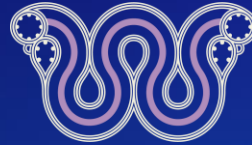




Waipapa
Taumata Rau
**University
of Auckland**



PŪTAHI MANAWA
HEALTHY HEARTS FOR
AOTEAROA NEW ZEALAND

Thank you!

Patients &
whānau

Translating inherited cardiac disease research into clinical care



Rare Disorders Research Forum



August 2026



Dr Polona Le Quesne Stabej, Senior Research Fellow
Dr Zoe Ward, Research Fellow

Inherited heart diseases



Cardiomyopathies



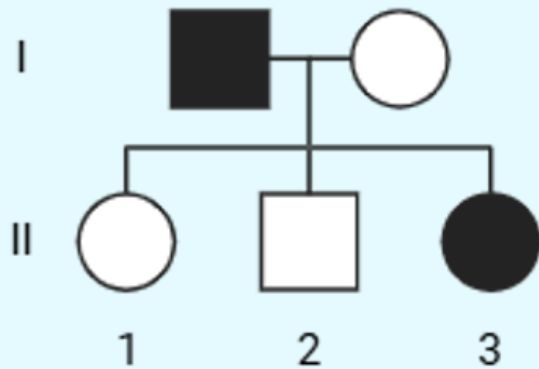
Channelopathies



Sudden cardiac death



Aortopathies (TADs, syndromic)

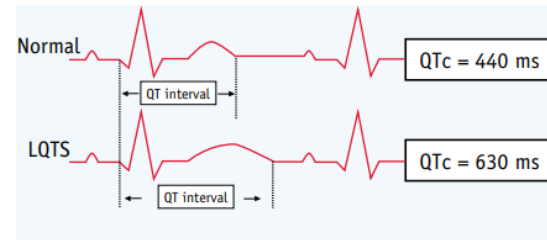


Channelopathies



Long QT Syndrome:

- 1 / 2,000
- Highly treatable; most deaths are preventable



Brugada syndrome

- 1 / 2,000

CPVT (Catecholaminergic Polymorphic Ventricular Tachycardia)

- 1 / 10,000

Arrhythmogenic cardiomyopathy (ACM)

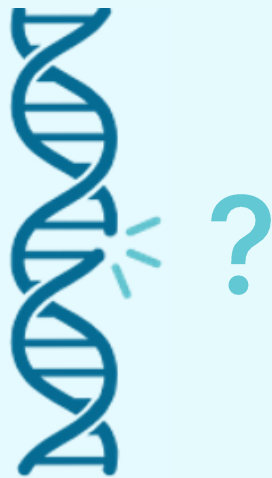
- 1 / 5,000

Sudden Cardiac Death

- ~ 1.3-2.9 / 100,000

Inherited heart diseases

Diagnostic testing leaves
~ 60% of patients / families
without a genetic diagnosis



Registry of patients and
families ~ 6500 consented

Why genetic testing



Refine/confirm/establish diagnosis



Identify at-risk relatives (cascade screening)

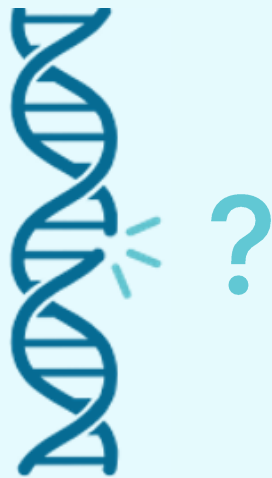


Preventative measures, precision medicine

Inherited heart diseases

Diagnostic testing leaves

~ 60% of patients / families
without a genetic diagnosis



Genome sequencing can reveal hidden genetic causes

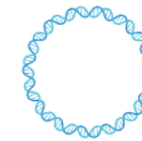


Panel/exome



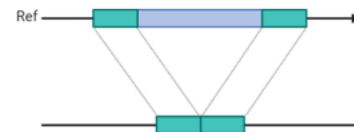
Genome

Intronic, UTRs



Mitochondrial

Long read sequencing technology



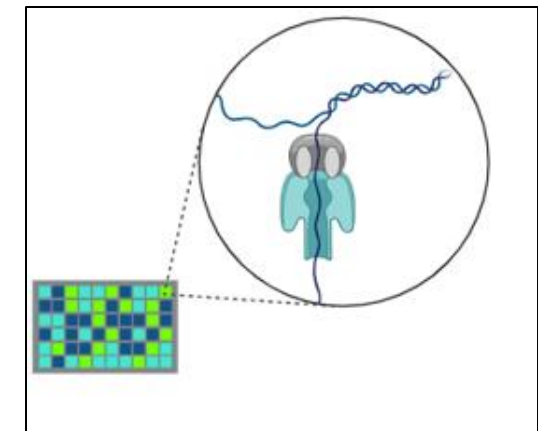
Structural variants



DNA modifications

CTG CTG CTG CTG

Repeat expansions



Rōpū Kaitiaki

- **Dr Karaitiana Taiuru**, Ngāi Tahu, Ngāti Kahungunu, Ngāti Toa (Lead)
- Saraya Hogan, Ngāti Hako, genetic counsellor
- Arahia Harawira, Te Whanau A Apanui, Whakatohea, patient representative
- Lisa Warbrick, Ngāti Awa, Ngāti Rangitihi, Te Atihaunui a Pāpārangi, IGI Director
- Dr Joshua Agnew, paediatrician, Cook Island Māori (Pacific seat)



- Governance over study protocols and patient-facing material (Patient Information Sheet, Consent)
- Ensure tikanga (correct procedure) and traditional values are considered by researchers when conducting research
- Advise on return of results

Cultural considerations

For Māori, biological samples e.g. DNA and genomic data are Taonga (treasured possession) representing Mauri (life force), Tapu (sacred) and Whakapapa (genealogy).

The research team has obligations under Te Tiriti, such as being a kaitiaki (intergenerational guardian) of the Taonga

I understand that I can request to have the **research sample** returned to me or destroyed at the end of the study. I would like **(tick (✓) one)**:

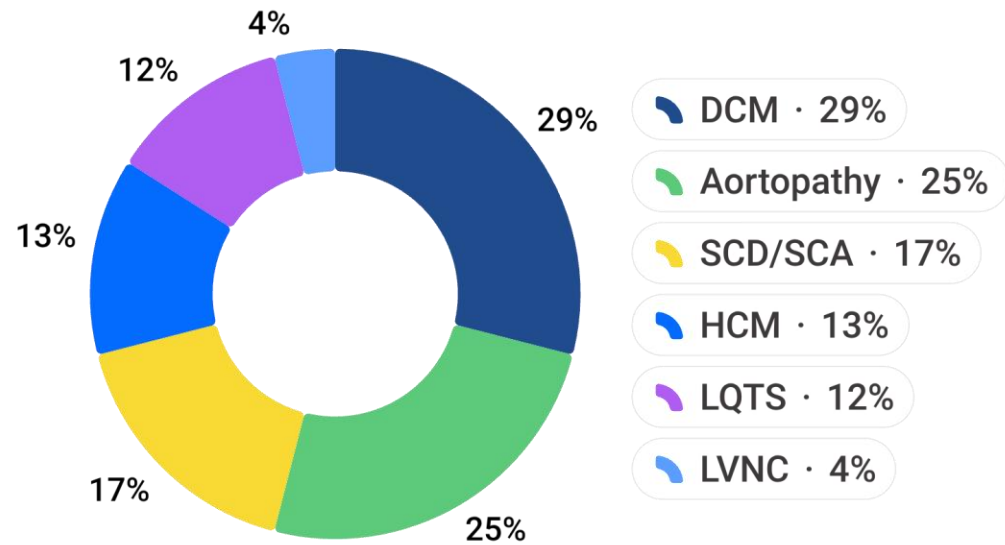
- ☐ My/My relative's (whanaunga's) remaining sample disposed of using standard disposal methods.
- ☐ My/My relative's (whanaunga's) remaining sample disposed of with an appropriate karakia. Procedure and karakia are available on request.
- ☐ My/My relative's (whanaunga's) remaining sample returned to me.

Please tick (✓) one:

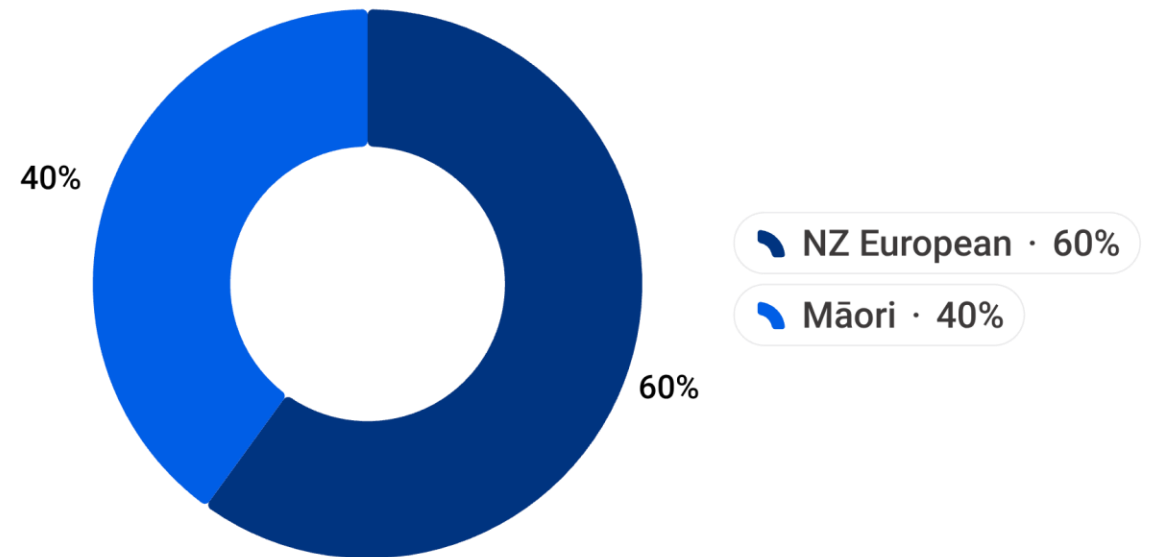
- ☐ I am aware that my sample may be sent overseas for sequencing, and any leftover sample will be returned to Aotearoa New Zealand.
- ☐ I would like all genetic testing on my sample to be done in Aotearoa New Zealand. I understand this might require an additional blood/saliva sample to be taken.

Participant Demographics: Phenotype & Ethnicity

Phenotype by Family (N=24)



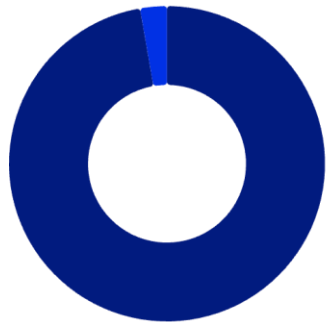
Ethnicity (N=73)



Sample & Incidental Findings Summary (N=73)



Samples Sent Overseas

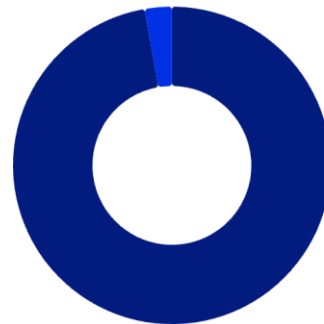


Yes (97%)
No (3%)

71 of 73 participants consented to overseas transfer



Incidental Findings Return

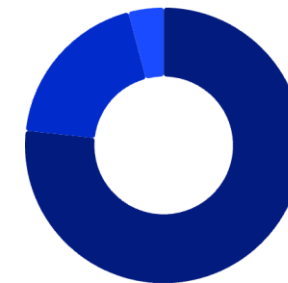


Yes (97%)
No (3%)

71 of 73 agreed to receive incidental findings.



Sample Disposal Method



Standard (77%)
Karakia (19%)
Return (4%)

56 of 73 selected standard disposal;
14 chose Karakia,
3 chose Return.

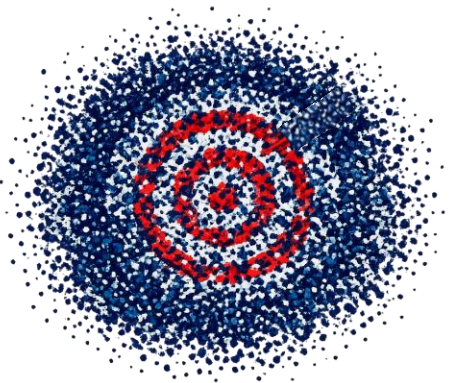
From ~7 million variant calls to one family-specific candidate

19 inherited cardiac
disease families

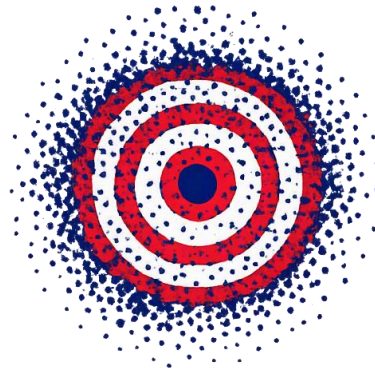
2–5 relatives
sequenced per family

Illumina SRGS + Oxford
Nanopore LRGS

Short read (Illumina)
Long read (Oxford Nanopore)



Population filtering



Rare variants
gnomAD



Biological prioritisation



Shortlist
In house db
Predicted consequence
Gene-disease validity

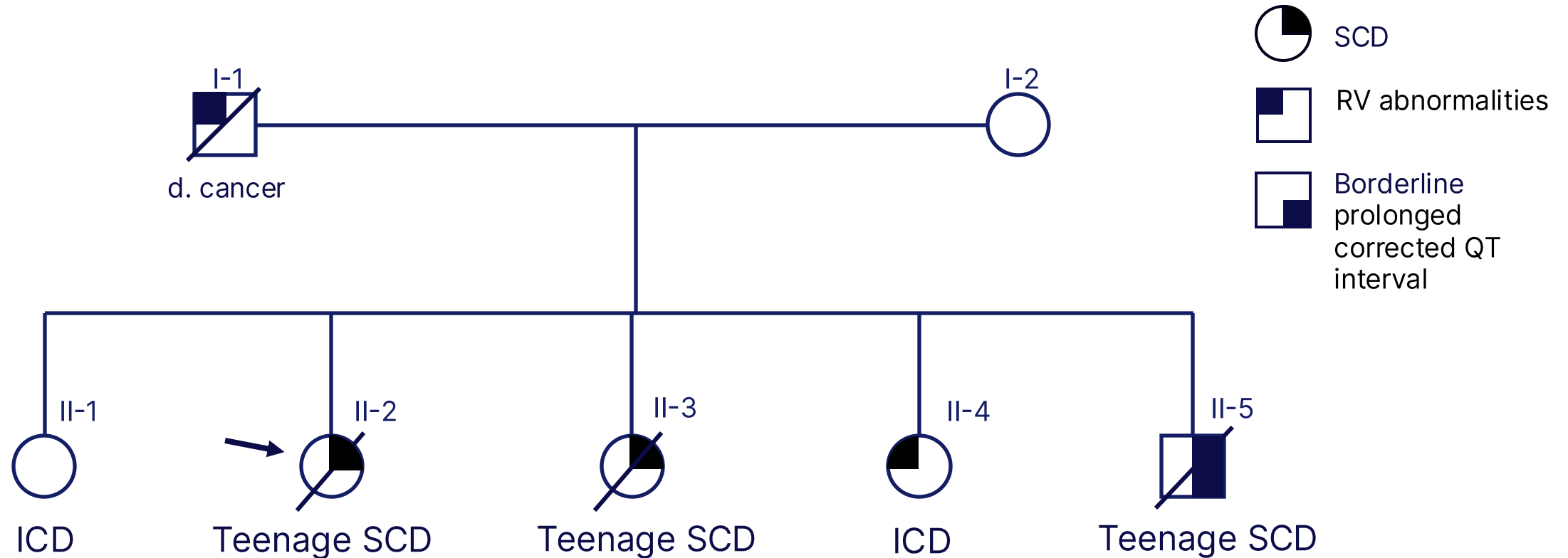


Family-disease specific
candidate



Leading candidate(s)
Segregation
He Kāhano Aotearoa Māori
Variome
No other compelling alternatives

Introduction to the Whānau



- Dad + II-4 'right ventricular (RV) abnormalities' on MRI
- No conduction disease seen in children and mum (ECG, Exercise test, Holter monitoring)
- II-5 a had borderline prolonged QT interval
- II-3, II-5 normal hearts on autopsy
- II-3, II-5 DNA panel LQTS + CPVT genetic testing - uninformative
- II-3, II-5 Whole Exome Sequencing UK (2016)+ UoA (2019) - uninformative
- Recruited into genome inherited cardiac disease research project (2024)

Sequencing of Whānau 1

Illumina (I-2, II-3, II-4, II-5)

Single Nucleotide Variants

Insertions/Deletions

Structural Variants

Copy Number Variants

Short Tandem Repeats

Nanopore (II-5)

Single Nucleotide Variants

Insertions/Deletions

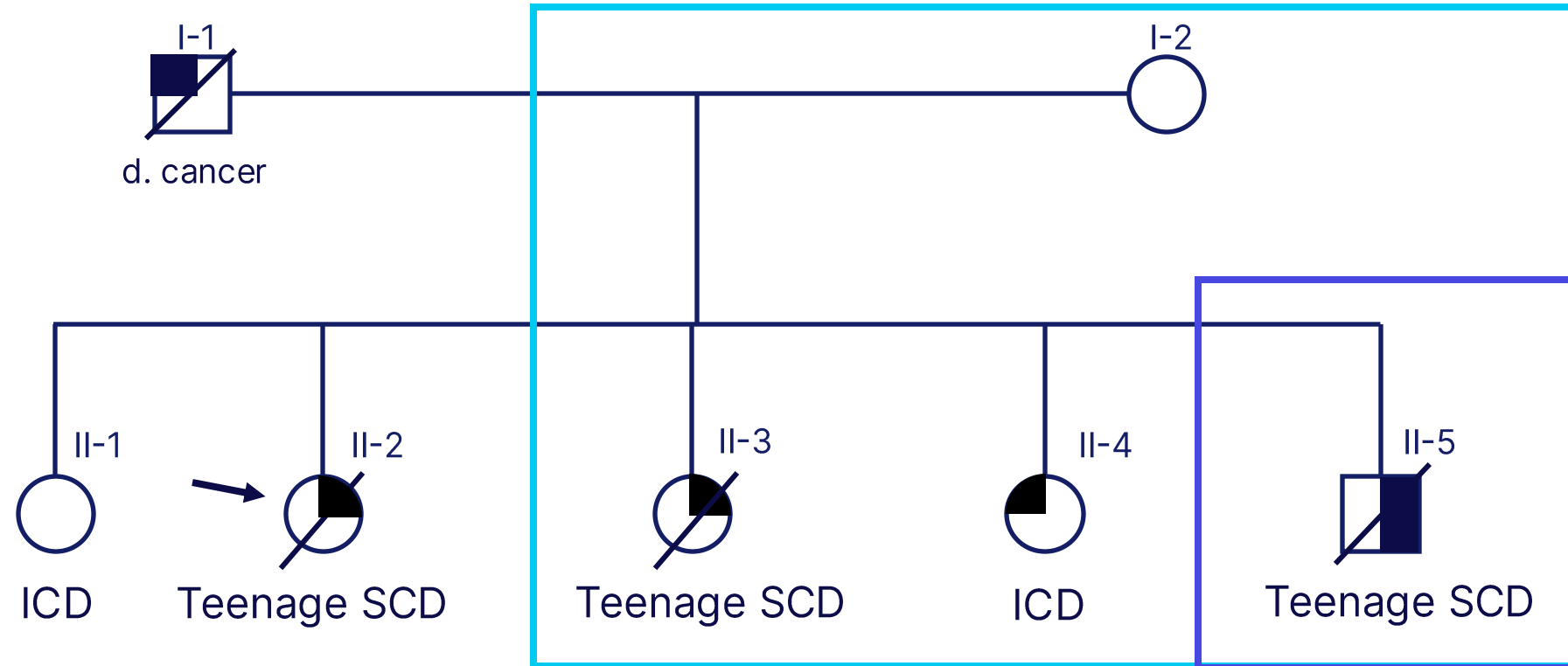
Structural Variants

Copy Number Variants

Short Tandem Repeats

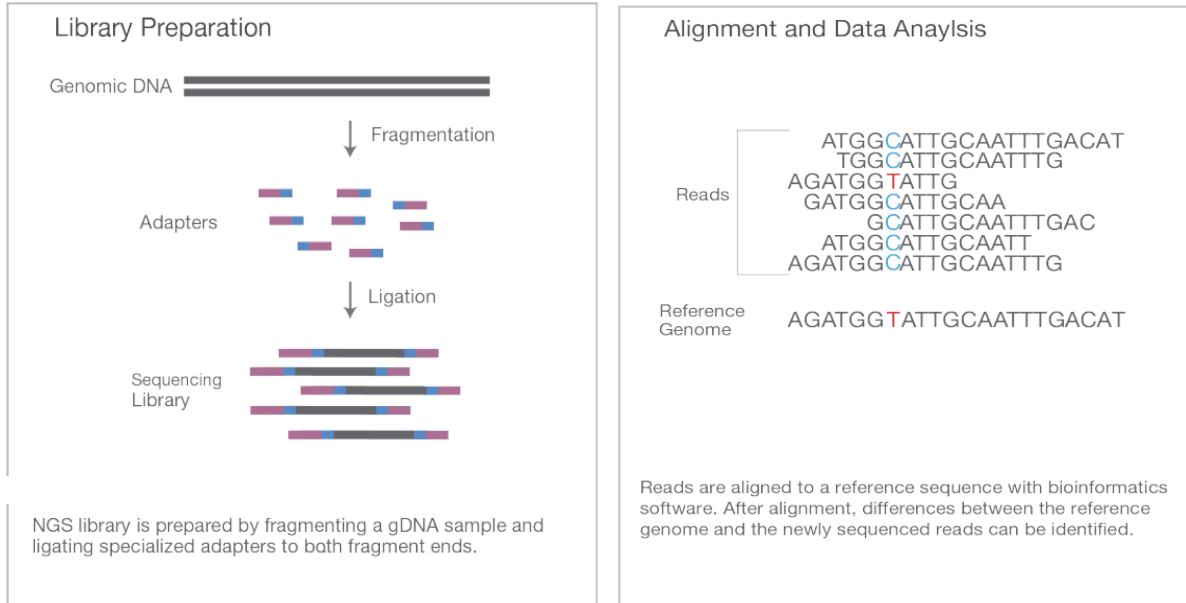
Phasing

Methylation

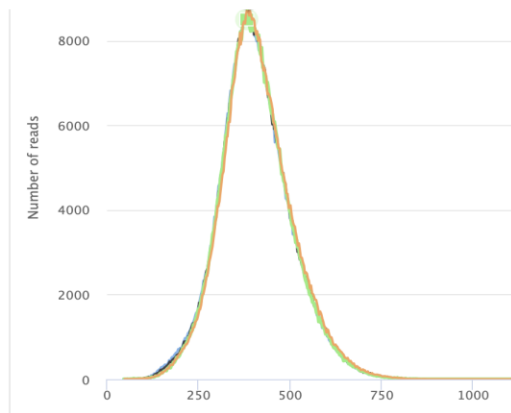


Illumina vs Nanopore Sequencing

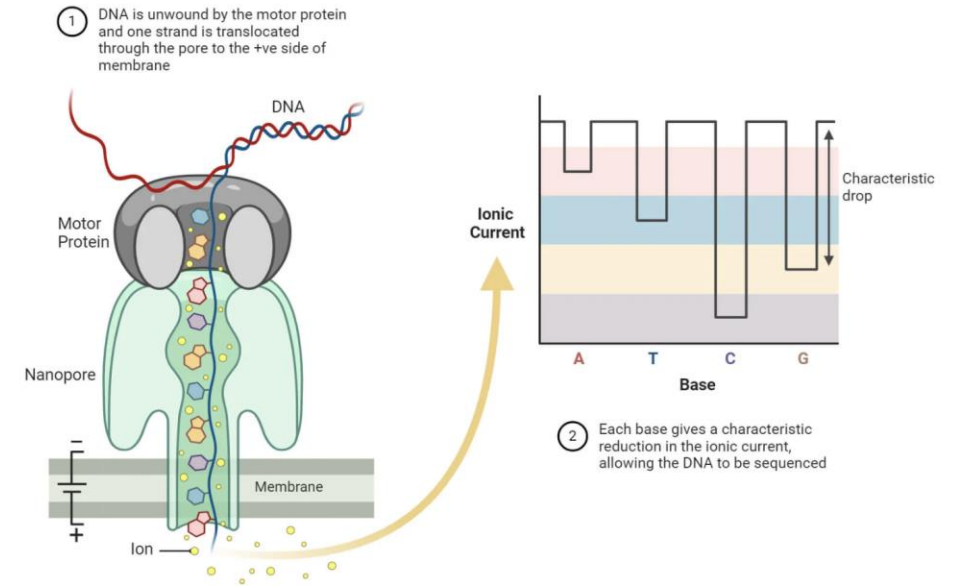
Illumina



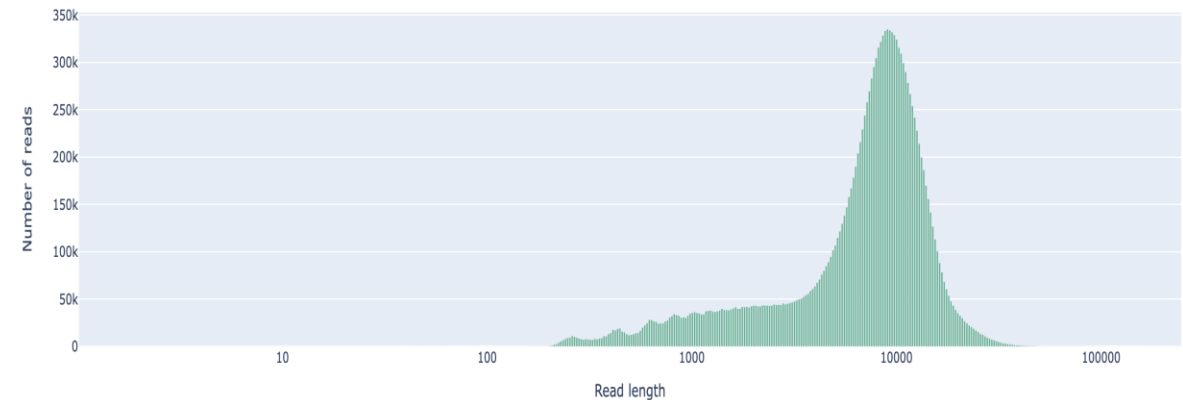
Mean length Illumina 384bp



Nanopore

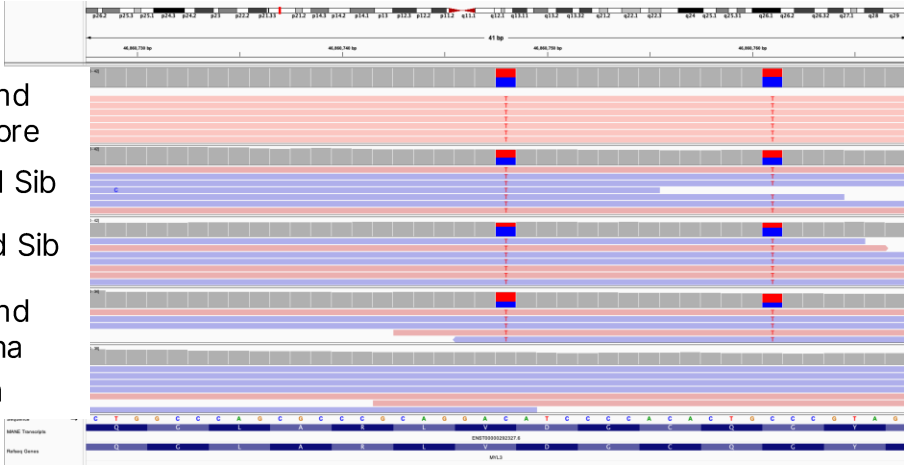
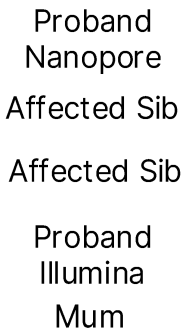


Mean length Nanopore 8152bp



Illumina vs Nanopore Sequencing Results

MYL3 NM_000258.3 c.235G>A p.Val79Ile



Illumina

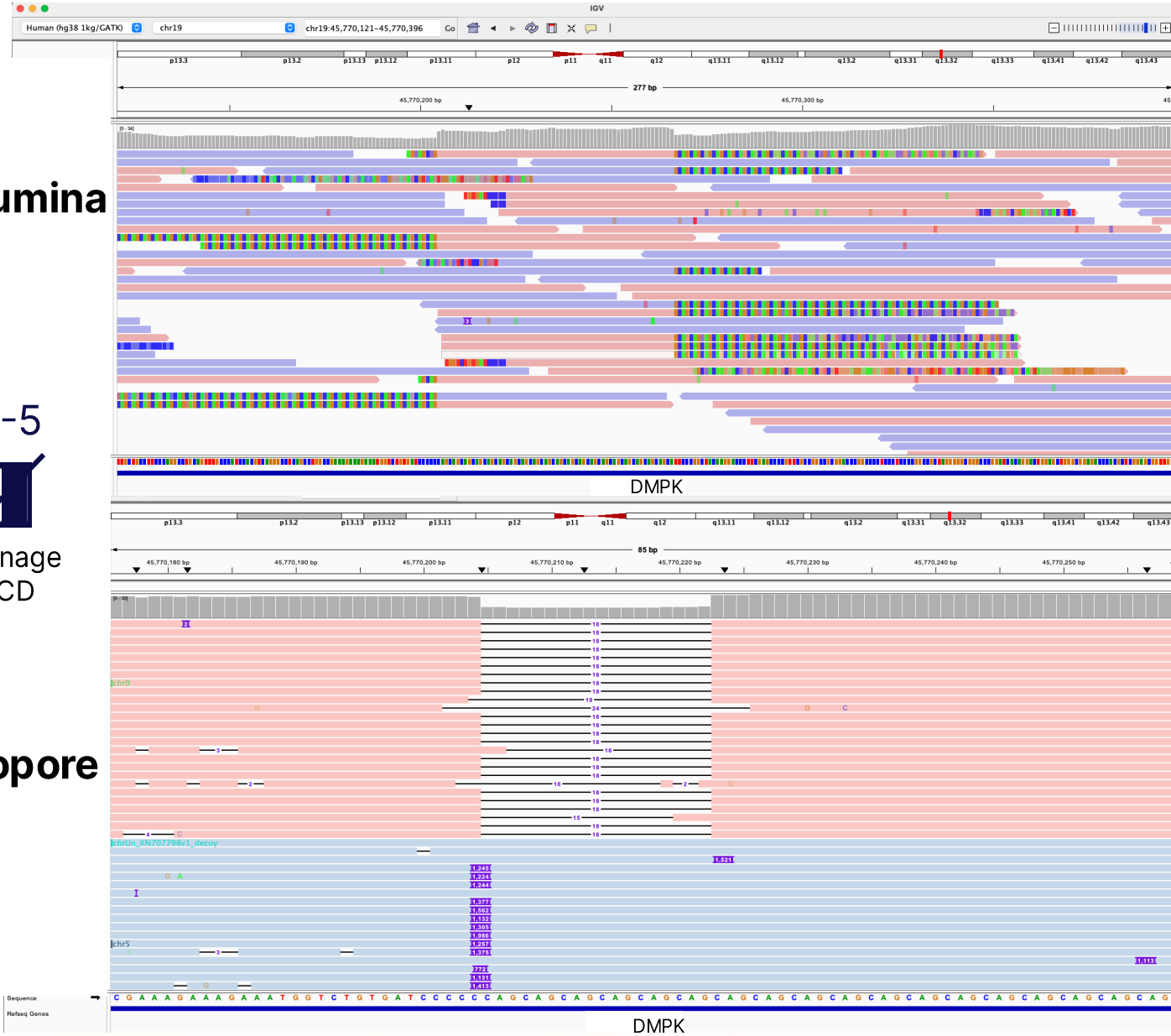
11-5



Teenage SCD

Nanopore

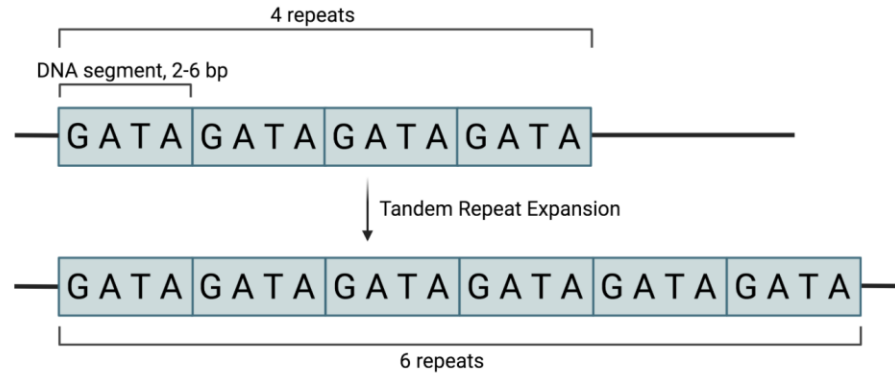
	Gene	Repeat	Allele 1	Allele2
Illumina	DMPK	CTG	14 (42 bp)	125 (375 bp)
ONT	DMPK	CTG	14 (42 bp)	424 (1272 bp)



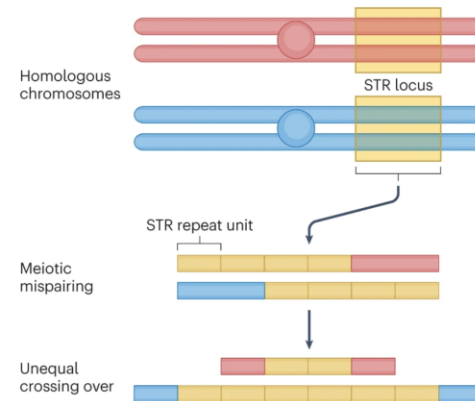
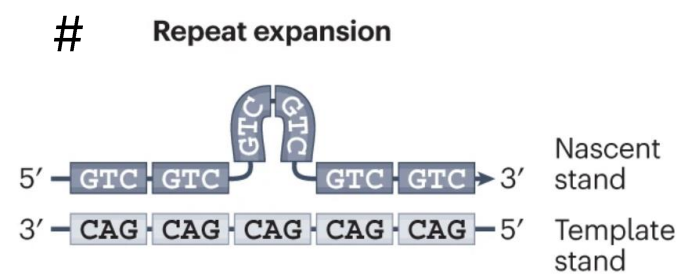
Repeat expansions

- > 1 million STR loci - regulate gene expression and influence complex traits

Short Tandem Repeat (STR)



Repeat expansion



* PolyQ			PolyA		
HD	(CAG) _n	HTT	SPD1	(GCG) _n	HOX13D
HDL2	(CAG/CTG) _n	JPH3	BCCD	(GCN) _n	RUNX2
SCA1	(CAG) _n	ATXN1	OPMD	(GCG) _n	PABPN1
SCA2	(CAG) _n	ATXN2	HFGS	(GCN) _n	HOXA13
SCA3	(CAG) _n	ATXN3	BPES	(GCN) _n	FOXL2
SCA6	(CAG) _n	CACNA1A	HPE5	(GCN) _n	ZIC2
SCA7	(CAG) _n	ATXN7	EIEE1	(GCN) _n	ARX
SCA17	(CAG) _n	TBP	MRGH	(GCN) _n	SOX3
SBMA	(CAG) _n	AR	CCHS	(GCN) _n	PHOX2B
DRPLA	(CAG) _n	ATN1			

DM1 (CTG)_n
SCA8 (CTG/CAG)_n

DMPK
ATXN8OS/ATXN8

Promoter / 5' UTR

exon

intron

exon

3' UTR

FXS	(CGG) _{n>200}	FMR1	ALS/FTD	(GGGGCC) _n	C9ORF72
FXTAS	(CGG) ₅₀₋₂₀₀	FMR1	FEC3D	(CTG) _n	TCF4
FRA1E	(CCG) _n	AFF2	DM2	(CAG) _n	CNBP
EPH1	(CCCCGCCGCCG) _n	CSTB	FRDA	(GAA) _n	FXN
SCA12	(CAG) _n	PPP2R2B	SCA10	(ATTCT) _n	ATXN10
NIID	(CGG) _n	NOTCH2NLC	SCA31	(TGGAA) _n	BEAN
OPDM1	(CGG) _n	LRP12	SCA36	(GGCCTG) _n	NOP56
OPDM2	(CGG) _n	GIPC1	CANVAS	(AAGGG) _n	RFC1
BSS	(CGG) _n	XYLT1	XDP/DYT3	(CCCTCT) _n	TAF1
GDPAG	(GCA) _n	GLS	SCA37	(ATTTT/ATTTC) _n	DAB1
			FAME1	(ATTTT/ATTTC) _n	SAMD12
			FAME2	(ATTTT/ATTTC) _n	STARD7
			FAME3	(ATTTT/ATTTC) _n	MARCHF6
			FAME4	(ATTTT/ATTTC) _n	YEATS2
			FAME6	(ATTTT/ATTTC) _n	TNRC6A
			FAME7	(ATTTT/ATTTC) _n	RAPGEF2
			XDP	(CCCTCT) _n	TAF1 (SVA)

* Depienne C, Mandel JL. **30 years of repeat expansion disorders: What have we learned and what are the remaining challenges?** Am J Hum Genet. 2021 May 6;108(5):764-785. PMID: 33811808

Tanudisastro HA, Deveson IW, Dashnow H, MacArthur DG. **Sequencing and characterizing short tandem repeats in the human genome.** Nat Rev Genet. 2024 Jul;25(7):460-475. PMID: 38366034

Myotonic Dystrophy type 1

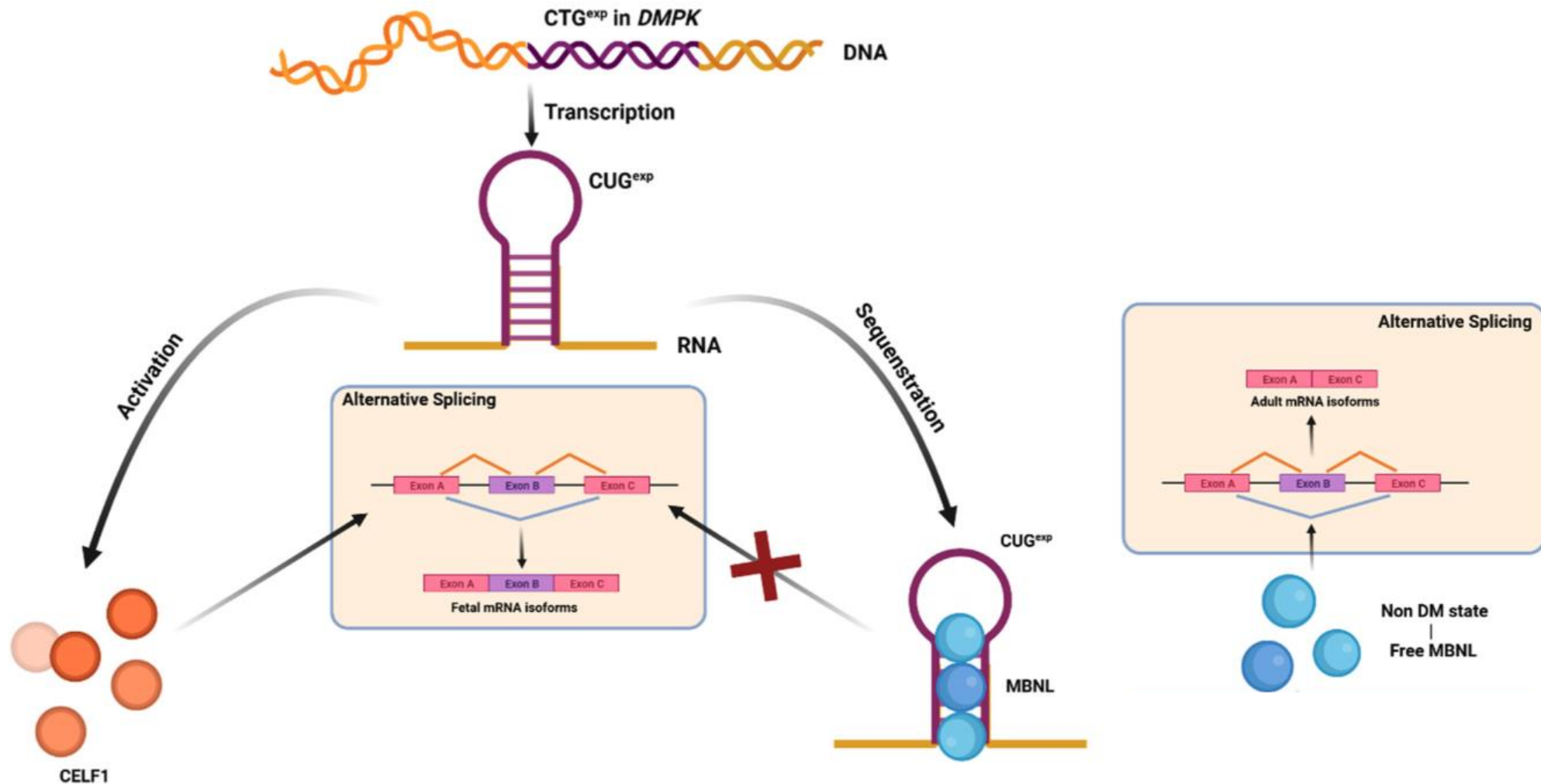
- Autosomal dominant multi-system disorder that was first recognised more than a century ago
- Highly variable phenotypic expression - muscle degeneration, cataracts, cardiac and central nervous involvement
- Most common form of muscular dystrophy with onset in adulthood
- Incidence: 1 / 2,100 (Johnson et al, 2021, PMID: 33472919)
- CTG repeats in the 3' untranslated region of *DMPK*
- Healthy = ~5-34 repeats; 'Premutation' = ~35-49; Disease range = >50
- 'Anticipation' - the trinucleotide is mitotically and meiotically unstable with a bias toward length increase in the next generation
- Unstable at both the somatic and intergenerational levels - biased towards increasing during lifetime and over successive generations

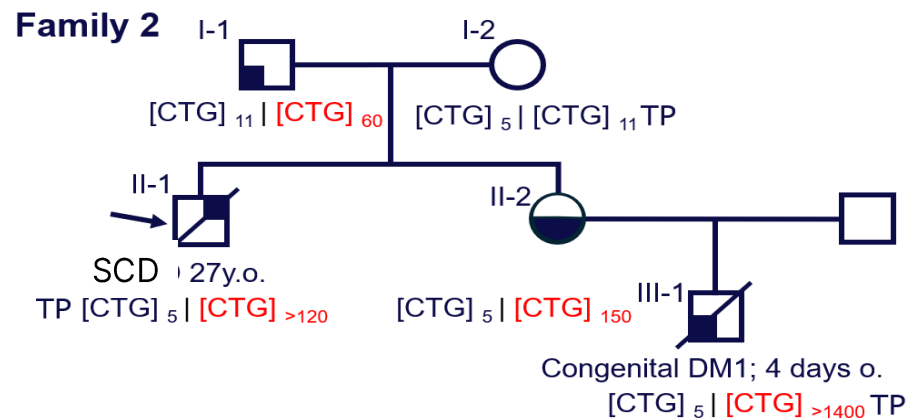
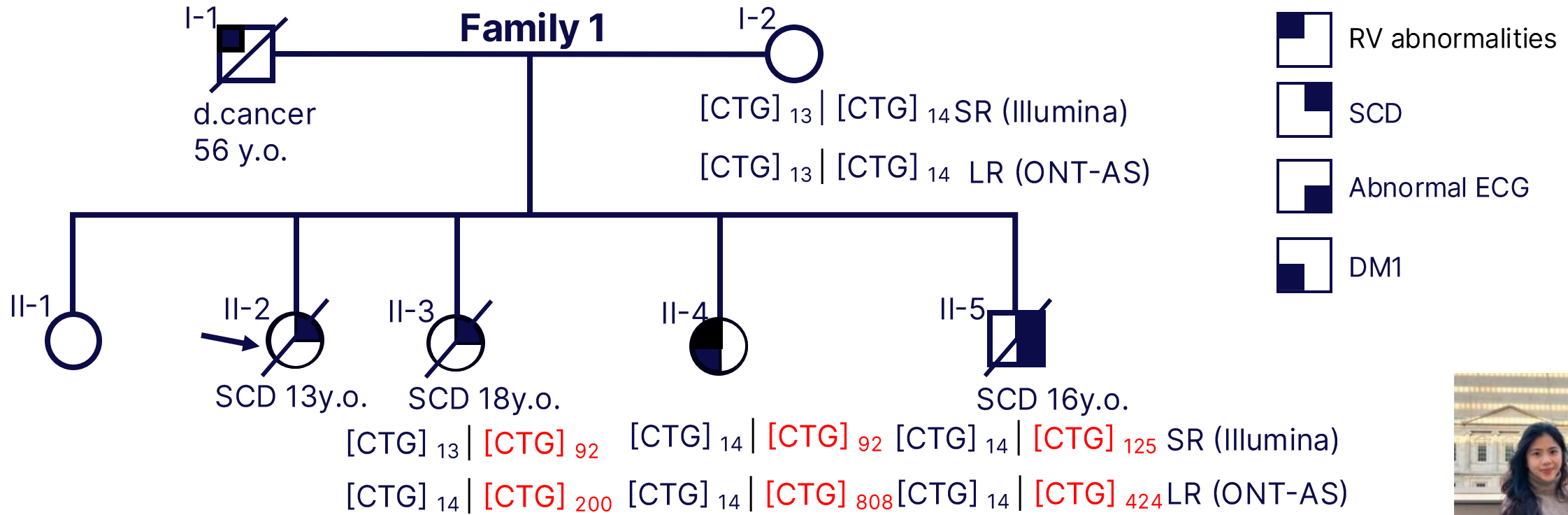
Myotonic Dystrophy 1 Clinical types

Phenotype	Clinical Features	Repeat Size	Age of Onset
Mild/Adult Onset	• Cataracts • Mild myotonia	50 ~ 100	20 - 70 years
Classical	• Muscle weakness • Myotonia • Cataracts • Cardiac arrhythmia	~100~1000	10 - 30 years
Congenital	• Infantile hypotonia • Respiratory deficits • Intellectual disability • Classic signs develop later	~700 ->1000	Birth to 10 years

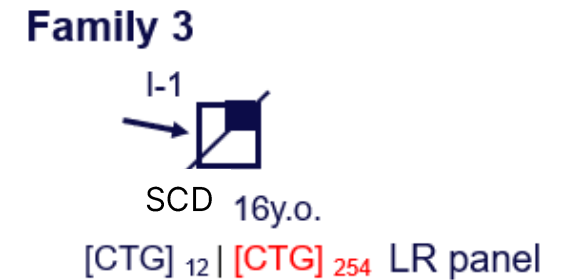
- Cardiac complications second most common cause of death in DM1 (after respiratory causes)
- Among cardiovascular causes of death in DM1 patients 43% = sudden cardiac death

Mechanism of DMPK repeat expansion





Prof Richard Bagnall

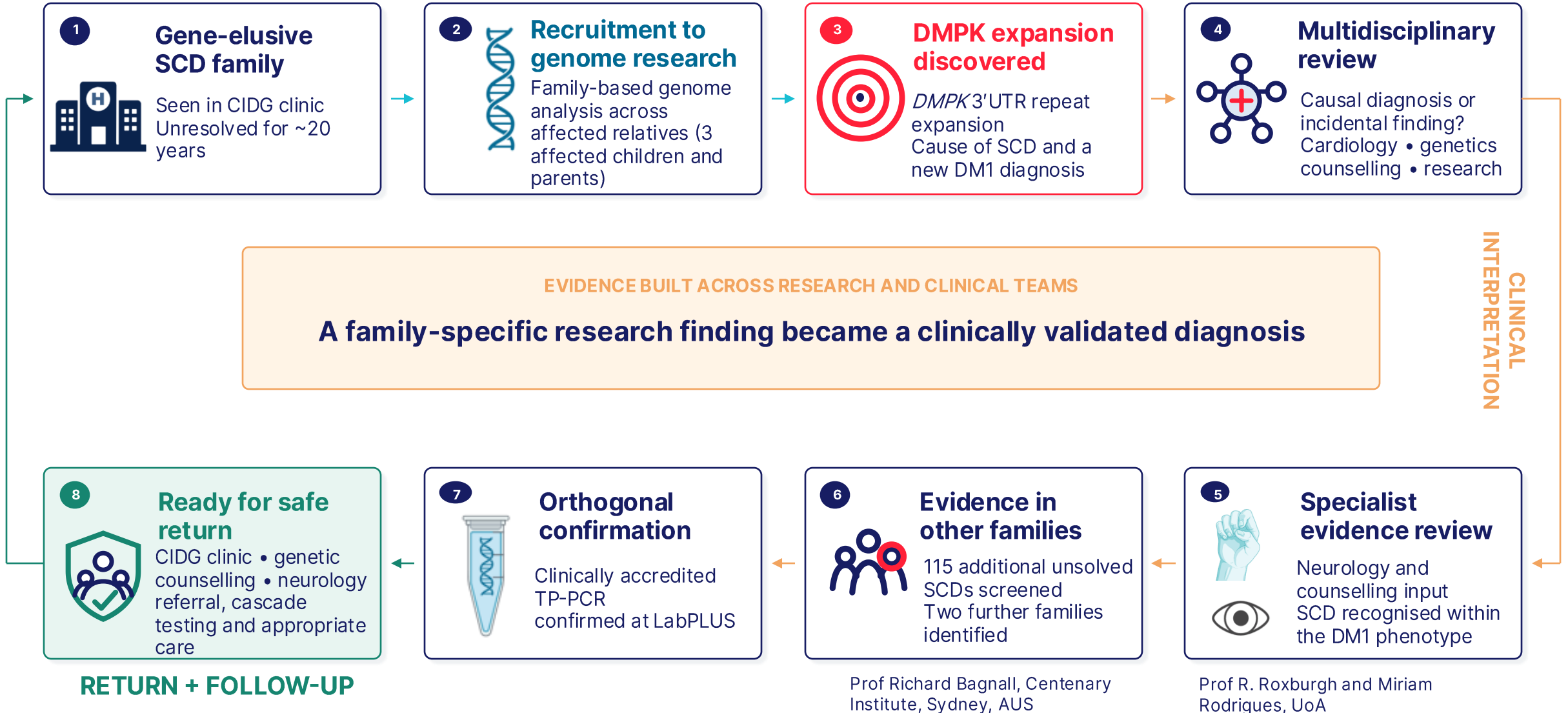


Conclusions

- We report five SCD in the young from three families, in whom initial genetic testing was uninformative
- Our study suggests that *DMPK* repeat expansions should be considered as a potential cause of unexplained SCD in the young
- The *DMPK* repeat region is not typically included in cardiac or SCD gene panels and is challenging to size using short-read sequencing
- Given the age-related penetrance of DM1, young individuals with pathogenic *DMPK* repeat expansions may lack overt clinical features but remain at risk for SCD
- It is unclear whether *DMPK* repeat length alone is predictive of sudden death risk, or whether repeat methylation status, repeat interruptions, or other genetic variants influence risk (potential role of the *MYL3* variant in family is uncertain)

From a gene-elusive SCD family to a clinical diagnosis

Clinic → genome research → evidence building → accredited confirmation → safe return



Genome sequencing is a long-term clinical and family resource

Value comes from the genome, the family, the team and the ability to revisit evidence over time



CHOICE & KAITIAKITANGA

Consent is an ongoing process

- Offer clear choices about participation, findings returned, and sample management.
- Be transparent: sequencing may not identify the cause now, or for several years.
- Uphold Te Tiriti obligations to Māori and extend manaakitanga through Pacific engagement.

**CLEAR CHOICES
REALISTIC EXPECTATIONS**



TEAM-BASED CARE

A team, not just a test

- Complex findings require joint clinical and research review before return.
- A research genetic counsellor enables recontact and careful return of evolving results.

**COMPLEX TEST
COMPLEX RETURN**



EVIDENCE GAINED

1/19 immediately returnable result

- Most require further ACMG evidence before clinical return.

**FROM CANDIDATE TO
CLINICAL EVIDENCE**



ENDURING VALUE

Answers can emerge over time

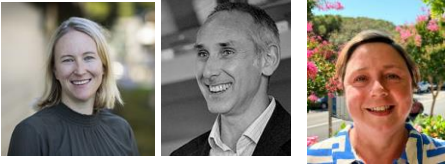
- Unresolved genomes remain a reusable diagnostic resource as knowledge develops.

**REANALYSIS
FUTURE VALUE**

Genome sequencing creates enduring opportunities for diagnosis, even when answers are not immediate.

The University of Auckland
Dr Polona Le Quesne Stabej (Principal Investigator)
Dr Nikki Earle (Principal Investigator)
Dr Zoe Ward, bioinformatician

Prof Cris Print
 Dr Simone Watkins



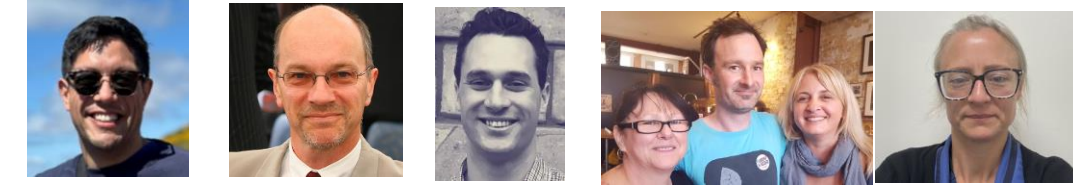
Genetic Health Service NZ
Steph Burcher, genetic counsellor
Dr Ian Hayes, clinical geneticist
 Romy Kerr, Genetic Insight



Pūnaha Io (Neurogenetic registry)

Prof Richard Roxburgh
Miriam Rodrigues

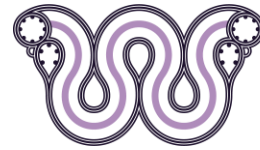
Precision Medicine Initiative, The University of Auckland



Dr Martin Stiles, Dr Andrew Martin, Dr Josh Agnew, Prof Jon Skinner, Dr Manar Khashram, Rachael Stiles, Tom Donoghue, Sarah Pilkington
 Jackie Crawford, Louise and Mary Neil

Māori data sovereignty and Rōpu Kaitiaki Lead

Dr Karaitiana Taiuru, Ngāi Tahu, Ngāti Kahungunu, Ngāti Toa



PŪTAHI MANAWA

HEALTHY HEARTS FOR AOTEAROA NEW ZEALAND

Pacific engagement lead

Terisa Vula



University of Otago
Prof Stephen Robertson
Dr Ben Halliday
Prof Martin Kennedy
A/Prof Anna Pilbrow
Dr Allamanda Faatoese



Students

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Auroiana Glenda Etelei,
 University of Technology Sydney
 Jolene Mok, BBioMedSci
 honours, University of Auckland

Centenary Institute, Sydney

A/Prof Richard Bagnall

Garvan Institute, Sydney

A/Prof Jodie Ingles lab

Victor Chang Cardiac Research Institute

Prof Jamie Vandenberg

Monash University

Fabrice Jaffré



University of Otago
Functional Work

Prof Pete Jones
 Dr Megan Leask



Rachel Sanders, Anna Pilbrow, Judy Heslop & Alison Weaver

Diagnostic laboratories

LabPLUS (Mark Greenslade, Saraya Hogan, Neha Kumar)

Canterbury Health Laboratories, Dr Kylie Drake

Technologies:

Liam Williamson, Jack Rolfe



The Liggins Institute
Hui Hui Phua, senior technologist