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

Presenter
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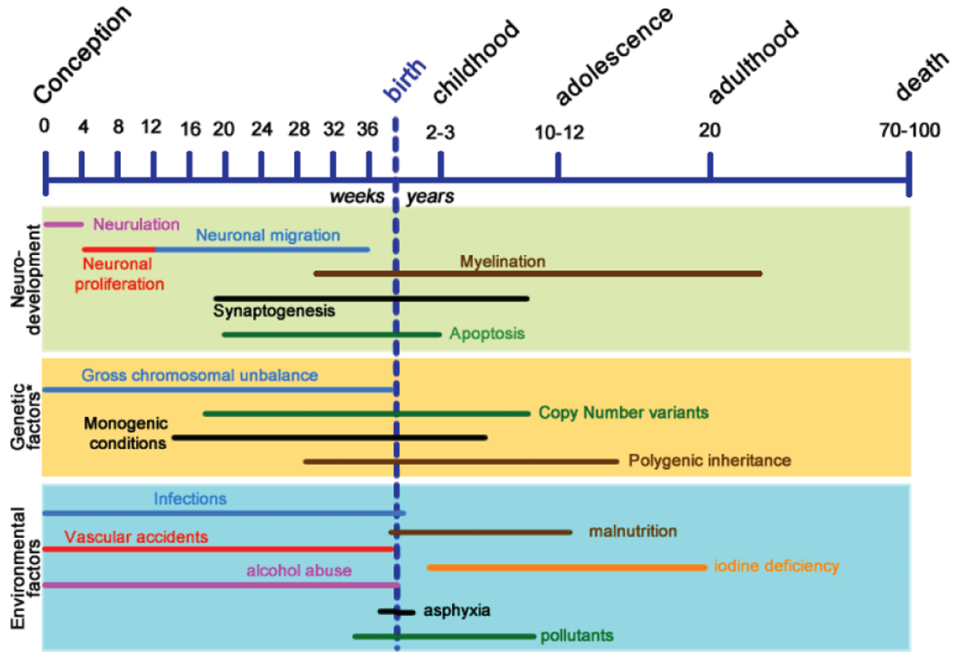
Talk Overview

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?

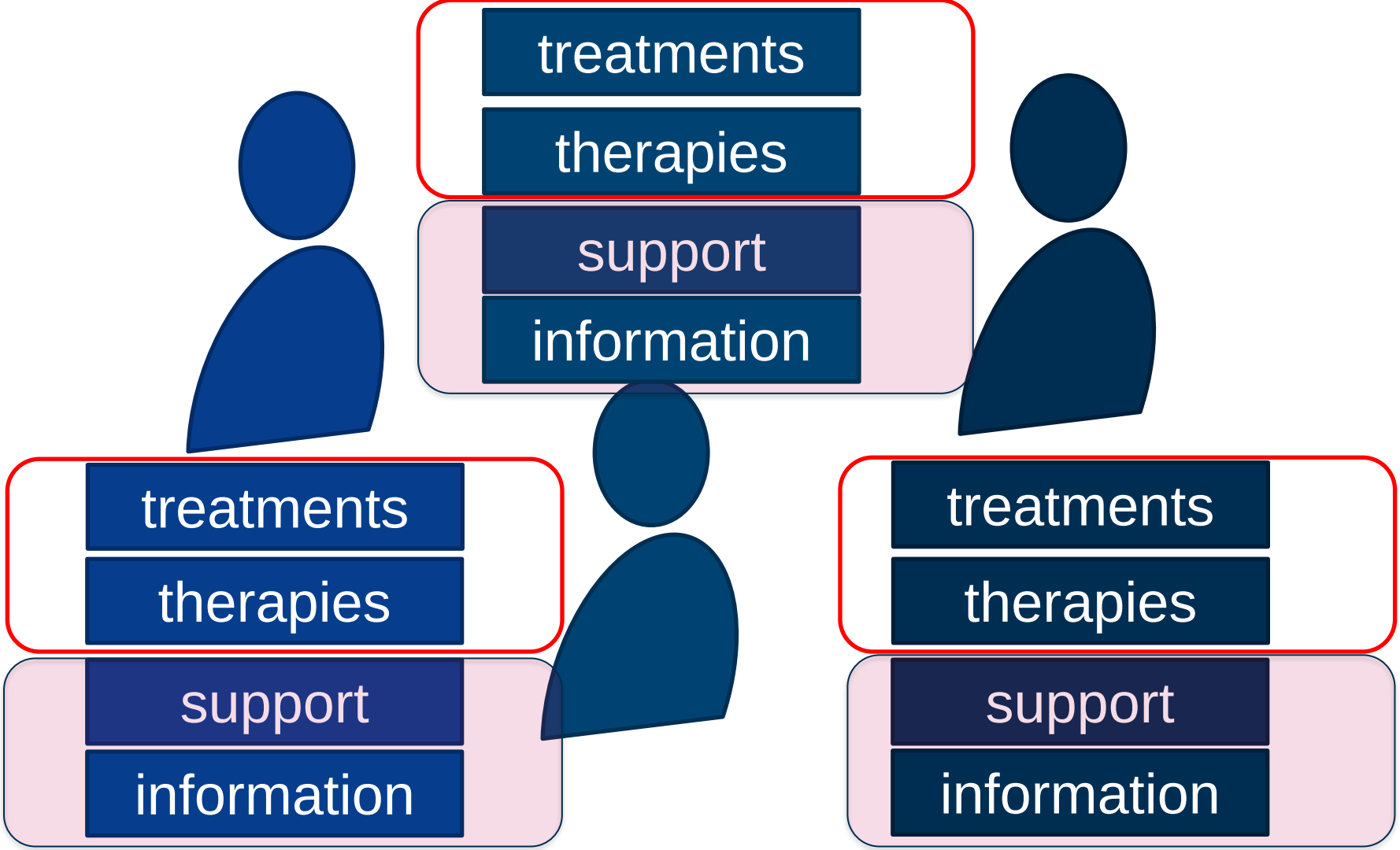


ID caused by a variety of environmental and genetic causes, often combined with each other.

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

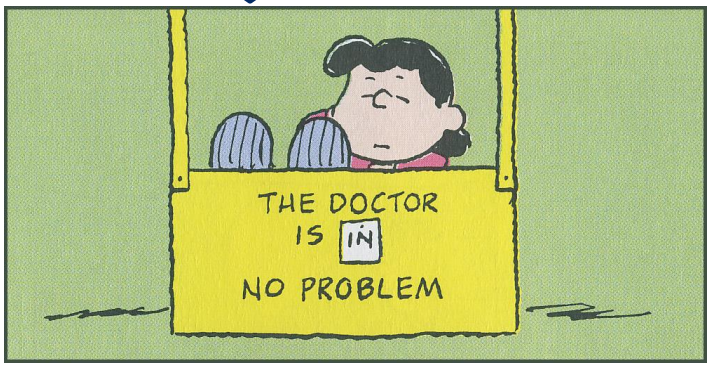
But….genetics can be

confusing a different language worrying

…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



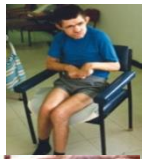
The genetic test did not find anything

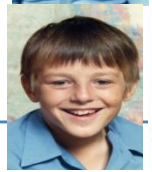
But when it works….. it can be magic

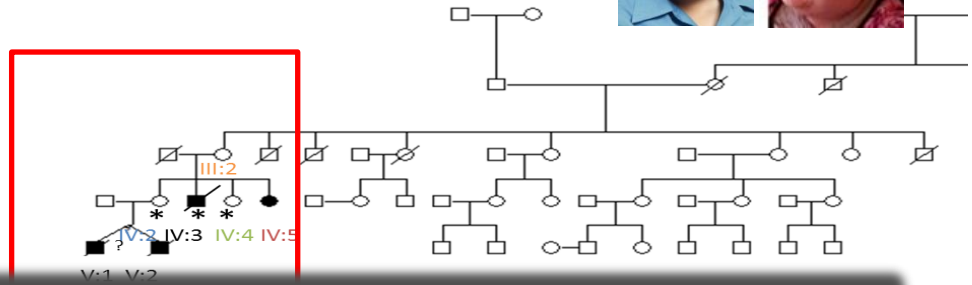
One family's story

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

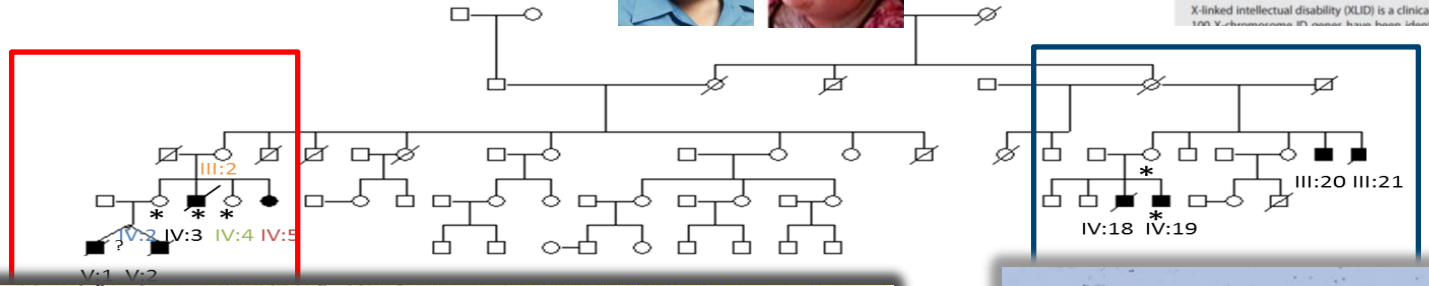
www.nature.com/mp

ORIGINAL ARTICLE

X-exome sequencing of 405 unresolved famil
novel intellectual disability genes

H Hu[1,41], SA Haas[2,41], J Chelly[3,4], H Van Esch[5], M Raynaud[6,7,8], APM de Brouwer[9], S Weinert[10], F Laumonnier[6,7], T Zemojtel[2], MI Love[2], H Richard[2], A-K Emde[2], M Bienek[1], C Jensen[1], M Han M Feldkamp[10], W Wissink-Lindhout[9], N Lebrun[3,4], L Castelnau[3,4], J Rucci[3,4], R Montjean[3,4], O D M Shaw[16,17], MA Corbett[16,17], A Gardner[16,17], S Willis-Owen[16,18], C Tan[16], KL Friend[19], S Belet[1] M Jimenez-Pocquet[6], M-P Moizard[6,7,8], N Ronce[6,7,8], R Sun[2], S O'Keeffe[2], R Chenna[2], A van Bo L Christie[20], J Boyle[20], E Haan[16,19], J Nelson[21], G Turner[20], G Baynam[21,22,23,24], G Gillessen-Kaes B Budny[28], M Badura-Stronka[29], A Latos-Bieleńska[29], LB Ousager[30], P Wieacker[31], G Rodríguez A Dufke[34], M Cohen[35], L Van Maldergem[36], C Vincent-Delorme[37], B Echenne[38], B Simon-Bouy K Devriendt[5], R Ullmann[1,42], M Vingron[2], K Wrogemann[1,40], TF Wienker[1], A Tzschach[1], H van W Chen[1,10], H-H Ropers[1] and VM Kalscheuer[1]

X-linked intellectual disability (XLID) is a clinically and genetically heterogeneous disorder. Dur



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20th-2-1980

Dear Doctor,

While reading the Subnormal Child News welfare news, I came across an article written by you. Named X-linked mental retardation. I find this article is connected to the mental retardation 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[1,2], T Stuhlmann[3,4], S Weinert[3,4], E Haan[5,6], H Van Esch[7], M Holvoet[7], J Boyle[1], M Leffler[1], M Raynaud[8,9,10], C Moraine[8,9,10], H van Bokhoven[11], T Kleefstra[11], K Kahrizi[12], H Najmabadi[12], H-H Ropers[13], MR Delgado[14,15], D Sirsi[14], S Golla[14], A Sommer[16], MP Pietryga[16], WK Chung[17], J Wynn[17], L Rohena[18], E Bernardo[18], D Hamlin[18], BM Faux[18], DK Grange[19], L Manwaring[19], J Tolmie[20], S Joss[20], DDD Study[21], JM Cobben[22], FAM Duijkers[23], JM Goehringer[24], TD Challman[24], F Hennig[25], U Fischer[25], A Grimme[25], V Suckow[25], L Musante[13], J Nicholl[26], M Shaw[5,27], SP Lodh[2], Z Niu[28], JA Rosenfeld[28], P Stankiewicz[28], TJ Jentsch[3,4], J Gecz[5,27], M Field[1] and VM Kalscheuer[13,25]

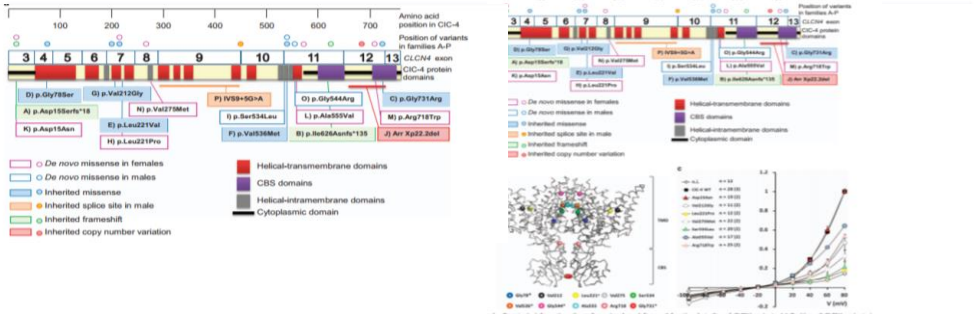

Table 1. Summary of phenotypic characteristics of male hemizygotes and female heterozygotes with *CLCN4* variants

	Affected males (n = 29) Proportion of total cohort (56%)	Heterozygous females with de novo variants (n = 5) Proportion of total cohort (10%)	Heterozygous females with inherited variants (n = 18) Proportion of total cohort (34%)
ID	29/29 (100%)	5/5 (100%)	2/18 (11%)
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%)	2/5 (40%)	0/2 (0%)
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%)	1/5 (20%)	2/18 (11%)
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.

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Questions ?

HNEkidshealth
Children, Young People & Families

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.

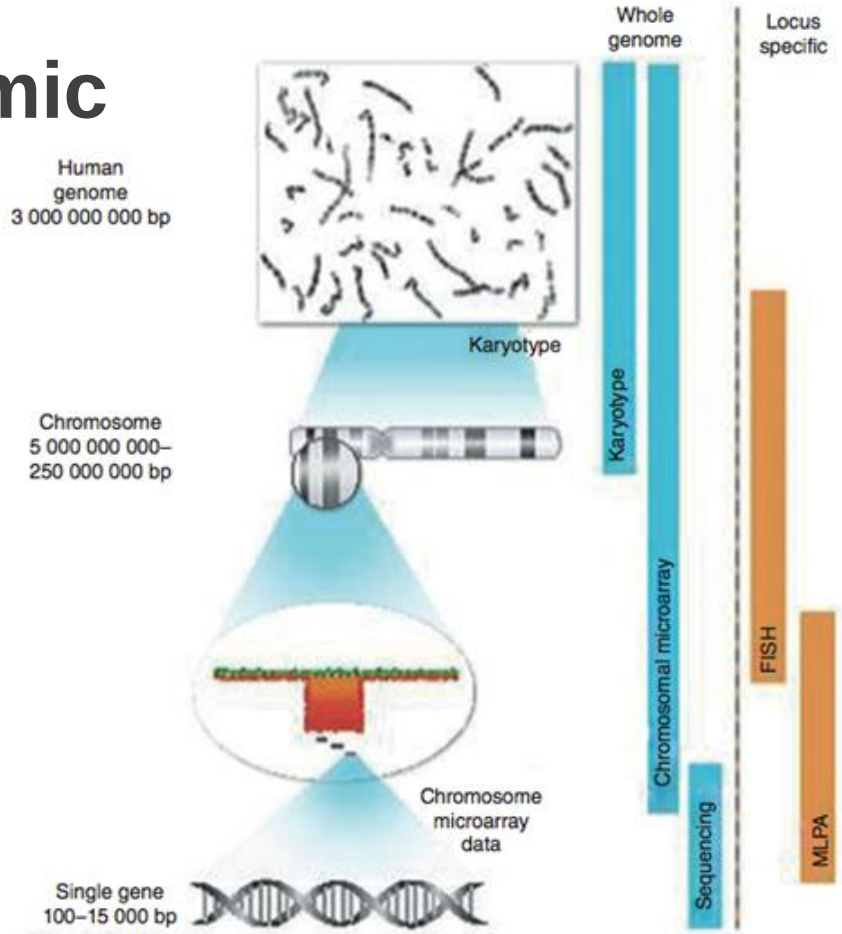
From the data, teams of scientists and doctors try to identify 1 or 2 variants that may be causing a medical condition.

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



Chromosomal microarray in Australia: a guide for paediatricians
Palmer, Peters and Mowat, 2012

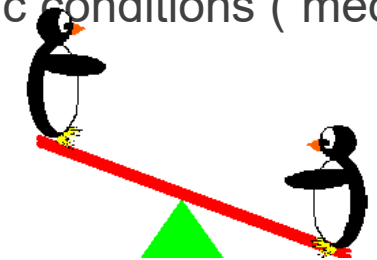
Your patients will be asking these questions

Questions to ask your doctor/genetic counsellor

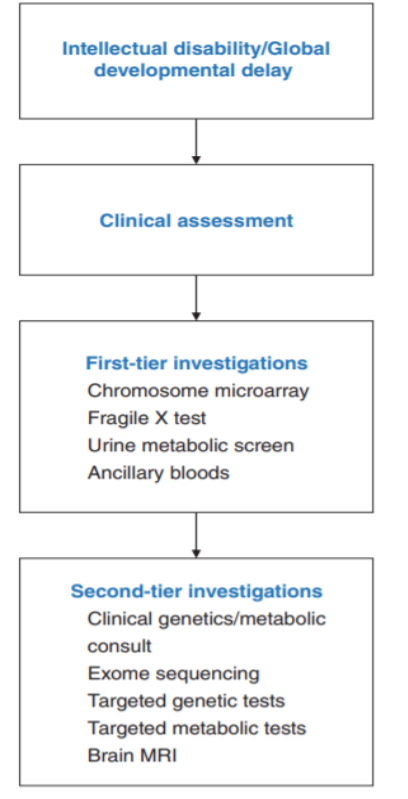
- What is the chance that the genomic test will identify the cause of my/my child's condition?
- How long will it take to get a result?
- Who will give me the result and how?
- Where will my genomic test be done?
- What is the cost to me (if any) of my genomic test?
- *What can this mean for other members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

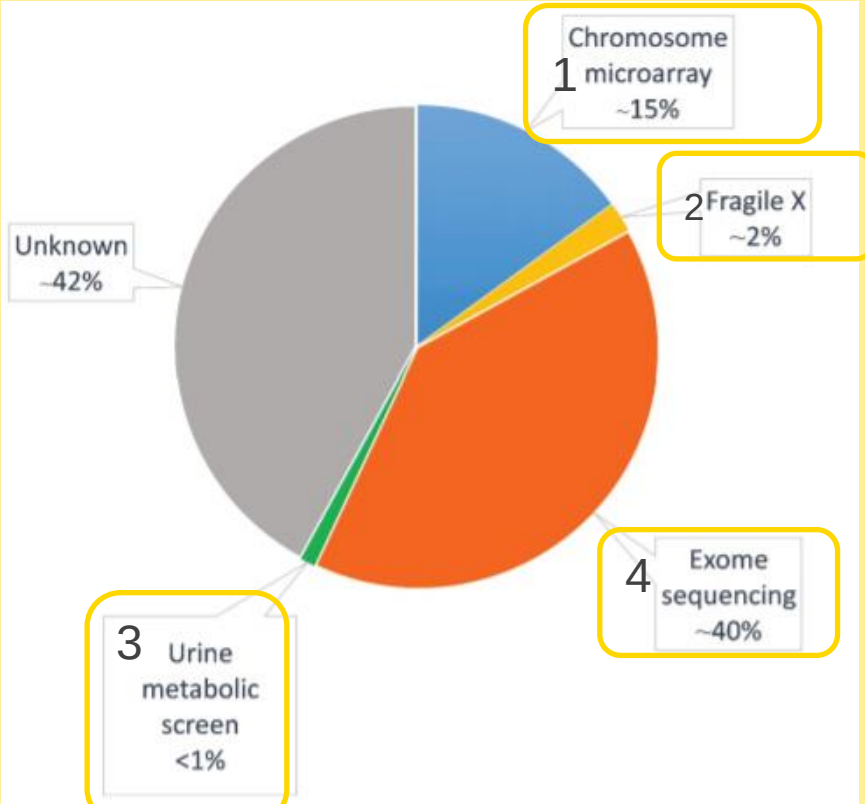
The best test for each patient is a balance of:

- 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





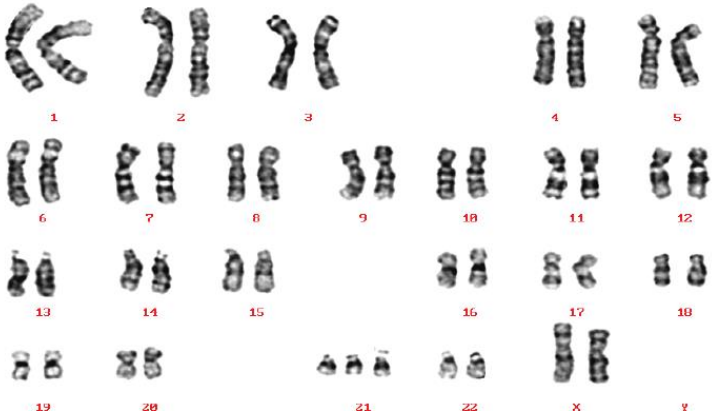
Amor DJ. J Paediatr Child Health. 2018 Oct;54(10):1154-1158. Investigating the child with intellectual disability.

Test 1: chromosomal microarray

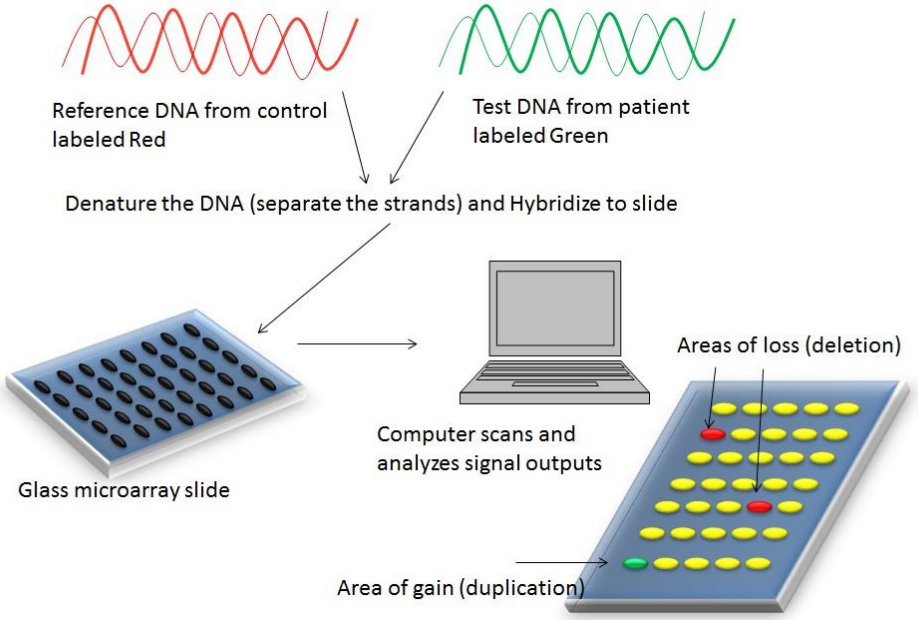
This test finds deletions or duplications of chromosomal material:

- **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[1]. 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,[1] Greg B Peters[2] and David Mowat[1,3]

[1]Department of Medical Genetics, Sydney Children's Hospital, Randwick, a
[3]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 eneration sequencing

toria McKay,[1] Daryl Efron,[1,2,3] Elizabeth E Palmer,[4,5,6] Susan M White,[3,7] Chris Pearson[8] and rgie Danchin[1,2,3]

partment of General Medicine, Royal Children's Hospital, [2]Murdoch Children's Research Institute, [3]Department of Paediatrics, University of Melbourne, torian Clinical Genetics Service, Murdoch Children's Research Institute, Melbourne, Victoria, [4]Sydney Children's Hospital, [5]Department of Women and ldren's Health, Randwick Campus, University of New South Wales, Sydney, [6]Genetics of Learning Disability Service, Newcastle, New South Wales and partment of General Medicine, Women's and Children's Hospital, Adelaide, South Australia, Australia


Journal of Paediatrics and Child Health

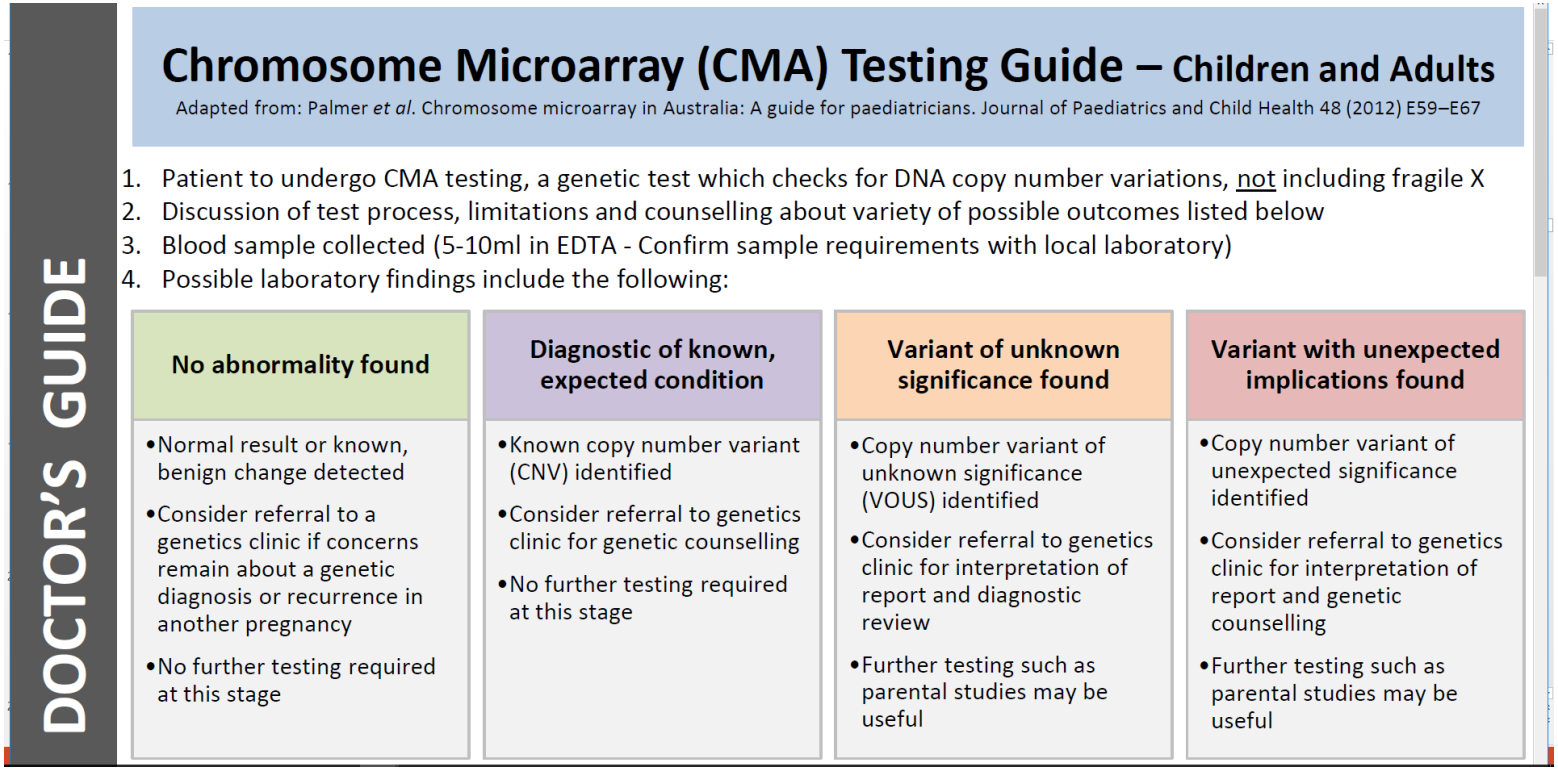
doi:10.1111/jpc.13869

VIEWPOINT

Chromosome microarray analysis: A soothing guide

Anne Ronan [1,2]

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
•Normal result or known, benign change detected •Consider referral to a genetics clinic if concerns remain about a genetic diagnosis or recurrence in another pregnancy •No further testing required at this stage	•Known copy number variant (CNV) identified •Consider referral to genetics clinic for genetic counselling •No further testing required at this stage	•Copy number variant of unknown significance (VOUS) identified •Consider referral to genetics clinic for interpretation of report and diagnostic review •Further testing such as parental studies may be useful	•Copy number variant of unexpected significance identified •Consider referral to genetics clinic for interpretation of report and genetic counselling •Further testing such as parental studies may be useful

Flow chart

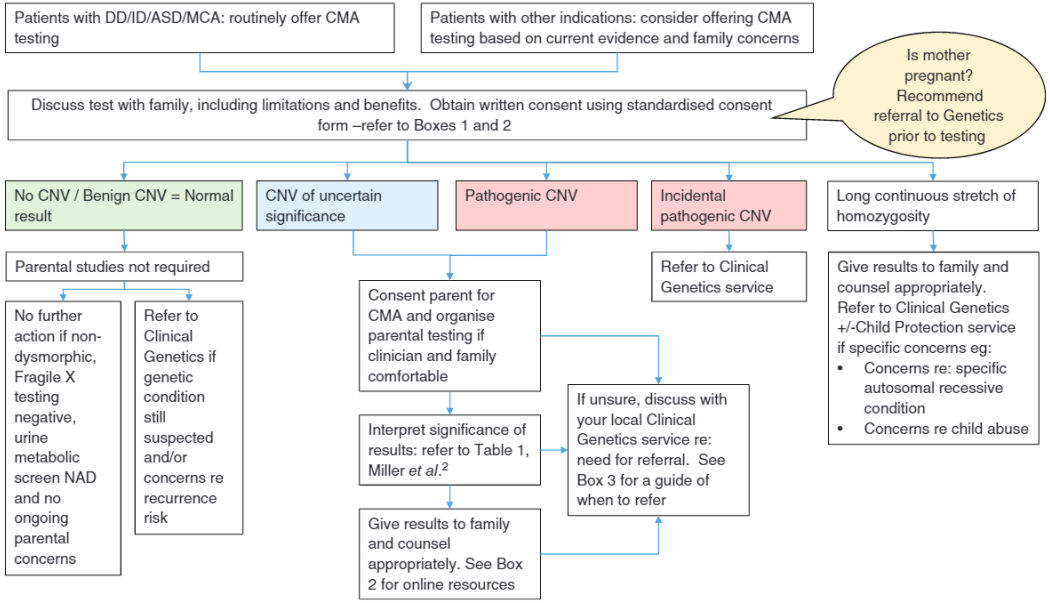


Fig. 1 Guide for paediatricians ordering CMA. ASD, autism spectrum disorder; CMA, chromosomal microarray; CNV, copy number variant; DD, developmental delay; ID, intellectual disability; MCA, multiple congenital anomalies; NAD, no abnormality detected.

When to consider referral to clinical genetics

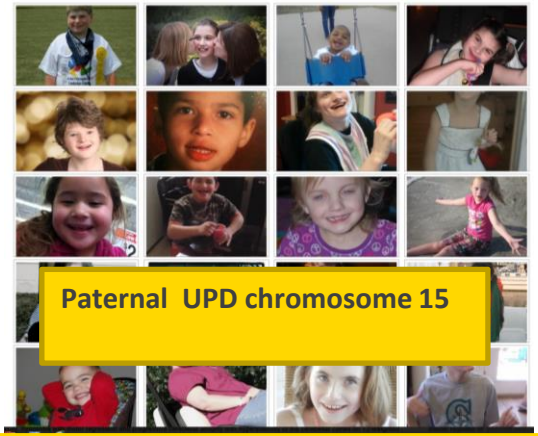
- Uncertainty interpreting a laboratory report
- Uncertainty re significance of CNV–especially for variants of uncertain or unknown significance, and variants on the X chromosome
- Uncertainty re need to test relatives–especially for parent with neurocognitive phenotype
- If CMA is normal (i.e. no CNV 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

UNSW SYDNEY

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/

Microdeletions

Understanding chromosome disorders Unique

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

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

Microduplications

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.

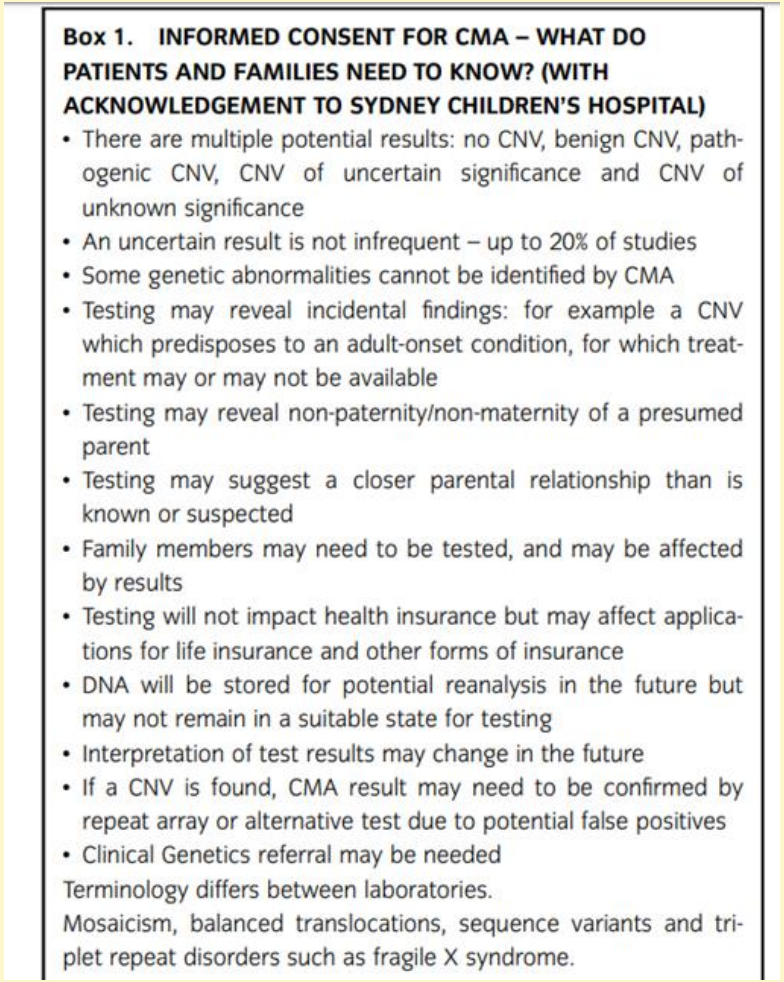
At the moment, it's uncertain whether the 22q11.2 duplication is a natural genetic variant - we are all different - or whether it's a real syndrome whose effects can be highly variable.

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.

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

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Questions ?

HNEkidshealth
Children, Young People & Families

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

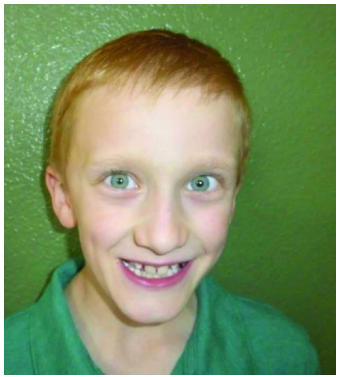
Clinical information should be included on the test request form to ensure rebate. Rebate is available for this test under the following clinical situations:

(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.

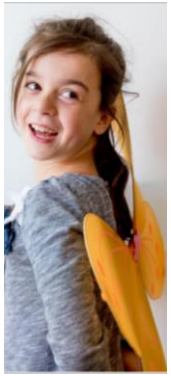
Q: which of these individuals have Fragile X syndrome

A: All of them



Male with Fragile X syndrome

Hagerman et al., 2009



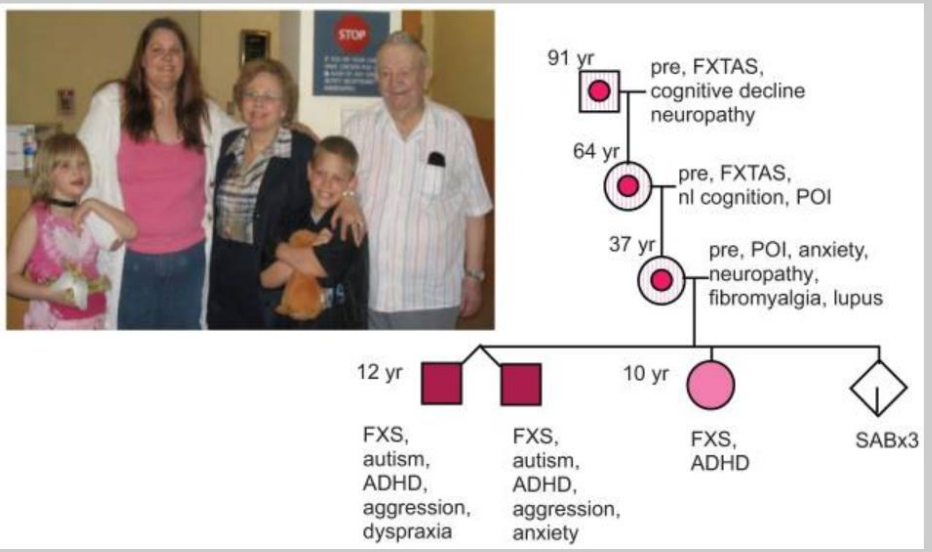
Female with full mutation in *FMR1*

Fragile X Association Australia

Female with Fragile X Tremor Ataxia syndrome

Fragile X Association USA

A family affair



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.

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.

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

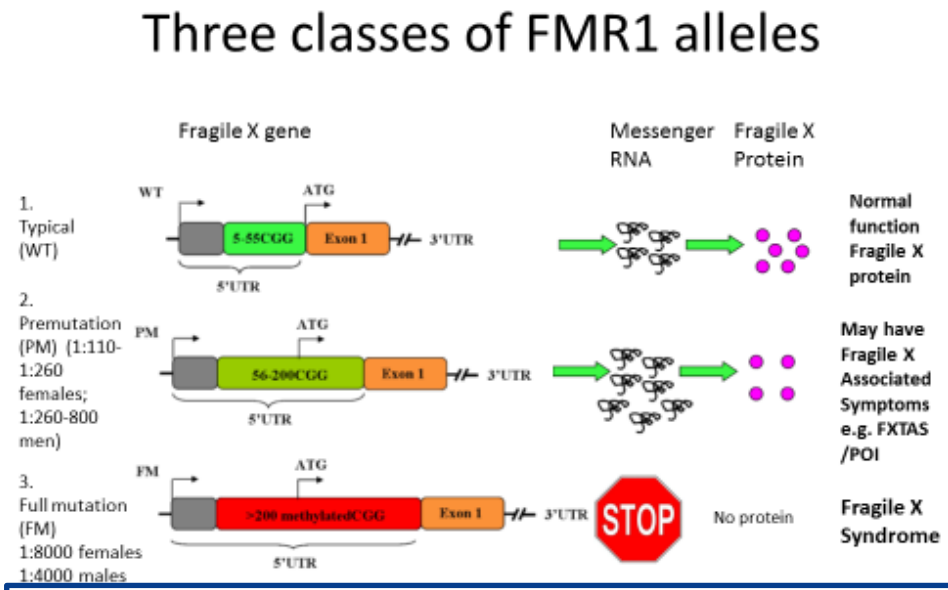
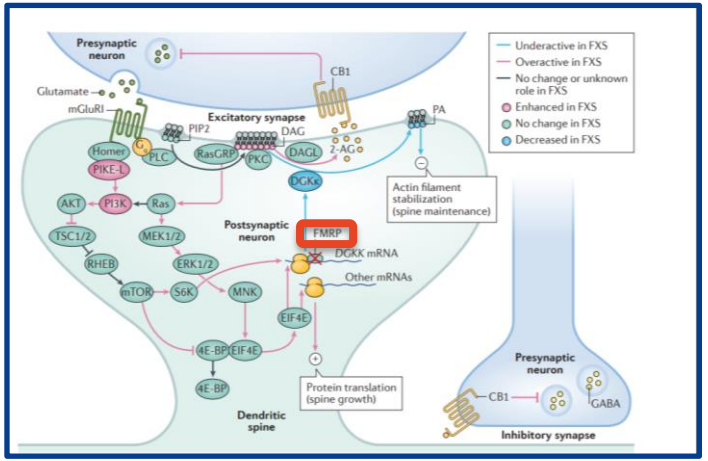


Figure courtesy of Melanie Leffler, GOLD Service

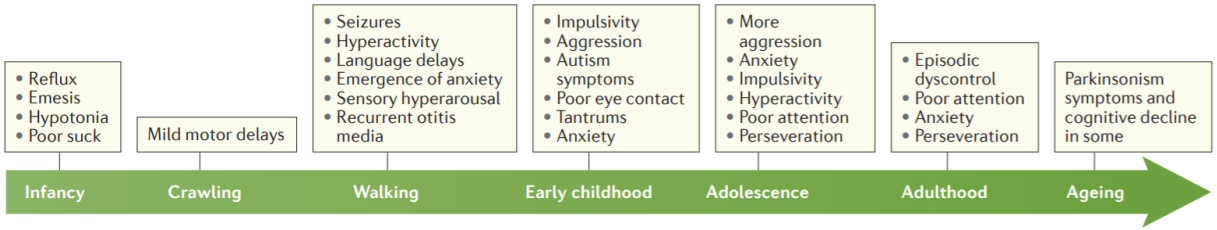
See also video https://fragilex.org.au/what-is-fragile-x/what-causes-fragile-x/

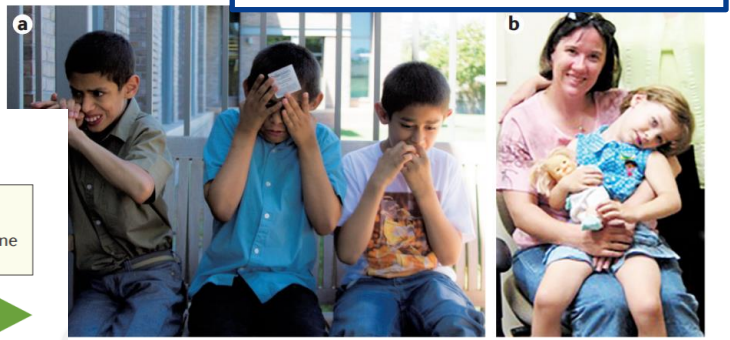


Fragile X protein (FMRP) has key role in neurodevelopment and function (Hagerman et al., 2017)

Hagerman et al., 2017

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.

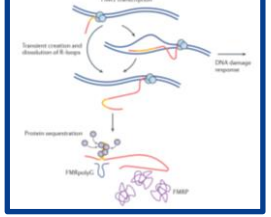
Long narrow face, prominent ears and larger testicles (in older males)

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 syndrome
Hagerman et al., Nature Reviews Disease Primer, 2017.

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[36,37]	67% of 100 with FXTAS 42% of 67 without FXTAS	61% of 18 with FXTAS 16% of 128 without FXTAS
Migraine[11,38]	27% of 122	54% of 203
Fibromyalgia[37,39,40]	ND	44% of 16 with FXTAS 8% of 121 without FXTAS
Thyroid dysfunction[37,39,41]	ND	50% of 18 with FXTAS 17% of 121 without FXTAS
Sleep disturbances[42,43]		63% of 110
Sleep apnoea[44]	31.4% of 118 males and females	
Restless legs syndrome[43]	33.1% of 127 males and females	
Central pain sensitivity syndrome[11,40]	ND	75% of 33
Tandem gait abnormalities[11,63]	100% with FXTAS	30% of 33
Neuropathy[11,37,45–47]	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

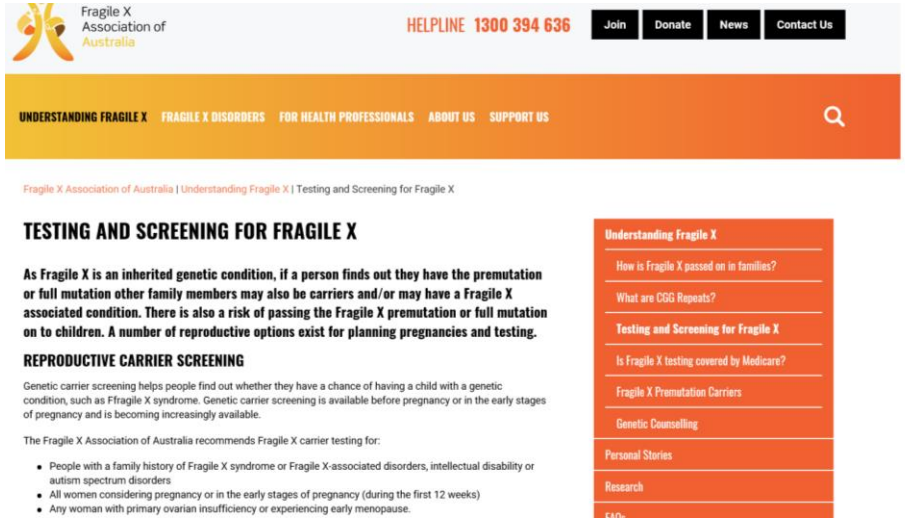
As a minimum verbal consent should be documented in the medical notes. An information sheet should be provided to all families and these important points covered:

- 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/



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

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Questions ?

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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 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

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Questions ?

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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

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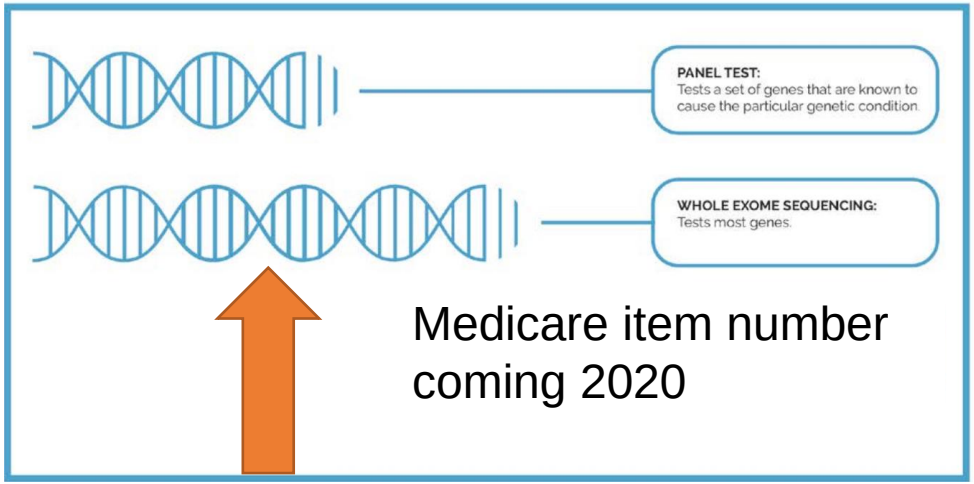
- **Exome sequencing**: can test most coding genes. Often exome sequencing is limited to genes currently known to cause a medical condition and may be referred to as a 'Clinical Exome' or 'Mendeliome'.



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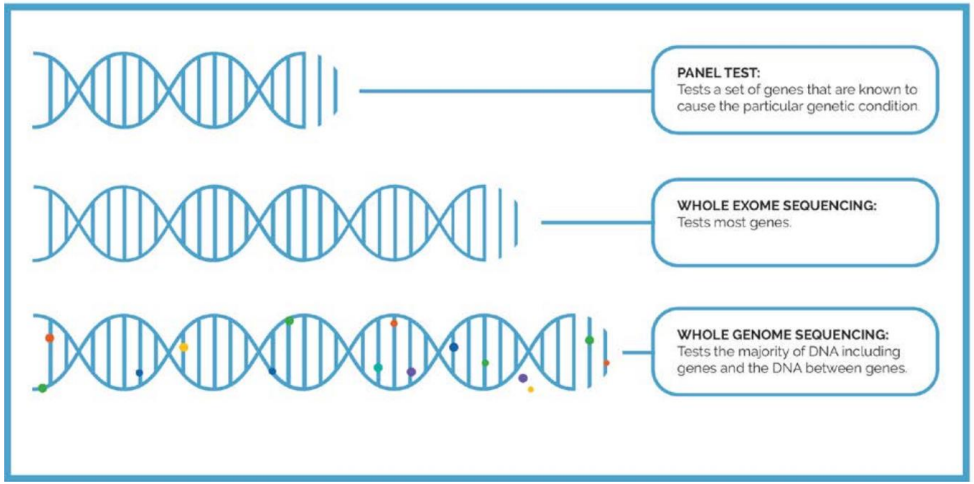
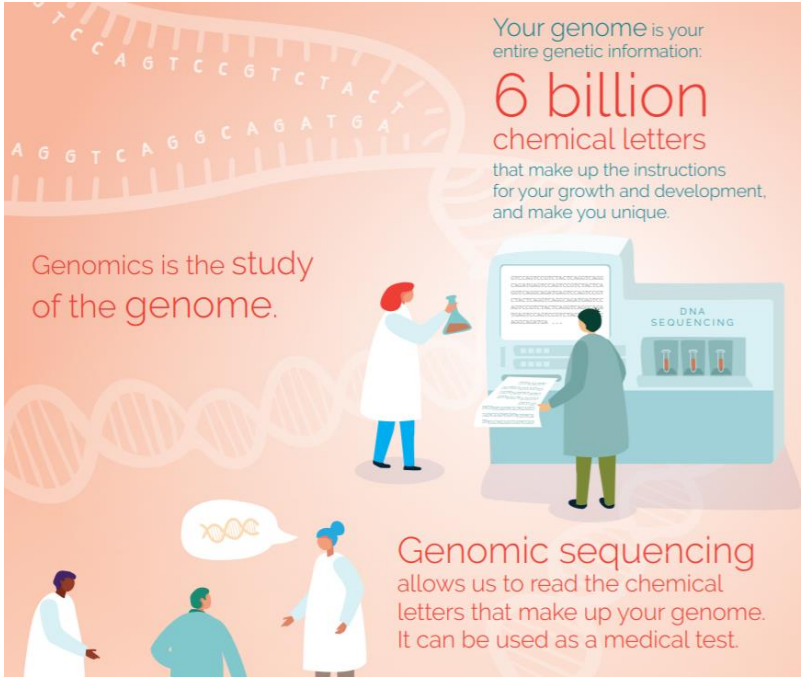
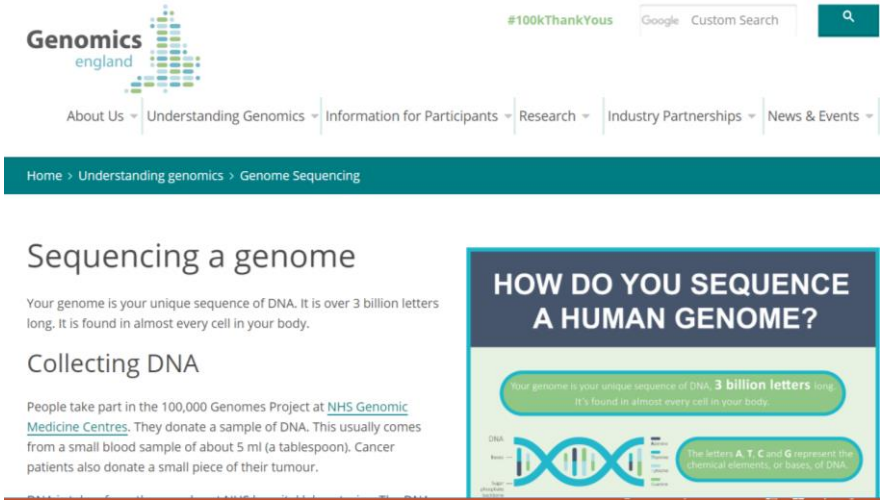
- **Whole genome sequencing (WGS)**: tests the majority of DNA, including coding genes and the DNA between genes. WGS has the potential to detect complex structural genetic rearrangements that may not be detected by chromosomal microarray, and variants in the mitochondrial DNA.



https://www.australiangenomics.org.au

Great resources about Next gen testing





www.genomicsengland.co.uk/

https://www.genomicsinfo.org.au

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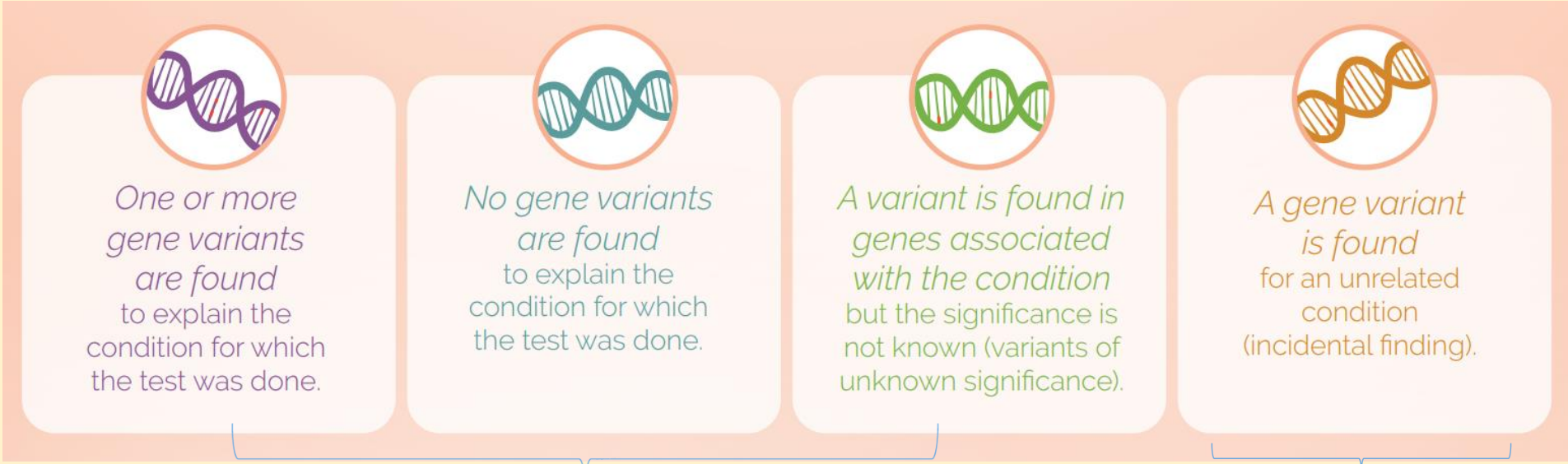
Possible results of genomic test?



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 what to know. You can discuss this with your doctor before you have the test and choose not to find out.

Some possible pitfalls

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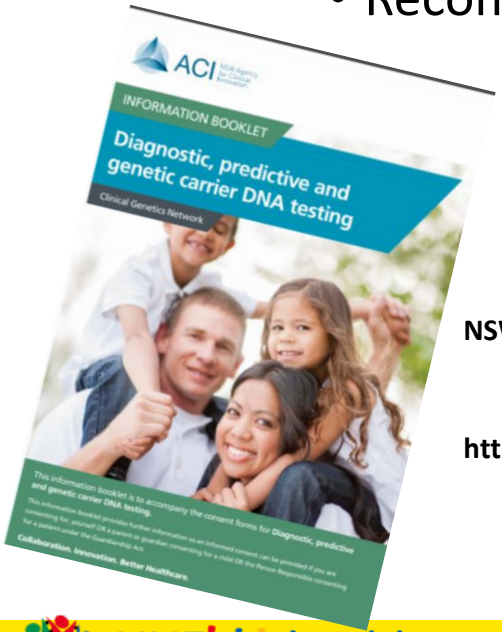
- **Insurance** – In Australia, genomic testing will not affect your health insurance policy. However genomic testing in you or your child may affect how easy it is for you or other family members to get income protection, travel or life insurance; or the price of your premium.

Moratorium on genetic tests in life insurance (July 2019 -June 2024 +): during moratorimu 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

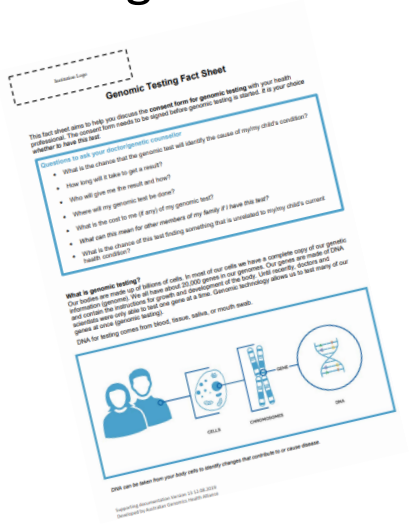
Which consent form to use?

- 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



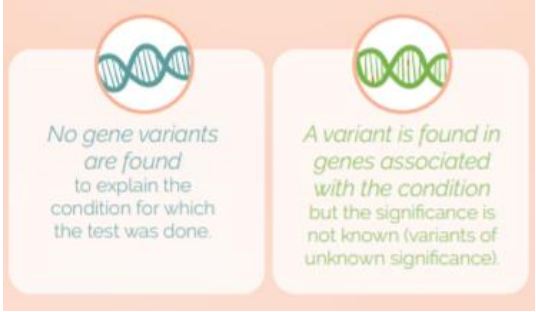
For other states look at the newly released National Consent forms.

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

•Questions ?

UNCERTAIN OR NO DIAGNOSIS – what next?

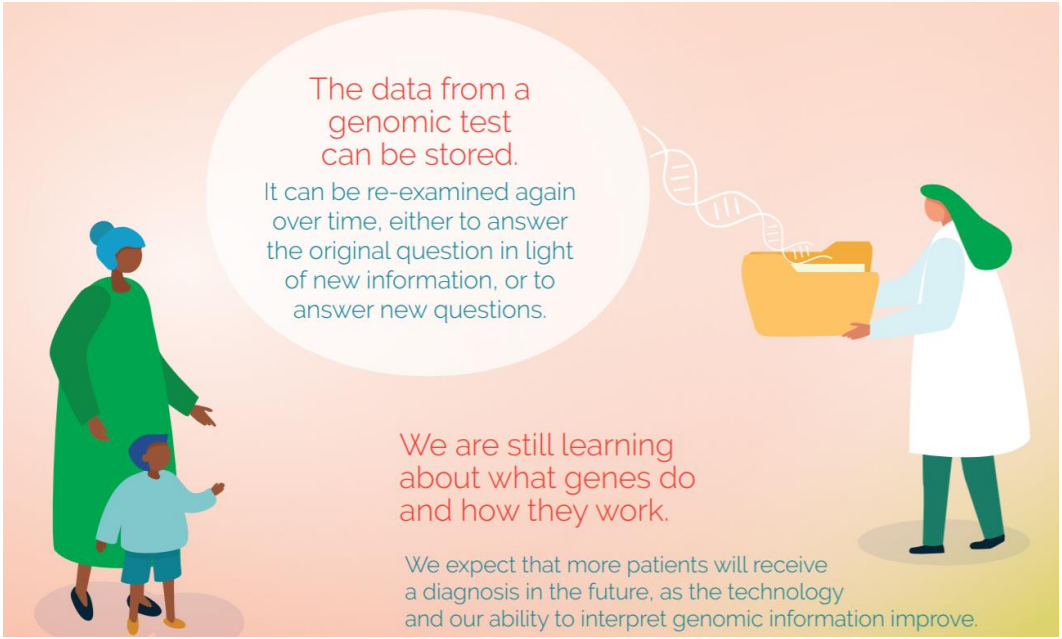
- ¼ - ½ children



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

RE-ANALYSIS

Re-analysis



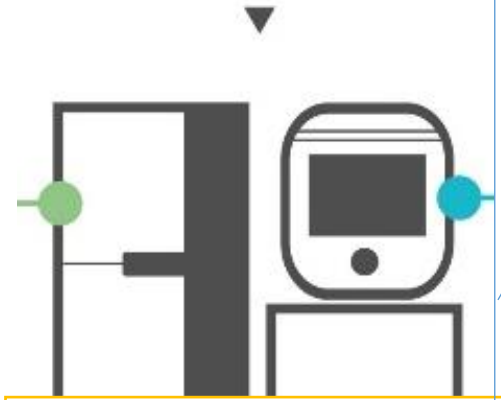
Genetic testing is more advanced than our ability to interpret it.

Enrol in genetic research

Girl with severe epilepsy condition

Born | 6 years | 8 years

Girl with severe epilepsy condition



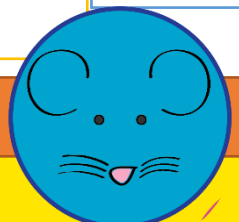
DNA sent for exome sequencing

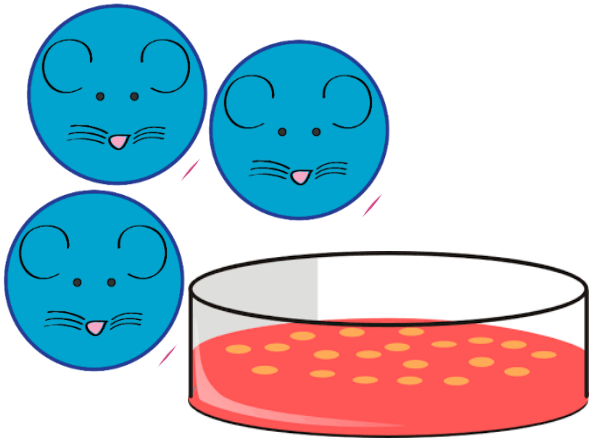
NO answer in >600 genes known to cause brain conditions.

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

Born

6 years

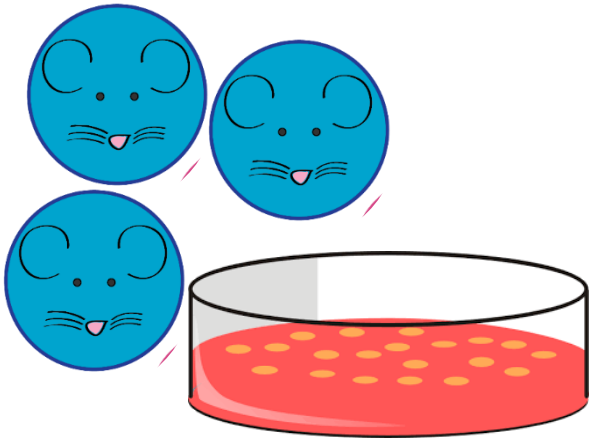




Scientists do more work on gene in mouse and cell culture

10 years

12 years



International collaborations to find more patients

Scientists do more work on gene in mouse and cell culture

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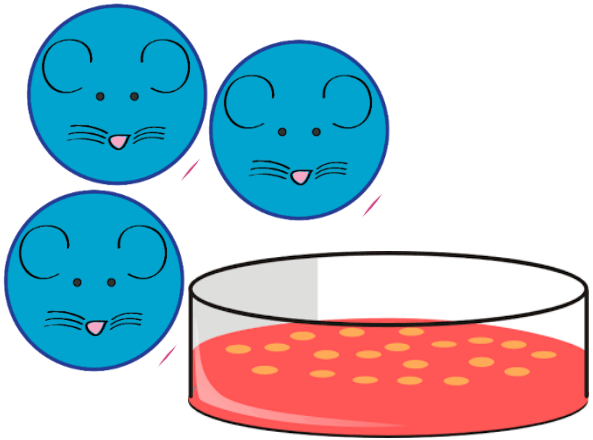

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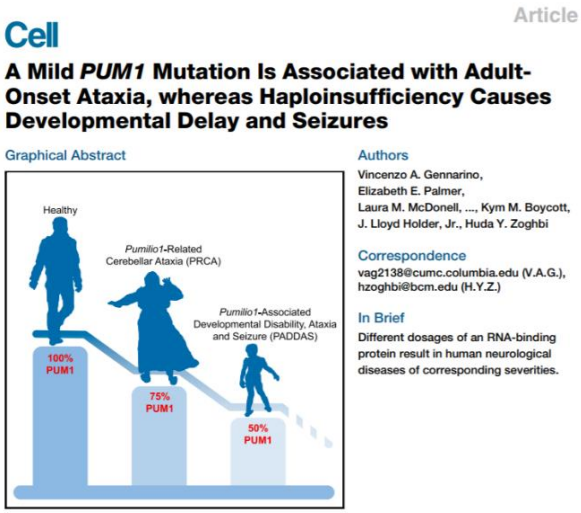
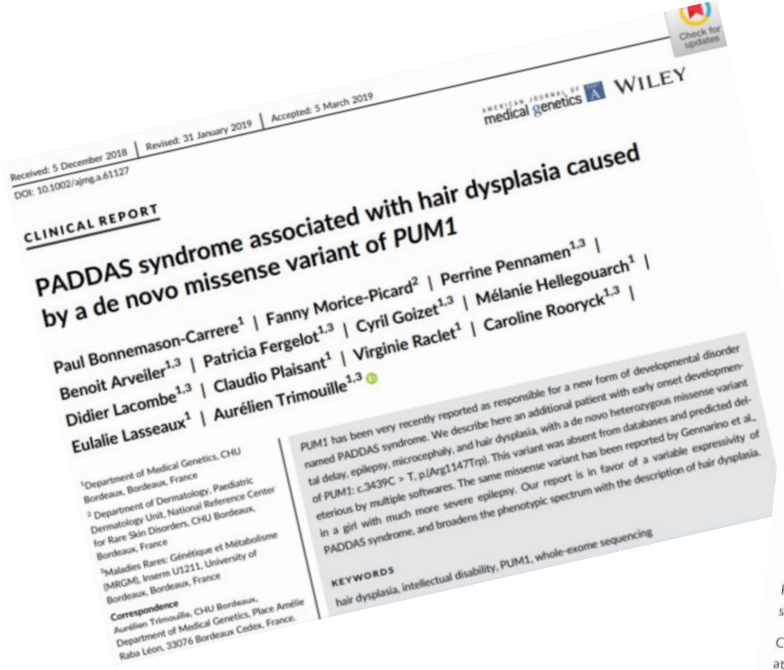


Scientists do more work on gene in mouse and cell culture

Scientific article published -> report back to family

10 years

12 years



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American Journal of medical genetics A WILEY

CLINICAL REPORT

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

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[3]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 Gennarino 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.

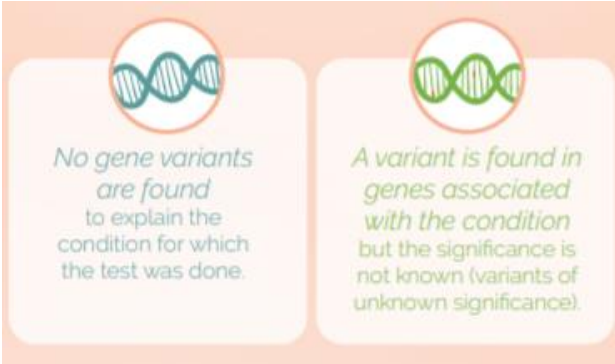
A/Professor Vincenzo Alessandro Gennarino, PhD, Department of Genetics and Development, Columbia University Medical Canter, New York, USA, vag2138@cumc.columbia.edu

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

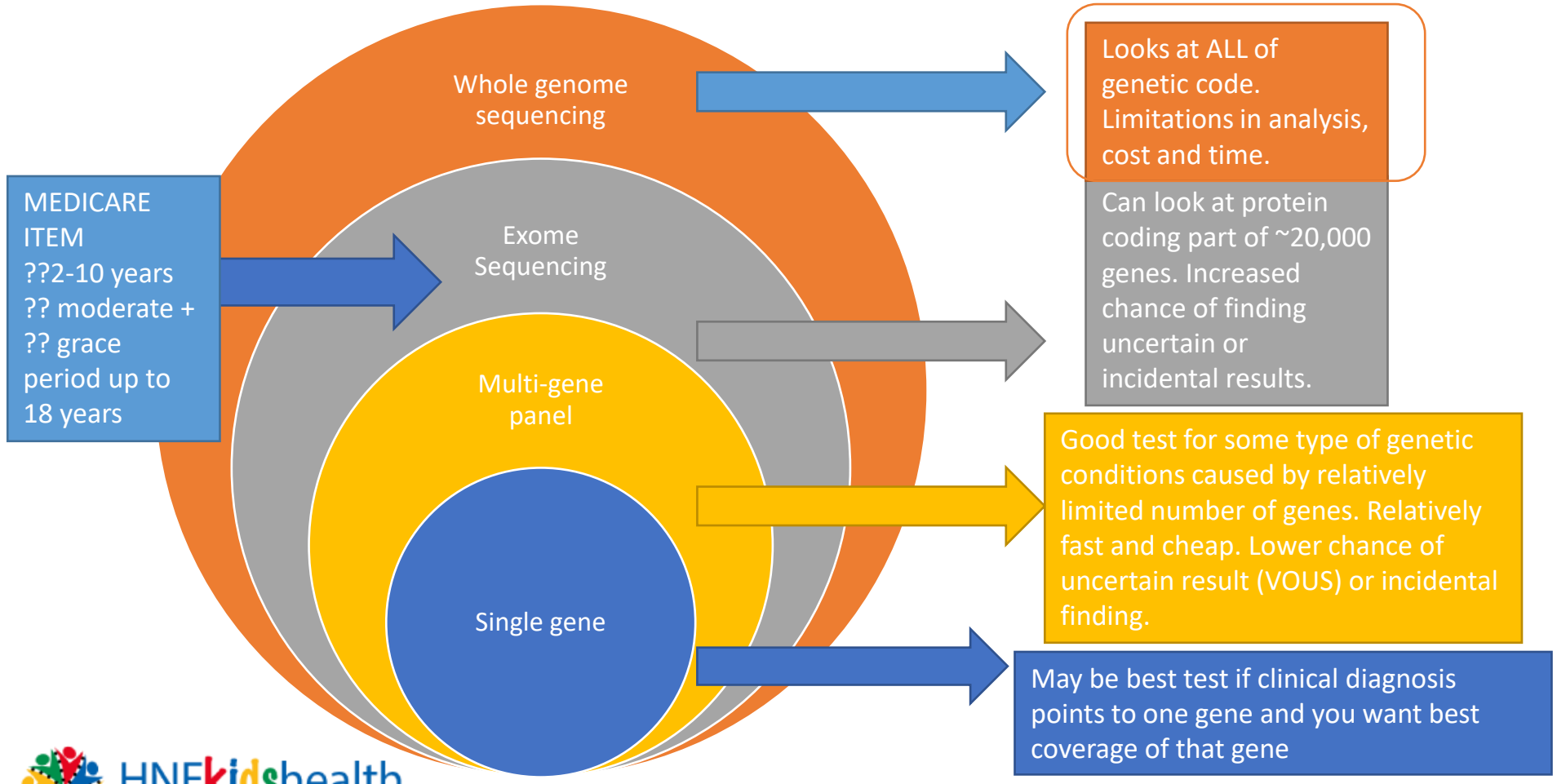
UNCERTAIN OR NO DIAGNOSIS – what next?

- ¼ - ½ children



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

RETEST



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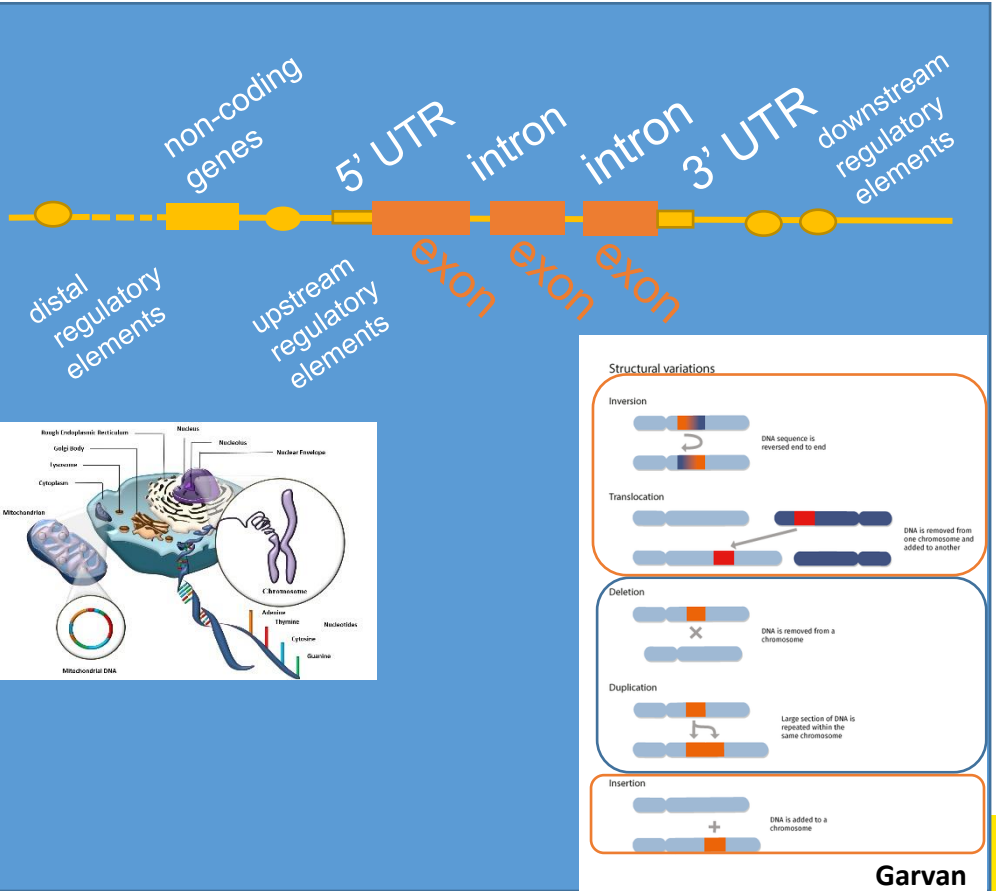
WGS potential



•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

Cost

(>$3,500 per patient)

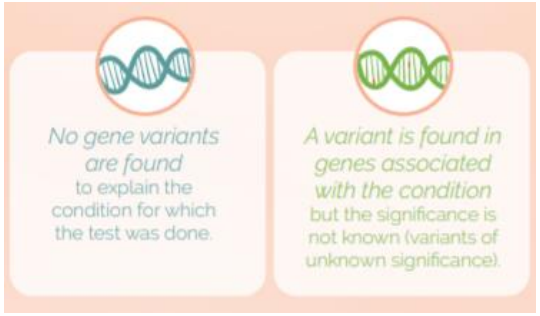
Assessment of pathogenicity of non coding variants

(MANY variants of uncertain significance)

Dark Emu, Black Seeds. Bruce Pascoe

UNCERTAIN OR NO DIAGNOSIS – what next?

- ¼ - ½ 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

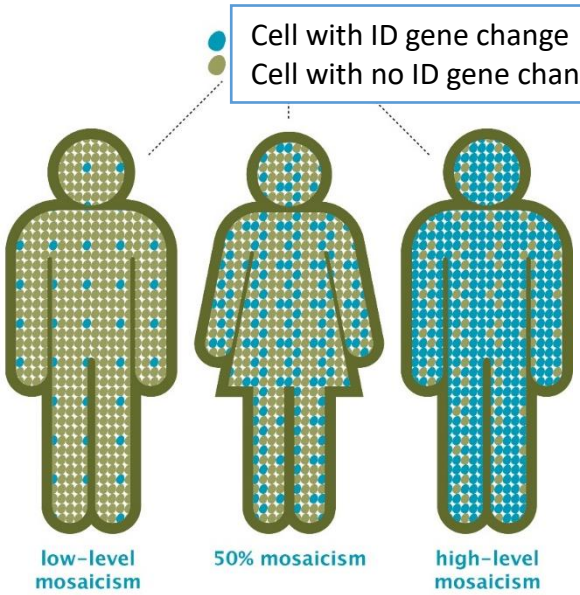
- The condition is **not genetic** or is more complex

CONSIDER RESEARCH

Mosaicism?

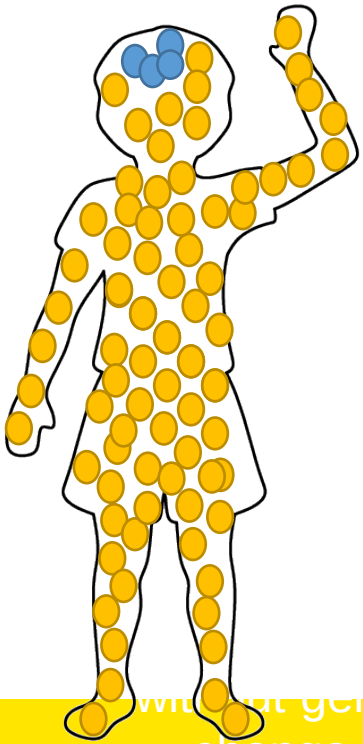
- This cat has mosaicism
- Some of it's hair cells carry a gene change for fur pigment, some don't

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

More than one gene change, gene-environment interactions

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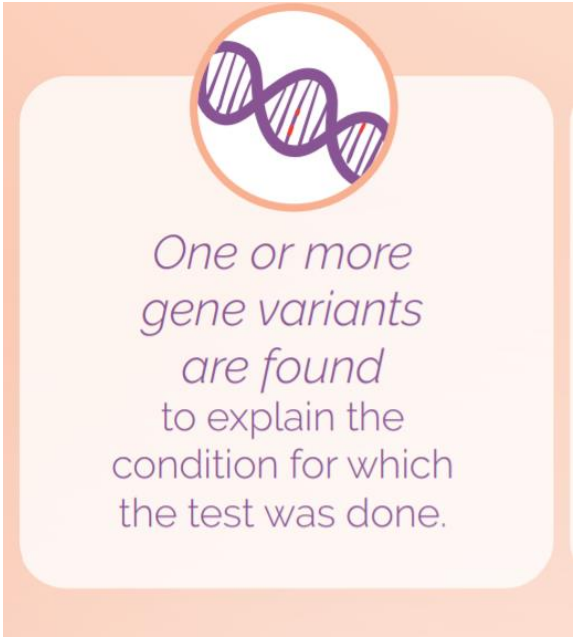
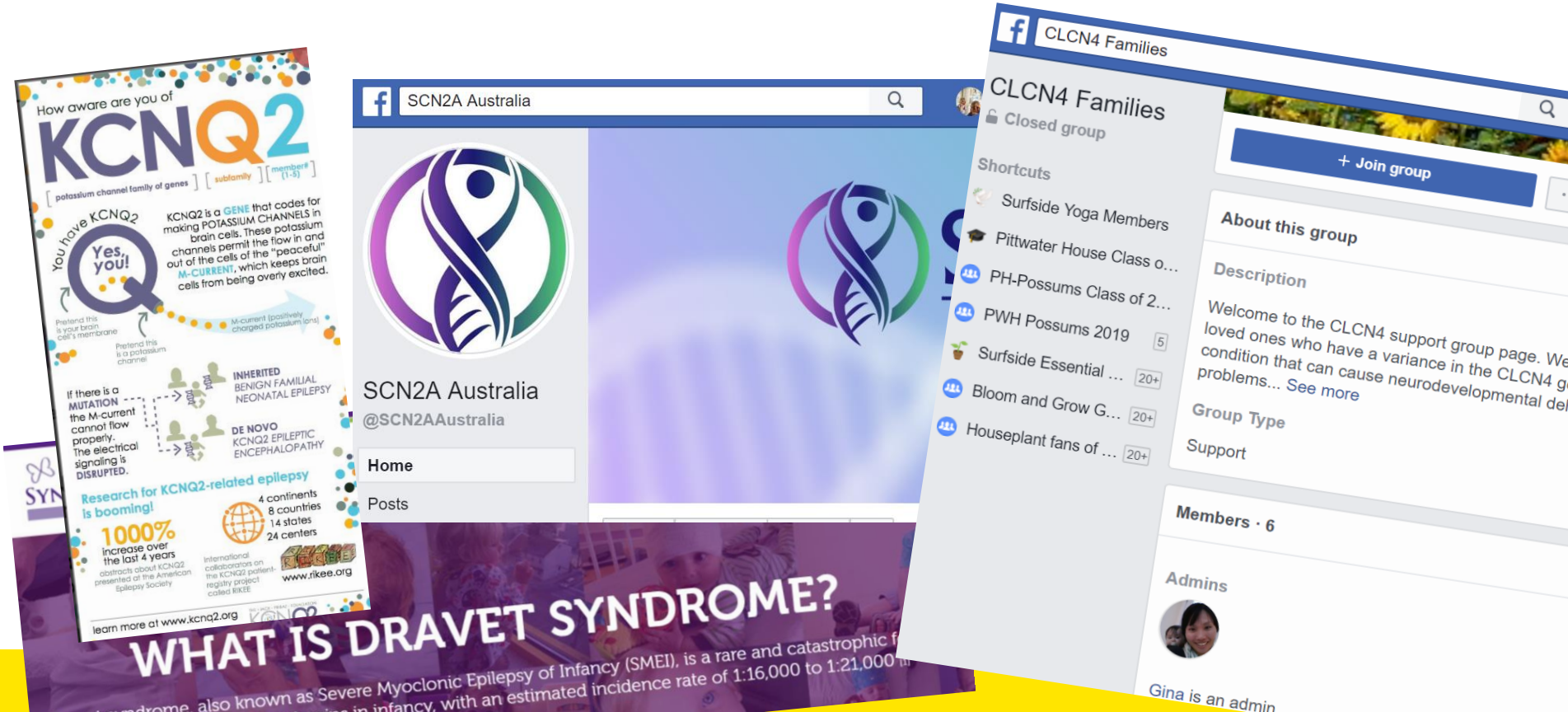
A sure diagnosis…what next?



Parent developed resources can be great start



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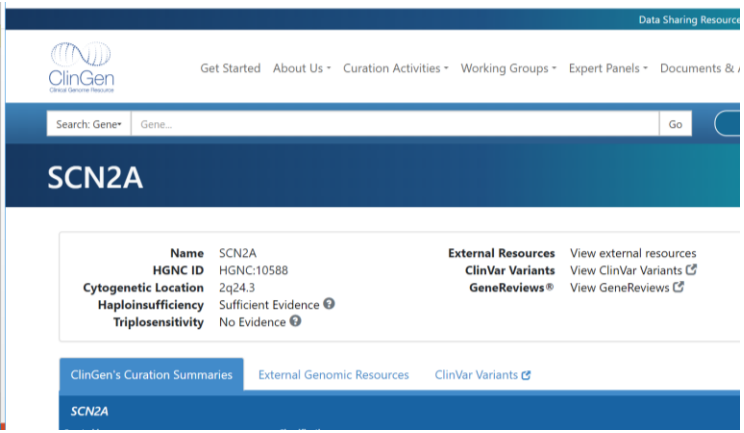
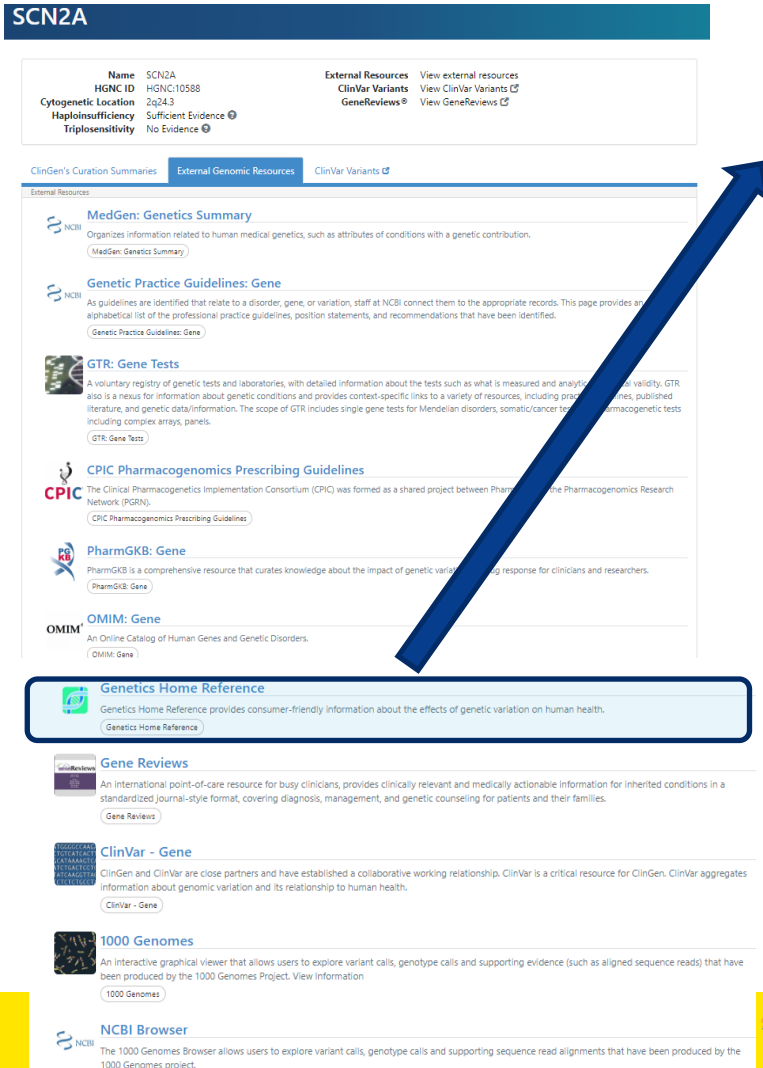


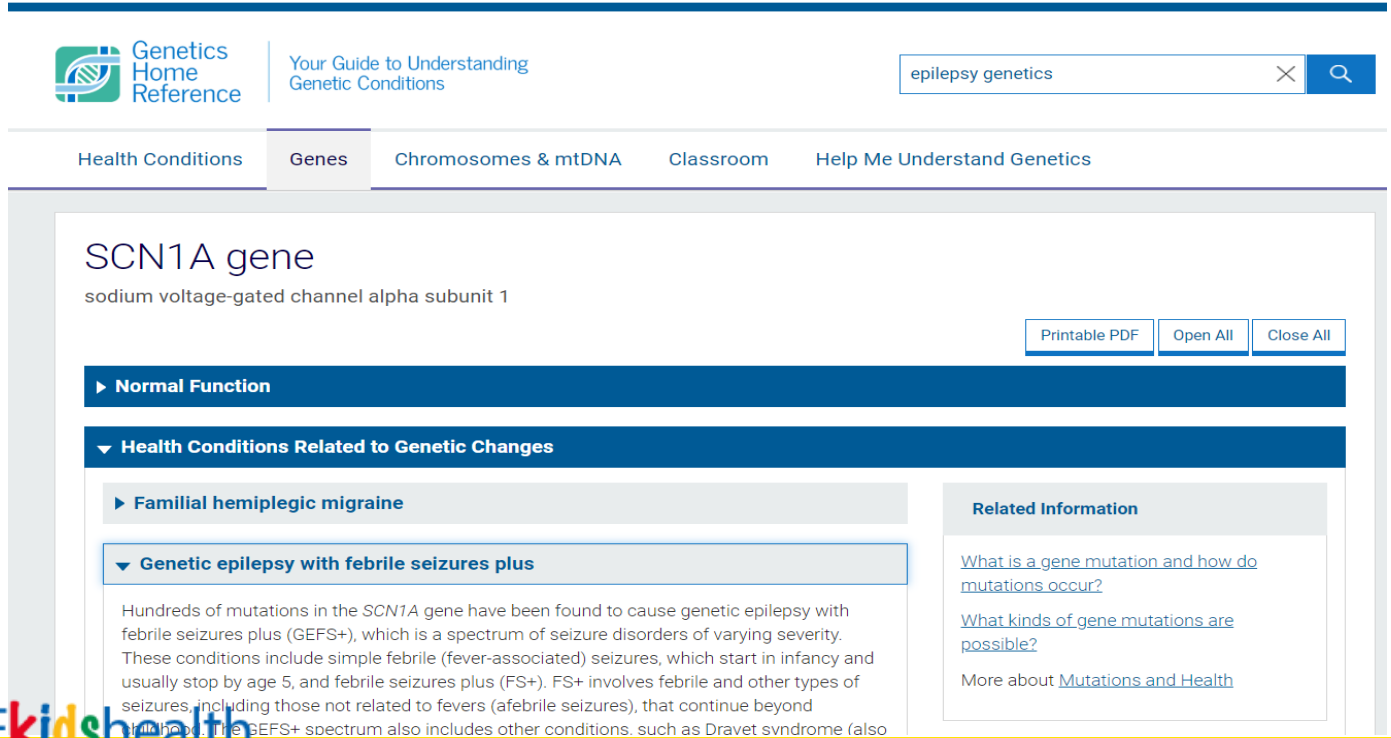
https://www.clinicalgenome.org/



Genetics Home Reference: patient information

Number included genes increasing

GENETICS HOME REFERENCE : GENE SPECIFIC INFORMATION



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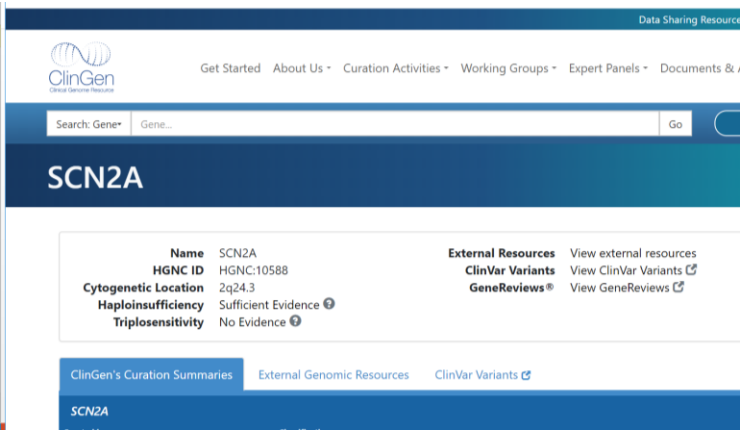

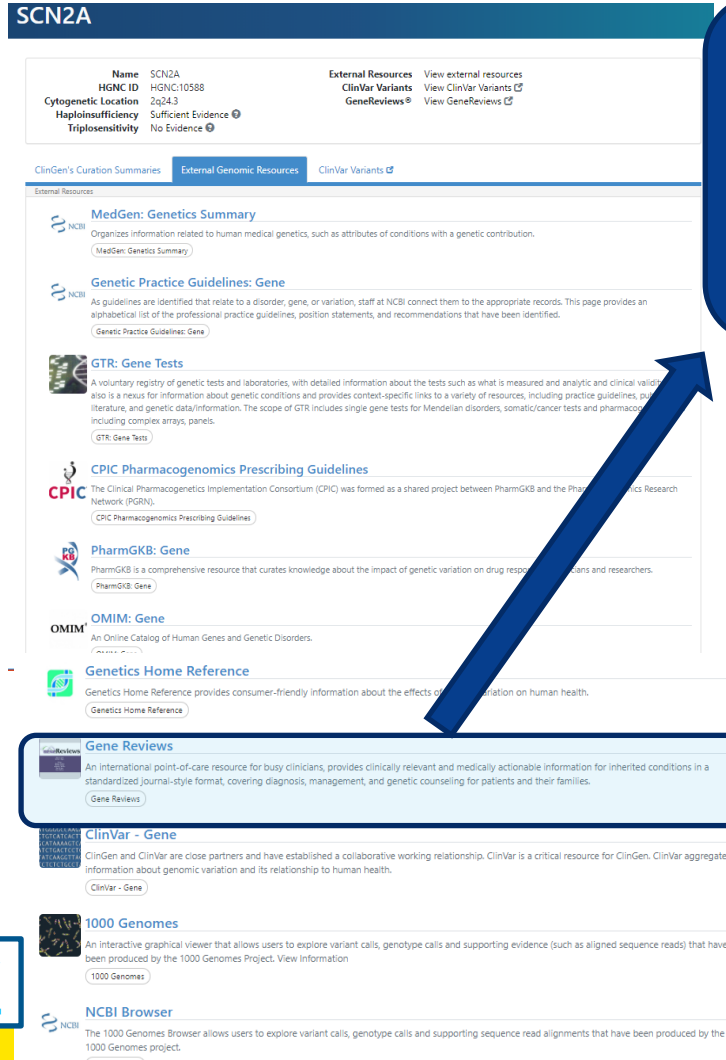

GeneReviews: Expert written clinical summaries

https://www.clinicalgenome.org/

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GeneReviews® [Internet].

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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 centrotemporal 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:

ividual 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).

enetic 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].

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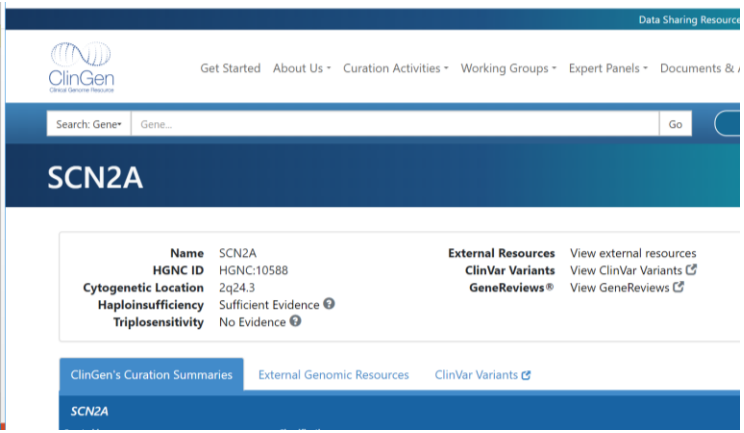
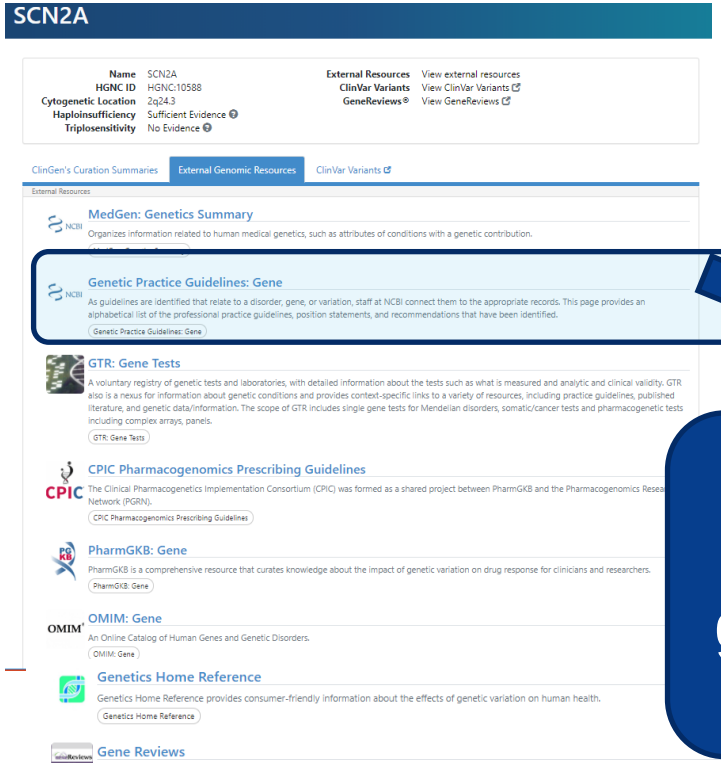




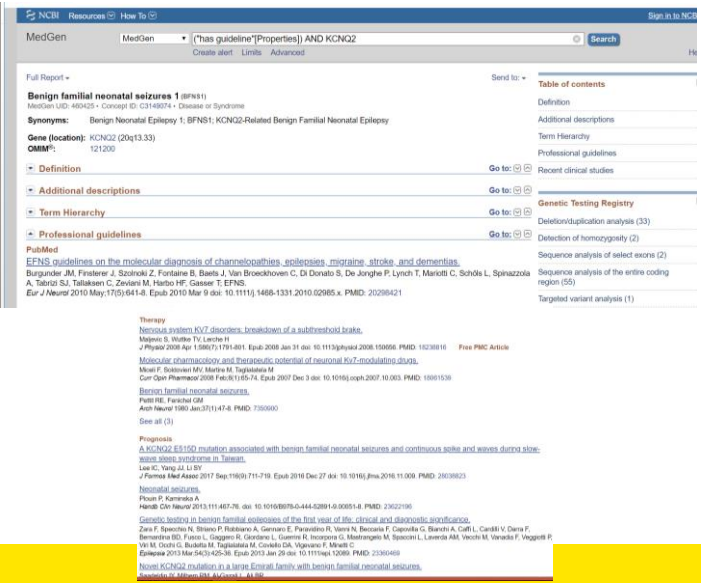
Practice guidelines

https://www.clinicalgenome.org/

MEDGEN: LINK TO PRECISION MEDICINE

MedGen

Organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.



- Diagnosis
- Therapy
- Prognosis
- Clinical prediction guides
- Management Guidelines

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

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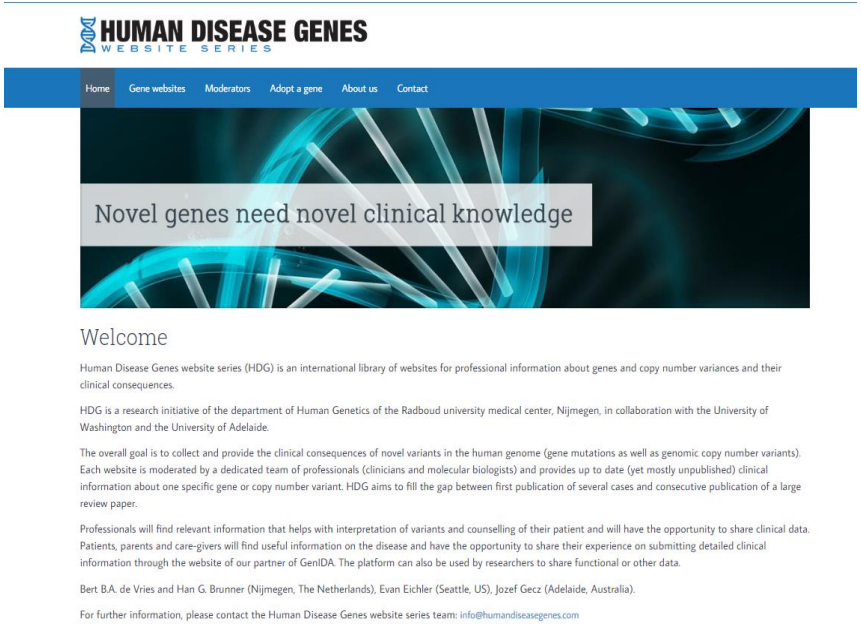
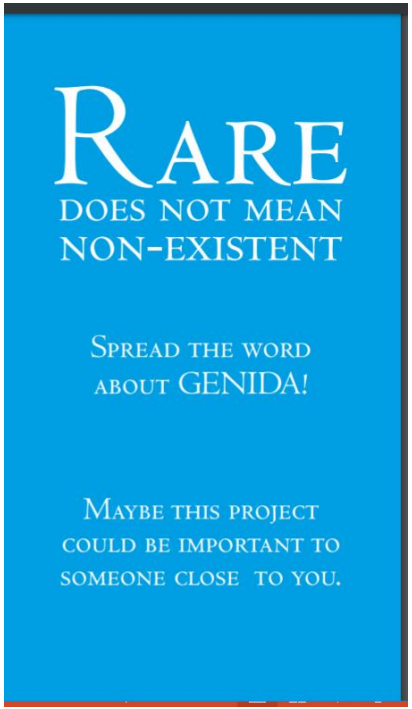
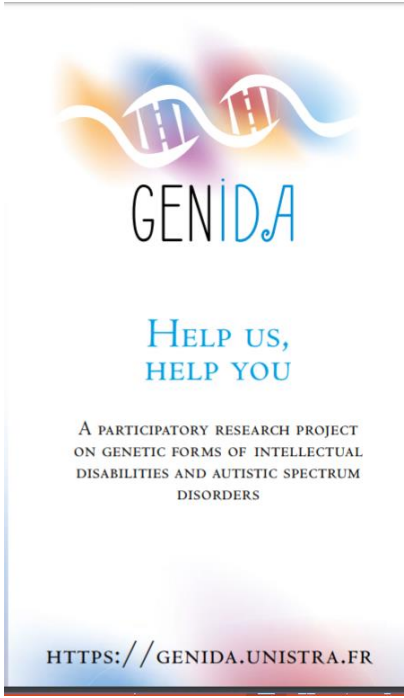
VERY NEW GENES







HUMAN DISEASE GENES
WEBSITE SERIES

CLCN4

Home | Professionals | Parents | Graph and chart | Contact

Clinical Characteristics

Gensites 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.

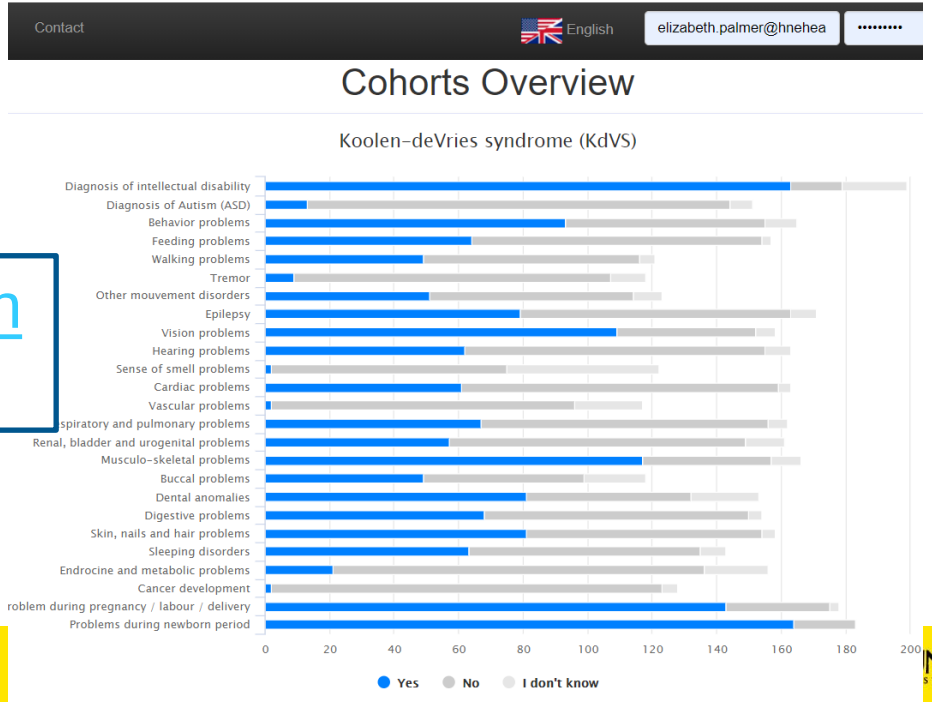
Approximately, 50% of individuals with a *CLCN4* disorder will have seizures. These may not be a major concern and easy to treat with medication. However some patients have severe seizure patterns (epileptic encephalopathies). Some individuals have been described to have difficulties with an unsteady 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/



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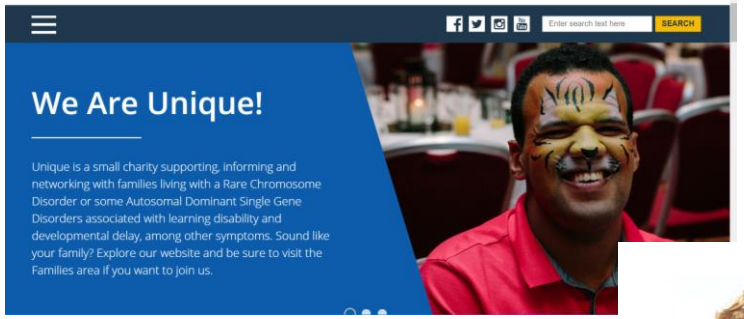
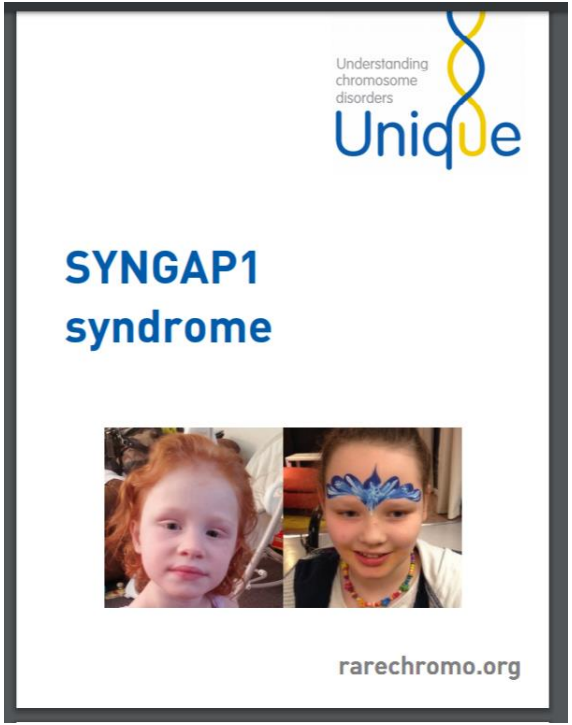


" For all of her delays Autumn is a smart little girl who knows how to manipulate situations to get what she desires. She is a toddler at heart, and while her body progresses much faster than her mind, we are often reminded to approach the world much more slowly, and to look at things differently, as 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



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Questions ?

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

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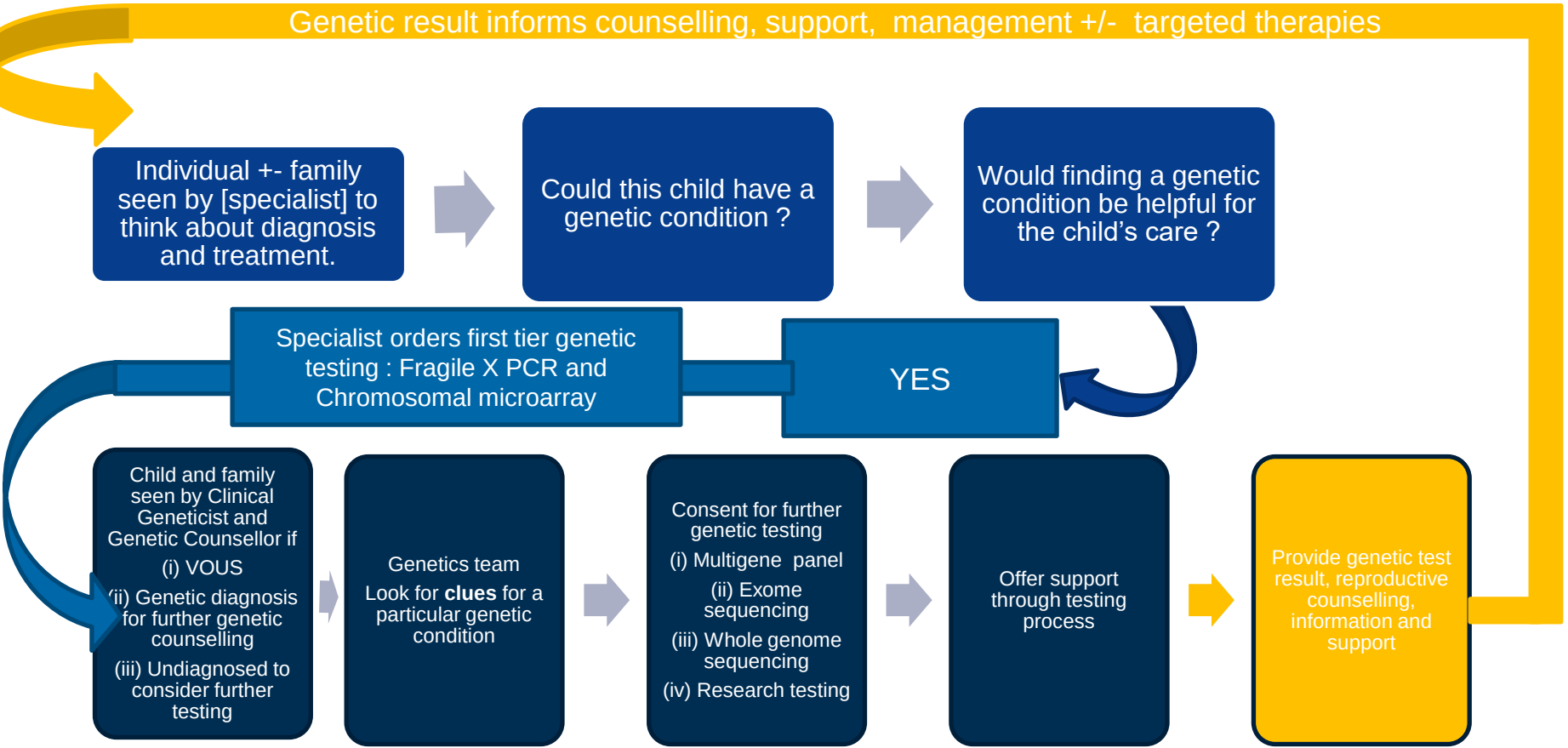
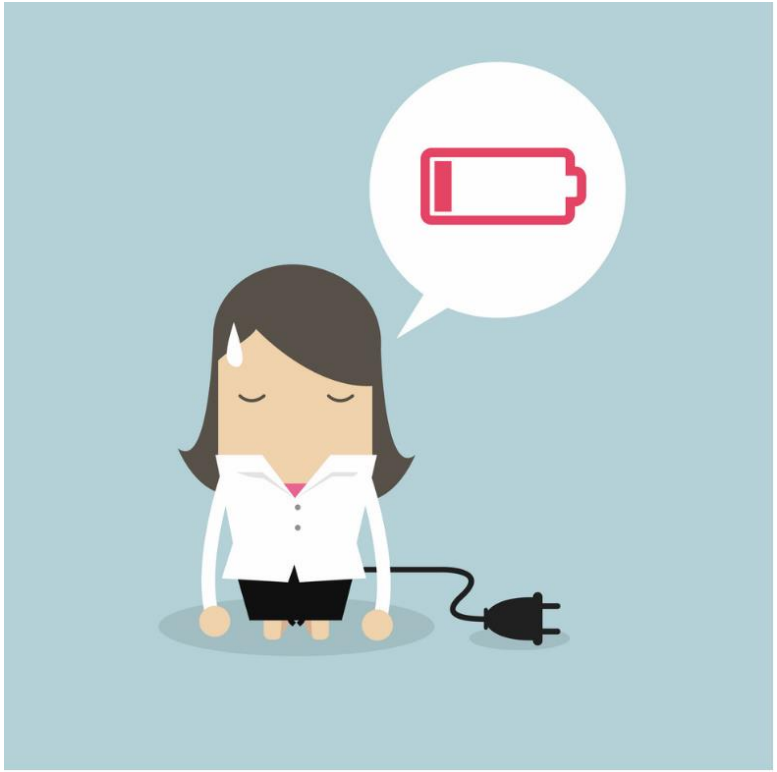
Traditional genetic testing process



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

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.

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Questions ?

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