

# Integrating genomics into the diagnosis and personalized care of individuals with Intellectual Disability

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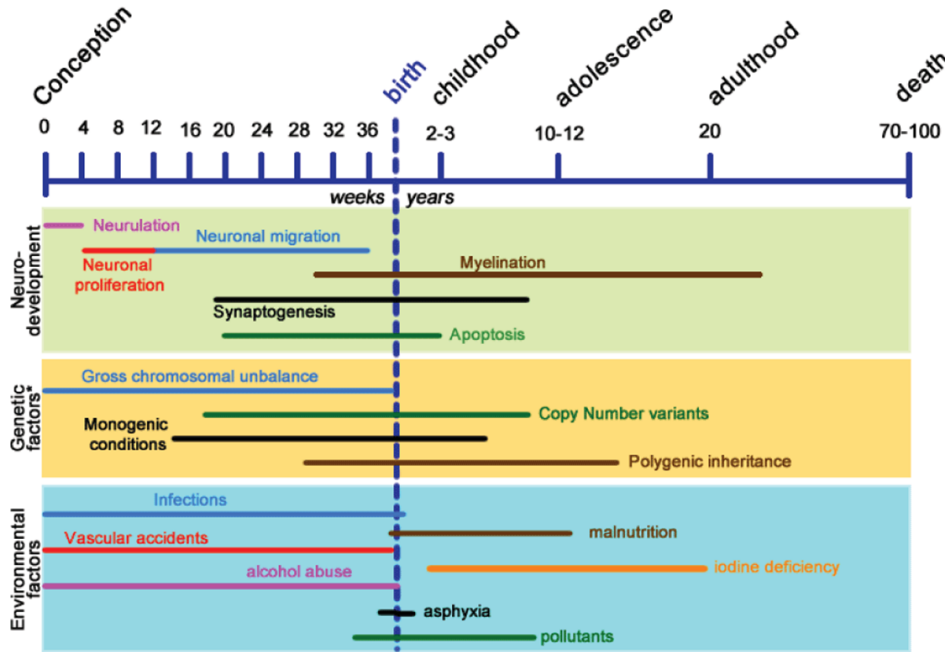


# Talk Overview

1. Why consider genetics for intellectual disability
2. Genetic testing 101
  - a practical guide to the key genetic tests for my patient
  - what do I need to cover in pretest counselling
  - how do I read the reports
3. Where can I go for resources for my patient with a genetic condition



# Why think about genetics for intellectual disability?



ID caused by a variety of environmental and genetic causes, often combined with each other.

Chiurazzi P and Pirozzi F. Advances in understanding – genetic basis of intellectual disability  
F1000 Research 2016, 5



# Genetics can improve holistic care

- **Management:** May provide information about expected **natural history** and avoid the need for other investigations/procedures. For some disorders, **condition-specific management and surveillance guidelines** are available.
- **Genetic counselling:** A diagnosis also provides information about **chance of recurrence** in future pregnancy and, where necessary, the options of prenatal diagnosis and pre-implantation genetic testing.
- **Support:** May help patients and families access **condition-specific family support**. Can help alleviate guilt, provide an explanation.
- ? Targeted therapies



treatments

therapies

support

information

treatments

therapies

support

information

treatments

therapies

support

information

# But...genetics can be



confusing a different language worrying

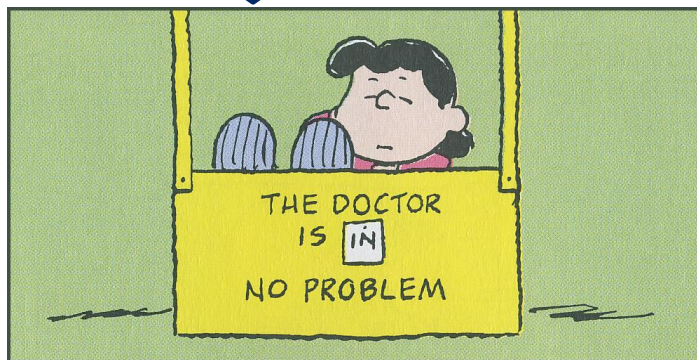
HNE Kids Health

# ...and genetic test reports can be disappointing

Your child has  
Rhubarb Custard  
Disease...  
I don't know anything  
about RCD...  
There's no support  
group for RCD...  
There's no treatment  
for RCD...  
There are only 10  
children in the world  
with RCD

The genetic test  
shows ... your child  
**MIGHT** have RCD

The genetic  
test did not find  
anything



But when it works..... it can be  
magic



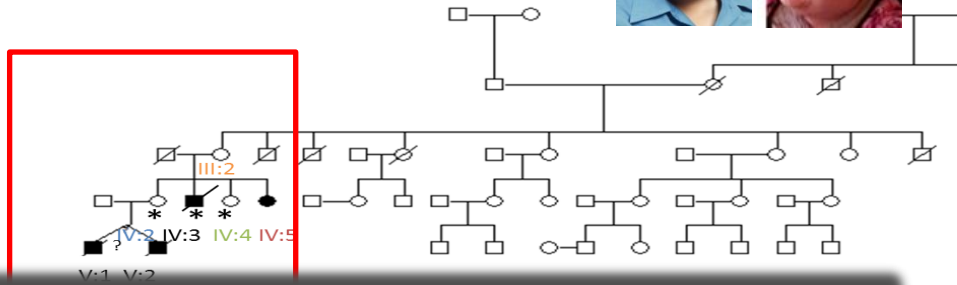


# One family's story

1950s



1970-90s



10th December, 1976

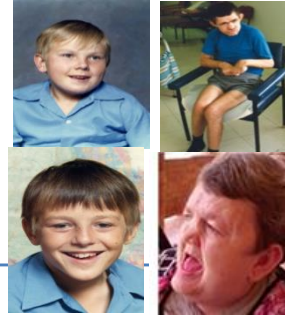
I first visited Mrs. at home, in May 1976, to do an investigation of her family history, following up on Dr. Turner's research on Renpenning's Syndrome - and it's X-linked inheritance patterns. This family were followed up because there were two male children in the family who were retarded,

# X linked CLCN4 related condition

1950s



1970-90s



2000s



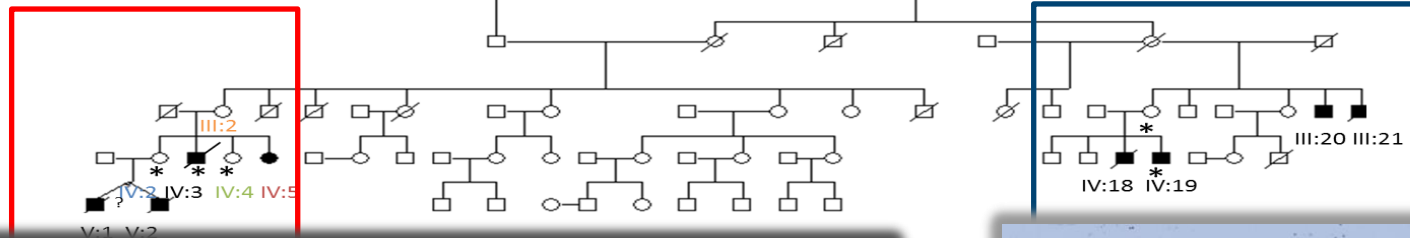
2016

## ORIGINAL ARTICLE

### X-exome sequencing of 405 unresolved families with novel intellectual disability genes

H Hu<sup>1,41</sup>, SA Haas<sup>3,41</sup>, J Chelly<sup>3,4</sup>, H Van Esch<sup>3</sup>, M Raynaud<sup>3,7,8</sup>, APM de Brouwer<sup>9</sup>, S Weinert<sup>10</sup>, F Laumonier<sup>2,7</sup>, T Zemojtel<sup>1</sup>, M Love<sup>1</sup>, H Richard<sup>1</sup>, A-K Emde<sup>1</sup>, M Bieneke<sup>1</sup>, C Jensen<sup>1</sup>, M Han<sup>1</sup>, M Feldkamp<sup>10</sup>, W Wissink-Lindhout<sup>1</sup>, N Lebrun<sup>1,11</sup>, L Castelneau<sup>1,12</sup>, J Rucil<sup>1,13</sup>, R Montjean<sup>1,14</sup>, O D M Shaw<sup>15,17</sup>, MA Corbett<sup>16,17</sup>, A Gardnau<sup>16,17</sup>, S Willis-Owen<sup>16,18</sup>, C Tan<sup>19</sup>, KL Friend<sup>1,7</sup>, S Belet<sup>1</sup>, M Jimenez-Pocquet<sup>1</sup>, M-P Molard<sup>2,8</sup>, N Ronce<sup>3,7,8</sup>, R Sun<sup>7</sup>, S O'Keeffe<sup>2,8</sup>, R Chennu<sup>2</sup>, A van Boven<sup>1</sup>, L Christie<sup>20</sup>, J Boyle<sup>20</sup>, E Haan<sup>16,19</sup>, J Nelson<sup>21</sup>, G Turner<sup>20</sup>, G Baynam<sup>21,22,23,24</sup>, G Gillesen-Kaesl<sup>1</sup>, B Budny<sup>25</sup>, M Badura-Stronka<sup>26</sup>, A Latos-Bieleiska<sup>25</sup>, LB Ousager<sup>30</sup>, P Wieacker<sup>31</sup>, G Rodriguez<sup>32</sup>, A Dufke<sup>33</sup>, M Cohen<sup>34</sup>, L Van Maldergem<sup>35</sup>, C Vincent-Delorme<sup>1,7</sup>, B Echenne<sup>36</sup>, B Simon-Bouy<sup>37</sup>, K Devriendt<sup>38</sup>, R Ullmann<sup>1,42</sup>, M Vingron<sup>3</sup>, K Wrogemann<sup>1,40</sup>, TF Wienker<sup>1</sup>, A Tzschach<sup>1</sup>, H van W Chen<sup>1,10</sup>, H-H Ropers<sup>1</sup> and VM Kalscheuer<sup>1</sup>

X-linked intellectual disability (XLID) is a clinically and genetically heterogeneous disorder. During 1990s, various X-linked genes have been identified. Yet, a large number of families remained



10th December, 1976

I first visited Mrs. [redacted] at home, in May 1976, to do an investigation of her family history, following up on Dr. Turner's research on Renpenning's Syndrome - and it's X-linked inheritance patterns. This family were followed up because there were two male children in the family who were retarded,

20th-2-1980

Dear Doctor,

While reading the subnormal children's welfare news, I came across an article written by you. Named 'X-linked mental retardation'. I find this article is connected to the mental retardations in my family.

# Family participating in ongoing studies to better understand this condition

OPEN

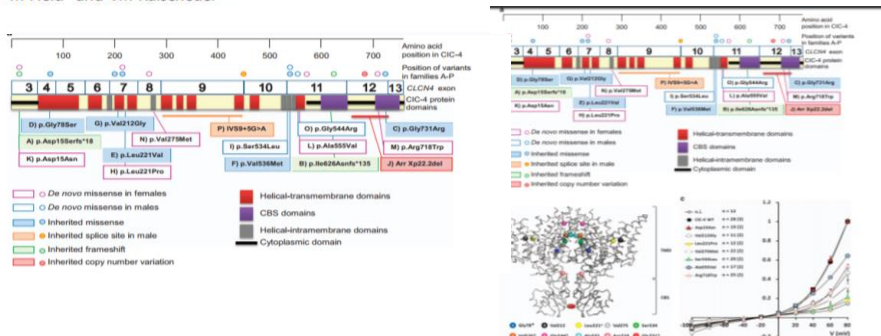
Molecular Psychiatry (2016) 00, 1–9

www.nature.com/mp

## ORIGINAL ARTICLE

*De novo* and inherited mutations in the X-linked gene *CLCN4* are associated with syndromic intellectual disability and behavior and seizure disorders in males and females

EE Palmer<sup>1,2</sup>, T Stuhlmann<sup>3,4</sup>, S Weinert<sup>3,4</sup>, E Haan<sup>5,6</sup>, H Van Esch<sup>7</sup>, M Holvoet<sup>7</sup>, J Boyle<sup>1</sup>, M Leffler<sup>1</sup>, M Raynaud<sup>8,9,10</sup>, C Moraine<sup>8,9,10</sup>, H van Bokhoven<sup>11</sup>, T Kleefstra<sup>11</sup>, K Kahrizi<sup>12</sup>, H Najmabadi<sup>12</sup>, H-H Ropers<sup>13</sup>, MR Delgado<sup>14,15</sup>, D Sirsi<sup>14</sup>, S Golla<sup>14</sup>, A Sommer<sup>16</sup>, MP Pietryga<sup>16</sup>, WK Chung<sup>17</sup>, J Wynn<sup>17</sup>, L Rohena<sup>18</sup>, E Bernardo<sup>18</sup>, D Hamlin<sup>18</sup>, BM Faux<sup>18</sup>, DK Grange<sup>19</sup>, L Manwaring<sup>19</sup>, J Tolmie<sup>20</sup>, S Joss<sup>20</sup>, DDD Study<sup>21</sup>, JM Cobben<sup>22</sup>, FAM Duijkers<sup>23</sup>, JM Goehring<sup>24</sup>, TD Challman<sup>24</sup>, F Hennig<sup>25</sup>, U Fischer<sup>25</sup>, A Grimme<sup>25</sup>, V Suckow<sup>25</sup>, L Musante<sup>13</sup>, J Nicholl<sup>26</sup>, M Shaw<sup>5,27</sup>, SP Lodh<sup>28</sup>, Z Niu<sup>28</sup>, JA Rosenfeld<sup>28</sup>, P Stankiewicz<sup>28</sup>, TJ Jentsch<sup>3,4</sup>, J Gecz<sup>5,27</sup>, M Field<sup>1</sup> and VM Kalscheuer<sup>13,25</sup>



**Table 1. Summary of phenotypic characteristics of male hemizygotes and female heterozygotes with *CLCN4* variants**

	Affected males (n=28) Proportion of total cohort (54%)	Heterozygous females with <i>de novo</i> variants (n=5) Proportion of total cohort (10%)	Heterozygous females with inherited variants (n=18) Proportion of total cohort (34%)
ID	26/28 (100%)	5/5 (100%)	21/18 (117%)
Borderline	1/29 (4%)	1/5 (20%)	0/2 (0%)
Mild	7/29 (24%)	0/5 (0%)	1/2 (50%) of those with ID
Moderate	9/29 (31%)	3/5 (60%)	9/2 (90%)
Severe/profound	12/29 (41%)	2/5 (40%)	1/2 (50%) of those with ID
Seizure disorder	15/29 (52%)	2/5 (40%)	1/18 (6%)
Well controlled	7/15 (47% of those with seizures)	1/2 (50% of those with seizures)	0/1 (0%)
Intractable seizures	8/15 (53% of those with seizures)	1/2 (50% of those with seizures)	1/1 (100% of those with seizures)
Behavioral issues/mental health disorders	19/29 (66%)	3/5 (60%)	3/18 (17%)
Infantile hypotonia	8/29 (27%)	3/5 (60%)	0/18 (0%)
Progressive neurological symptoms	6/29 (21%)	3/5 (60%)	1/18 (6%)
Cortical atrophy, corpus callosum hypoplasia or white matter hyperintensities on neuroimaging	7/11 (64% of tested)	2/4 (50% of tested)	1/1 (100% of tested)

Abbreviation: ID, intellectual disability.

Palmer et al., 2018

# One mother's thoughts on finding “the gene”

“Oh what can I say?....It's the end of a life time of searching for answers”

End Diagnostic Odyssey

“If I was in my twenties, I would have the choice.....I would not have chosen to bring handicapped children into the world.....I'm so happy that other women will have choices.”

Reproductive Choices

Slides courtesy Jackie Boyle, GC GoLD, with permission of the family for photographs to be used for teaching purposes.



# We can use clinical matchmaking to find new diagnoses



# and connect and empower families.



**HUMAN DISEASE GENES**  
WEBSITE SERIES

Genes: [ATN1](#) Home > Parents > Clinical characteristics

**Clinical characteristics**

ATN1-related neurodevelopmental condition is due to very small 'spelling mistakes' in the gene that stop it from working properly. Only 10 children, the oldest being 9 years old, are currently known around the world with this type of ATN1-related condition, and we are still learning more about this condition.

**Features of ATN1-related neurodevelopmental condition can include:**

- Delayed motor (movement) skills:** To date, all individuals with ATN1-related condition have had a diagnosis of 'global developmental delay' which means that they have been slower to gain all their motor milestones, such as the ability to roll, sit, or stand.
- Delayed cognitive (thinking) skills:** All individuals have had a diagnosis of 'global developmental delay' which means that they have been slower to gain all their cognitive milestones, such as the ability to use simple words to communicate.
- Delayed speech and language (communication) skills:** All affected individuals have delays in their speech and language development. Some individuals are able to communicate using different sounds, and one child so far has the ability to use simple words to communicate.
- Gastrointestinal difficulties:** Some individuals have developed epileptic seizures, which typically have been able to be well controlled with medication. Some children have needed to be fed by gastrostomy (G-tube).
- Sensory:** Some individuals have difficulties hearing, seeing, or feeling things. Some individuals have had bladder or urinary tract infections, needing treatment with antibiotics, and some have had differences in the appearance of the base of the skull and part of the spine have been noted on their checks.
- Brain and spine:** Some individuals with ATN1-related condition have had bladder or urinary tract infections, needing treatment with antibiotics, and some have had differences in the appearance of the base of the skull and part of the spine have been noted on their checks.
- Cardiovascular:** Some individuals with ATN1-related condition have had difficulties with their breathing and sleeping patterns, and have needed treatment with antibiotics, and some support of their breathing, for example with oxygen or special breathing support (CPAP).
- Eyes and vision:** Some individuals with ATN1-related condition have had difficulties with their hearing, for example with hearing aids or cochlear implants.
- Hearing and vision:** Some individuals with ATN1-related condition have had difficulties with their hearing, for example with hearing aids or cochlear implants.
- Respiratory and sleep:** Some individuals with ATN1-related condition have had difficulties with their breathing and sleeping patterns, and have needed treatment with antibiotics, and some support of their breathing, for example with oxygen or special breathing support (CPAP).
- Considerable & noticeable features of facial features** may also be present. Some individuals have been described as having 'fish face' or 'fish mouth'.

**ATN1 related disorder support group**

10 Group created on 4 September 2019

**De novo variants disrupting the HX Repeat Motif of ATN1 Cause a Recognizable Non-Progressive Neurocognitive Syndrome**

Who said "North" was "UP"?

# Questions ?



**So now we agree it is important .. Buckle up  
for genetic testing 101 in  
neurodevelopmental disorders!**








A genomic test produces vast amounts of data.

Each person's genome contains millions of genetic differences called **variants**.  
Most of them are harmless.



From the data, teams of scientists and doctors try to identify 1 or 2 variants that may be causing a medical condition.

This is a complex and time-consuming task, and many checks and balances are in place to ensure the test is done correctly.



Genetic variation is the rule, finding the pathogenic variant is hard work!

The cat sat on  
the mac



# A smorgasbord of genomic tests

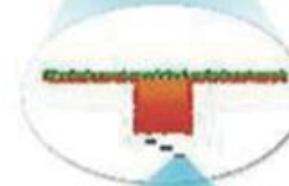


Human genome  
3 000 000 000 bp



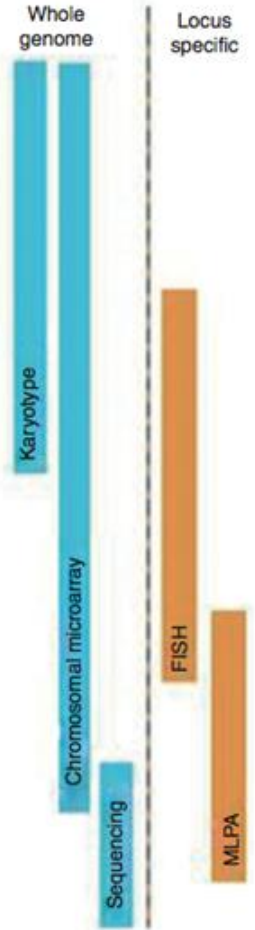
Karyotype

Chromosome  
5 000 000 000–  
250 000 000 bp



Chromosome microarray data

Single gene  
100–15 000 bp



# Your patients will be asking these questions

## Questions to ask your doctor/genetic counsellor

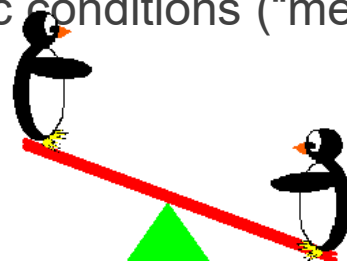
- What is the chance that the genomic test will identify the cause of my/my child's condition?
- How long will it take to get a result?
- Who will give me the result and how?
- Where will my genomic test be done?
- What is the cost to me (if any) of my genomic test?
- *What can this mean for other members of my family if I have this test?*
- What is the chance of this test finding something that is unrelated to my/my child's current health condition?



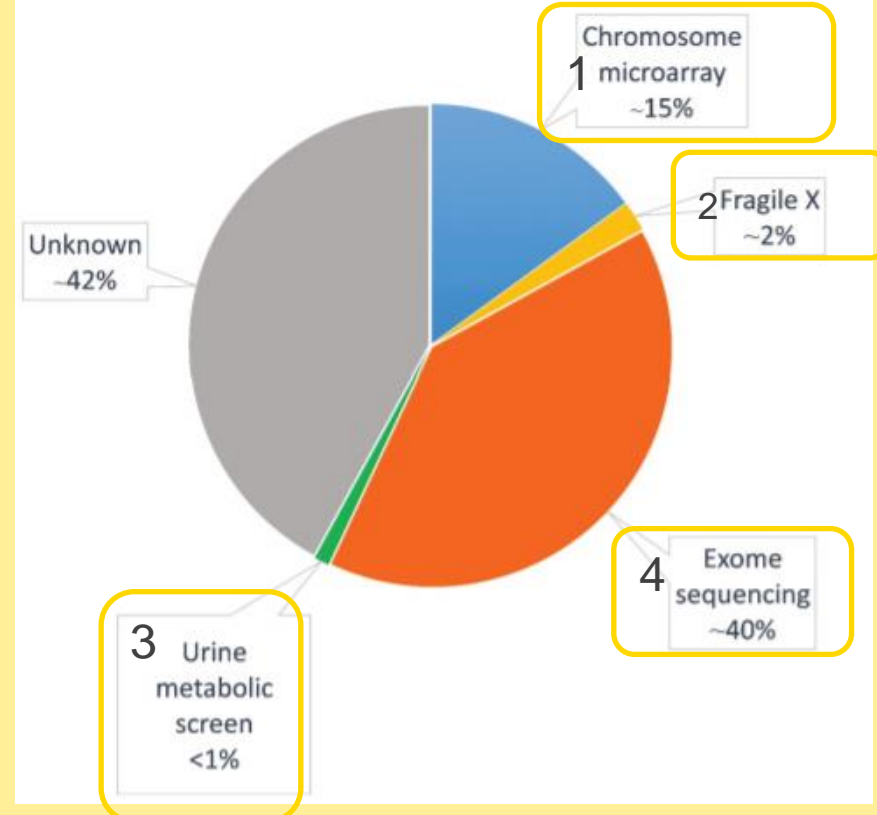
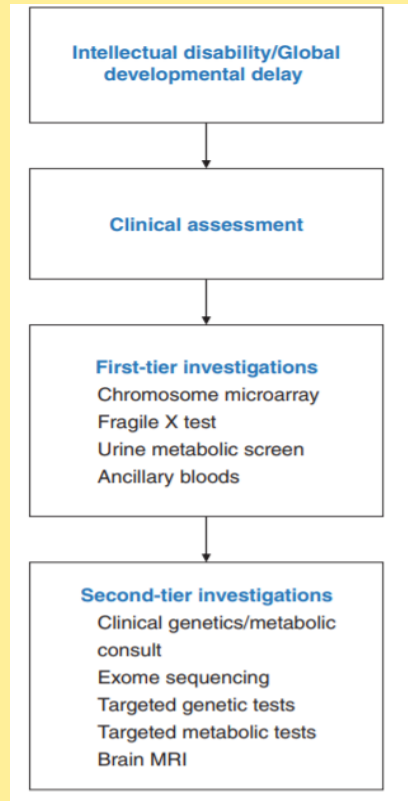


# The best test for each patient is a balance of:

- Chance of test getting a diagnosis for this patient (sensitivity)
- Chance of test finding a variant of uncertain significance (specificity)
- Chance of test providing about other unrelated genetic conditions (“medically actionable results”) [consent]
- Time
- Cost
- Availability
- Medicare



# Diagnostic pathway for intellectual disability

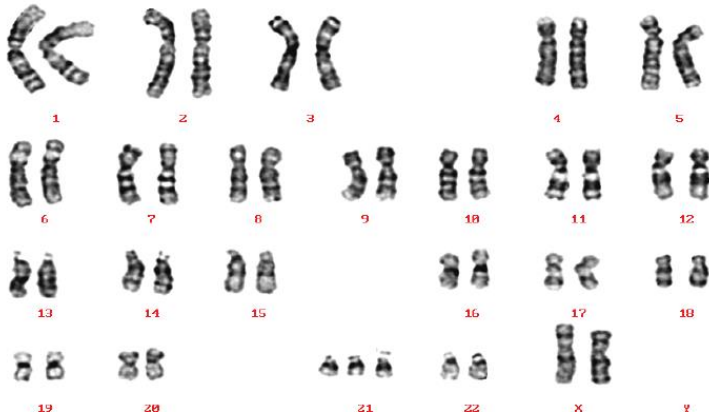


# Test 1: chromosomal microarray

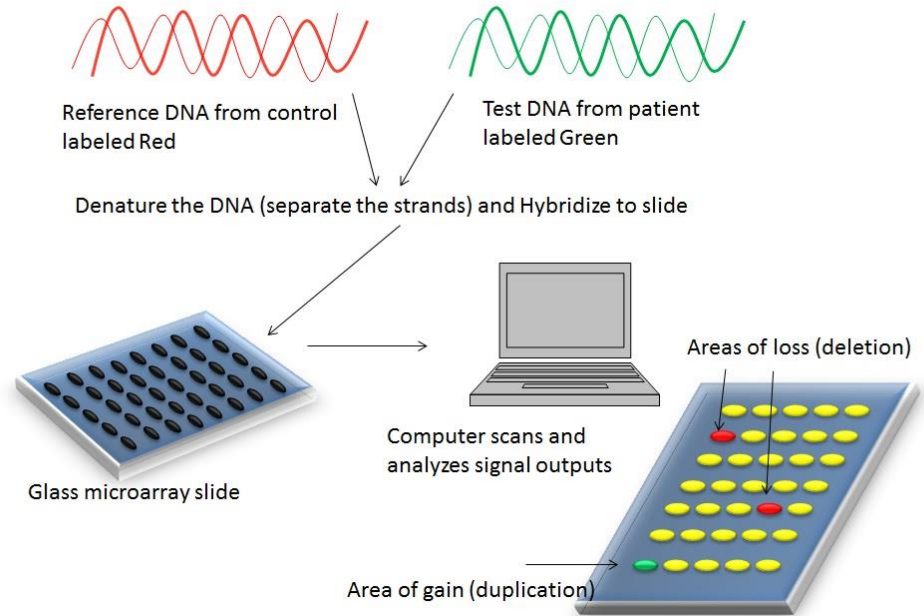
This test finds deletions or duplications of chromosomal material:

- **Use:** CMA is a first-line test for developmental delay/intellectual disability/ autism, with or without epilepsy. This test cannot screen for all genetic causes. It does not screen for Fragile X syndrome which has a separate Medicare item.
- **Yield:** CMA has a diagnostic yield of 10-15% for intellectual disability/autism<sup>1</sup>. The yield is lower if cognition is normal.
- **Sample requirements:** Important to check with individual genetic laboratories. Most labs require 5-10ml EDTA but some can provide saliva collection kits.
- **Result turnaround:** typically, 4-6 weeks.
- **Medicare:** rebate is available for this test [item number 73292] if the affected patient has developmental delay/intellectual disability and/or autistic spectrum disorder and / or two or more congenital abnormalities. To ensure Medicare rebate is provided, and to aid result interpretation, **clinical informationchrom should be included in request forms.**

# Chromosomal microarrays(CMA) now (largely) replace karyotypes



Karyotype diagnoses about 1-3% of children with a suspected genetic condition (e.g. Down syndrome)



CMA diagnoses about 10-15% of children with a suspected severe genetic condition (due to extra or missing chromosomal segments)

# More information

Journal of Paediatrics and  
Child Health



doi:10.1111/j.1440-1754.2011.02081.x

## REVIEW ARTICLE

### Chromosome microarray in Australia: A guide for paediatricians

Elizabeth E Palmer,<sup>1</sup> Greg B Peters<sup>2</sup> and David Mowat<sup>1,3</sup>

<sup>1</sup>Department of Medical Genetics, Sydney Children's Hospital, Randwick, ar

<sup>3</sup>Department of Medical Genetics, School of Women's and Child Health Uni

Journal of Paediatrics and  
Child Health



doi:10.1111/jpc.13523

## ORIGINAL ARTICLE

### Current use of chromosomal microarray by Australian paediatricians and implications for the implementation of next generation sequencing

Stacia McKay,<sup>1</sup> Daryl Efron,<sup>1,2,3</sup> Elizabeth E Palmer,<sup>4,5,6</sup> Susan M White,<sup>3,7</sup> Chris Pearson<sup>8</sup> and  
Argie Danchin<sup>1,2,3</sup>

<sup>1</sup>Department of General Medicine, Royal Children's Hospital, <sup>2</sup>Murdoch Children's Research Institute, <sup>3</sup>Department of Paediatrics, University of Melbourne, <sup>4</sup>Paediatric Clinical Genetics Service, Murdoch Children's Research Institute, Melbourne, Victoria, <sup>5</sup>Sydney Children's Hospital, <sup>6</sup>Department of Women and Children's Health, Randwick Campus, University of New South Wales, Sydney, <sup>7</sup>Genetics of Learning Disability Service, Newcastle, New South Wales and <sup>8</sup>Department of General Medicine, Women's and Children's Hospital, Adelaide, South Australia, Australia

Journal of Paediatrics and  
Child Health



doi:10.1111/jpc.13869

## VIEWPOINT

### Chromosome microarray analysis: A soothing guide

Anne Ronan <sup>1,2</sup>

# Printable guide: <https://www.genetics.edu.au/testing-guide-chromosome-microarray-cma-children-and-adults>

## DOCTOR'S GUIDE

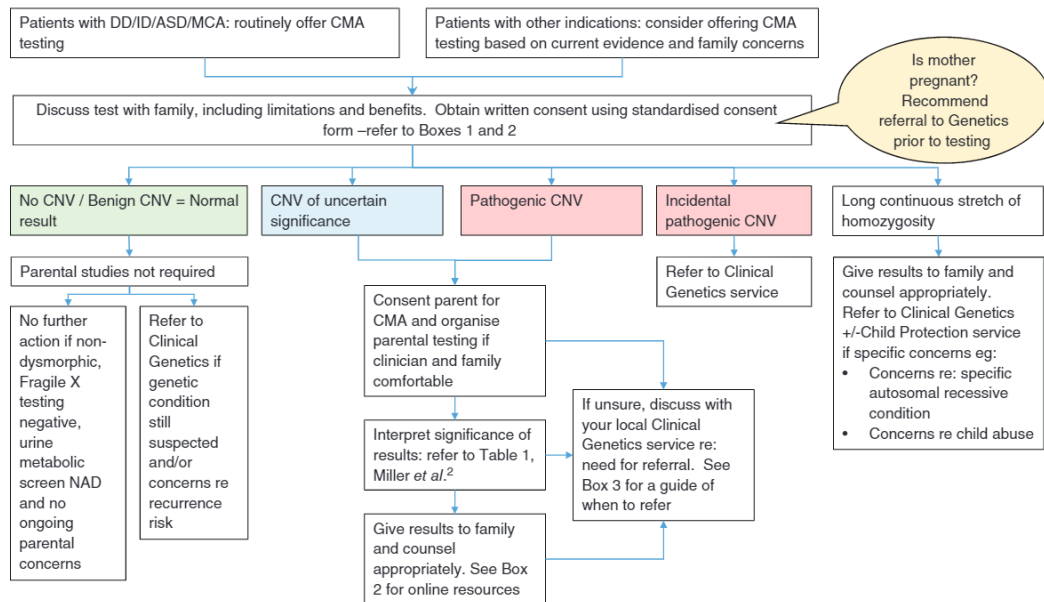
### Chromosome Microarray (CMA) Testing Guide – Children and Adults

Adapted from: Palmer *et al.* Chromosome microarray in Australia: A guide for paediatricians. Journal of Paediatrics and Child Health 48 (2012) E59–E67

1. Patient to undergo CMA testing, a genetic test which checks for DNA copy number variations, not including fragile X
2. Discussion of test process, limitations and counselling about variety of possible outcomes listed below
3. Blood sample collected (5-10ml in EDTA - Confirm sample requirements with local laboratory)
4. Possible laboratory findings include the following:

No abnormality found	Diagnostic of known, expected condition	Variant of unknown significance found	Variant with unexpected implications found
<ul style="list-style-type: none"><li>• Normal result or known, benign change detected</li><li>• Consider referral to a genetics clinic if concerns remain about a genetic diagnosis or recurrence in another pregnancy</li><li>• No further testing required at this stage</li></ul>	<ul style="list-style-type: none"><li>• Known copy number variant (CNV) identified</li><li>• Consider referral to genetics clinic for genetic counselling</li><li>• No further testing required at this stage</li></ul>	<ul style="list-style-type: none"><li>• Copy number variant of unknown significance (VOUS) identified</li><li>• Consider referral to genetics clinic for interpretation of report and diagnostic review</li><li>• Further testing such as parental studies may be useful</li></ul>	<ul style="list-style-type: none"><li>• Copy number variant of unexpected significance identified</li><li>• Consider referral to genetics clinic for interpretation of report and genetic counselling</li><li>• Further testing such as parental studies may be useful</li></ul>

# Flow chart



**Fig. 1** Guide for paediatricians ordering CMA. ASD, autism spectrum disorder; CMA, chromosomal microarray; CNV, copy number variant; DD, developmental delay; ID, intellectual disability; MCA, multiple congenital anomalies; NAD, no abnormality detected.

## When to consider referral to clinical genetics

- Uncertainty interpreting a laboratory report
- Uncertainty re significance of CNV—especially for variants of uncertain or unknown significance, and variants on the X chromosome
- Uncertainty re need to test relatives—especially for parent with neurocognitive phenotype
- If CMA is normal (i.e. no CNV or benign CNV) but genetic condition is still suspected and/or family concerned re recurrence in future pregnancies
- Prior to genetic testing if mother is pregnant
- Family require more detailed information re: recurrence risk/prognosis
- Long continuous stretch of homozygosity: is there are concerns re child protection or a specific recessive condition



# Not all lab tests and reports are created equal!

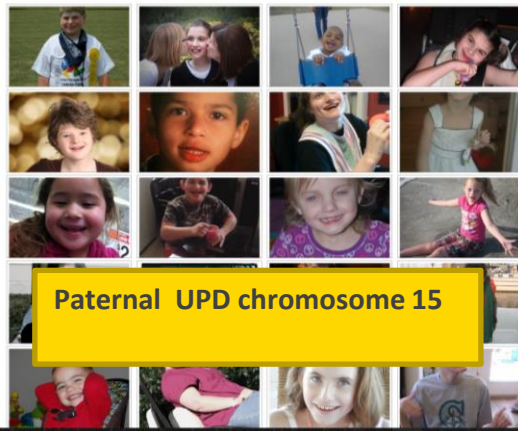




# My lab uses a SNP array what does that mean?

Can detect: **COPY NUMBER NEUTRAL CHANGES**

such as uniparental isodisomy (UPD) where *both* of a pair of chromosomes inherited from *one* parent



<https://www.angelman.org/individuals-with-as-photo-gallery>

Prader-Willi syndrome association of Victoria

# SNP arrays also reveal degree of parental relatedness



In known consanguineous partnerships – can be helpful in narrowing down regions of loss of homozygosity where more likely gene causing autosomal recessive condition may be present.

Can also be red flag for possible child protection issue

# Where to go if a microdel or dup detected



<https://www.rarechromo.org/>



**MEF2C**  
**haploinsufficiency**  
**syndrome**  
(MRD20/chromosome 5q14.3  
deletion syndrome)



## Microdeletions

Deletion of the MEF2C gene causing ID, severely impaired language development, Autism (50%)/stereotypical behaviours,



## 22q11.2 duplications at a glance

People with the typical 22q11.2 duplication have a very tiny extra bit of chromosome 22.

Any effects of having this extra bit of chromosome 22 appear to be generally mild and highly variable, even within the same family.

At the moment, it's uncertain whether the 22q11.2 duplication is a natural genetic variant - we are all different - or whether it's a real syndrome whose effects can be highly variable.

About 70 per cent of people with the extra bit of chromosome 22 have inherited it from one of their parents. Most of the parents were completely unaware that they had the extra bit of chromosome 22 until they were tested after their child was found to have the extra bit.

Anyone who has the extra bit of chromosome 22 has a 50 per cent chance of passing it on to any child of theirs. They have a 50 per cent chance of having a child without the duplication. This is true for each pregnancy.

It isn't possible to say in advance how mildly or severely a baby with the duplication will be affected - or whether they will be affected at all.

## Microduplications

# Consent

## **Box 1. INFORMED CONSENT FOR CMA – WHAT DO PATIENTS AND FAMILIES NEED TO KNOW? (WITH ACKNOWLEDGEMENT TO SYDNEY CHILDREN'S HOSPITAL)**

- There are multiple potential results: no CNV, benign CNV, pathogenic CNV, CNV of uncertain significance and CNV of unknown significance
- An uncertain result is not infrequent – up to 20% of studies
- Some genetic abnormalities cannot be identified by CMA
- Testing may reveal incidental findings: for example a CNV which predisposes to an adult-onset condition, for which treatment may or may not be available
- Testing may reveal non-paternity/non-maternity of a presumed parent
- Testing may suggest a closer parental relationship than is known or suspected
- Family members may need to be tested, and may be affected by results
- Testing will not impact health insurance but may affect applications for life insurance and other forms of insurance
- DNA will be stored for potential reanalysis in the future but may not remain in a suitable state for testing
- Interpretation of test results may change in the future
- If a CNV is found, CMA result may need to be confirmed by repeat array or alternative test due to potential false positives
- Clinical Genetics referral may be needed

Terminology differs between laboratories.

Mosaicism, balanced translocations, sequence variants and triplet repeat disorders such as fragile X syndrome.

Similar principles to consent  
for any genomic test

J Paediatr Child Health. 2017  
Jul;53(7):650-656.

Current use of chromosomal microarray  
by Australian paediatricians and  
implications for the implementation  
of next generation sequencing.

McKay V, Efron D, Palmer EE, White SM,  
Pearson C, Danchin M

# CMA for other disorders

CMA is being investigated for use in other patient populations, and its uses will expand over time. In these cases it may be especially useful when other tests have failed to yield a diagnosis such as :

- Unexplained seizure disorder
- Growth delay
- Psychiatric illness
- Neuromuscular conditions

Yield ranges based on condition (6-20%).

- The yield is low for ASD or psychiatric disorders *without* intellectual disability.  
**Guidelines would be helpful.**
- For these conditions, a panel or exome might be a better test, with array reserved to look for larger deletions and duplications that the test can't pick up



# Questions ?



# Test 2: screening for Fragile X syndrome



Fragile X Association of  
Australia



# Fragile X PCR

This test checks for expansion in the Fragile X gene (*FMR1*) and is a screen for Fragile X syndrome.

**Use:** Fragile X PCR is a first-tier test for both boys and girls with unexplained intellectual disability. Fragile X syndrome is NOT screened for by chromosomal microarray (CMA) and needs to be separately requested.

**Yield:** Fragile X syndrome is the most common known cause of inherited intellectual disability, affecting around 1 in 4000 males and about 1 in 6,000 females. Testing is not recommended for children with epilepsy who do not have developmental delay or intellectual disability.

**Sample requirements:** Important to check with individual genetic laboratories. Most labs require 5-10ml EDTA but some can provide saliva collection kits.

**Result turnaround:** typically 2- 4 weeks.



# Medicare rebate

Clinical information should be included on the test request form to ensure rebate. Rebate is available for this test under the following clinical situations:

- (a) The patient exhibits intellectual disabilities, ataxia, neurodegeneration, or premature ovarian failure consistent with a FMR1 mutation; or
- (b) The patient has a relative with the FMR1 mutation.

# Q: which of these individuals have Fragile X syndrome



# A: All of them



Male with Fragile  
X syndrome  
Hagerman et al., 2009



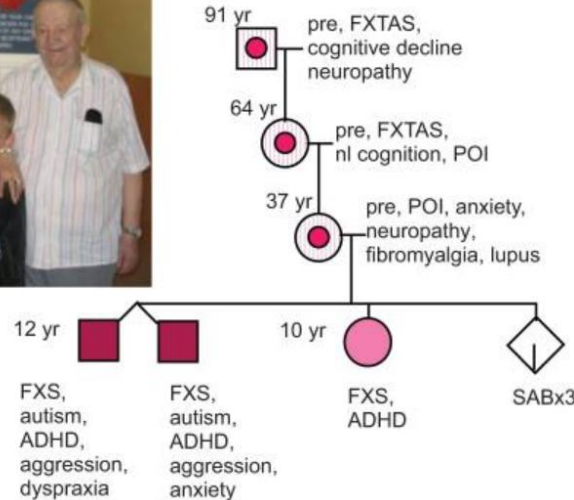
Female with full  
mutation in *FMR1*  
Fragile X Association Australia



Female with Fragile X  
Tremor Ataxia syndrome  
Fragile X Association USA



# A family affair



## Fragile X syndrome

- 'Full mutation' in the Fragile X gene: leading cause of inherited intellectual disability / autism in males **and females**

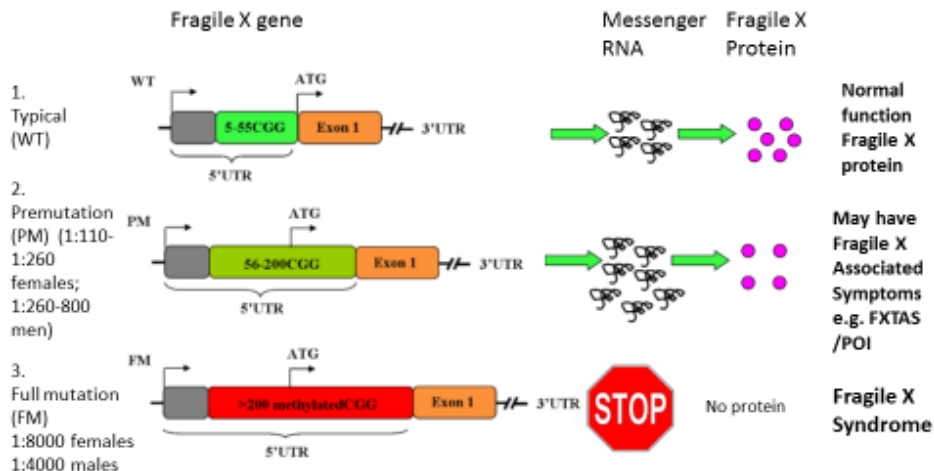
## Fragile X related conditions

- 'Pre-mutation' in Fragile X gene linked to array of medical and psychological conditions in females and males.

Advances in the treatment of fragile X syndrome.  
Hagerman RJ1, Berry-Kravis E, Kaufmann WE, Ono MY, Tartaglia N, Lachiewicz A, Kronk R, Delahunty C, Hessl D, Visootsak J, Picker J, Gane L, Tranfaglia M. Pediatrics. 2009 Jan;123(1):378-90. doi: 10.1542/peds.2008-0317.

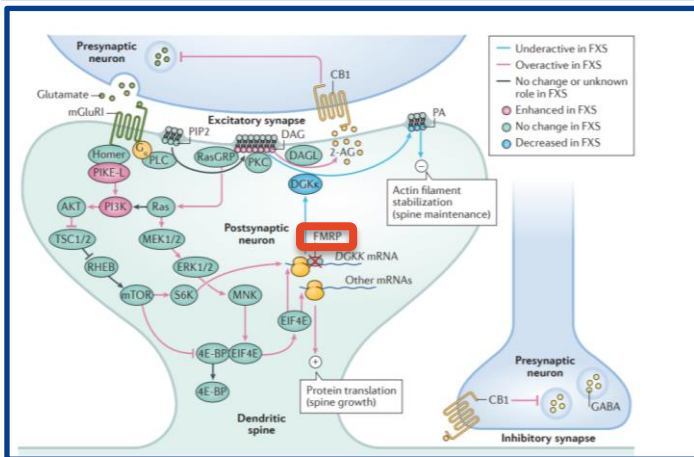
# Molecular underpinnings of Fragile X related conditions: a triplet repeat expansion disorder

## Three classes of FMR1 alleles



See also video

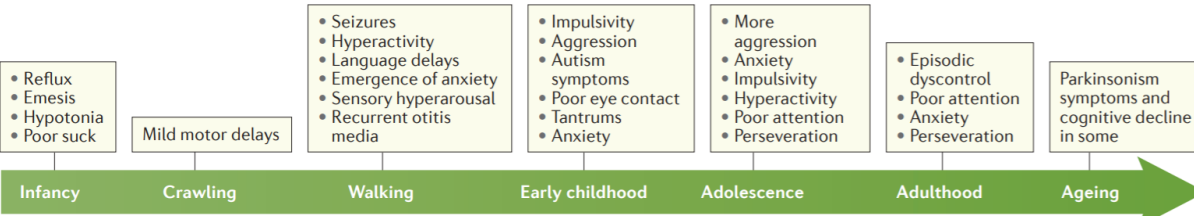
<https://fragilex.org.au/what-is-fragile-x/what-causes-fragile-x/>



Fragile X protein (FMRP) has key role in neurodevelopment and function (Hagerman et al., 2017)

Figure courtesy of Melanie Leffler, GOLD Service

# Characteristics of Fragile X



## Intellectual disability

Ranges from mild – severe. 2/3 females have IQ in normal range.

## Behavioural and Emotional features

Anxiety and shyness

Attention Deficit Hyperactivity Disorder (ADHD)

Autistic type and challenging behaviours often linked to hyperarousal and anxiety.

## Physical features

Physical features may be **subtle or not present** they can include

Low muscle tone and loose joints, high palate.

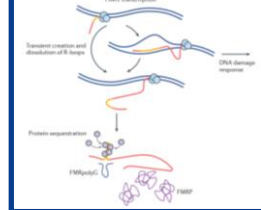
Long narrow face, prominent ears and larger testicles (in older males)

Important to screen for otitis media, hearing loss, mitral valve prolapse

Extensive research efforts on targeted therapeutics. SSRI can help learning through reduction anxiety.



# Fragile X premutation associated disorders



Postulated to be progressive toxic pathophysiology

## Fragile X Associated Tremor and Ataxia (FXTAS)

- Up to two in five (20-40%) male carriers over the age of 50 develop Fragile X Tremor Ataxia Syndrome (FXTAS).
- FXTAS is a neurological condition similar to Parkinson's disease that causes ataxia intention tremor and memory problems. It is seen less commonly in females carrying a premutation.

## Premature Ovarian Insufficiency (FXPOI)

- Approximately one in five (20%) female carriers experience early menopause
- Important implication for genetic counselling: early review with fertility specialist recommended.

Table 1 | Phenotypes associated with *FMR1* premutations besides FXTAS and FXPOI

Phenotype	Prevalence in individuals with premutation	
	Males	Females
Hypertension <sup>36,37</sup>	67% of 100 with FXTAS 42% of 67 without FXTAS	61% of 18 with FXTAS 16% of 128 without FXTAS
Migraine <sup>11,38</sup>	27% of 122	54% of 203
Fibromyalgia <sup>37,39,40</sup>	ND	44% of 16 with FXTAS 8% of 121 without FXTAS
Thyroid dysfunction <sup>37,39,41</sup>	ND	50% of 18 with FXTAS 17% of 121 without FXTAS
Sleep disturbances <sup>42,43</sup>		63% of 110
Sleep apnoea <sup>44</sup>	31.4% of 118 males and females	
Restless legs syndrome <sup>43</sup>	33.1% of 127 males and females	
Central pain sensitivity syndrome <sup>11,40</sup>	ND	75% of 33
Tandem gait abnormalities <sup>11,63</sup>	100% with FXTAS	30% of 33
Neuropathy <sup>11,37,45-47</sup>	88% of 16 with FXTAS 36% without FXTAS	53% of 17 with FXTAS 12% of 116 without FXTAS

FXPOI, fragile X-associated primary ovarian insufficiency; FXTAS, fragile X-associated tremor/ataxia syndrome; ND, not determined.

Hagerman and Hagerman, Nature Reviews Neurology, 2016



# Consent for Fragile X testing should cover

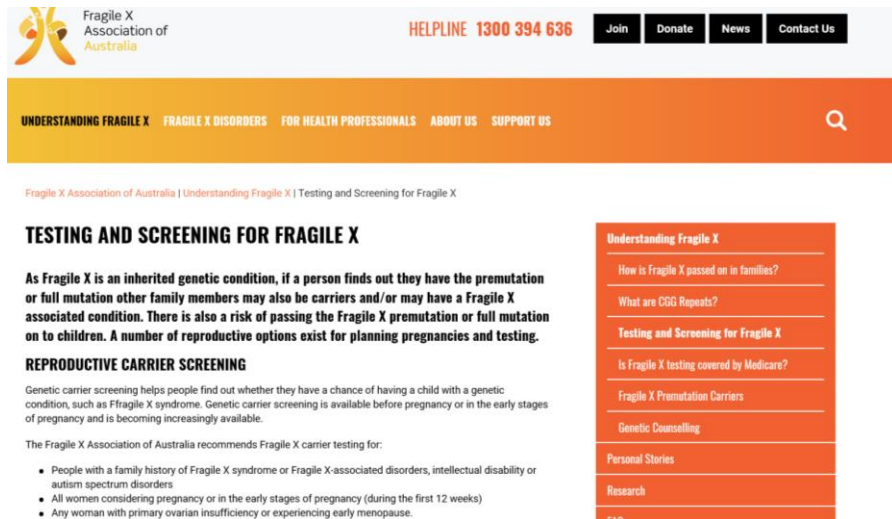
As a minimum verbal consent should be documented in the medical notes. An information sheet should be provided to all families and these important points covered:

- The test screens for Fragile X Syndrome (FXS), the most common cause of inherited intellectual disability.
- People with FXS can have developmental delay, learning difficulties, anxiety, autism and epilepsy.
- The features of FXS vary from mild to severe with males more likely to be severely affected than females because the gene is found on the X-chromosome.
- Screening can also reveal carrier status (intermediate or premutation expansion) which can have implications for the health of the child and other members of the family, as well as genetic counselling implications.

# Patient factsheets

## [Fragile X PCR Testing guide](https://www.fragilex.org.au/understanding-fragile-x/testing-and-screening-for-fragile-x/)

[https://www.fragilex.org.au/  
understanding-fragile-  
x/testing-and-screening-for-  
fragile-x/](https://www.fragilex.org.au/understanding-fragile-x/testing-and-screening-for-fragile-x/)



The screenshot shows the website of the Fragile X Association of Australia. The header includes the organization's logo, name, and a helpline number (1300 394 636). Navigation links for 'Join', 'Donate', 'News', and 'Contact Us' are present. A main navigation bar lists categories: 'UNDERSTANDING FRAGILE X', 'FRAGILE X DISORDERS', 'FOR HEALTH PROFESSIONALS', 'ABOUT US', and 'SUPPORT US'. The main content area is titled 'TESTING AND SCREENING FOR FRAGILE X' and contains a paragraph explaining that Fragile X is an inherited genetic condition and a risk of passing the premutation or full mutation to children. It also mentions reproductive options. Below this is a section for 'REPRODUCTIVE CARRIER SCREENING' which explains the purpose of genetic carrier screening and lists three categories of people recommended for testing: those with a family history, women considering pregnancy, and women with primary ovarian insufficiency. On the right side, there is a sidebar with a table of contents for the 'Understanding Fragile X' section, listing topics like 'How is Fragile X passed on in families?', 'What are CGG Repeats?', 'Testing and Screening for Fragile X', 'Is Fragile X testing covered by Medicare?', 'Fragile X Premutation Carriers', 'Genetic Counselling', 'Personal Stories', and 'Research'.

Fragile X Association of Australia

HELPLINE 1300 394 636

Join Donate News Contact Us

UNDERSTANDING FRAGILE X FRAGILE X DISORDERS FOR HEALTH PROFESSIONALS ABOUT US SUPPORT US

Fragile X Association of Australia | Understanding Fragile X | Testing and Screening for Fragile X

### TESTING AND SCREENING FOR FRAGILE X

As Fragile X is an inherited genetic condition, if a person finds out they have the premutation or full mutation other family members may also be carriers and/or may have a Fragile X associated condition. There is also a risk of passing the Fragile X premutation or full mutation on to children. A number of reproductive options exist for planning pregnancies and testing.

#### REPRODUCTIVE CARRIER SCREENING

Genetic carrier screening helps people find out whether they have a chance of having a child with a genetic condition, such as Fragile X syndrome. Genetic carrier screening is available before pregnancy or in the early stages of pregnancy and is becoming increasingly available.

The Fragile X Association of Australia recommends Fragile X carrier testing for:

- People with a family history of Fragile X syndrome or Fragile X-associated disorders, intellectual disability or autism spectrum disorders
- All women considering pregnancy or in the early stages of pregnancy (during the first 12 weeks)
- Any woman with primary ovarian insufficiency or experiencing early menopause.

#### Understanding Fragile X

- How is Fragile X passed on in families?
- What are CGG Repeats?
- Testing and Screening for Fragile X
- Is Fragile X testing covered by Medicare?
- Fragile X Premutation Carriers
- Genetic Counselling
- Personal Stories
- Research

# Fragile X and related conditions: key resources



Fragile X Association of Australia:  
<https://fragilex.org.au/>

Fragile X syndrome. Hagerman et al., Nature reviews. Disease primers. , 2017, Vol.3

**Gene reviews:** FMR1-Related Disorders Robert A Saul, MD, and Jack C Tarleton

Fragile X-associated tremor/ataxia syndrome  
— features, mechanisms and management  
Randi J. Hagerman and Paul Hagerman Nature Reviews Neurology, 2016

# Questions ?





## Test 3: urine metabolic screen

This test involves an [extended urine metabolic screen](#) which includes an Amino Acid quantitation, Creatine metabolites, selected Purines and pyrimidines, Piperidine-6-carboxylate, GAG (Glycoasaminoglycan) screen and Organic Acids.

The test is available in NSW through the NSW Biochemical Genetics Department at the Children's Hospital at Westmead. For other states contact your local Biochemical genetics team.

**Use:** this testing can screen for metabolic causes of intellectual disability, including conditions with targeted treatments such as specialist diet. Should be especially considered when there is regression of skills, coarse features, organomegaly and additional neurological signs.

**Yield:** although overall yield is less than 1%, the screen may quickly reveal conditions (>80) with targeted therapies.

**Sample requirement:** random urine, 10 mL (minimum 2 mL), which the collection centre needs to deliver immediately on ice or freeze within 2 hours of collection and transport on dry ice with no added preservative to the NSW Biochemical Genetics Department at the Children's Hospital at Westmead.

**Result turnaround:** typically, 2-3 days.

**Medicare:** Partial rebate is available for this testing (metabolic profile, amino acid – please refer to the Medicare website). Clinical information should be included on test form to aid interpretation and for Medicare rebate.

### **Resources/links:**

[Urine Metabolic Screen](http://www.schn.health.nsw.gov.au/find-a-service/laboratory-services/nsw-biochemical-genetics-service) information: <http://www.schn.health.nsw.gov.au/find-a-service/laboratory-services/nsw-biochemical-genetics-service>

Other specialist metabolic tests may be organised by a neurologist or metabolic specialist

# Treatable-ID.org

TREATABLE INTELLECTUAL DISABILITY - AN INTERACTIVE TOOL FOR THE CLINICIAN

HOME DISEASES SIGNS & SYMPTOMS DIAGNOSIS TREATMENT ALL

Start the tool via the menu above



## Treatable ID.org

81 treatable metabolic disorders causally related to Intellectual Disability...

“ ”

*Treatable diseases should be prioritized in the diagnostic work-up of any individual with Intellectual Disability. Early diagnosis & treatment improves outcomes.*

### What is Treatable-ID.org?

A systematic literature review, performed by *Dr. Clara van Karnebeek* & *Dr. Sylvia Stockler* in B.C. Children's Hospital (Vancouver, Canada) identified 81 inborn errors of metabolism which are causally related to Intellectual Disability and amenable to therapy. These diseases are presented on this website as an interactive tool for the clinician and related to:

### Treatable-ID on mobile devices

When you visit this website from any mobile device or tablet you will access a mobile version of the app. Additionally you can download the Treatable ID app for iPhone or iPad from the Apple App Store free of charge.

### How does it work?

The information is presented in several different ways: ranging from the biochemical categories, signs & symptoms, diagnostic tests, to therapies & evidence. For each condition a disease page has been created as information portal with access to specific genetics, biochemistry, phenotype, diagnostic tests and therapeutic advice. *Get the full story here*

Download on the App Store

Quick tour / Help

Help us to improve the functionality of this free app.

Register / Feedback

About

FAQ

# Questions ?



# OK first tier testing was normal– what do I do now?





# Test 4: Next generation sequencing

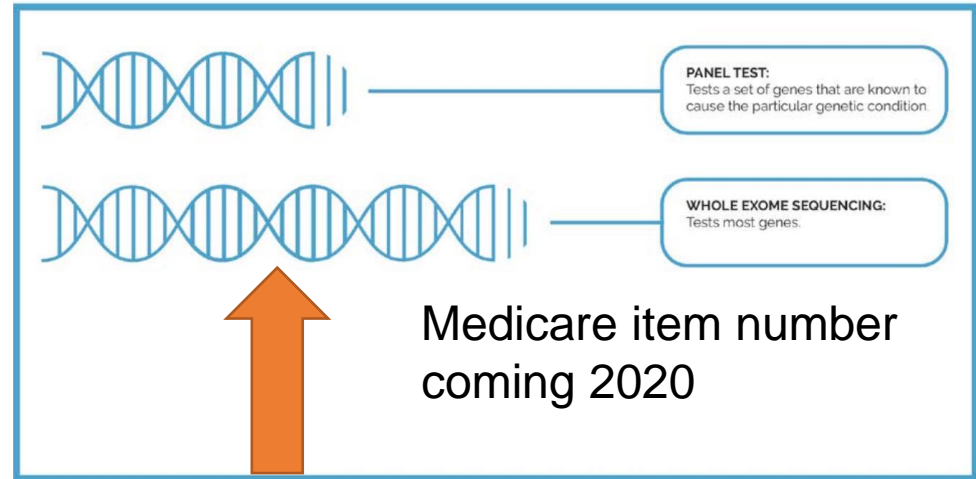
- **Panel tests:** test a set of genes causing a NDD. Gene panels vary widely in the genes that are included and will identify variants in the more common NDD genes, but may not include rarer or only recently described NDD genes.



<https://www.australiangenomics.org.au>

# Test 4: Next generation sequencing

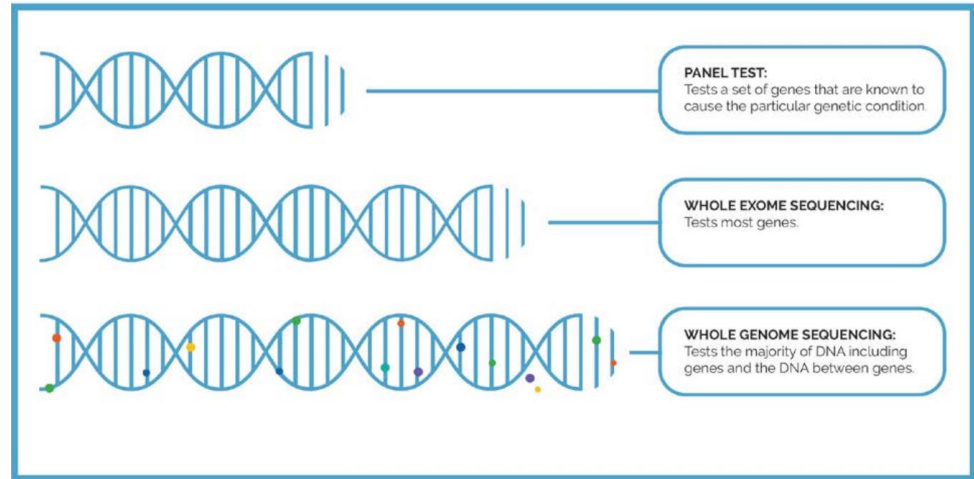
- **Panel tests:** test a set of genes causing a NDD. Gene panels vary widely in the genes that are included and will identify variants in the more common NDD genes, but may not include rarer or only recently described NDD genes.
- **Exome sequencing:** can test most coding genes. Often exome sequencing is limited to genes currently known to cause a medical condition and may be referred to as a 'Clinical Exome' or 'Mendeliome'.



<https://www.australiangenomics.org.au>

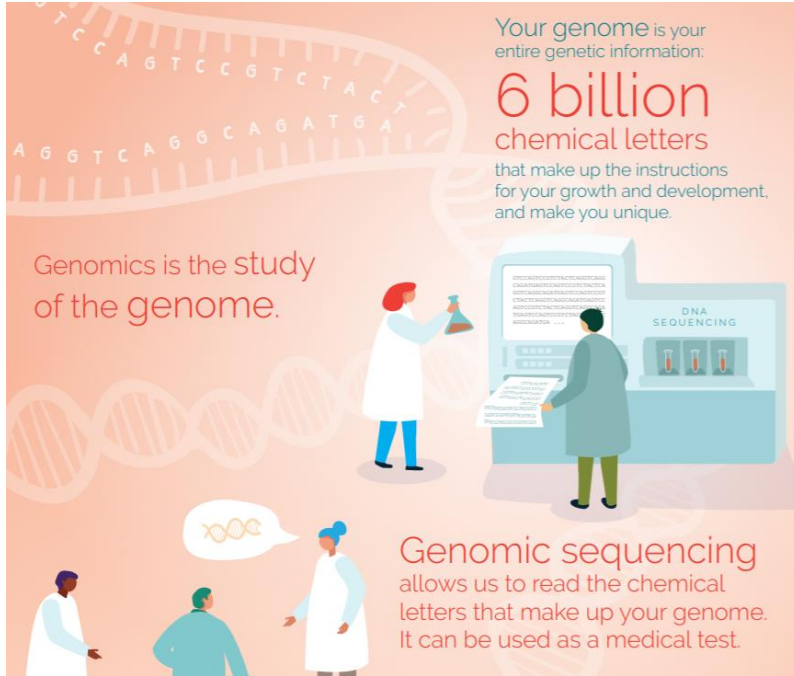
# Test 4: Next generation sequencing

- **Panel tests:** test a set of genes causing a NDD. Gene panels vary widely in the genes that are included and will identify variants in the more common NDD genes, but may not include rarer or only recently described NDD genes.
- **Exome sequencing:** can test most coding genes. Often exome sequencing is limited to genes currently known to cause a medical condition and may be referred to as a 'Clinical Exome' or 'Mendeliome'.
- **Whole genome sequencing (WGS):** tests the majority of DNA, including coding genes and the DNA between genes. WGS has the potential to detect complex structural genetic rearrangements that may not be detected by chromosomal microarray, and variants in the mitochondrial DNA.



<https://www.australiangenomics.org.au>

# Great resources about Next gen testing



AGGTCAGGCAGATGA  
TCCAGTCCGTCTACT

Your genome is your entire genetic information:

**6 billion** chemical letters

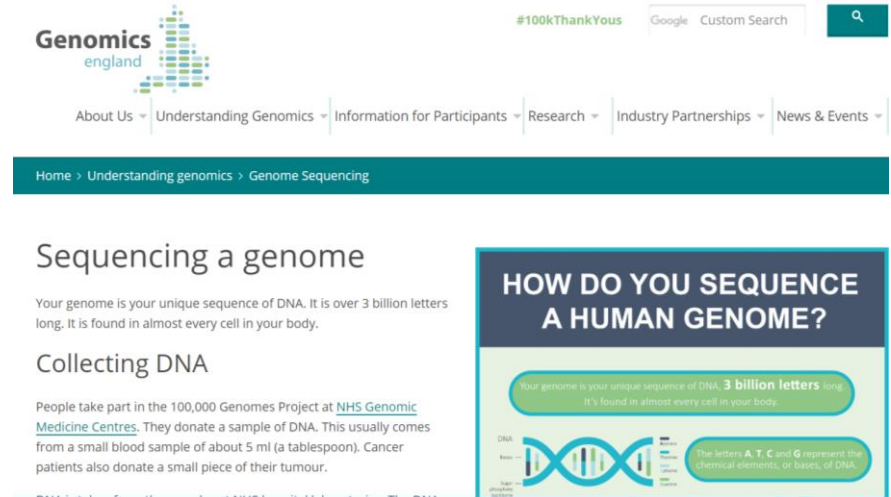
that make up the instructions for your growth and development, and make you unique.

Genomics is the study of the genome.

DNA SEQUENCING

Genomic sequencing allows us to read the chemical letters that make up your genome. It can be used as a medical test.

<https://www.genomicsinfo.org.au>



Genomics  
england

#100kThankYou

Google Custom Search

About Us Understanding Genomics Information for Participants Research Industry Partnerships News & Events

Home > Understanding genomics > Genome Sequencing

## Sequencing a genome

Your genome is your unique sequence of DNA. It is over 3 billion letters long. It is found in almost every cell in your body.

### Collecting DNA

People take part in the 100,000 Genomes Project at NHS Genomic Medicine Centres. They donate a sample of DNA. This usually comes from a small blood sample of about 5 ml (a tablespoon). Cancer patients also donate a small piece of their tumour.

### HOW DO YOU SEQUENCE A HUMAN GENOME?

Your genome is your unique sequence of DNA. **3 billion letters** long. It's found in almost every cell in your body.

DNA

The letters **A, T, C** and **G** represent the chemical elements, or bases, of DNA.

[www.genomicsengland.co.uk/](http://www.genomicsengland.co.uk/)

# Possible results of genomic test?



*One or more gene variants are found to explain the condition for which the test was done.*



*No gene variants are found to explain the condition for which the test was done.*



*A variant is found in genes associated with the condition but the significance is not known (variants of unknown significance).*



*A gene variant is found for an unrelated condition (incidental finding).*

**Any genetic test**

**Array, gene panel, exome or genome sequencing**

<https://www.genomicsinfo.org.au/wp-content/uploads/2019/02/What-is-genomic-testing-v9.pdf>



# Some possible pitfalls


There are some potential risks to consider relating to genomic testing:


- **Incidental findings** – In genomic testing, we are looking at many genes at once, so there is a small chance doctors will find a variant in a gene that is not related to your health condition. This could give you health information that you may not want to know. You can discuss this with your doctor before you have the test and choose not to find out.



# Some possible pitfalls

There are some potential risks to consider relating to genomic testing:

- 
- **Incidental findings** – In genomic testing, we are looking at many genes at once, so there is a small chance doctors will find a variant in a gene that is not related to your health condition. This could give you health information that you may not want to know. You can discuss this with your doctor before you have the test and choose not to find out.
  - **Insurance** – In Australia, genomic testing will not affect your health insurance policy. However genomic testing in you or your child may affect how easy it is for you or other family members to get income protection, travel or life insurance; or the price of your premium.



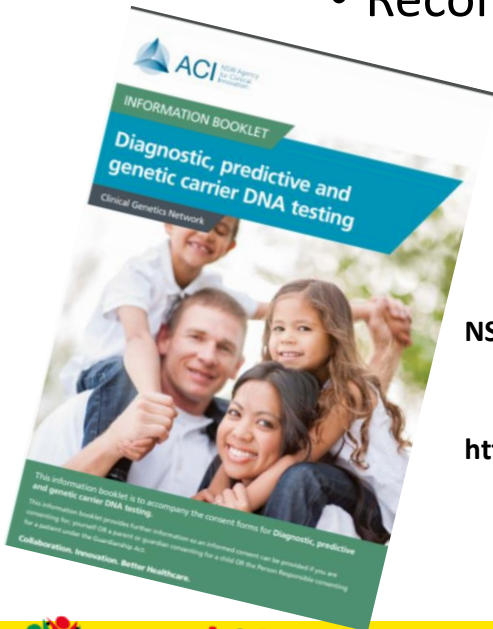
Moratorium on genetic tests in life insurance (July 2019 -June 2024 +): during moratorium life insurance companies cannot use genetic test *up to certain financial limits*. results

More information <https://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-20-life-insurance-products-and-genetic-testing-in-australia>



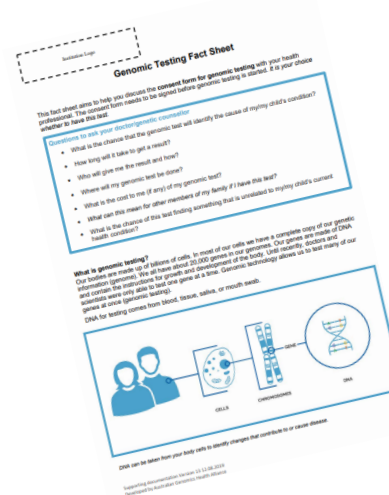
# Which consent form to use?

- Can be a little confusing, different forms in different hospitals, laboratories and states.
- Recommend discuss with local genetics service/ lab



NSW has own consent forms and patient booklets available through ACI:

[https://www.aci.health.nsw.gov.au/networks/clinical\\_genetics/genetic-and-genomic-testing-consent-forms](https://www.aci.health.nsw.gov.au/networks/clinical_genetics/genetic-and-genomic-testing-consent-forms)



For other states look at the newly released National Consent forms.

<https://www.australiangenomics.org.au/resources/for-professionals/national-clinical-consent/>

# •Questions ?



# UNCERTAIN OR NO DIAGNOSIS

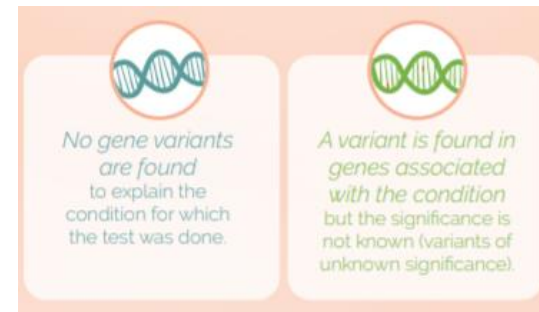
## — what next?

- $\frac{1}{4}$  -  $\frac{1}{2}$  children

There is a genetic condition but the **ANALYSIS** is not yet good enough to pick it up

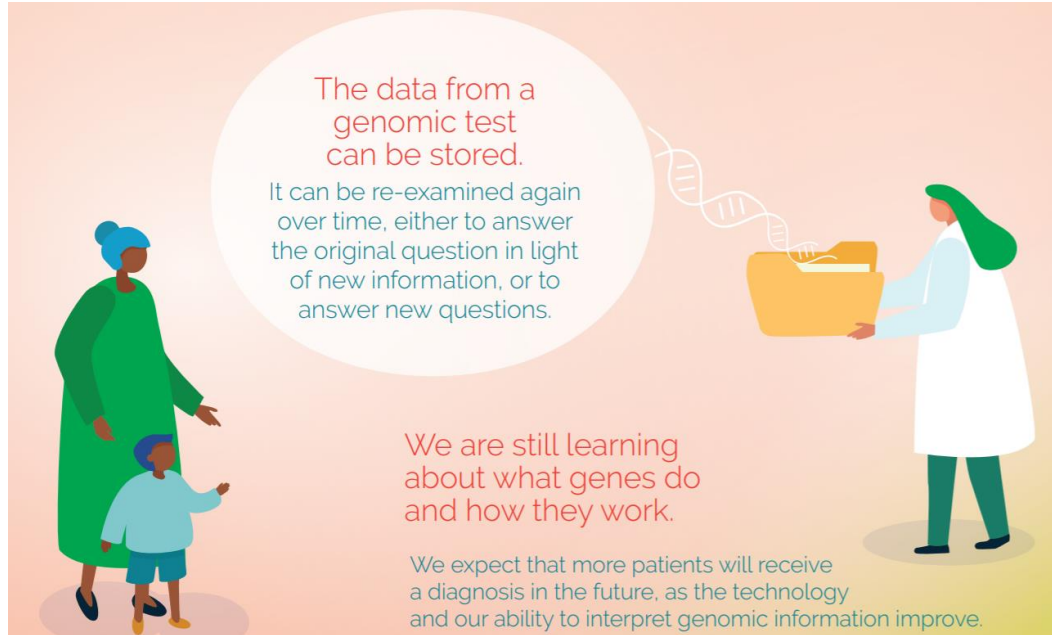


RE-ANALYSIS





# Re-analysis



Genetic testing is more advanced than our ability to interpret it.

# Enrol in genetic research

Girl with  
severe  
epilepsy  
condition

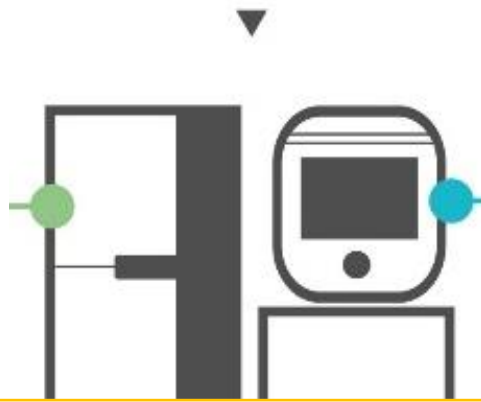


Born

6 years

8 years

Girl with  
severe  
epilepsy  
condition



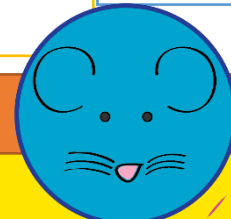
DNA sent for exome  
sequencing

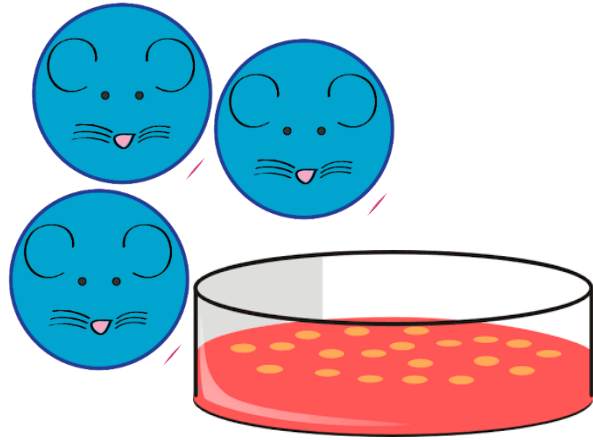
NO answer in >600  
genes known to  
cause brain  
conditions.

? Maybe damaging  
genetic variant in  
gene reported to  
cause brain  
condition in mice

Born

6 years

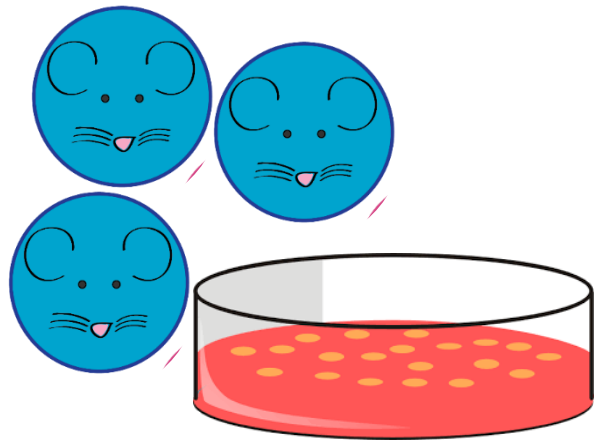




Scientists do  
more work on  
gene in mouse  
and cell culture

10 years

12 years



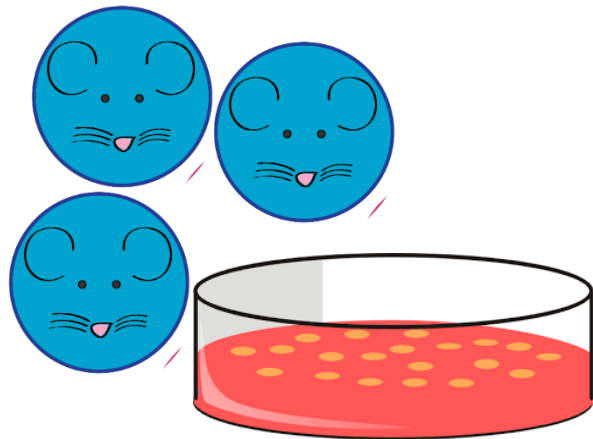
International  
collaborations to  
find more patients

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10 years

12 years



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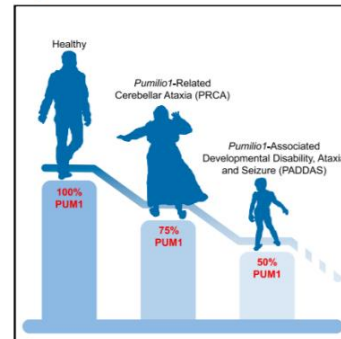
Scientists do  
more work on  
gene in mouse  
and cell culture



## Cell

**A Mild *PUM1* Mutation Is Associated with Adult-Onset Ataxia, whereas Haploinsufficiency Causes Developmental Delay and Seizures**

Graphical Abstract



Authors

Vincenzo A. Gennarino,  
Elizabeth E. Palmer,  
Laura M. McDonnell, ..., Kym M. Boycott,  
J. Lloyd Holder, Jr., Huda Y. Zoghbi

Correspondence

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hzoghbi@bcm.edu (H.Y.Z.)

In Brief

Different dosages of an RNA-binding protein result in human neurological diseases of corresponding severities.

Scientific article  
published ->  
report back to  
family

10 years

12 years



## CLINICAL REPORT

# PADDAS syndrome associated with hair dysplasia caused by a de novo missense variant of PUM1

Paul Bonnemas-Carrere<sup>1</sup> | Fanny Morice-Picard<sup>2</sup> | Perrine Pennamen<sup>1,3</sup> |  
Benoit Arveiler<sup>1,3</sup> | Patricia Fergelot<sup>1,3</sup> | Cyril Goizet<sup>1,3</sup> | Mélanie Hellegouarch<sup>1</sup> |  
Didier Lacombe<sup>1,3</sup> | Claudio Plaisant<sup>1</sup> | Virginie Raclet<sup>1</sup> | Caroline Rooryck<sup>1,3</sup> |  
Eulalie Lasseaux<sup>1</sup> | Aurélien Trimouille<sup>1,3</sup>

<sup>1</sup>Department of Medical Genetics, CHU Bordeaux, Bordeaux, France  
<sup>2</sup>Department of Dermatology, Paediatric Dermatology Unit, National Reference Center for Rare Skin Disorders, CHU Bordeaux, Bordeaux, France  
<sup>3</sup>Maladies Rares: Génétique et Métabolisme (MRGM), Inserm U1211, University of Bordeaux, Bordeaux, France

Correspondence  
Aurélien Trimouille, CHU Bordeaux, Department of Medical Genetics, Place Amélie Raba Léon, 33076 Bordeaux Cedex, France.

PUM1 has been very recently reported as responsible for a new form of developmental disorder named PADDAS syndrome. We describe here an additional patient with early onset developmental delay, epilepsy, microcephaly, and hair dysplasia, with a de novo heterozygous missense variant of PUM1: c.3439C > T, p(Arg1147Trp). This variant was absent from databases and predicted deleterious by multiple softwares. The same missense variant has been reported by Genovino et al. in a girl with much more severe epilepsy. Our report is in favor of a variable expressivity of PADDAS syndrome, and broadens the phenotypic spectrum with the description of hair dysplasia.

## KEYWORDS

hair dysplasia, intellectual disability, PUM1, whole-exome sequencing

## HUMAN DISEASE GENES WEBSITE SERIES

Home Professionals Parents Graph and Chart Contact

PUM1

To share and collect information about clinic management and research projects.

## Welcome

This website provides information on patients with mutations in the PUM1 gene, including clinical data, molecular data, and management and research options. PUM1 plays an important role in the development and function of neurons (brain cells). When the PUM1 gene does not function properly, due to a change in its DNA sequence (known as a mutation or pathogenic variant), it can lead to a range of neuropsychiatric difficulties, depending on the severity of the mutation.

Currently two distinct PUM1-related disorders are recognised. The more severe disease is an early-onset syndrome called Pumilio1-associated developmental disability, ataxia, and seizures (PADDAS). The features of this disease can vary from one individual to the next. A milder PUM1 mutation has been found in one family with a slowly progressive, adult-onset ataxia. This disease is called Pumilio1-related cerebellar ataxia, or PRCA.

This website was created to share and collect information about clinical and research projects on PUM1 and to gather more knowledge about patients with mutations in PUM1 with the goal of developing better treatments.

A/Professor Vincenzo Alessandro Genovino, PhD, Department of Genetics and Development, Columbia University Medical Center, New York, USA, vag2138@cumc.columbia.edu

Dr (Elizabeth) Emma Palmer (Clinical Geneticist), MD, Genetics of Learning Disability Service, Hunter Genetics, Waratah, NSW 2298, Sydney, Australia, Elizabeth.palmer1@health.nsw.gov.au

A/Professor Jimmy Lloyd Holder, Jr, MD (Pediatric Neurology), Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA, holder@bcm.edu

# UNCERTAIN OR NO DIAGNOSIS

— what next?

- $\frac{1}{4}$  -  $\frac{1}{2}$  children

There is a genetic condition but the **TEST** is not yet good enough to pick it up

RETEST



*No gene variants are found to explain the condition for which the test was done.*



*A variant is found in genes associated with the condition but the significance is not known (variants of unknown significance).*

MEDICARE  
ITEM  
??2-10 years  
?? moderate +  
?? grace  
period up to  
18 years

Whole genome  
sequencing

Exome  
Sequencing

Multi-gene  
panel

Single gene

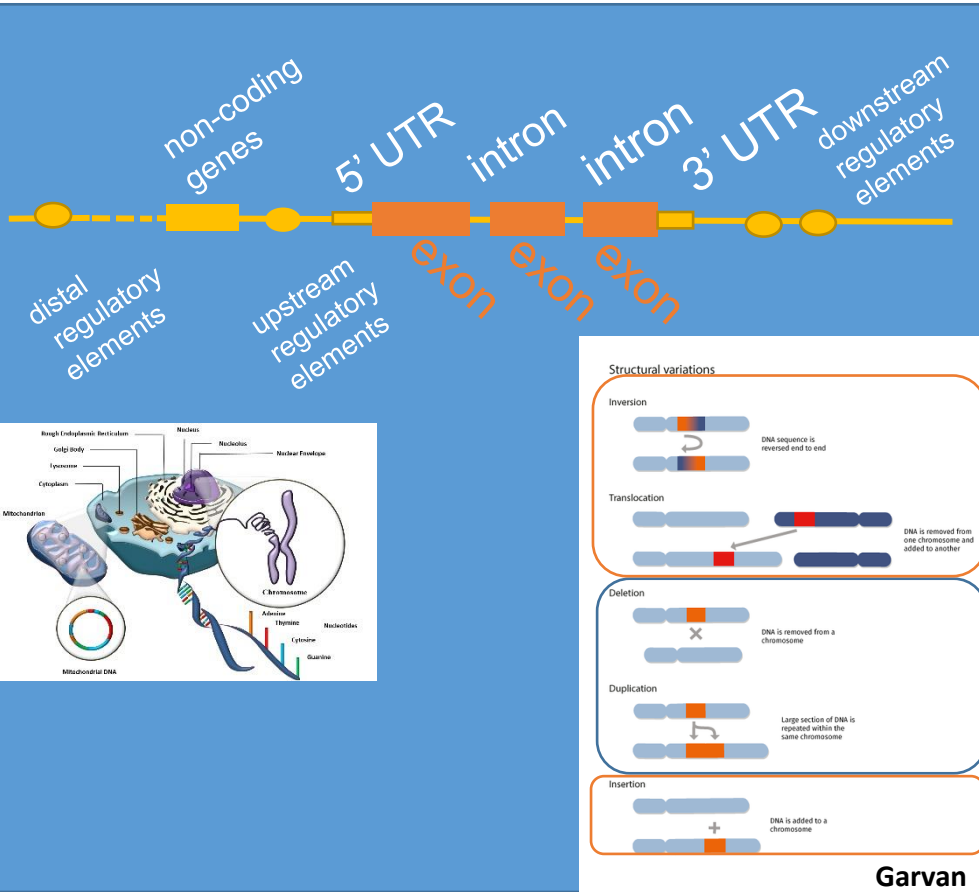
Looks at ALL of  
genetic code.  
Limitations in analysis,  
cost and time.

Can look at protein  
coding part of ~20,000  
genes. Increased  
chance of finding  
uncertain or  
incidental results.

Good test for some type of genetic  
conditions caused by relatively  
limited number of genes. Relatively  
fast and cheap. Lower chance of  
uncertain result (VOUS) or incidental  
finding.

May be best test if clinical diagnosis  
points to one gene and you want best  
coverage of that gene

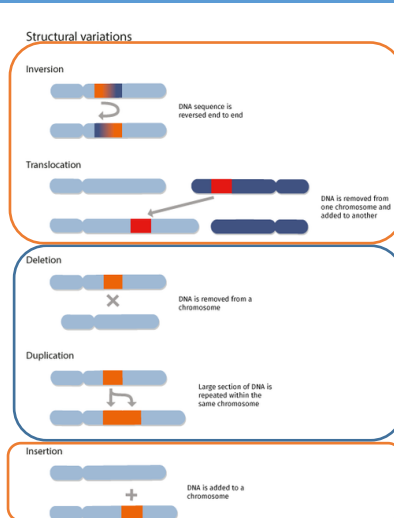
# WGS potential



- Broadest detection of genetic alterations which can cause a disease in one single test

## Why?

- (regions of) genes not covered by multigene panel (MGP) or exome
- non-coding variants
- variants in mitochondrial genome
- structural variants
  - small and large deletions/ duplications
  - complex e.g. inversions, translocations, insertions
- others e.g. expansion variants



Garvan



**HNEkidshealth**  
Children, Young People & Families



## Cost

(>\$3,500 per patient)

## Assessment of pathogenicity of non coding variants

(MANY variants of uncertain significance)





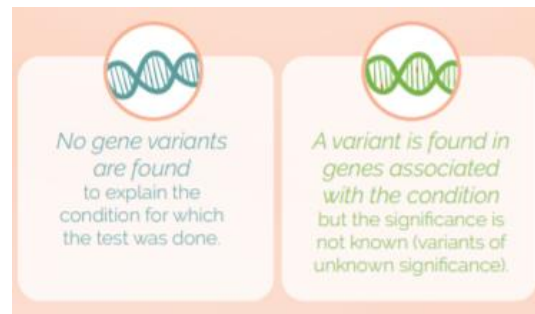




# UNCERTAIN OR NO DIAGNOSIS

– what next?

- $\frac{1}{4}$  -  $\frac{1}{2}$  children



There is a genetic condition but the **ANALYSIS** is not yet good enough to pick it up

There is a genetic condition but the **TEST** is not yet good enough to pick it up

- The condition is **not genetic** or is more complex



CONSIDER RESEARCH

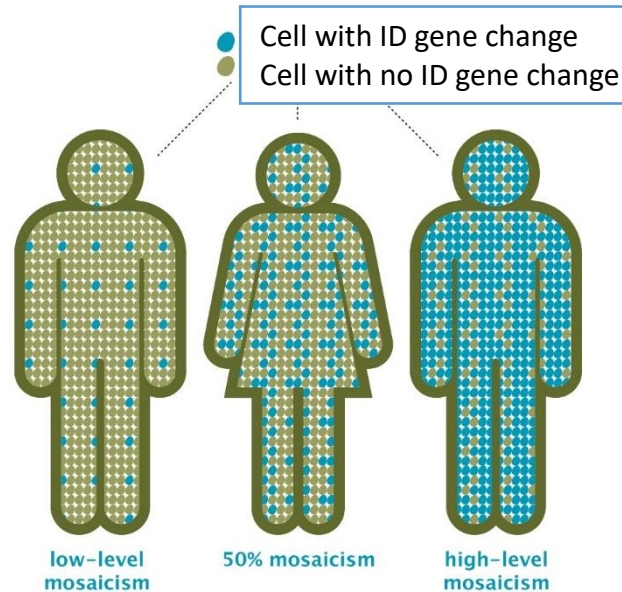


# Mosaicism?

- This cat has mosaicism
- Some of it's hair cells carry a gene change for fur pigment, some don't

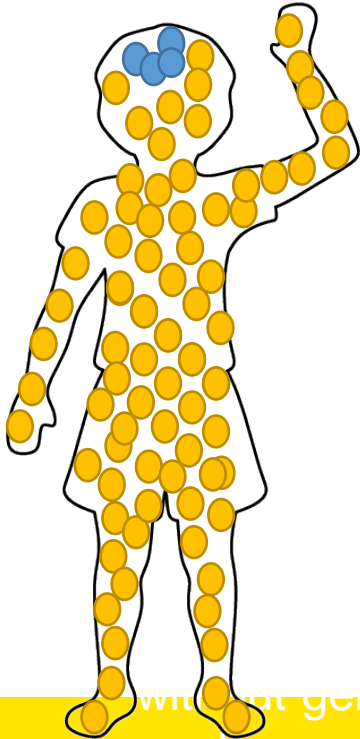


The same can be true for people



Standard blood testing can 'miss' genetic mosaicism

# A child may be undiagnosed from a blood test because they have mosaicism



- Here the gene change is just in the child's brain
- A standard genetic blood test is not likely to find the change
- More specialist testing may be required

without gene  
change



**HNEkidshealth**  
Children, Young People & Families

# More than one gene change, gene-environment interactions



Connect Hub ,  
Search Autism CRC  
Our programs Knowledge Centre Get involved News About us Contact us

Home > Our programs

## Early Years Program 1

In Program 1: Early Years, we are working on earlier and more accurate diagnosis of autism to achieve the right interventions as early as possible. By harnessing existing knowledge of autism to improve diagnosis, as well as using breakthroughs in biological research to identify subtypes of autism and the most effective interventions for these subtypes, we aim to provide detailed information on the most effective interventions for children on the spectrum. This is an exciting revolution in the way in which we understand and support children with autism.

### Where did we

- Parents' concerns
- GP reluctantly referring
- Autism undiagnosed
- Trial and error of

### Where we are going?

...ed by early childhood healthcare professionals and ... appropriate clinician ... using a standardised national

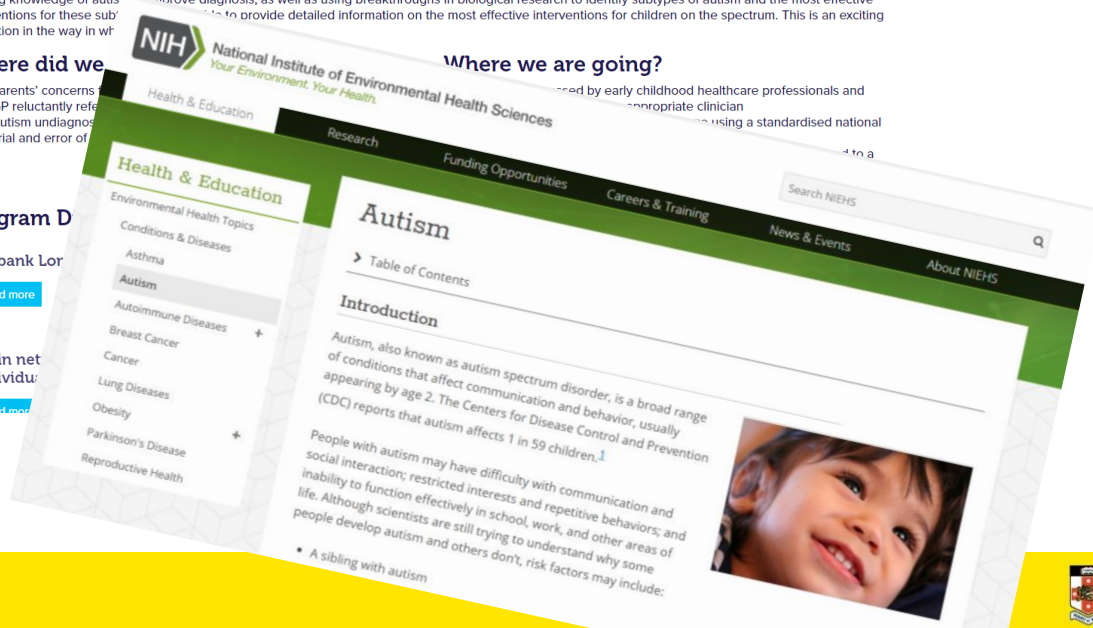
### Program D

Biobank Lor

[Read more](#)

Brain net  
individu

[Read more](#)

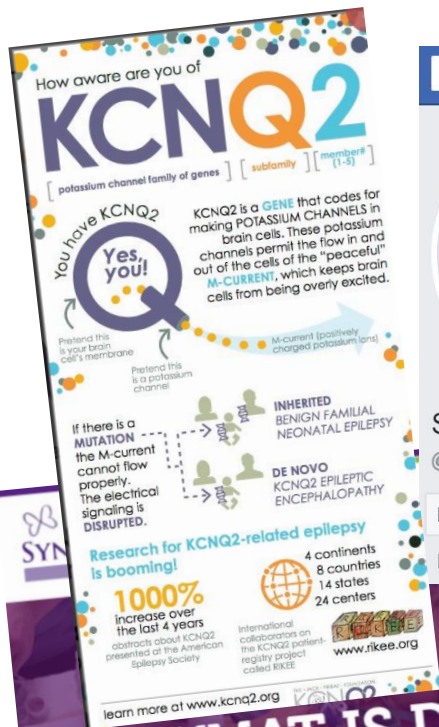


# A sure diagnosis...what next?



*One or more  
gene variants  
are found  
to explain the  
condition for which  
the test was done.*

# Parent developed resources can be great start



## WHAT IS DRAVET SYNDROME?

Dravet syndrome, also known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a rare and catastrophic form of epilepsy that begins in infancy, with an estimated incidence rate of 1:16,000 to 1:21,000 in the general population.



# CLINGEN

Search: Gene\* Gene... Go

## SCN2A

<b>Name</b>	SCN2A	<b>External Resources</b>	View external resources
<b>HGNC ID</b>	HGNC:10588	<b>ClinVar Variants</b>	View ClinVar Variants
<b>Cytogenetic Location</b>	2q24.3	<b>GeneReviews</b>	View GeneReviews
<b>Haploinsufficiency</b>	Sufficient Evidence		
<b>Triplosensitivity</b>	No Evidence		

ClinGen's Curation Summaries External Genomic Resources ClinVar Variants

SCN2A



<https://www.clinicalgenome.org/>

## SCN2A

<b>Name</b>	SCN2A	<b>External Resources</b>	View external resources
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ClinGen's Curation Summaries External Genomic Resources ClinVar Variants

External Resources

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Organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.  
(MedGen: Genetics Summary)
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Genetics  
Home  
Reference:  
patient  
information



Number  
included  
genes  
increasing

# GENETICS HOME REFERENCE : GENE SPECIFIC INFORMATION



Genetics Home Reference  
Your Guide to Understanding Genetic Conditions

epilepsy genetics

Health Conditions

Genes

Chromosomes & mtDNA

Classroom

Help Me Understand Genetics

## SCN1A gene

sodium voltage-gated channel alpha subunit 1

Printable PDFOpen AllClose All

► Normal Function

▼ Health Conditions Related to Genetic Changes

► Familial hemiplegic migraine

▼ Genetic epilepsy with febrile seizures plus

Hundreds of mutations in the *SCN1A* gene have been found to cause genetic epilepsy with febrile seizures plus (GEFS+), which is a spectrum of seizure disorders of varying severity. These conditions include simple febrile (fever-associated) seizures, which start in infancy and usually stop by age 5, and febrile seizures plus (FS+). FS+ involves febrile and other types of seizures, including those not related to fevers (afebrile seizures), that continue beyond childhood. The GEFS+ spectrum also includes other conditions, such as Dravet syndrome (also

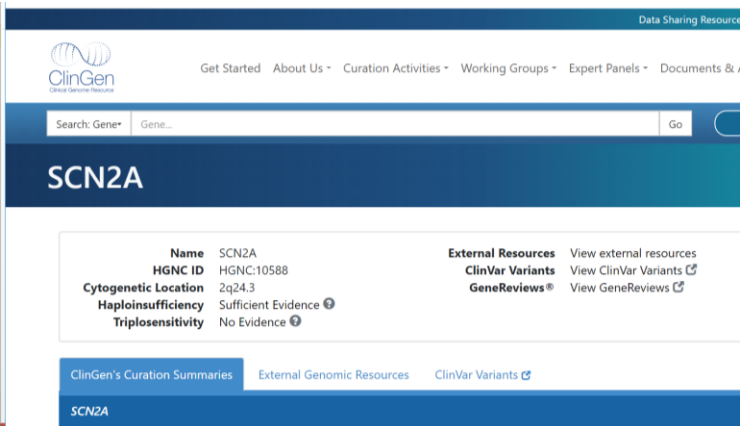
Related Information

[What is a gene mutation and how do mutations occur?](#)

[What kinds of gene mutations are possible?](#)


More about [Mutations and Health](#)

# CLINGEN



The screenshot shows the ClinGen website interface. At the top, there's a navigation bar with links like 'Get Started', 'About Us', 'Curation Activities', 'Working Groups', 'Expert Panels', and 'Documents &'. Below this is a search bar with 'SCN2A' entered. The main content area displays gene information for SCN2A, including HGNC ID (HGNC:10588), Cytogenetic Location (2q24.3), Haploinsufficiency (Sufficient Evidence), and Triplosensitivity (No Evidence). There are also links to 'External Resources', 'ClinVar Variants', and 'GeneReviews'. A blue arrow points from this section towards the URL at the bottom.

## SCN2A



The screenshot shows the GeneReviews website interface for the SCN2A gene. It features a table with gene information: Name (SCN2A), HGNC ID (HGNC:10588), Cytogenetic Location (2q24.3), Haploinsufficiency (Sufficient Evidence), and Triplosensitivity (No Evidence). There are also links to 'External Resources', 'ClinVar Variants', and 'GeneReviews'. Below this, there's a section titled 'ClinGen's Curation Summaries' with tabs for 'External Genomic Resources' and 'ClinVar Variants'. The 'External Genomic Resources' tab is active, showing a list of resources: MedGen: Genetics Summary, Genetic Practice Guidelines: Gene, GTR: Gene Tests, CPIC Pharmacogenomics Prescribing Guidelines, PharmGKB: Gene, OMIM: Gene, Genetics Home Reference, Gene Reviews, ClinVar - Gene, 1000 Genomes, and NCBI Browser. A blue arrow points from the ClinGen website screenshot to the GeneReviews website screenshot.

**GeneReviews:**  
Expert written  
clinical  
summaries

<https://www.clinicalgenome.org/>



<https://www.ncbi.nlm.nih.gov/books/NBK1116/>

## GRIN2A-Related Speech Disorders and Epilepsy

Kenneth A Myers, MD, PhD, FRCPC and Ingrid E Scheffer, FAA, FAHMS, FRACP, MBBS, PhD.

► [Author Information](#)

Initial Posting: September 29, 2016.

*Estimated reading time: 21 minutes*

### Summary

[Go to:](#) ▼

**Clinical characteristics.** *GRIN2A*-related speech disorders and epilepsy are characterized by speech disorders in all affected individuals and a range of epilepsy syndromes present in about 90%. Severe speech disorders observed can include dysarthria and speech dyspraxia, and both receptive and expressive language delay/regression; more mildly affected individuals may display subtly impaired intelligibility of conversational speech. Epilepsy features include seizure onset usually between ages three and six years, focal epilepsy with language and/or global developmental regression, and electroencephalogram (EEG) showing continuous spike-and-wave discharges in sleep or very active centroparietal discharges. Seizure types include seizures associated with aura of perioral paresthesia, focal or focal motor seizures (often evolving to generalized tonic-clonic), and atypical absence seizures. Epilepsy syndromes can include: Landau-Kleffner syndrome (LKS), epileptic encephalopathy with continuous spike-and-wave during sleep

[Go to:](#) ▼

individual diagnosed with a *GRIN2A*-related speech disorder and

logist

f initial assessment)

o capture slow-wave sleep (if not done at the time of initial  
r excluding continuous spike-and-wave in sleep (CSWS).

netic counselor

at speech/language deficits may benefit from therapy by a speech  
o the specific speech disorder, often include linguistic  
nication [Murray et al 2014].

tic drugs (AEDs). Many different AEDs may be effective, and  
no one medication has been demonstrated to be effective specifically for *GRIN2A*-related disorders.

In one individual a good response to refractory epilepsy was achieved with topiramate [Venkateswaran et al 2014].

# CLINGEN

CLINGEN  
Genetic Genomics Resource

Get Started About Us Curation Activities Working Groups Expert Panels Documents & Reports

Search: Gene\* Gene... Go

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SCN2A



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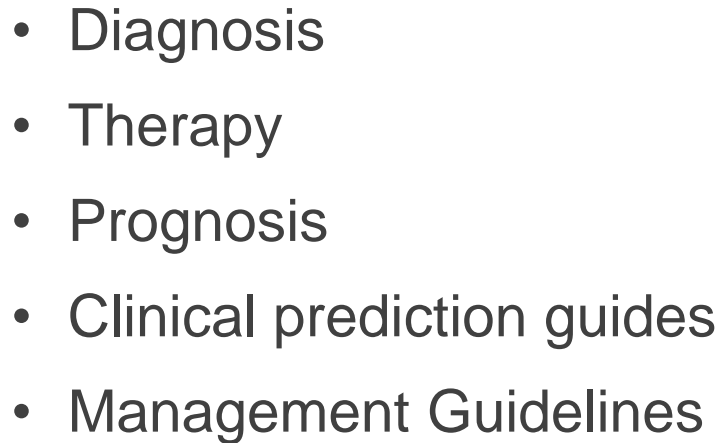
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Practice  
guidelines

<https://www.clinicalgenome.org/>

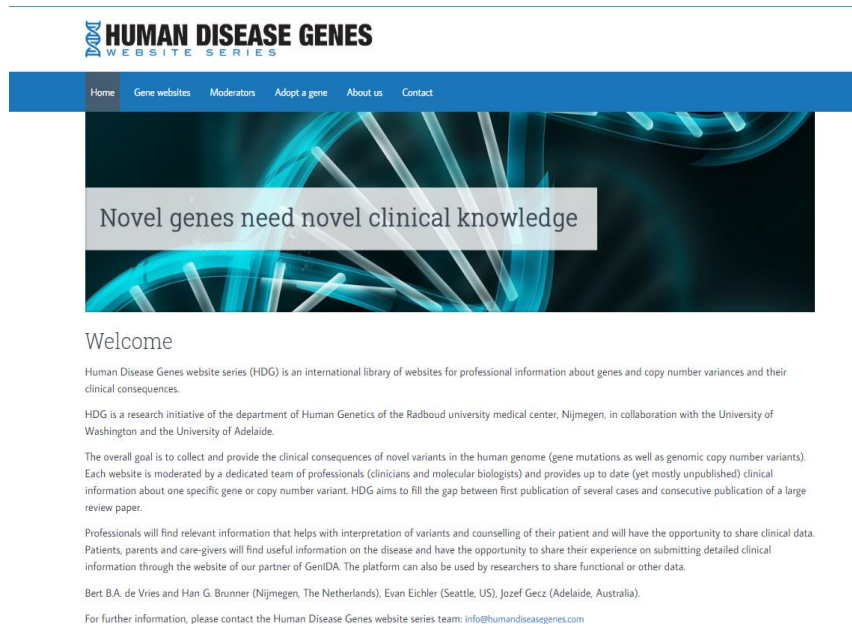
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<https://www.ncbi.nlm.nih.gov/medgen/>



# VERY NEW GENES



**HUMAN DISEASE GENES**  
WEBSITE SERIES

Home Gene websites Moderators Adopt a gene About us Contact

Novel genes need novel clinical knowledge

Welcome

Human Disease Genes website series (HDG) is an international library of websites for professional information about genes and copy number variations and their clinical consequences.

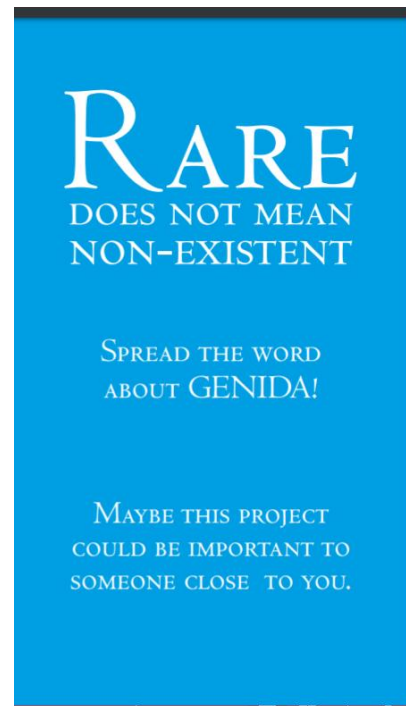
HDG is a research initiative of the department of Human Genetics of the Radboud university medical center, Nijmegen, in collaboration with the University of Washington and the University of Adelaide.

The overall goal is to collect and provide the clinical consequences of novel variants in the human genome (gene mutations as well as genomic copy number variants). Each website is moderated by a dedicated team of professionals (clinicians and molecular biologists) and provides up to date (yet mostly unpublished) clinical information about one specific gene or copy number variant. HDG aims to fill the gap between first publication of several cases and consecutive publication of a large review paper.

Professionals will find relevant information that helps with interpretation of variants and counselling of their patient and will have the opportunity to share clinical data. Patients, parents and care-givers will find useful information on the disease and have the opportunity to share their experience on submitting detailed clinical information through the website of our partner of GENIDA. The platform can also be used by researchers to share functional or other data.

Bert B.A. de Vries and Han G. Brunner (Nijmegen, The Netherlands), Evan Eichler (Seattle, US), Jozef Gecz (Adelaide, Australia).

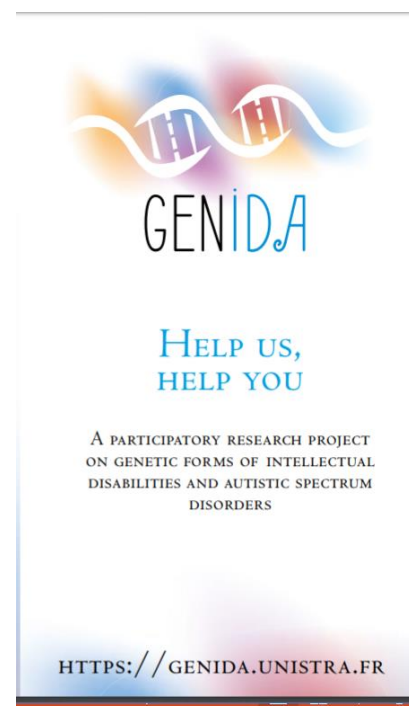
For further information, please contact the Human Disease Genes website series team: [info@humandiseasegenes.com](mailto:info@humandiseasegenes.com)



**RARE**  
DOES NOT MEAN  
NON-EXISTENT

SPREAD THE WORD  
ABOUT GENIDA!

MAYBE THIS PROJECT  
COULD BE IMPORTANT TO  
SOMEONE CLOSE TO YOU.



**GENIDA**

HELP US,  
HELP YOU

A PARTICIPATORY RESEARCH PROJECT  
ON GENETIC FORMS OF INTELLECTUAL  
DISABILITIES AND AUTISTIC SPECTRUM  
DISORDERS

[HTTPS://GENIDA.UNISTRA.FR](https://genida.unistra.fr)

## Clinical Characteristics

Genesites Sites > Home > Parents > Clinical Characteristics

### Features of CLCN4 related genetic disorder

Male individuals with a *CLCN4*-related disorder will have some degree of developmental delay/ intellectual disability. The severity of learning difficulty can also vary within individuals with the same *CLCN4* gene change, even within the same family. Females who carry a *CLCN4* gene changes have been reported to have normal intelligence, borderline intellectual disability/ learning difficulties, or more severe intellectual disability. Intellectual disability is more common in females if the genetic change is a new genetic change for that individual ('de novo' change), rather than an inherited genetic change.

It is relatively common for individuals with a *CLCN4*-related condition to have particular delays in their speech and language development. Some individuals have ongoing speech difficulties causing stutters/indistinct speech (articulation difficulties).

Autistic behaviours have been reported in some individuals with *CLCN4* gene changes. Other behavioural differences reported in some people with *CLCN4* gene changes include a degree of hyperactivity, aggression and/or mood swings. Other individuals are described to be more introverted or have no significant behavioural issues. There is probably an increased chance of mental health conditions (for example anxiety and depression) in both males and females with a *CLCN4* gene change.

Approximately 50% of individuals with a *CLCN4* disorder will have seizures. These may not be a major concern and easy to treat with medication. However some patients have severe seizure patterns (epileptic encephalopathies). Some individuals have been described to have difficulties with an unsteady gait (ataxia) or have increased reflexes in their limbs and a tendency to walk on their toes (lower limb spasticity). Other individuals have a completely normal neurological examination. Many individuals with a *CLCN4*-related condition were described as being quite floppy as a baby (infantile hypotonia). Some older individuals with *CLCN4*-related condition have had brain imaging suggestive of a smaller brain size with age (cortical atrophy) or changes in the appearance of the white matter in their brains. Other individuals have had normal brain imaging.

Some adult males with *CLCN4*-related disorder have been described as having a slightly longer face with a more prominent chin, but generally individuals do not look significantly different from other (unaffected) members of their family and we are not aware of a particularly increased chance of other medical conditions.

Most of these features become present by early childhood. This is a genetic condition and is not related to environmental exposures or events during pregnancy or in early infant life.

<https://humandiseasegenes.nl/>

<https://genida.unistra.fr/>

Contact



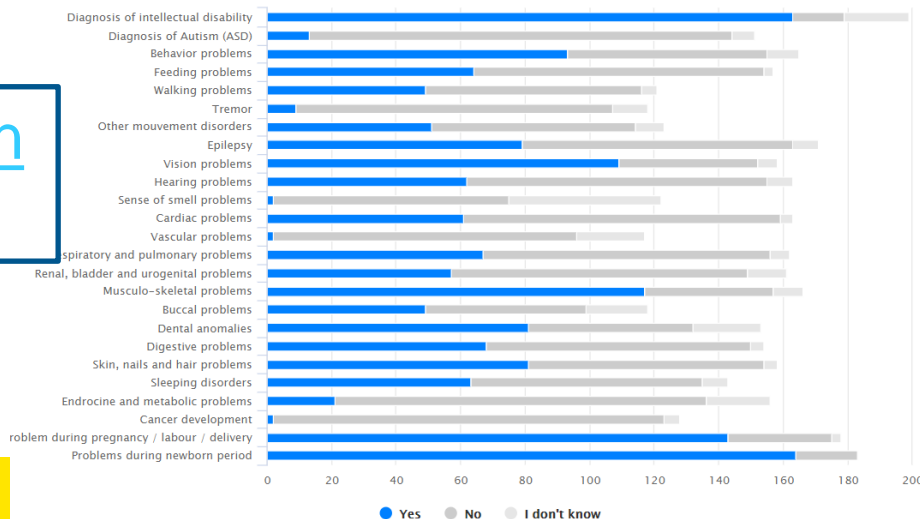
English

elizabeth.palmer@hnehea

\*\*\*\*\*

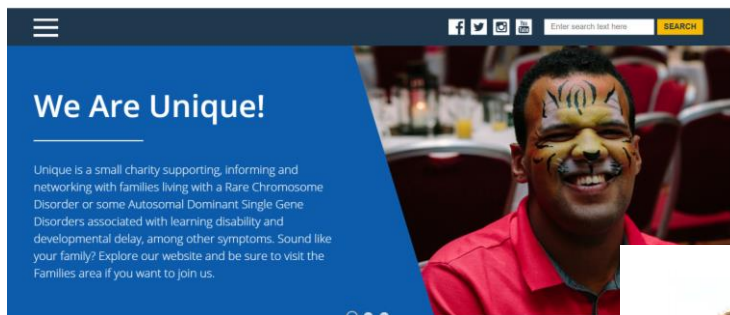
## Cohorts Overview

### Koolen-deVries syndrome (KdVS)



# UNIQUE

<https://www.rarechromo.org/>



"For all of her delays Autumn is a smart little girl who knows how to manipulate situations to get what she desires. She is a toddler at heart, and while her body progresses much faster than her mind, we are often reminded to approach the world much more slowly, and to look at things differently, as she would see them. Autumn functions at varying degrees between a 1 and 2½ year old child in a 6 year old's body. Physically she is mostly capable, and although she cannot yet run she is quite a power walker - so we focus on her areas of greatest need. She needs a lot of repetition to really learn something. What might take typical kids 10 tries will take her 100: consistency and constancy are important. Her receptive language (understanding) is more advanced than her expressive language (talking) and she clings to key words and phrases that she understands. If you happen to say 'shoes', she will get her shoes, and want you to put them on with the expectation that you are now going out. We have to be selective in our wording so as to not create a situation that will cause her to melt down." - age 6

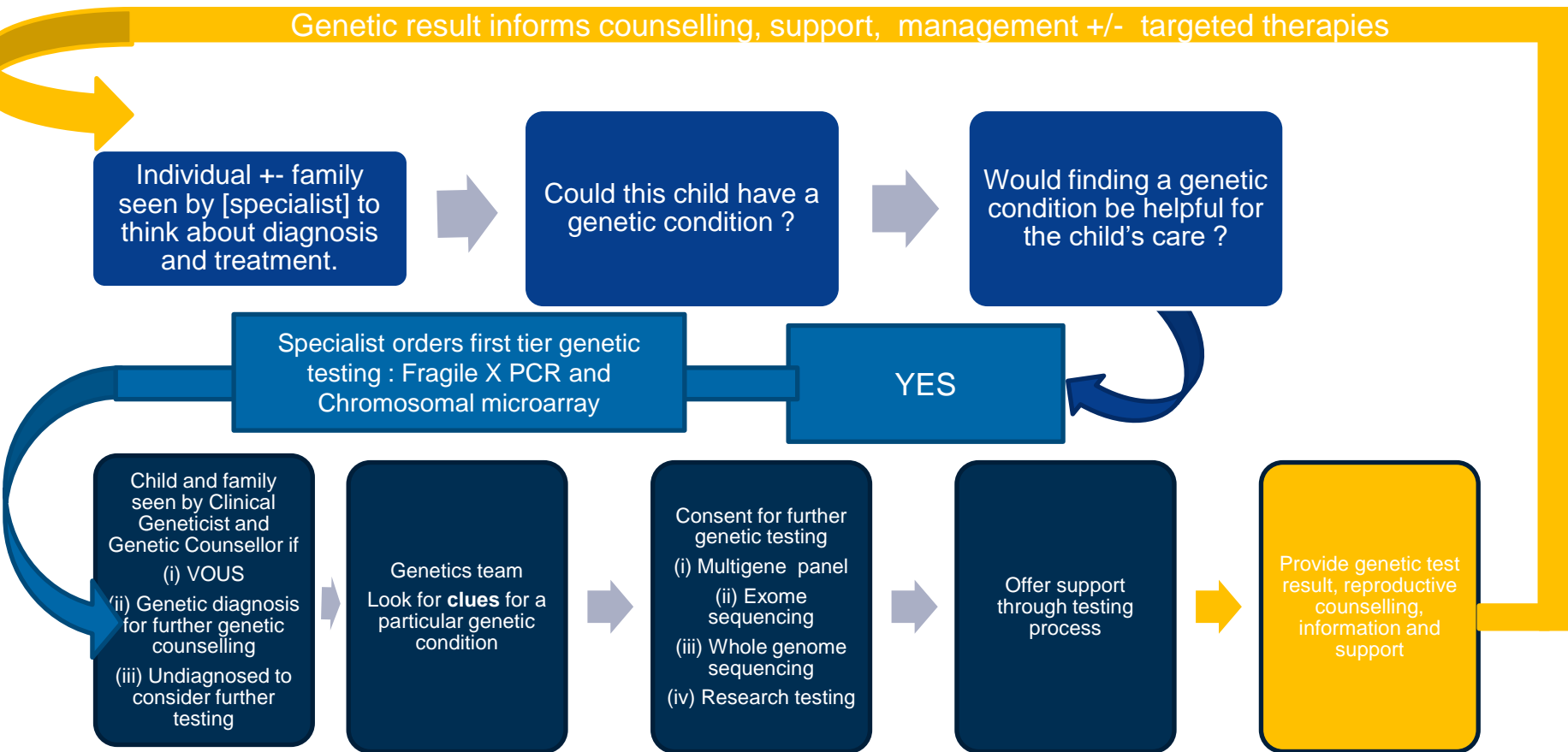


# Questions ?



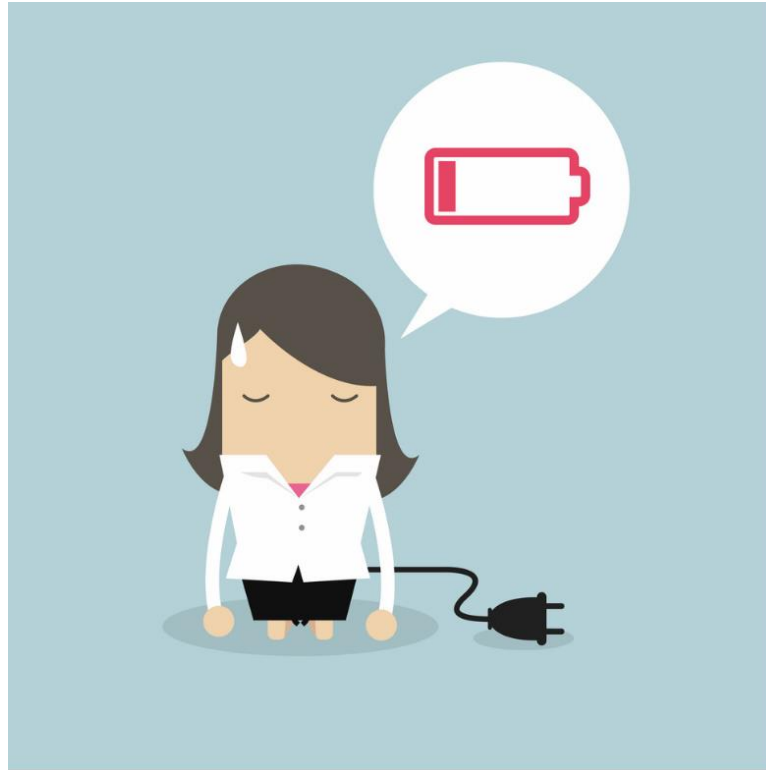
Why should I bother about this: why  
don't I just refer to Clinical  
Genetics for all testing?

# Traditional genetic testing process





# But this is unsustainable

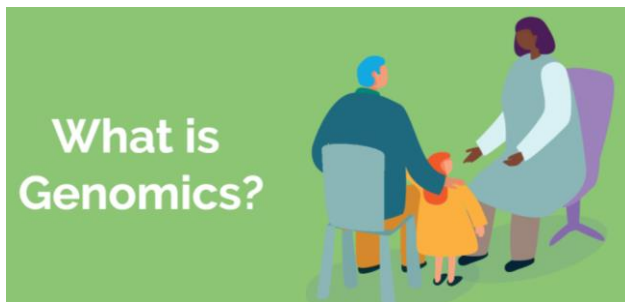


# Upskilling yourself

Two great starting points:

Australian Genomics Health Alliance

<https://www.genomicsinfo.org.au>



Centre for Genetics Education:

<https://www.genetics.edu.au>

## Genes and Genetics



Your **genes** are the instructions for building your body and they tell your body how to work. They determine things like your eye colour, your height or your risk for a health condition.

You have around 20,000 genes. Each of your genes are made up of **DNA**, which contains a four-letter chemical code (**A, T, C and G**). Each gene has thousands of letters, and your entire genetic code contains 6 billion letters. It would take 57 years to read out your DNA sequence.



Your genes act as templates for messages, which cells in your body use to make **proteins**. These proteins are the building blocks of your body. Only about 2% of the genetic information you have, is actually used for making proteins.

Most genes come in two copies, one inherited from your mother, the other from your father.



Your genes are arranged along large tightly-packed structures called **chromosomes**. Most of us have 46 chromosomes, in 23 pairs. Each of your chromosomes contains many genes. If unravelled, the chromosomes from just one of your cells, would stretch for 2 metres.

You share 99.9% of your genetic information with other people. It is the other 0.1% that **makes you unique**.

The genetic differences you have can be inherited from your parents or can happen randomly. Generally, these genetic differences are part of normal human variation, and each person's genome contains millions of these variants.

However, sometimes genetic variants can disrupt the normal function of genes and cause health problems. For example, through gaining an extra chromosome, or having single letters changed, missing or duplicated in the genetic code. These variants are sometimes called mutations.



Your genes are just one element that contributes to your appearance, your body function, or your risk of developing a condition. Your diet, lifestyle and environment also come into play.

However, as we gain more understanding of genes, we can also better understand the role of genetics in health and disease, and improve healthcare for you, and all Australians.

# Summary: We owe this to our patients.

- Genomic testing should be considered as part of clinical care for individuals with neurodevelopmental disorders
  - it dramatically improves diagnostic yield
  - It has important impacts for child and their family
  - It is required to be 'precision medicine' ready
- To deliver genomic medicine we need to understand the capabilities, limitations and possible pitfalls of the tests we order.
- We need to better understand most appropriate testing when cognition normal.
- ...thank you for listening.



# Questions ?

