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

Presenter
(Elizabeth) Emma Palmer

Clinical Geneticist
Genetics of Learning Disability Service,
NSW
Sydney Children’s Hospital (Honorary)

Lecturer, School of Women’s and
Children’s Health, UNSW.

Elizabeth.palmer@health.nsw.gov.au
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
But... genetics can be confusing, a different language to worry about.
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

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 Rempenning’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...
I first visited Mrs. [Name] at home in May 1976, to do an investigation of her family history, following up on Dr. Turner’s research on Rassmussen’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.
Family participating in ongoing studies to better understand this condition

**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 Palmer1,2, T Stuhlmann3,4, S Weinert3,4, E Haan3,6, H van Esch7, M Holvoet7, J Boyle1, M Leffler1, M Raynaud8,10, C Moraine8,10, H van Bokhoven11,12, K Kleefstra11,12, K Kahrizi12, H Najmabadi12, HHH Ropers13, MR Delgado16,17, D Sisirak14, S Golla12, A Sommer14, MP Pietrzyga18, WK Chung19, J Wynn19, LRohena12, E Bernardo12, DHamlin19, BM Faux19, DGRange19, L Manwaring19, JTolmie20, SS Joss20, DDD Study20, JMBobbin20, FAM Duijkers20, JMGoeihinger21, TDChallman21, FHennig10, UFischer10, AGrimme10, VSuckow10, LMusante10, JNicholl22, WSnow10, SLPodh10, ZNiu10, JRAronfeld10, PStankiewicz10, TJJentsch14, JGecz10, MField10, and VMKalscheuer10

**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”

“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.”

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.
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.

https://www.genomicsinfo.org.au
Genetic variation is the rule, finding the pathogenic variant is hard work!

The cat sat on the macC
A smorgasbord of genomic tests
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?

https://www.australiangenomics.org.au
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\(^1\). 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 information 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

REVIEW ARTICLE

Chromosome microarray in Australia: A guide for paediatricians
Elizabeth E Palmer,1 Greg B Peters2 and David Mowat1,3
1Department of Medical Genetics, Sydney Children's Hospital, Randwick, Australia
2Department of Medical Genetics, School of Women's and Child Health University of New South Wales, Westmead, Sydney, Australia
3Department of Paediatrics, University of New South Wales, Sydney, Australia

ORIGINAL ARTICLE

Current use of chromosomal microarray by Australian paediatricians and implications for the implementation of next generation sequencing
Corina McKay,1,2 Daryl Elfon,1,3,5,6 Elizabeth E Palmer,1,4,6 Susan M White,5,7 Chris Pearson8 and Argie Danchin1,2,3
1Department of Paediatrics, University of New South Wales and the Children's Hospital at Westmead, Westmead, Sydney, Australia
2Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia
3Department of Paediatrics, Murdoch Children's Research Institute, Melbourne, Victoria, Australia
4Department of Medical Genetics, University of New South Wales, Westmead, Sydney, Australia
5Department of Paediatrics, Murdoch Children's Research Institute, Melbourne, Victoria, Australia
6Department of Paediatrics, University of New South Wales, Westmead, Sydney, Australia
7Department of Paediatrics and Women's and Children's Health, Sydney, Australia

VIEWPOINT

Chromosome microarray analysis: A soothing guide
Anne Ronan1,2

1Department of Paediatrics, University of New South Wales, Westmead, Sydney, Australia
2Department of Paediatrics, Murdoch Children's Research Institute, Melbourne, Victoria, Australia


doi:10.1111/jptc.13869

Chromosome Microarray (CMA) Testing Guide – Children and Adults

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**
- 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

**Diagnostic of known, expected condition**
- Known copy number variant (CNV) identified
- Consider referral to genetics clinic for genetic counselling
- No further testing required at this stage

**Variant of unknown significance found**
- 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

**Variant with unexpected implications found**
- 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

Patients with DD/ID/ASD/MCA: routinely offer CMA testing

Discuss test with family, including limitations and benefits. Obtain written consent using standardised consent form – refer to Boxes 1 and 2

Is mother pregnant? Recommend referral to Genetics prior to testing

No CNV / Benign CNV = Normal result

Parental studies not required

No further action if non-dysmorphic, Fragile X testing negative, urine metabolic screen NAD and no ongoing parental concerns

Refer to Clinical Genetics if genetic condition still suspected and/or concerns re recurrence risk

Interpret significance of results: refer to Table 1, Miller et al. 2015

Give results to family and counsel appropriately. See Box 2 for online resources

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

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.
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

Microdeletions

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.

https://www.rarechromo.org/
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


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

What is Fragile X?

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 \textit{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.

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

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

Three classes of FMR1 alleles

- **1. Typical (WT)**
  - Fragile X gene
  - Messenger RNA
  - Fragile X Protein
  - Normal function

  - Fragile X gene
  - Messenger RNA
  - Fragile X Protein
  - May have Fragile X Associated Symptoms e.g. FXTAS/POI

- **3. Full mutation (FM)**
  - Fragile X gene
  - Messenger RNA
  - Fragile X Protein
  - No protein

Fragile X Syndrome

Figure courtesy of Melanie Leffler, GOLD Service

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

**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

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.

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.
Fragile X PCR Testing guide

Fragile X and related conditions: key resources

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


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

Questions ?

Questions ?

Questions ?

Questions ?

Questions ?

Questions ?

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:


Other specialist metabolic tests may be organised by a neurologist or metabolic specialist
Treatable-ID.org

Start the tool via the menu above

What is Treatable-ID.org?
A systematic literature review, performed by Dr. Clara van Karnebeek & Dr. Sylvie Stiekvoort in B.C. Children’s Hospital (Vancouver, Canada) identified 81 inborn errors of metabolism which are causally related to Intellectual Disability and are treatable. These diseases are presented on this website as an intellectual disability tool to improve outcomes.

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 an information portal with access to specific genetics, biochemistry, phenotype, diagnostic tests and treatment.

Treatable-ID on mobile devices
When you visit the 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.
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.

- **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](https://www.australiangenomics.org.au)
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Medicare item number coming 2020

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See more information here: [https://www.australiangenomics.org.au](https://www.australiangenomics.org.au)
Great resources about Next gen testing

https://www.genomicsinfo.org.au

www.genomicsengland.co.uk/
Possible results of genomic test?

1. One or more gene variants are found to explain the condition for which the test was done.
2. No gene variants are found to explain the condition for which the test was done.
3. A variant is found in genes associated with the condition but the significance is not known (variants of unknown significance).
4. A gene variant is found for an unrelated condition (incidental finding).

Any genetic test

Array, gene panel, exome or genome sequencing

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

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- **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.

- **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.*

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:

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

Born                                            6 years                                           8 years

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

? Maybe damaging genetic variant in gene reported to cause brain condition in mice
Scientists do more work on gene in mouse and cell culture.
Scientists do more work on gene in mouse and cell culture

International collaborations to find more patients

10 years

12 years
Scientists do more work on gene in mouse and cell culture

International collaborations to find more patients

Scientific article published -> report back to family
PADDAS syndrome associated with hair dysplasia caused by a de novo missense variant of PUM1

Paul Bonhomme-Carreras1 | Fanny Mercier-Picard2 | Perline Pernissan1,3 | 
Bertrand Berube1,3 | Patricia Fergerot1,3 | Cyril Gozari1,2 | 
Malézie Haefliger-Pixérécourt1 | Didier Lacombe1,3 | Chloé Piussan1 | 
Eudalie Lussenaerts1 | Aurélien Trimboule1,3

Department of Medical Genetics, CHU Réseau de Reference, France
Department of Dermatology, Pediatric Haematology and Oncology, CHU Réseau de Reference, France
Department of Medical Genetics, CHU Réseau de Reference, France
Institut Pasteur, Paris 8, France
University of Medicine, Brussels, Belgium
Institut Pasteur, Paris 8, France
Audrey Trimboule, CHU, Luxembourg
Audrey Trimboule, CHU, Luxembourg

Keywords:
Hair dysplasia, Intellectual disability, PUM1, whole-exome sequencing

PUM1 has been very rarely reported as responsible for a case of developmental disorder named PADDAS syndrome. We describe here an additional patient with early-onset developmentally delayed PADDAS syndrome. The patient presented with developmental delay, intellectual disability, and hair anomalies, with 18 de novo heterozygous missense variants in PUM1. No other mutations or microdeletions were observed in the genome of the patient. The patient's symptoms were overall consistent with PADDAS syndrome, including intellectual disability, developmental delay, and hair anomalies. The patient's symptoms were similar to those described in previous reports of PADDAS syndrome. The patient's symptoms were consistent with the diagnosis of PADDAS syndrome. The patient's symptoms were similar to those described in previous reports of PADDAS syndrome. The patient's symptoms were consistent with the diagnosis of PADDAS syndrome. The patient's symptoms were similar to those described in previous reports of PADDAS syndrome. The patient's symptoms were consistent with the diagnosis of PADDAS syndrome. The patient's symptoms were similar to those described in previous reports of PADDAS syndrome. The patient's symptoms were consistent with the diagnosis of PADDAS syndrome.

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 neuronal stem cells. When the PUM1 gene does not function properly, due to a change in its DNA sequence (known as a mutation or a genetic variant), it can lead to a range of neurodevelopmental difficulties depending on the severity of the mutation.

Currently, two distinct PUM1-related disorders are recognized: the more severe disease is an early onset syndrome called familial associated developmental disability, speech and seizure (FADDAS), the features of this disease can vary from one individual to the next.

A milder PUM1 mutation has been found in an individual with a slow progressive, adult onset ataxia. This disease is called familial-related cerebellar ataxia, or PCA.

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

Professor Vincente Alejandro Gennino, PhD, Department of Genetics and Development, Columbia University Medical Center, New York, USA.
Vig3135@cumc.columbia.edu

Dr. (Colombia) Emilia Palacios, Clinical Genetics, MD, Genetics of Learning Disability Service, Hunter Genetics, Wollongong, NSW 2528, Sydney, Australia.
Emilia.palacios@health.nsw.gov.au

Professor Jimmy Lloyd Holder, Jr, MD (Pediatric Neurology), Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA. jholder@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
Whole genome sequencing

Exome Sequencing

Multi-gene panel

Single gene

**Whole genome sequencing**
- Looks at ALL of genetic code.
- Limitations in analysis, cost and time.

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

**Multi-gene panel**
- 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.

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

**Medicare Item**
- 2-10 years
- Moderate +
- Grace period up to 18 years
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
Assessment of pathogenicity of non-coding variants

(MANY variants of uncertain significance)

Cost

(>$3,500 per patient)
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
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
SCN1A gene
sodium voltage-gated channel alpha subunit 1

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 infancy. 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

https://www.clinicalgenome.org/

GeneReviews: Expert written clinical summaries
GRIN2A-Related Speech Disorders and Epilepsy

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

Summary

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.
CLINGEN

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

VERY NEW GENES

Welcome

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

HDG is a research initiative of the department of Human Genetics of the Radboud university medical centre, 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 maintained 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 novel cases and consecutive publication of a large review paper.

Researchers 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 caregivers will find useful information on the disease and have the opportunity to share their experience by submitting updated clinical information through the website of our partner in GenIDa. The platform can also be used by researchers to share functional or other data.

Bert BA de Vries and Henk G. Bummert (Nijmegen, The Netherlands), Evan Eichler (Seattle, USA), Josef Goz (Adelaide, Australia).

For further information, please contact the Human Disease Genes website series team: 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.

Help us,
help you
A participatory research project
on genetic forms of intellectual
disabilities and autistic spectrum
disorders

https://genida.unistra.fr
HUMAN DISEASE GENES

CLCN4

Clinical Characteristics

Features of CLCN4 related genetic disorder

Most individuals with 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. Individuals with a CLCN4 gene change have been reported to have normal intelligence, borderline intellectual disability/learning difficulties, or a range of intellectual disabilities. Intellectual disability is more common in females if the genetic change is in the female parent (as a new mutation) rather than in an inherited genetic change.

It is relatively rare for individuals with a CLCN4-related condition to have particular delays in their speech and language development. Some individuals have ongoing speech difficulties causing stuttering and/or incoherent speech (stuttering difficulties). Anatomical features have been reported in some individuals with CLCN4 gene changes. These behavioral differences include in some people with CLCN4 gene changes to include a degree of hyperactivity, aggression and/or impulsiveness. Other individuals are described as being more introverted or having no significant behavioral issues. There is probably an increased chance of mental health conditions (for example anxiety and depression) in both boys and females with a CLCN4 gene change.

Approximately, 50% of individuals with a CLCN4 mutation will have seizures. These seizures may not be major seizures and may vary from individual to individual. However, some patients have severe seizure patterns (long-lasting, frequent). Some individuals have been described as having difficulties with an anxious, agitated and/or inattentive at times/difficulties with minor changes to their usual activity. Other individuals have a completely normal psychological examination. Many individuals with a CLCN4-related condition were described as being slow as a child (typically below average). Some students with CLCN4-related conditions have been very蠃ish with regard to a normal increase in age (mental age) or changes in the appearance of the adult mother in their brains. Other individuals have had normal brain imaging.

Some adult males with CLCN4-related disorders have been described as having a slightly larger than normal in their brains. However, studies have generally indicated that individuals do not look significantly different from other adults. Individuals of their family and we are not aware of a particularly increased chance of other neurological conditions.

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

https://humandiseasegenes.nhl/
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 cling 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

SYNGAP1 syndrome

rarechromo.org
Questions?
Why should I bother about this: why don’t I just refer to Clinical Genetics for all testing?
Traditional genetic testing process

Individual + family seen by [specialist] to think about diagnosis and treatment.

Could this child have a genetic condition?

Would finding a genetic condition be helpful for the child’s care?

Specialist orders first tier genetic testing: Fragile X PCR and Chromosomal microarray

Consent for further genetic testing:
(i) Multigene panel
(ii) Exome sequencing
(iii) Whole genome sequencing
(iv) Research testing

Genetics team look for clues for a particular genetic condition

Child and family seen by Clinical Geneticist and Genetic Counsellor if:
(i) VOUS
(ii) Genetic diagnosis for further genetic counselling
(iii) Undiagnosed to consider further testing

YES

Offer support through testing process

Provide genetic test result, reproductive counselling, information and support

Genetic result informs counselling, support, management +/- targeted therapies
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.
Questions ?