Cerebral Palsy

What it is, what causes it, and why we're now looking at genes

Dr Gina O'Grady
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Cerebral Palsy Society Webinar

Te Whatu Ora
Health New Zealand

Starship
Child Health

What is cerebral palsy?

The clinical definition

A group of early-onset lifelong conditions, characterized by limitations in activity, due to impaired movement and posture, attributed to **non-degenerative disturbances** in the **developing fetal or infant brain**.

— International Working Group, 2006

It's an umbrella term

CP is a description of what we see - not a single disease with a single cause.

The brain event is one-off

The underlying injury or difference doesn't get worse over time, though how it shows up can change.

It happens during development

Before, during, or in the first years after birth - while the brain is still being built.

No two people with CP are the same

CP is classified by the type of movement difficulty and which parts of the body are affected.

Spastic

~85%

Stiff, tight muscles. The most common form.

Dyskinetic

~7%

Involuntary movements — writhing or jerking.

Ataxic

~5%

Shaky, unsteady movements; balance affected.

And by which parts of the body are affected:

Hemiplegia

One side of the body

Diplegia

Mainly the legs

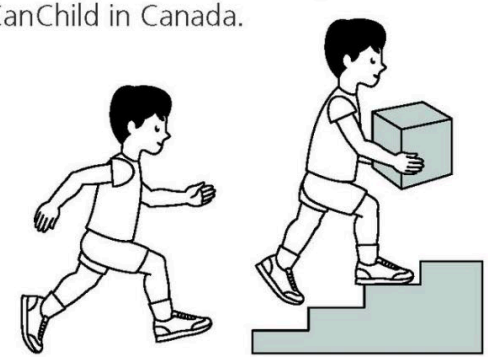
Quadriplegia

All four limbs, trunk, face

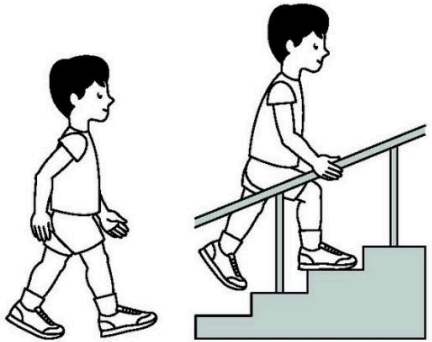
Severity also varies — from needing no mobility support, to full-time care. (GMFCS Levels I–V)

GROSS MOTOR SKILLS

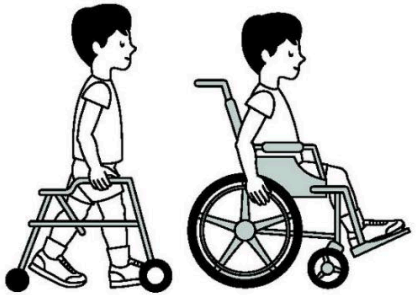
The gross motor skills (e.g. sitting and walking) of children and young people with cerebral palsy can be categorised into 5 different levels using a tool called the Gross Motor Function Classification System (GMFCS) developed by CanChild in Canada.



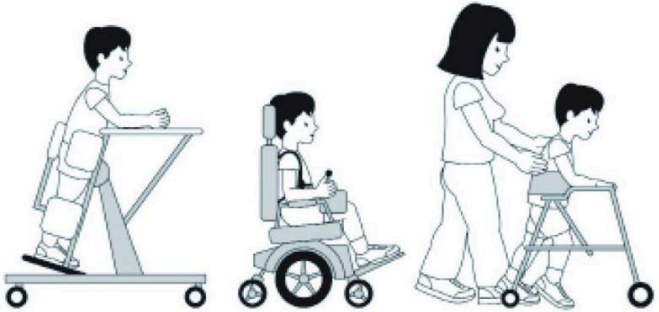
GMFCS Level I



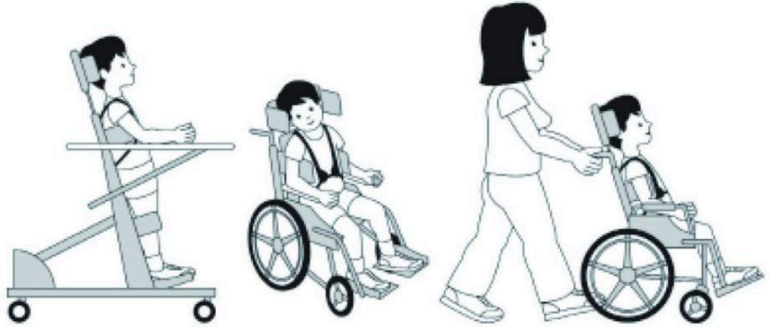
GMFCS Level II



GMFCS Level III



GMFCS Level IV



GMFCS Level V

How common is it?

1 in ~500
live births

Cerebral palsy is the most common physical disability of childhood

100-150 new diagnoses per year

Reducing from mid 90s

~10,000+

New Zealanders living with CP today

Sources: Australian Cerebral Palsy Register; Smithers-Sheedy et al., MJA 2024. NZ figure: estimate, Cerebral Palsy Society NZ.

The story we've told for 160 years

William Little (1862): children with these movement problems were affected by something that happened during a difficult birth — lack of oxygen, trauma, prematurity.

The conventional view of CP's causes:

Lack of oxygen at birth

Birth asphyxia — the baby gets into trouble during labour.

Prematurity

Brain damage in very preterm babies.

Birth trauma / infection

Physical injury or infection around delivery.

And for a long time, this is where the investigation stopped.

What changed the story

Large population studies, 1980s–2000s:

Only around 10% of CP cases had clearly documented problems during labour and delivery

And here's what really made researchers think again:

1. Rates of CP were falling even as maternity care improved but many cases remained that couldn't be explained by birth events.
2. Many babies with CP had brain scans showing abnormalities that clearly predated labour — brain malformations, strokes that happened in utero.
3. Some families had more than one child with CP — suggesting a heritable component, not just a difficult delivery.

The fuller picture of causes

CP can arise from disruptions at any point while the brain is developing and often more than one factor contributes.

Prenatal *during pregnancy*	Perinatal *around birth*	Neonatal *first weeks of life*	Postnatal *first 2 years*
• Brain malformations • Strokes in utero • Infections (CMV, rubella) • Placental issues • Genetic causes	• Lack of oxygen • Birth trauma • Infections • Extreme prematurity • Genetic causes	• Brain bleeds • Severe jaundice • Infections (meningitis) • Difficulty breathing • Genetic causes	• Accidents • Near-drowning • Stroke • Severe infections • Genetic causes

The majority of CP cases now trace back to something that happened before birth

Why genes have entered the picture

THE PROBLEM

In many children diagnosed with CP, no clear cause is ever found.

A healthy pregnancy, an uneventful birth — and yet the child has CP. We call this cryptogenic CP — 'hidden cause.'

WHAT CHANGED

We can now analyse the human genetic code.

Genetic testing with gene panels and whole exome sequencing has become increasingly availalbe.

When we now apply genetic sequencing to children with CP, we find a genetic cause in up to 1 in 4

What does a “genetic cause” actually mean?

Three main ways genes contribute to CP

1

A single-gene change

“Monogenic” causes

A small spelling error in ONE important gene is enough to disrupt brain development. Most are brand new (de novo) changes not inherited from either parent.

Examples: CTNNB1, TUBA1A, KANK1

2

Missing or extra chunks of DNA

Copy number variants (CNVs)

A whole section of DNA is duplicated or deleted, affecting many genes at once. Often seen in children whose CP comes alongside other developmental differences.

Detected by chromosomal microarray

3

Genetic vulnerability

Predisposition, not direct cause

Genes that don't cause CP by themselves but make a baby's brain more vulnerable to other stresses - prematurity, infection, oxygen shortage. A 'double-hit.'

Clotting genes, inflammation genes, etc.

A genetic finding often explains WHY a baby was vulnerable - it doesn't always replace the other factors, it sits alongside them.

Who might be more likely to have a genetic cause?

Factors thought to increase the likelihood of a genetic cause

- No identifiable risk factors at delivery
- Normal MRI
- A very small head (microcephaly)
- A malformation of the brain on MRI
- “Dysmorphic” facial features
- Intellectual disability
- Low muscle tone

Factors which decrease the likelihood of a genetic cause

- Hemiplegic CP
- Prematurity (23-36 weeks)
- Normal intellect
- MRI findings compatible with clinical story

Tantsis, Esther M., et al. "Genetic testing in cerebral palsy with clinical and neuroimaging variables." *Developmental Medicine & Child Neurology* 67.11 (2025): 1443-1452.

Why a genetic diagnosis matters

An answer

For many families, just knowing why is profoundly important. The search for an explanation can end.

Recurrence risk

Genetic diagnosis offers a more precise risk of recurrence, important for family planning. But most monogenic CP is not inherited so future children are often at no increased risk.

Better care

Some genetic diagnoses come with specific recommendations: heart screening, vision checks, monitoring for seizures.

Personalised treatment

For a small but growing number of genes, there are already targeted therapies — and more are in trials.

For many adults and older children living with CP, these questions have never been answered. Genetic testing can still offer that, decades later.

What a genetic finding does NOT change

The diagnosis of CP stays the same

Finding a gene does not mean the child “doesn't really have CP.” The CP label is about how someone lives, moves, and needs support. That doesn't change.

It doesn't rewrite the past

A genetic diagnosis isn't blame. It doesn't mean something was missed at birth, or that clinicians did anything wrong.

It doesn't mean the condition is progressive

A genetic cause does not turn CP into a worsening disease. The non-progressive nature of CP is about how the condition behaves not its cause.

Supports and services are unchanged

Funding, therapy, equipment, and community support are tied to the CP diagnosis which remains. None of that goes away.

Where we go from here

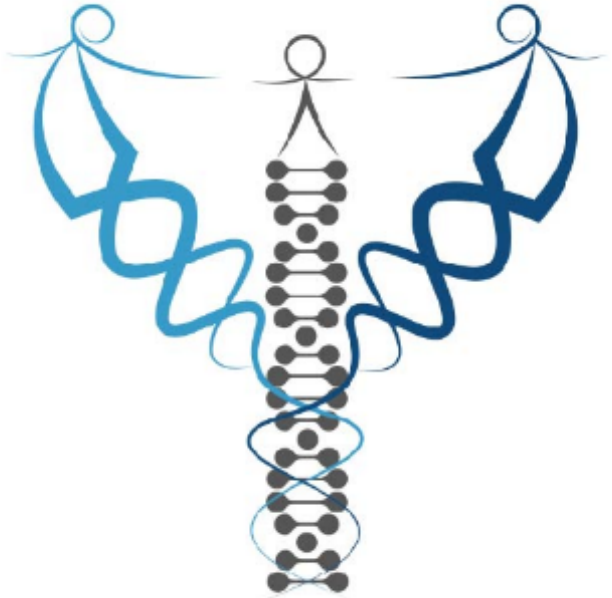
Cerebral palsy is an umbrella term, not a single disease and for a meaningful proportion of people given that diagnosis, we can now identify a specific genetic cause that had never been looked for before.

Cerebral Palsy Project

A study offering genetic testing to New Zealanders with undiagnosed cerebral palsy

Handing over to: Professor Justin O'Sullivan

Newborn Genomics Programme



Te Ira ō te Arai | DNA beyond the veil

A community working to individualize diagnosis, predict outcomes, inform patient treatment and management

Dines Family Trust

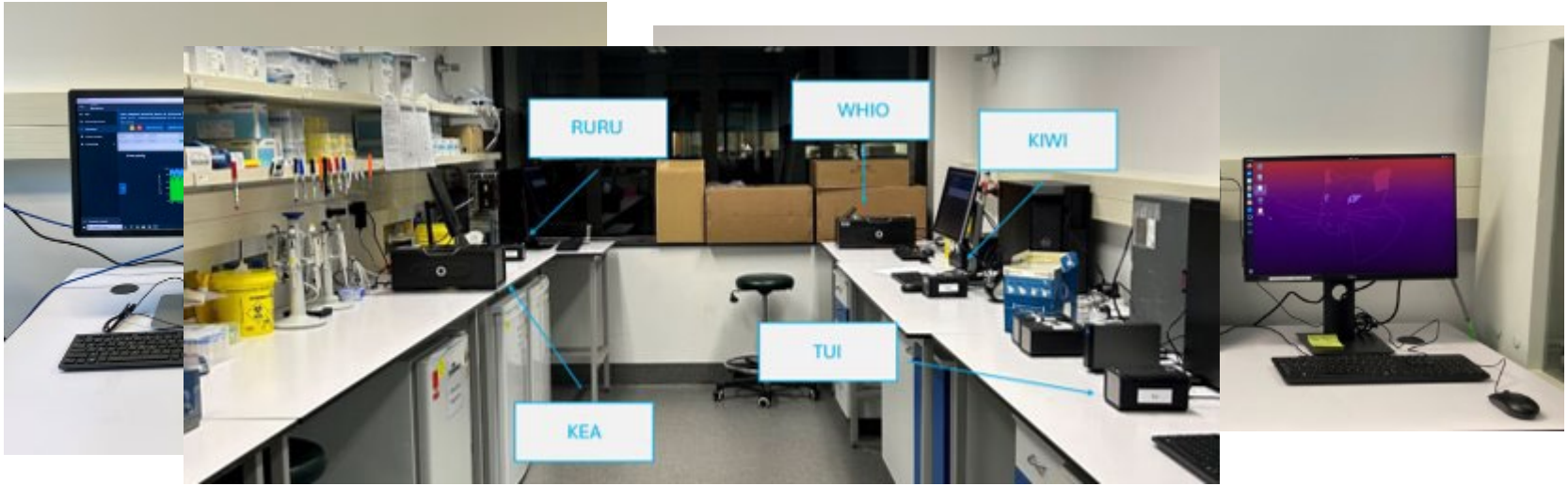
Kelliher Charitable Trust

Peter Gibson via The Tautoko Trust

Neurological Foundation

- Ethics: Study title: Cerebral Palsy project.
- Approval from Health and Disability Ethics Committee (2025 FULL 24103)
- Locality approval: underway

We have established powerful sequencing facilities in New Zealand



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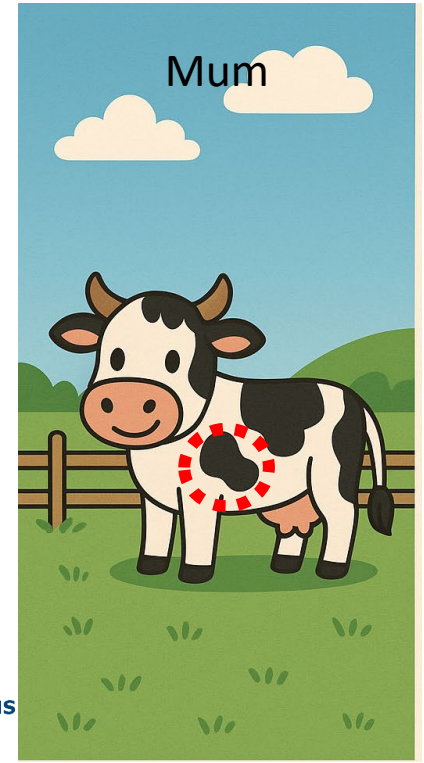
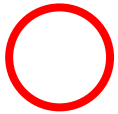
We use these facilities to play spot the difference between DNA sequences – to identify changes that link to disease





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We have demonstrated that these systems help diagnoses in acute and non-acute care

npj | genomic medicine

Article

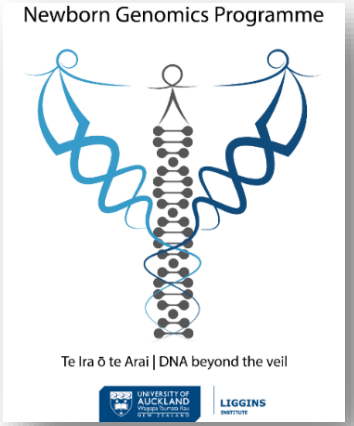
Published in partnership with CEGMR, King Abdulaziz University

https://doi.org/10.1038/s41525-024-00445-5

Benchmarking nanopore sequencing and rapid genomics feasibility: validation at a quaternary hospital in New Zealand

Check for updates

Denis M. Nyaga[1,8], Peter Tsai[1,2,8], Clare Gebbie[1,8], Hui Hui Phua[1,8], Patrick Yap[3,8], Polona Le Quesne Stabej[1,2], Sophie Farrow[1], Jing Rong[1], Gergely Toldi[1,4], Eric Thorstensen[1], Zornitza Stark[5,6], Sebastian Lunke[5,6], Kimberley Gamet[3], Jodi Van Dyk[1], Mark Greenslade[7] & Justin M. O'Sullivan[1] ✉



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Newborn Genomics Programme

Te Ira ō te Arai | DNA beyond the veil

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25 cases analysed

In 18 cases a genetic cause for the patient's condition was found – 72% diagnostic rate

Te Whatu Ora
Health New Zealand

In this project we will sequence DNA from families in an attempt to identify genetic causes of Cerebral Palsy

The Trio

Mother
Sample M

Father
Sample F

Child
Sample C

Why the Trio Helps

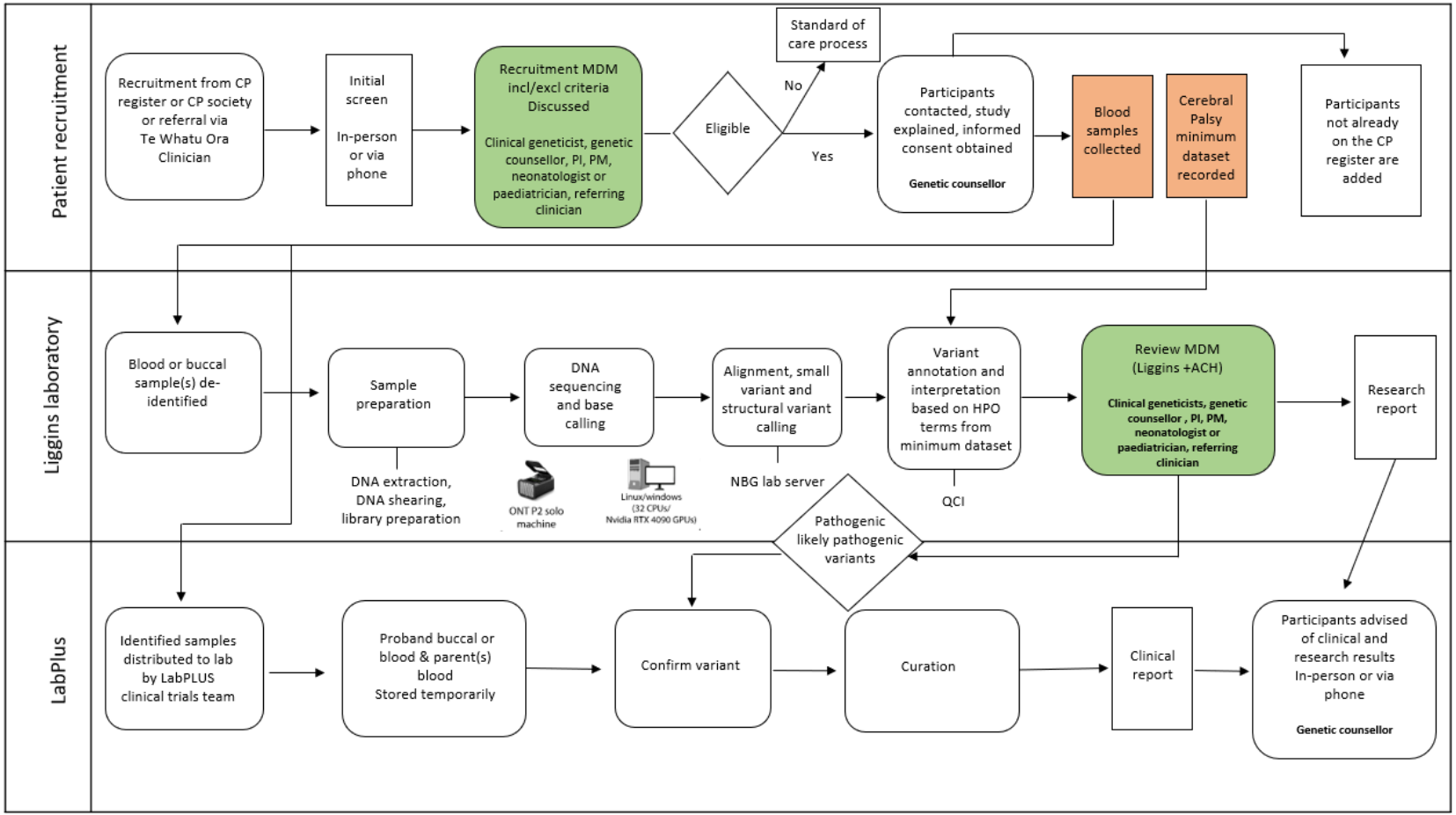
Disentangles ancestry from inheritance
Shared differences from the reference that are present in parents are likely ancestral (population) variants.

Improves variant interpretation
Focus clinical interpretation on variants that are de novo or not explained by parental genotypes.

Reduces false positives
Helps avoid misclassifying common ancestral differences as disease causing.

Key Takeaway: A trio provides the inheritance context needed to separate true variants from ancestral DNA differences relative to the reference genome, leading to more accurate and confident conclusions.

How it will work



What do we think the outcome will be?

We predict that **>27%** of patients will receive an accurate genetic diagnosis through the sequencing programme

>8% of patients may have a treatment or therapeutic change because of diagnosis

Together we can:

1. Demonstrate the use of genetic diagnosis to help improve the quality of life of the children and families who live with Cerebral Palsy

2. Improve the analysis of the genetic variation and treatment responses for CP

3. Help the sustainable development of the NZ Cerebral Palsy Register as a conduit for patients to connect to international trials

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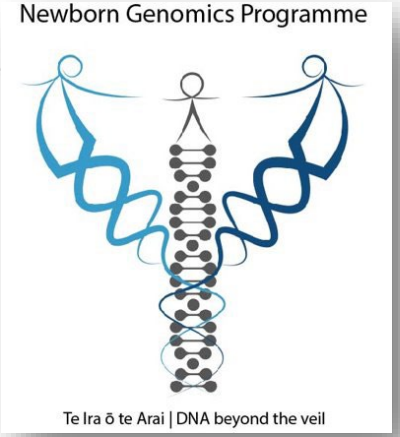
Stage 1: sequence 50 individuals living with CP

Launch – June 2026

Contact: cpgenes@auckland.ac.nz

Cerebral Palsy project



Principal Investigator

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Project manager

- Jodi Van Dyk (Project manager, Liggins Institute, University of Auckland)

Technical team

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Collaborators

- Rare Disorders New Zealand
- New Zealand Cerebral Palsy Register
- Cerebral Palsy Society of New Zealand

Funder:

Kelliher Trust

Neurological Foundation

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Trial steering group

- Professor Stuart Dalziel, Paediatric Emergency Medicine Specialist, Waipapa Taumata Rau | University of Auckland, Cure Kids Chair of Child Health Research, Cure Kids
- Laura Lane – Lived experience representative
- Amy Hogan – Lived experience representative
- Professor Andrew Shelling, Professor of Obstetrics, gynaecological and Reproductive Science, Waipapa Taumata Rau | University of Auckland
- Chris Higgins, Chief Executive Rare Disorders New Zealand
- Haunui Royal, Kaiarahi, Liggins Institute, Waipapa Taumata Rau | University of Auckland
- Professor Justin M. O'Sullivan, Professor of Genetics and Systems Biology, Director, Liggins Institute, Waipapa Taumata Rau | University of Auckland
- Jodi Van Dyk, Project Manager, Liggins institute, Waipapa Taumata Rau | University of Auckland

A FAMILY'S DIAGNOSTIC JOURNEY

Oscar's Genetic Journey

Following the process of elimination — from a cerebral palsy diagnosis to a candidate gene.

Presented by Merryn Straker

May 2026

How we got here

Years of investigation — a process of elimination

Early years — **Cerebral palsy diagnosed**
Spastic-ataxic CP (GMFCS 2), with strabismus and dysarthria.

~2009 · age 2 — **First genetics clinic — while Merryn was pregnant**
Clinic had only one family on record with two children with CP. Recurrence risk estimated at 10% or lower.

2010s — **Investigations — all unremarkable**
Array of tests including a molecular karyotype — all normal. Chromosomal causes ruled out.

2013 · age 8 — **Enrolled in international genetics study**
Sample sent to the Kruer Lab in Phoenix, USA — part of a worldwide research project investigating the genetic causes of CP.

2019 — **Repeat MRI: no structural cause**
Brain MRI showed myelination now normal. Conclusion: "No cause found for symptoms."

2020 – 21 · age 13 — **Follow-up genetics — WES declined locally**
Previous tests had all been normal; whole exome sequencing was not pursued. Next genetics review scheduled for age 25.

Aug 2021 — **Kruer Lab results returned**
Whole exome sequencing identified a candidate variant in the KCNE5 gene.

The Kruer Lab study

An international research effort to find genetic causes of cerebral palsy — published in Nature Genetics.

250
children with CP and their parents

20,000+
genes screened (whole exome sequencing)

3
countries — USA, China, Australia

What they found

12%

De novo (spontaneous) variants
Brand-new genetic changes not inherited from either parent — found across 75 different genes, mostly involved in brain development and brain wiring.

2%

Inherited recessive variants
Variants in genes already known to cause Hereditary Spastic Paraplegia, where both parents carried the same recessive change.

30%

Overlap with intellectual disability
Many genes implicated in CP also appear in conditions that often co-occur — including epilepsies (10%) and autism (5%).

4 families

Treatment changes from research
Genetic findings led directly to changes in clinical care and access to personalised treatments for four children in the study.

Oscar's result: a variant in KCNE5

A compelling clue — but not yet a definitive diagnosis.

THE VARIANT

KCNE5 `c.G55T (p.E19*)`

Hemizygous, X-linked · Detected via whole exome sequencing

Variant of Unknown Significance

What does it mean?

KCNE5 codes for a potassium-channel protein. It's a **compelling candidate** for Oscar's symptoms, but it has **never before been linked to a human condition**.

That uncertainty is why it's classed as a *Variant of Unknown Significance*. For Oscar, it's the strongest clue we have — but research has to confirm whether this gene change is the cause.

What it changed for Oscar

- KCNE5 is associated with cardiac arrhythmia (long QT and possible cardiomyopathy).
- Dr Patel reframed Oscar's diagnosis to "probable KCNE5 disorder — ataxic CP with predisposition to arrhythmia."
- Oscar was referred to Cardiology — ECG and echocardiogram completed in 2023; results clear so far.
- Active monitoring continues, alongside ongoing research into KCNE5.

Not a final answer — but a meaningful clue, and a reminder that the diagnostic story is still being written.

Q & A

Thank you for attending

Email: cpgenes@auckland.ac.nz