494	24172	31	26	9	9	2.21	SubName: Full=Similar to Drosophila melanogaster Hsc70-3; Flags: Fragment; - OS=Drosophila yakuba (Fruit fly).
5	1	UNIPROT	B3MGF8_I	1425	50571	36	36	17	17	2.32	SubName: Full=GF12605; - OS=Drosophila ananassae (Fruit fly).
6	1	UNIPROT	B7Z143_D	984	62298	29	28	12	12	1.28	SubName: Full=CG11138, isoform D; - OS=Drosophila melanogaster (Fruit fly).
7	1	UNIPROT	B4I2C6_DI	900	43292	36	34	13	13	2.49	SubName: Full=GM18275; - OS=Drosophila sechellia (Fruit fly).
8	1	UNIPROT	M9MSL3_	785	92473	32	23	17	13	0.69	SubName: Full=Hsc70Cb, isoform G; SubName: Full=Hsc70Cb, isoform H; - OS=Drosophila melanogaster (Fruit fly).
9	1	UNIPROT	B3NR68_D	567	74257	16	16	11	11	0.61	SubName: Full=GG22433; - OS=Drosophila erecta (Fruit fly).
10	1	UNIPROT	B3LYC5_D	544	50561	16	15	10	10	0.88	SubName: Full=GF17649; - OS=Drosophila ananassae (Fruit fly).
11	1	UNIPROT	Q9VRJ4_D	401	33825	15	12	11	9	1.32	SubName: Full=CG10672; EC=1.1.-.-; SubName: Full=SD02021p; - OS=Drosophila melanogaster (Fruit fly).
12	1	UNIPROT	Q9V9T5_D	385	76752	11	10	10	9	0.46	SubName: Full=CG2118, isoform A; EC=6.4.1.4; SubName: Full=GM14617p; - OS=Drosophila melanogaster (Fruit fly).
13	1	UNIPROT	Q9VL68_D	313	31145	9	9	7	7	1.03	SubName: Full=CG4598, isoform A; EC=5.3.3.8; SubName: Full=CG4598, isoform B; EC=5.3.3.8; SubName: Full=RH73277p; SubN
14	1	UNIPROT	E1JJ99_DR	290	49408	7	7	5	5	0.38	SubName: Full=FI18101p1; SubName: Full=Scalloped, isoform H; SubName: Full=Scalloped, isoform I; SubName: Full=Scalloped,
15	1	UNIPROT	B3NF19_D	281	26930	9	9	5	5	1.26	SubName: Full=GG14898; - OS=Drosophila erecta (Fruit fly).
16	1	UNIPROT	B3NSB3_D	270	50561	17	14	6	5	0.37	RecName: Full=Elongation factor 1-alpha; - OS=Drosophila erecta (Fruit fly).
17	1	UNIPROT	B7Z0X1_D	258	51295	11	9	9	7	0.55	RecName: Full=Serine hydroxymethyltransferase; EC=2.1.2.1; - OS=Drosophila melanogaster (Fruit fly).
18	1	UNIPROT	B3MRI2_D	254	16312	5	5	2	2	0.46	SubName: Full=GF21290; - OS=Drosophila ananassae (Fruit fly).
19	1	UNIPROT	Q8IMF5_D	253	127049	5	4	4	3	0.08	SubName: Full=Microtubule-associated protein 205, isoform B; - OS=Drosophila melanogaster (Fruit fly).
20	1	UNIPROT	Q7K1U0_D	239	29087	7	7	5	5	0.72	SubName: Full=Arc1; SubName: Full=LD41905p; - OS=Drosophila melanogaster (Fruit fly).
21	1	UNIPROT	B3P0Z6_D	226	16242	8	7	5	4	1.14	RecName: Full=Single-stranded DNA-binding protein; - OS=Drosophila erecta (Fruit fly).
22	1	UNIPROT	B3MLU8_D	205	15005	12	8	4	4	1.27	SubName: Full=GF15052; - OS=Drosophila ananassae (Fruit fly).
23	1	UNIPROT	B4QJM4_D	199	34125	8	7	6	5	0.59	RecName: Full=Eukaryotic translation initiation factor 3 subunit H; Short=eIF3h; - OS=Drosophila simulans (Fruit fly).
24	1	UNIPROT	B4I8U9_D	193	51041	7	6	6	5	0.37	SubName: Full=GM15500; - OS=Drosophila sechellia (Fruit fly).



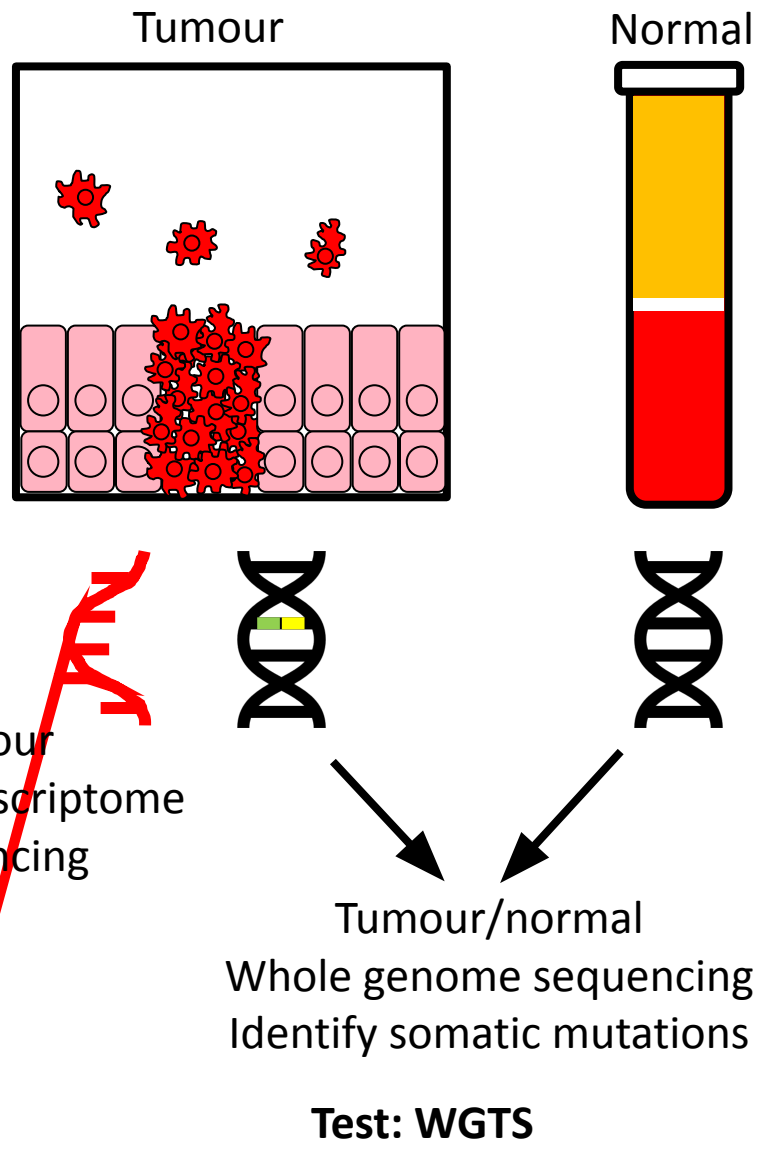


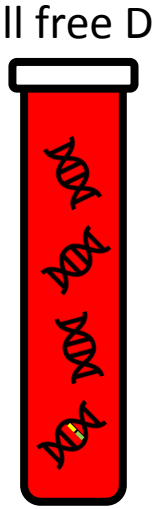
Notch	Hippo	Neurons	Neuroblasts	Metabolism
Notch	*warts*	*elav*	*miranda*	*Asparagine synthetase*
Serrate	*kibra*	*chinmo*	*deadpan*	*Glutaminase*
Delta	*expanded*	*erect wing*	*asense*	*Phospholipase D*
mastermind	*four-jointed*	*Lim3*	*worniu*	*Adenylate kinase 1*
su(H)	*lgl*	*SoxNeuro*	*klumpfuss*	*AMP deaminase*
numb	*karst*	*roundabout3*	*inscuteable*	*ATP synthase, subunit C*
E(spl) HLHm5	*Pez*		*zelda*	*Hexosaminidase 2*
E(spl) HLHm7				*CTP synthase*

Collaborate with bio-informaticians

Vissers et al, Genetics 2020
Vissers, Froldi et al, Cell Rep 2018

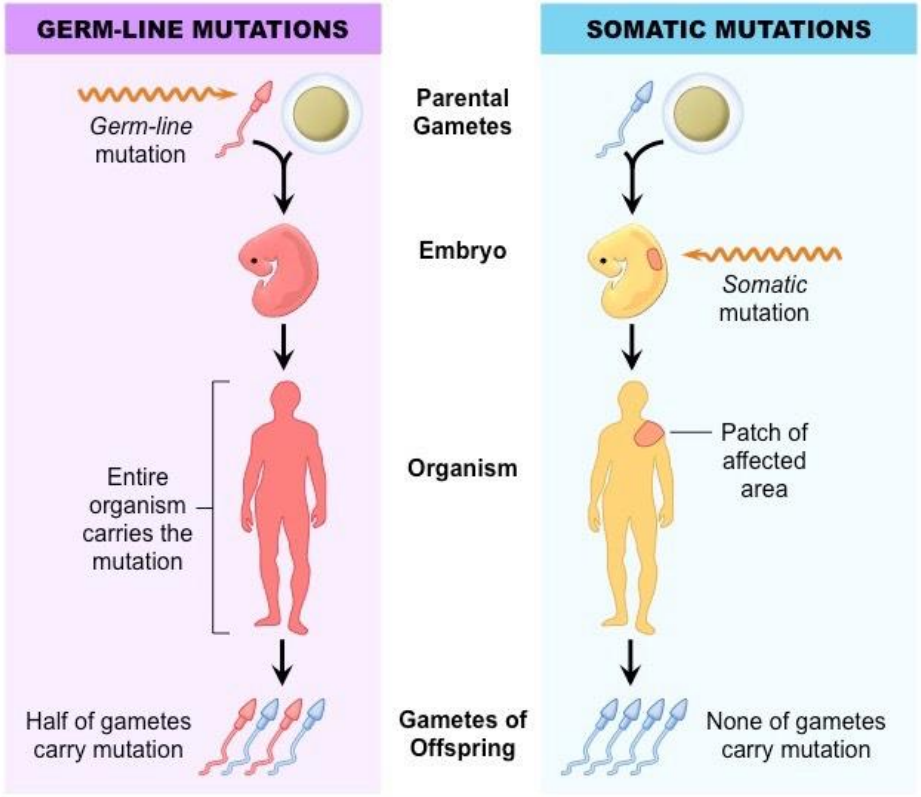
UMCCR genomic testing





Test:
ctTSO500
panel

Germline and somatic DNA variants



From: ib.bioninja.com.au

Germline

```
                1        10        20        30        4042
                |--------+---------+---------+---------+-|
Reference_genome ACTGTGTTAAGTCGCGAATTCATTCAGAATTGACCATGACAA
Patient_normal   ACTGTGTTAAGTCGCGAATACATTCAGAATTGACCATGACAA
```

Somatic

```
                1        10        20        30        40 43
                |--------+---------+---------+---------+--|
normal          ATGCAGCTAGTTTGCATGACAACATGTCAGTACCGTACAAAA
tumour          ATGCAGCTAGTTTGCATGACATACATGTCAGGGCCGTACAAAA
```

The Advanced Genomics Collaboration

A PARTNERSHIP BETWEEN illumina® THE UNIVERSITY OF MELBOURNE

The Advanced Genomics Collaboration

The Cancer Of Low sUrvival and unMet Need (COLUMN) initiative

Support thorough genomic investigation of challenging patients:

(i) Rare cancers (incidence <6/100,000)

(ii) Recalcitrant cancers (cancers that have poorest survival (<20% 5 year)

(iii) Relapsed cancers (cancers that have exhausted standard of care)

(iv) Enigmatic diagnoses (cancers with an ambiguous diagnosis or prognosis)

https://www.tagcaustralia.com/

Variant classification based on Clinical Significance

SPECIAL ARTICLE

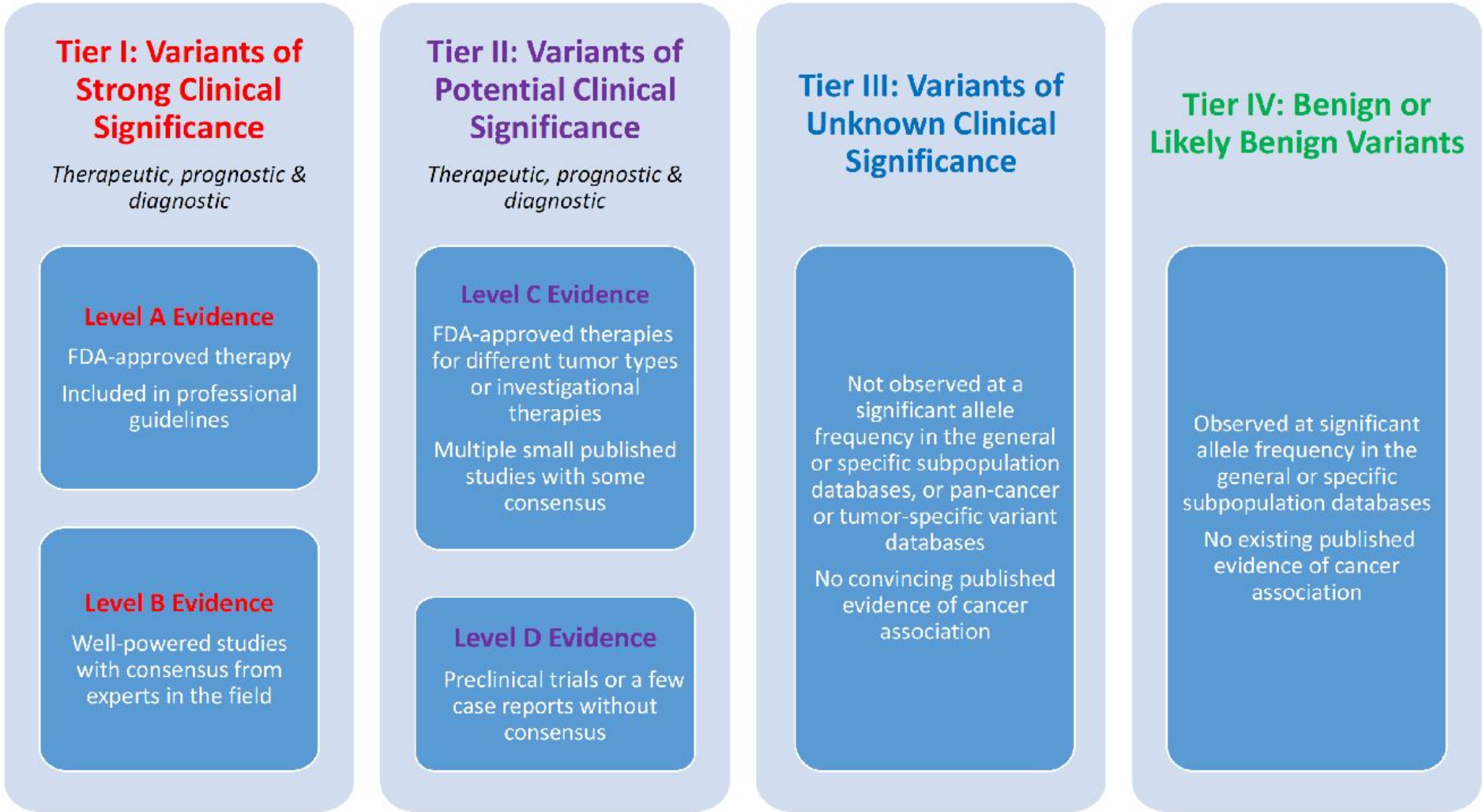
Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists

Marilyn M. Li,[*†] Michael Datto,[*‡] Eric J. Duncavage,[*§] Shashikant Kulkarni,[*¶] Neal I. Lindeman,[*‖] Somak Roy,[*,**] Apostolia M. Tsimberidou,[*††] Cindy L. Vnencak-Jones,[*‡‡] Daynna J. Wolff,[*§§] Anas Younes,[*¶¶] and Marina N. Nikiforova[*,**]

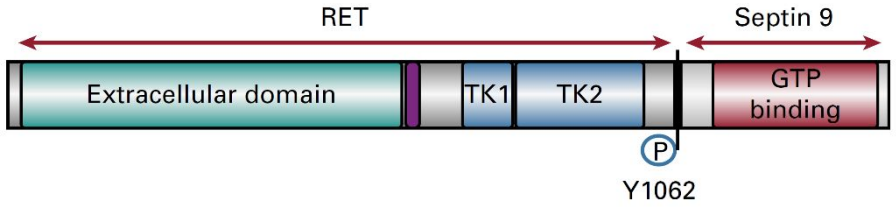
Li et al, J Mol Diagn 2017

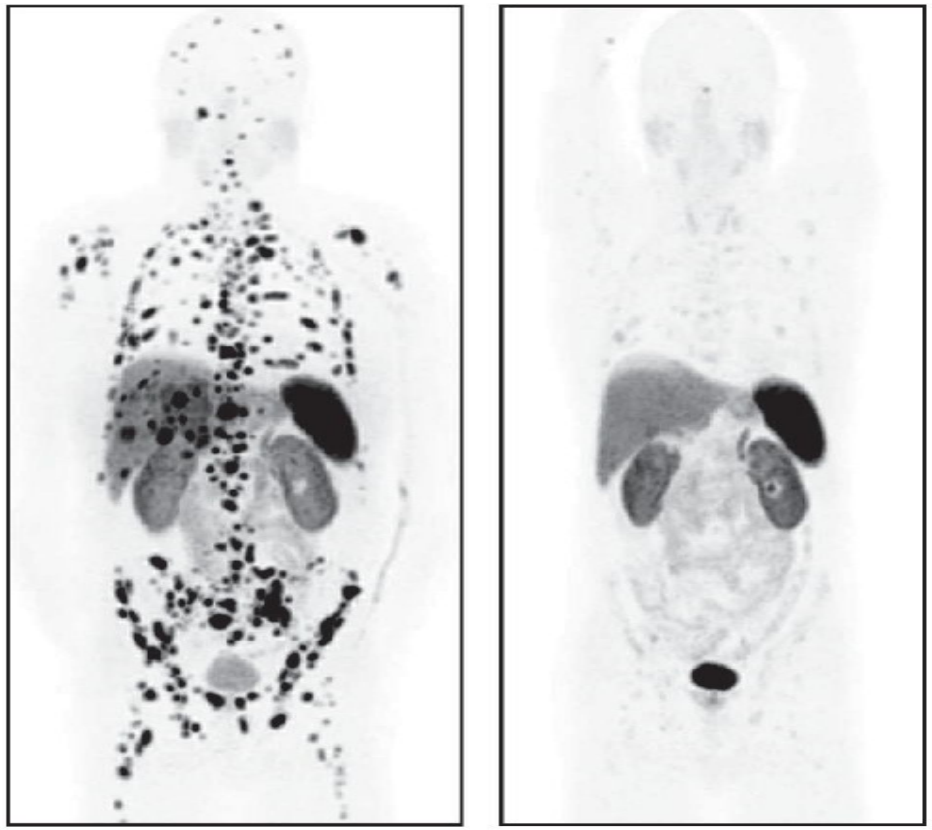
Variant classification based on Clinical Significance



Li et al, J Mol Diagn 2017

Clinical significance - Therapeutic

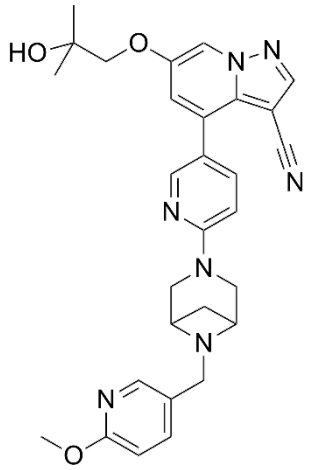




Before treatment

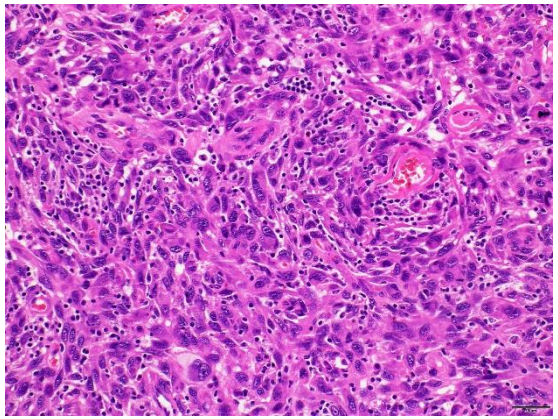
12 weeks treatment

RET kinase inhibitor:
Selpercatinib

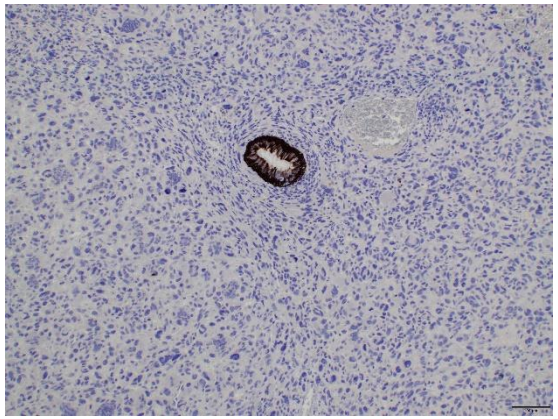


Mweempwa et al, JCO Precis Oncol 2021

Clinical significance - Diagnostic



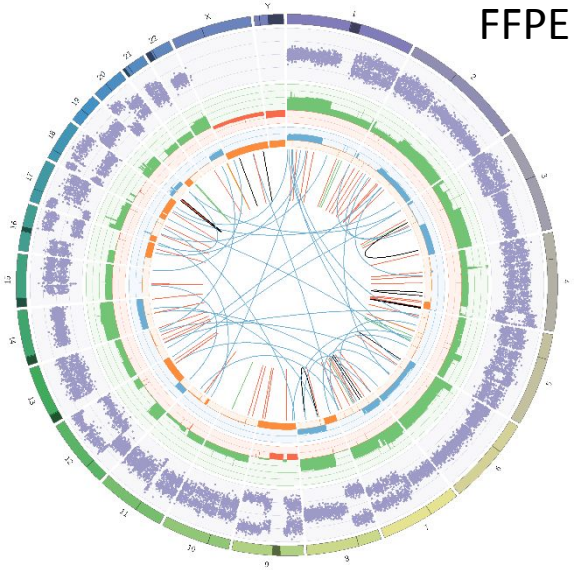
H&E



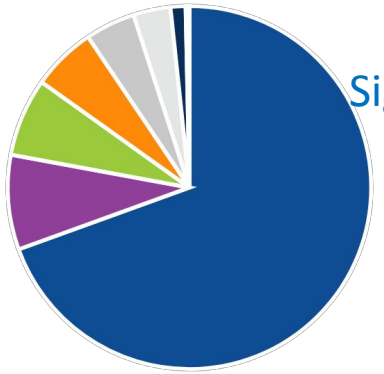
High molecular weight Cytokeratin (negative)

Lung lesion, Pleomorphic spindle cell morphology.

Pre-WGTS diagnostic differentials:
Carcinoma, sarcoma, melanoma or mesothelioma



FFPE sample



Signature 7 (UV) 69%

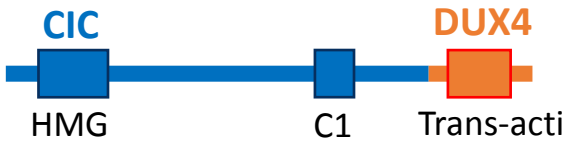
Mutational signatures

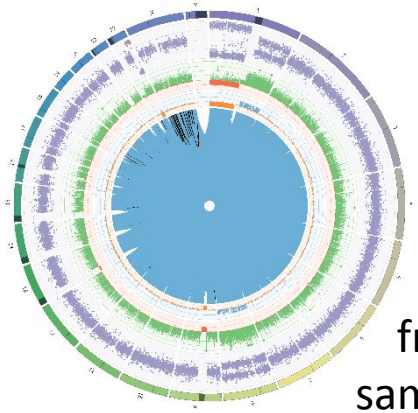
WGTS findings:
Tumour Mutational Burden:
88.85 mutations / Mb (HIGH)

Final diagnosis: skin cancer (cutaneous squamous cell carcinoma)

Research

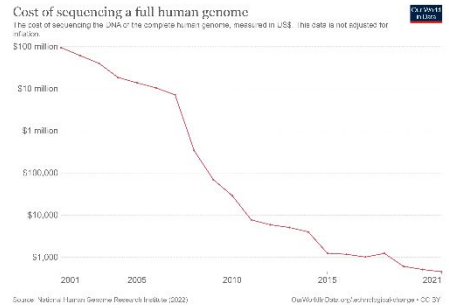
Unusual biology:





fresh sample

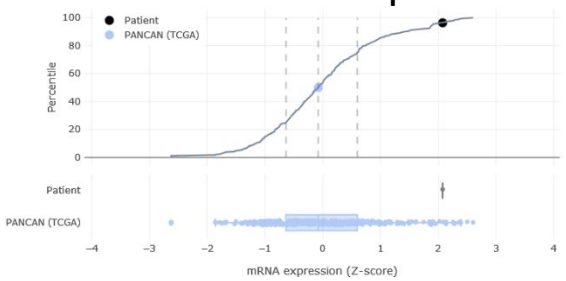
Feasibility:



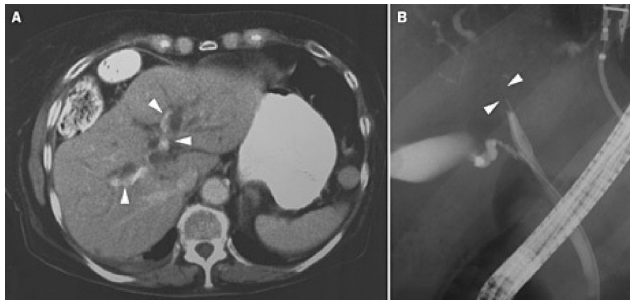
From: ourworldindata.org

The full clinical potential of WGTS:

NTRK3 RNA expression



Areas of clinical need for ctDNA testing:



From: www.hopkinsmedicine.org

Cholangiocarcinoma
Tissue biopsy:
no tumour
Liquid biopsy:
Microsatellite instability

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Ratana Lim

Damien Kee
Olga Kondrashova
Tony Papenfuss

SUPER NEXT
Richard Tothill
Linda Mileshkin
SUPER-NEXT team

Variant interpretation training

Amy Nisselle
Genomics Workforce Lead
Melbourne Genomics

Variant interpretation education programs

Scientists

Scientists working in genetics

Variant curators

Awareness-raising webinars
Genomics for medical/data scientists, careers in genomics

Self-directed online courses
Theory + practicals + cases

Introductory course

In-person workshops

Review online modules
Practice with tools
Review simple cases with experts

Advanced course

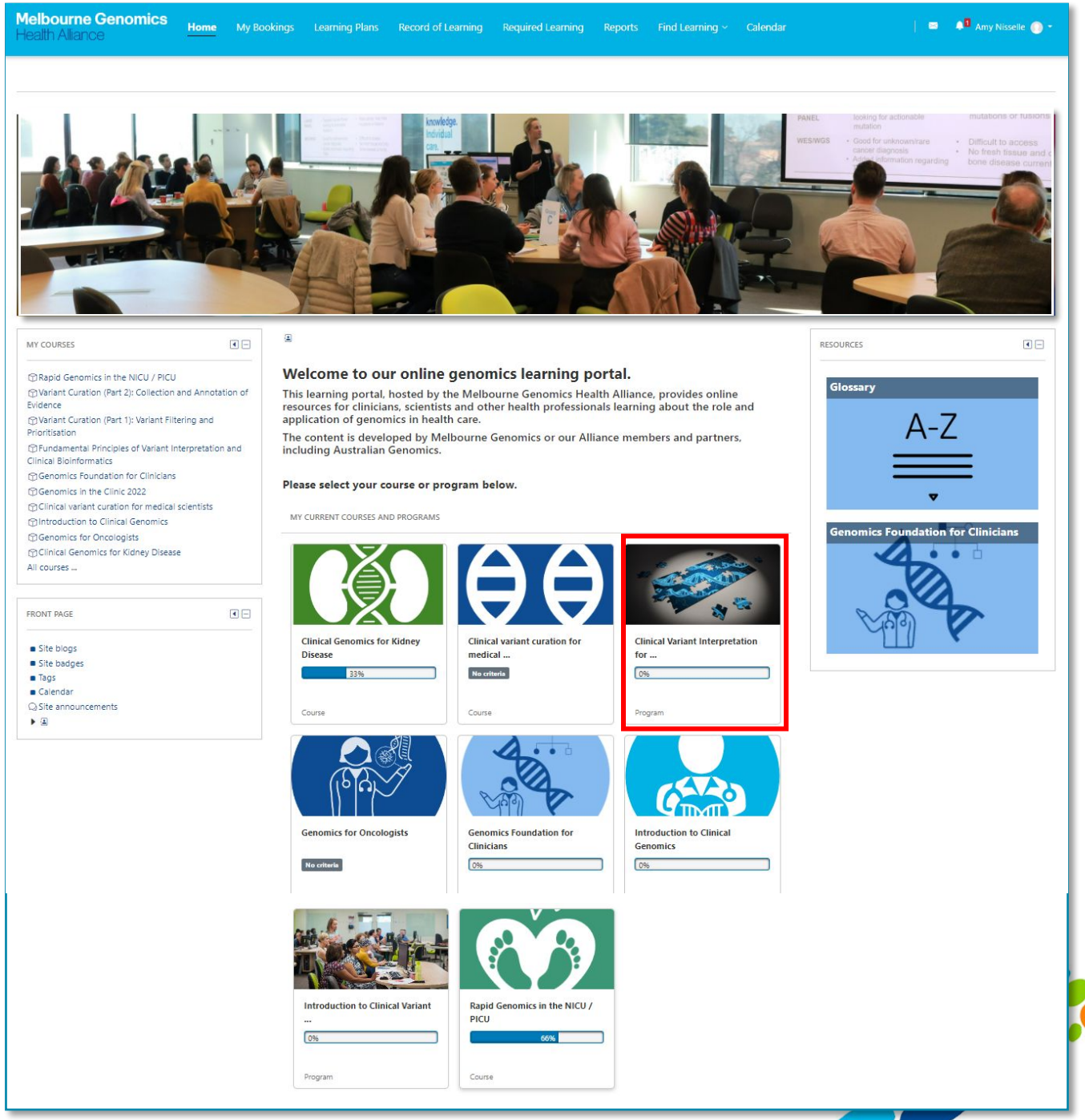
In-person workshops

Work through complex cases with experts

https://melbournegenomics.org.au/genomics-education
education@melbournegenomics.org.au

Melbourne Genomics Health Alliance

Melbourne Genomics learning management system



Melbourne Genomics Health Alliance

Melbourne Genomics
Health Alliance

Home / Find Programs / Melbourne Genomics / Clinical Variant Interpretation for Medical Scientists (self-directed)

Clinical Variant Interpretation for Medical Scientists (self-directed)

You are required to complete this program under the following criteria:

- Member of audience 'Clinical Variant Interpretation for Medical Scientists (Self-directed 2022)'.

Date assigned: 08 August 2022 Due date: No due date set

Progress:
0%

This self-directed online program provides an understanding of the principles and processes of variant interpretation pertinent to medical scientists specialising in genomic testing for rare germline disorders. To help us improve our education program, please complete this **SHORT SURVEY** before you begin.

What will I learn?

- The processes and limitations of germline variant interpretation
- How a clinical context is integrated into the variant interpretation process
- How to collect evidence to curate variants
- How to use evidence to classify variants
- How variant interpretation is integral to the generation of genomic test reports

How will I learn?

The program includes:

- **Theory modules** with learning content, knowledge checks and quizzes
- **Practical modules** with examples of software and tools, plus exercises to work through to consolidate understanding
- **Clinical case modules** with solutions, allowing you to put what you learn into practice.
- **Learning outcomes and quizzes** throughout for you to reflect and test your understanding as you go. The results can be included on a certificate of completion if needed to claim continuing professional development points.

Variant Interpretation Short Courses

All courses in this set must be completed (unless this is an optional set).

Course name	Actions
Fundamental Principles of Variant Interpretation and Clinical Bioinformatics	Launch course
Variant Curation (Part 1): Variant Filtering and Prioritisation	Launch course
Variant Curation (Part 2): Collection and Annotation of Evidence	Launch course
Variant Classification and Reporting	Launch course

Theory, pracs, exercises

Module 1: Genetics Theory for Clinical Variant Interpretation [v1.0]

33% COMPLETE

- Learning Outcomes
- Getting started
- The Human Genome
- Gene Structure and Expression
- Variation in the human genome
- Single nucleotide and small variants
- Application of genetics to the interpretation of variants
- Inheritance
- Quiz and Self-Reflection

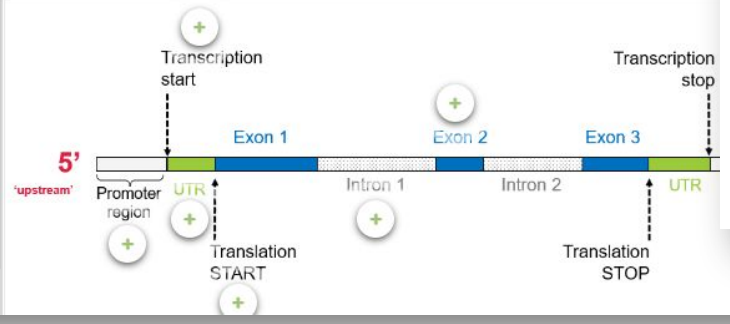
Lesson 4 of 9

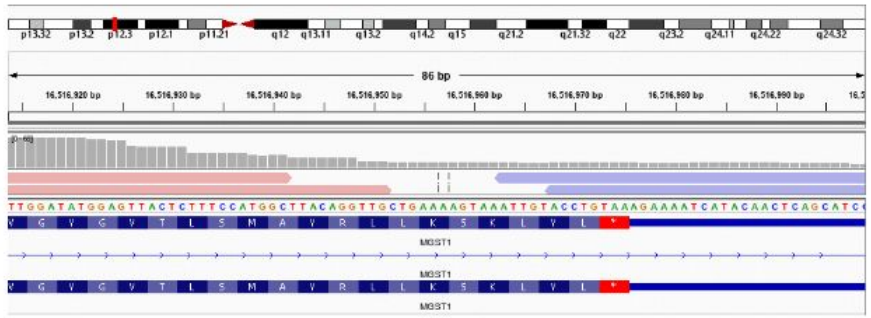
Gene Structure and Expression

Gene structure

The need to regulate gene expression is reflected in the structure
Genes contain coding regions (also referred to as 'structural' regi
encode polypeptides, as well as regulatory areas which control ge
expression.

**A gene sequence can be on either strand of the DNA; the seq
written in the 5' to 3' direction. This will become very import
when trying to interpret variants that are on either the forw
reverse strand.**

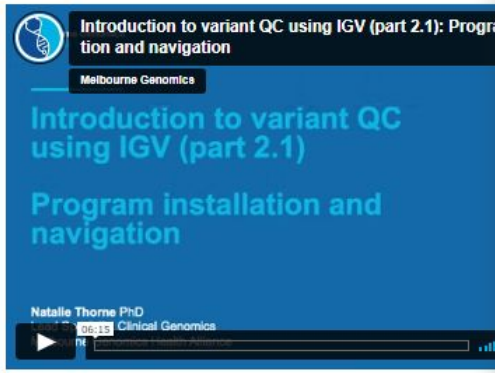




In the following 3 videos we take a deeper look at the various panels and functions of IGV that are used to explore genomic datasets and quality check variants.

You will learn how to:

- install IGV
- navigate around the program
- inspect the mRNA transcript(s) of a gene of interest
- distinguish true variants from artefacts



Lesson 9 of 24

Exercises

Amino acid physiochemical properties and conservation

Compare the physiochemical properties of the amino acids in each of the substitutions below. How do they differ?

Next, inspect the conservation of the two amino acid positions. Using the 'UCSC button' in Genomizer, link out to UCSC Genome Browser. The display should automatically be within a 21 bp window centred on the amino acid of interest. Select all species using the 'conservation' button, and then zoom out using the 3X and/or 1.5X button until you can see ~70-150bp. Make sure you check for homology in the region before you assess the level of conservation.

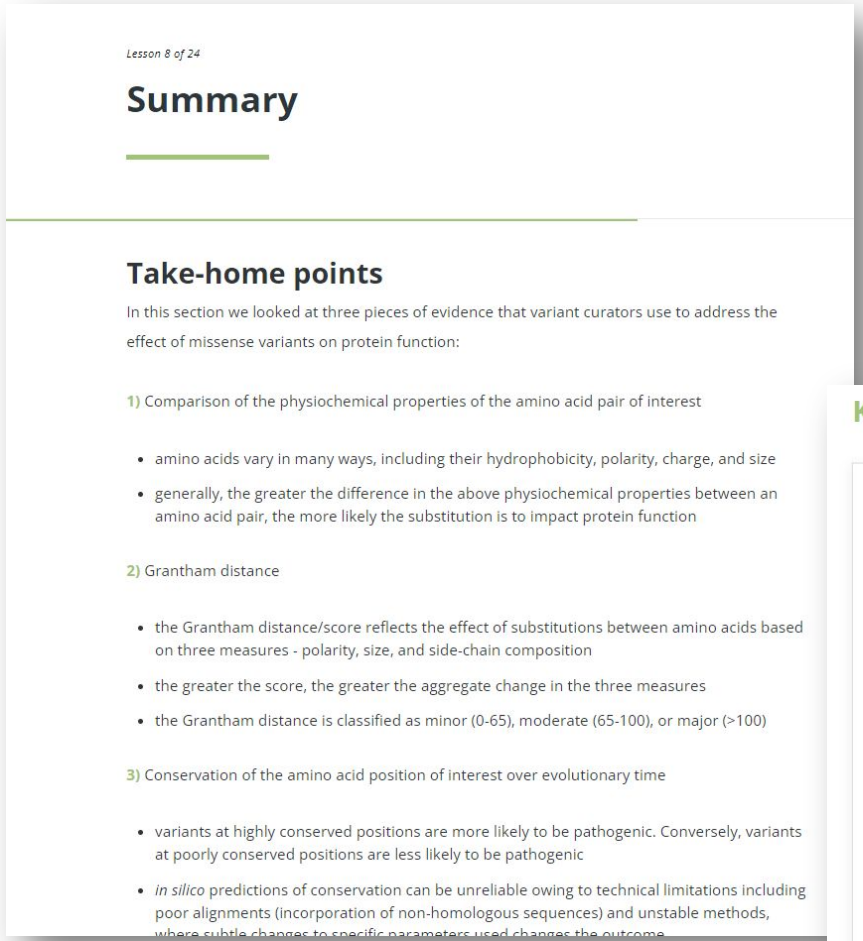
When you are ready to check your answer, click on the accordions below.

Genomizer links:

NM_005249.4(*FOXG1*):c.543G>T, p.(Lys181Asn)

NM_000249.3(*MLH1*):c.632C>A, p.Ser211Tyr

Summaries, knowledge checks, quizzes



Lesson 8 of 24

Summary

Take-home points

In this section we looked at three pieces of evidence that variant curators use to address the effect of missense variants on protein function:

1) Comparison of the physiochemical properties of the amino acid pair of interest

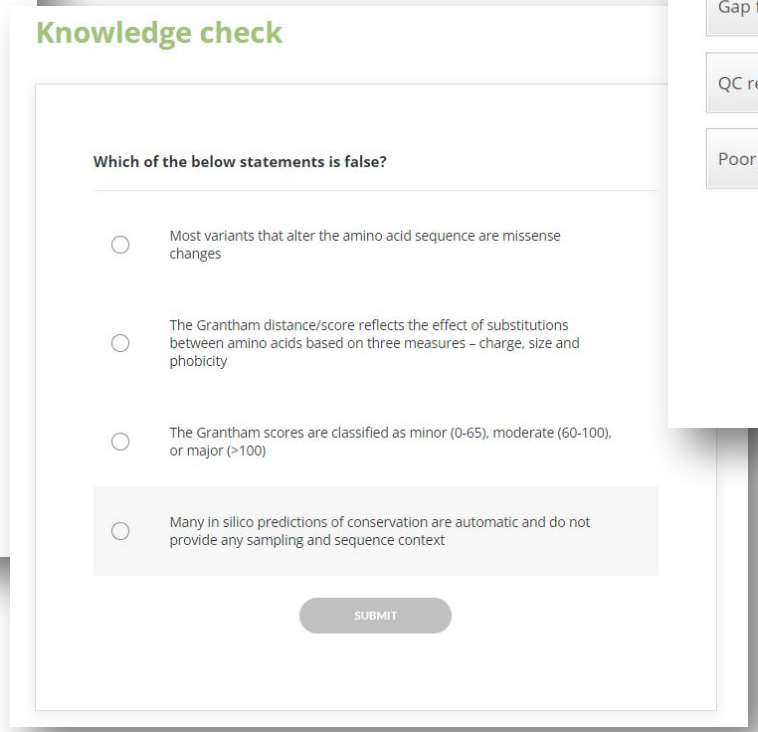
- amino acids vary in many ways, including their hydrophobicity, polarity, charge, and size
- generally, the greater the difference in the above physiochemical properties between an amino acid pair, the more likely the substitution is to impact protein function

2) Grantham distance

- the Grantham distance/score reflects the effect of substitutions between amino acids based on three measures - polarity, size, and side-chain composition
- the greater the score, the greater the aggregate change in the three measures
- the Grantham distance is classified as minor (0-65), moderate (65-100), or major (>100)

3) Conservation of the amino acid position of interest over evolutionary time

- variants at highly conserved positions are more likely to be pathogenic. Conversely, variants at poorly conserved positions are less likely to be pathogenic
- *in silico* predictions of conservation can be unreliable owing to technical limitations including poor alignments (incorporation of non-homologous sequences) and unstable methods, where subtle changes to specific parameters used changes the outcome

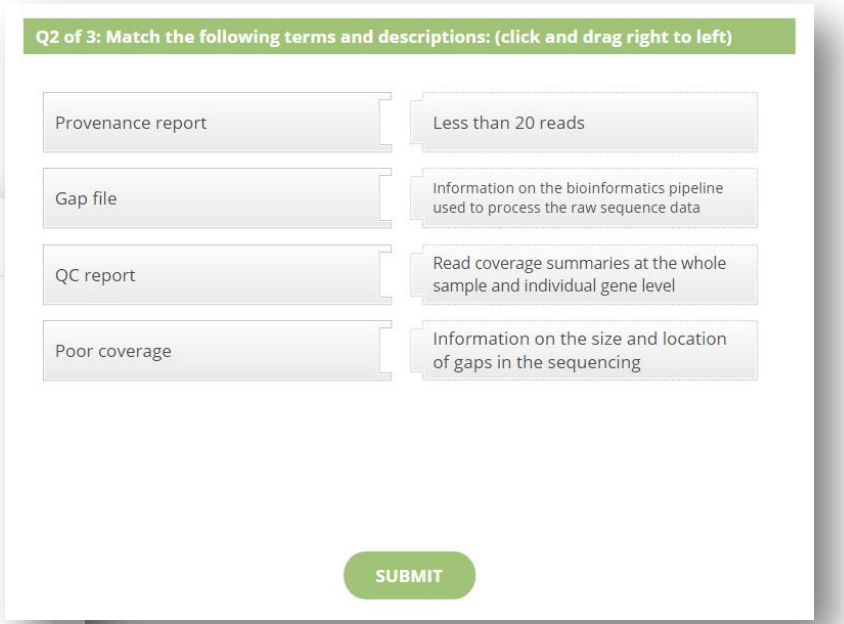


Knowledge check

Which of the below statements is false?

- Most variants that alter the amino acid sequence are missense changes
- The Grantham distance/score reflects the effect of substitutions between amino acids based on three measures – charge, size and phobicity
- The Grantham scores are classified as minor (0-65), moderate (60-100), or major (>100)
- Many in silico predictions of conservation are automatic and do not provide any sampling and sequence context

SUBMIT



Q2 of 3: Match the following terms and descriptions: (click and drag right to left)

Provenance report	Less than 20 reads
Gap file	Information on the bioinformatics pipeline used to process the raw sequence data
QC report	Read coverage summaries at the whole sample and individual gene level
Poor coverage	Information on the size and location of gaps in the sequencing

SUBMIT

Melbourne Genomics Health Alliance

Active learning throughout

Module 9: Transcript Selection and Variant Annotation Checking [v2.0]

50% COMPLETE

- Learning Outcomes
- Transcript selection
- Variant annotation checking
- Quiz and Self-Reflection

EXIT COURSE

Transcript selection

Recall that most genes are alternatively spliced, leading to the production of multiple mRNA transcripts. As such, you need to choose which transcript is relevant to the patient's phenotype. That is, you need to select the **condition-relevant transcript**. The process of transcript selection is introduced in the two videos below.

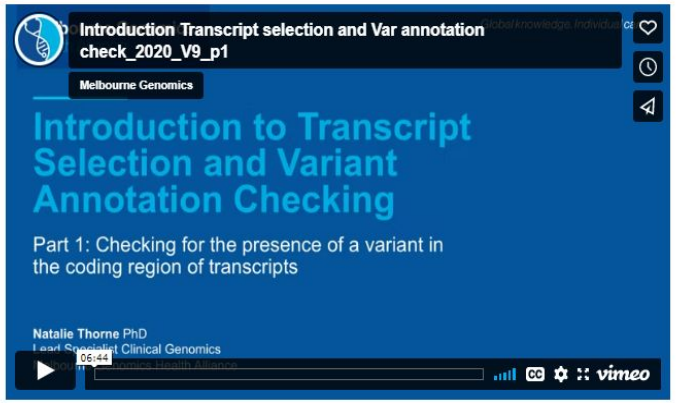
It's important to note that mRNA transcript reference sequences are periodically reviewed and updated. In turn, the relevant transcript for a condition will change occasionally. As such, every time you curate a variant the condition-relevant transcript must be checked, even if it's a condition you have work on before.

Following on from previous modules, we will continue with the CREBBP case. To work along with the below video you will need to open the bam files for the CREBBP V2 and V5 variant in IGV (links below). Remember, you'll need to have IGV open for the links to work.

***CREBBP* variant bam files:**

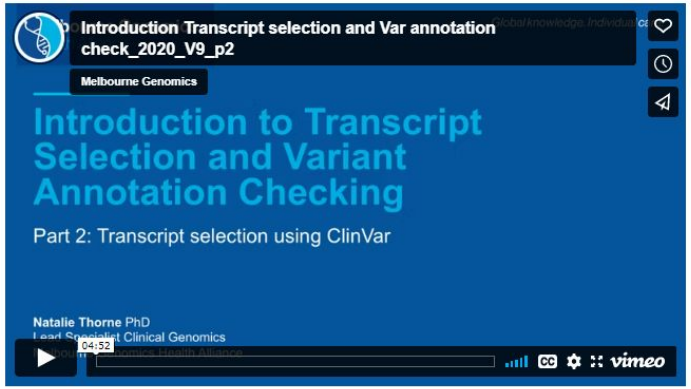
CREBBP V5 g.3808917G>A

CREBBP V2 g.3900336 C>T



Follow along with the next video to use ClinVar to select the CREBBP transcript relevant to Rubinstein-Taybi syndrome.

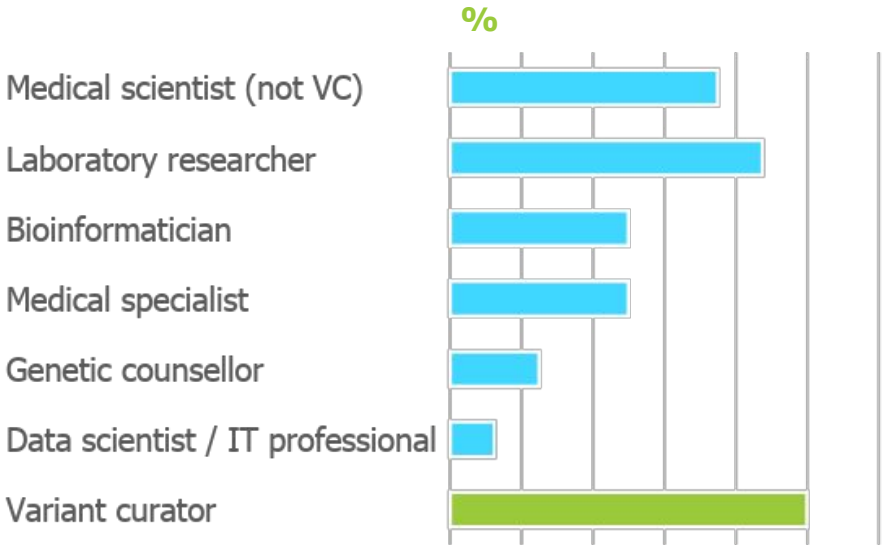
Question: There is a clear discrepancy between the ClinVar entries for CREBBP shown in the following video and what you will see yourself as you follow along. Can you see what it is? When you are ready to check your answer, click on the accordion below this video.

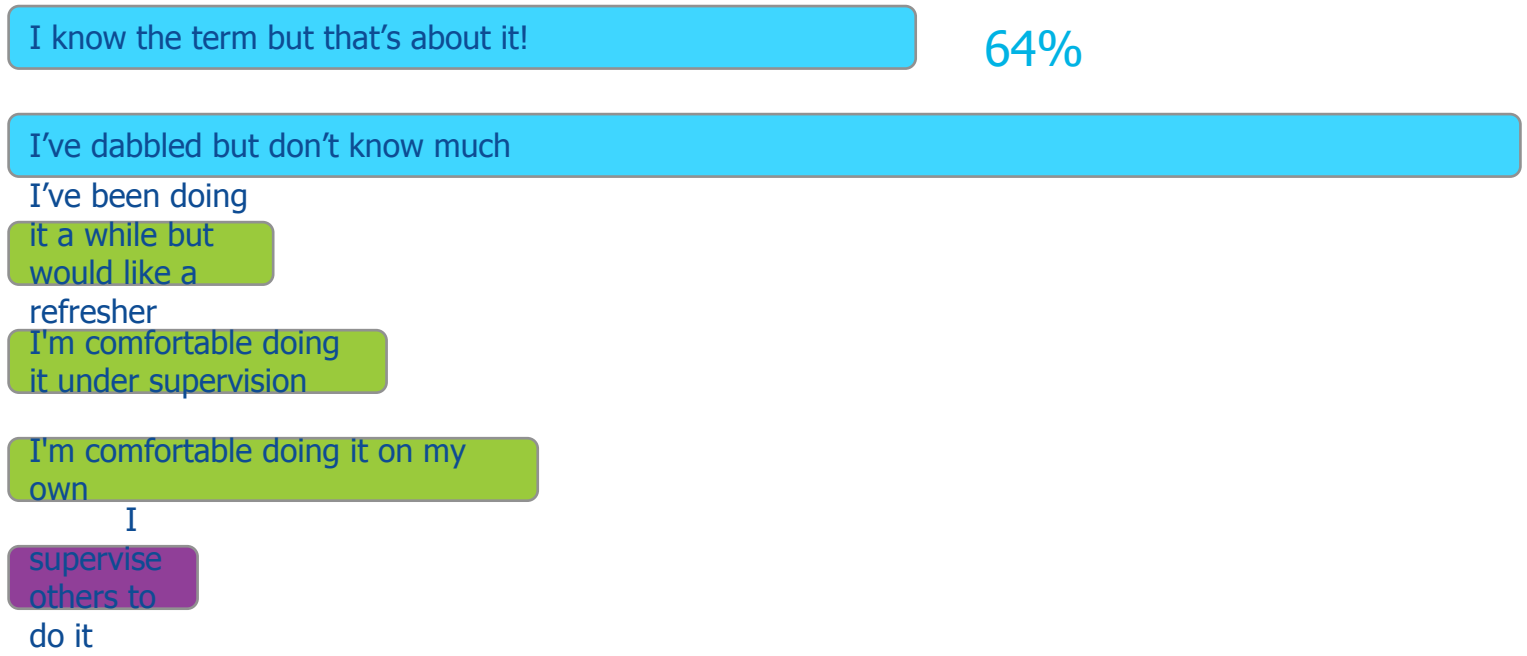


CREBBP ClinVar data discrepancy +

Lesson 3 - Variant annotation checking

Who typically completes our programs





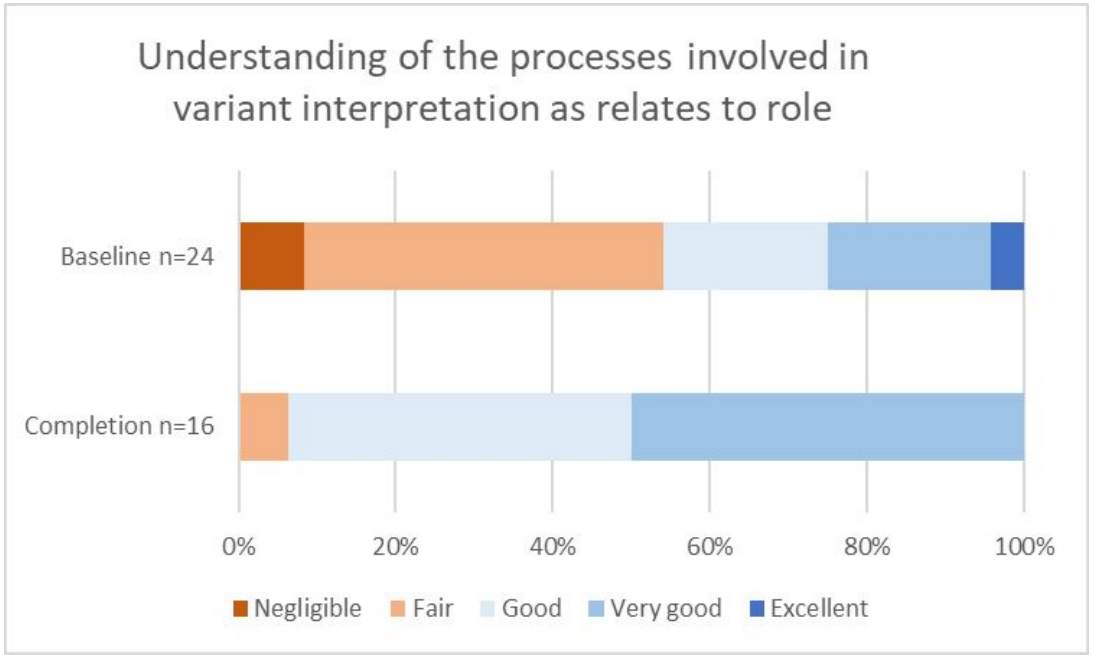
Why

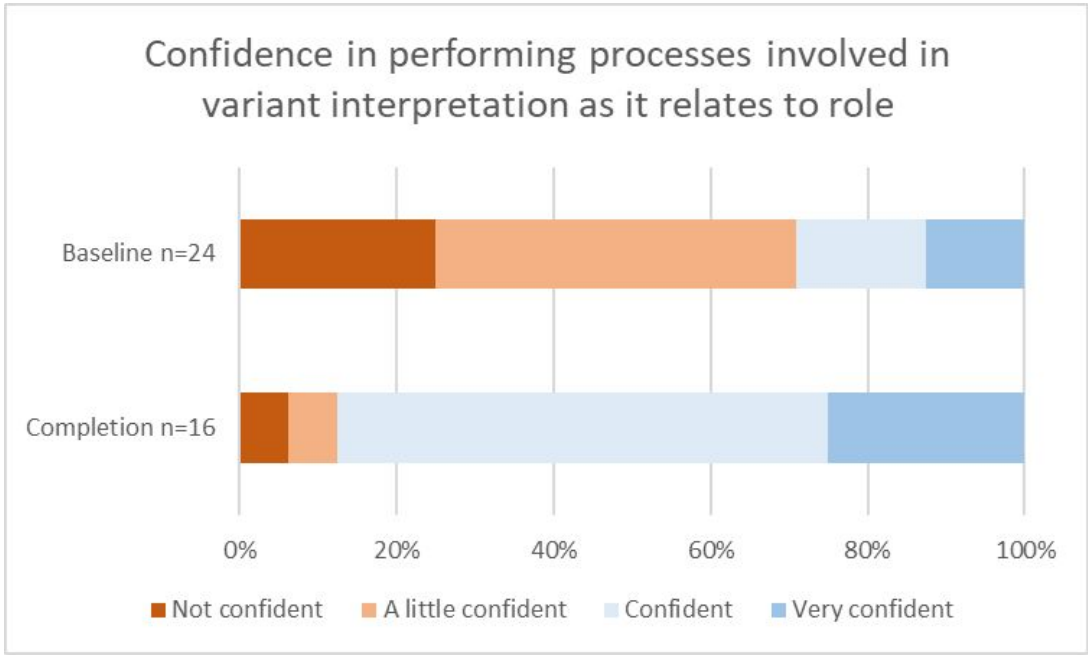
Foundations

Upskill in variant interpretation

Possibly move into the role

Improves understanding & confidence





*Good structure and **comprehensive** modules. Also enjoyed having **case studies** to apply the knowledge.*

PhD student (somatic)

*In-depth explanations and exercises for learning how to **navigate all the databases** used for variant interpretation.*

Medical scientist (not VC)

Melbourne Genomics Health Alliance

In-person workshops

with experts + multidisciplinary peer groups (in Melbourne)

Introductory

- Review online modules
- Work through pracs + simple case

Advanced

- Learn advanced topics
- Work through complex cases

www.melbournegenomics.org.au/genomics-education

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Health Alliance

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PMCC

Ain Roesley
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Ella Thompson
Victoria Bashay

Melbourne Genomics

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Clara Gaff
Donna Halton
Douglas Liddicoat
Melissa Martyn
Nat Thorne

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Melbourne Genomics education
www.melbournegenomics.org.au/genomics-education

University of Melbourne Centre for Cancer Research
https://mdhs.unimelb.edu.au/centre-for-cancer-research

The Advanced Genomics Collaboration
https://www.tagcaustralia.com/

Victorian Clinical Genetics Services
www.vcgs.org.au/tests/genomics

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The Royal Children's Hospital Melbourne
The University of Melbourne
WEHI brighter together
murdoch children's research institute
CSIRO
agrf
PeterMac Peter MacCallum Cancer Centre Victoria Australia
Austin Health
Monash Health

Supported by

Victoria State Government

Slide deck identification

Intended Audience

Name	Title
Australian BioCommons audience	

Contributing Authors

Name	Date
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Naomi Baker, VCGS	Nov 2022
Joep Vissers, UoM	Nov 2022

Purpose

Introduce Australian BioCommons audience to variant interpretation/ clinical genomics applications of big data concepts and processes

Reviewers

Name	Date