IALP Genetics in speech pathology

murdoch children's research institute

Through the lens of childhood apraxia of speech

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University of Melbourne
Murdoch Children's Research Institute

What do families want to know in clinic?

Symptom based approach to clinical management

Speech & language - motor speech, phon/linguistic, resonance, grammar, receptive vs expressive

Any co-occurring neurodevelopmental disorders

Careful history - other developmental challenges, cognition

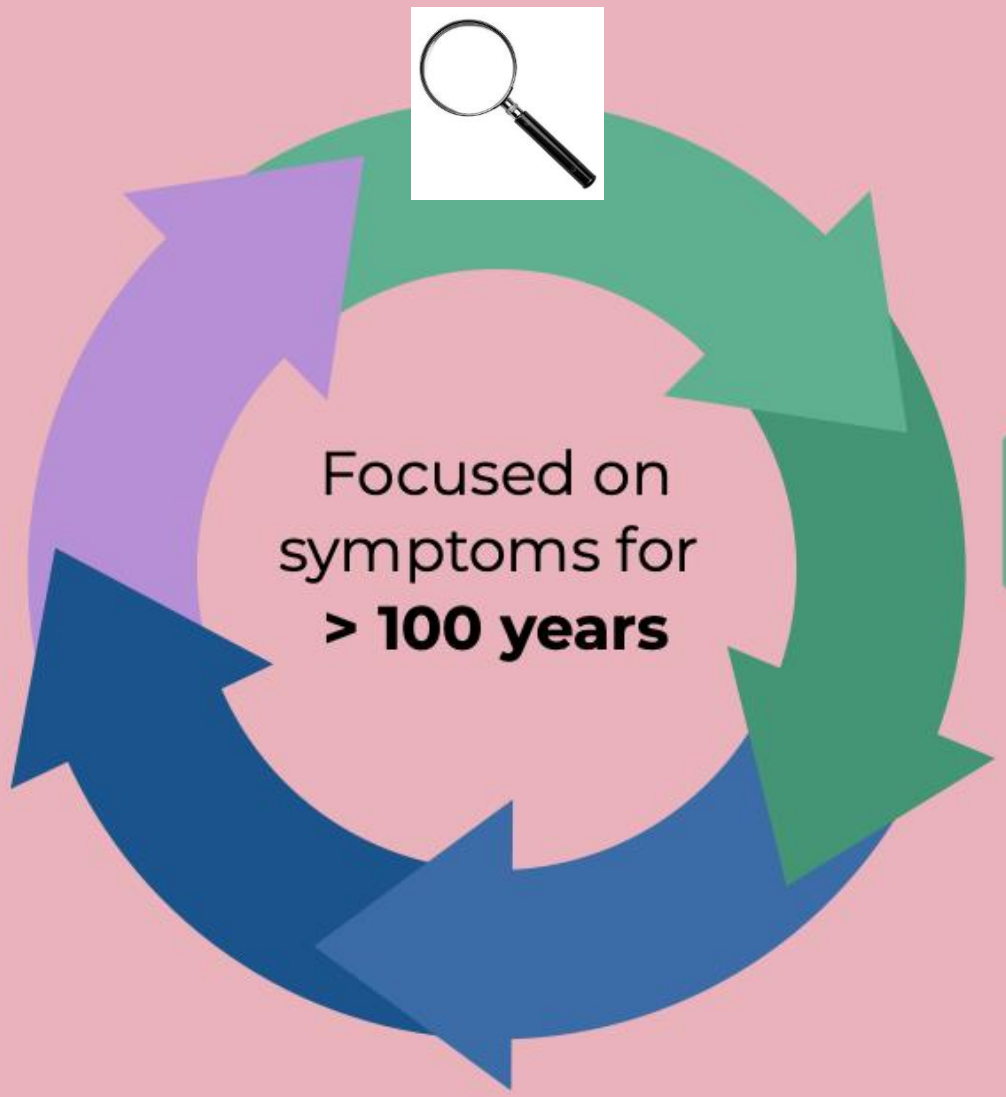
Issues in pregnancy or around time of birth

Other health & medical aspects. Hearing? MRI scan?

Family history, languages spoken at home, other ….

Targeted speech therapy
– limited or no ability to identify aetiology or prognosis

Symptom-based approach to speech pathology



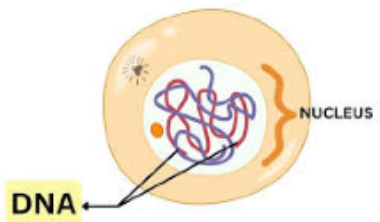
Genetic advances

Field is moving at a rapid pace re: aetiology - a new window into speech development

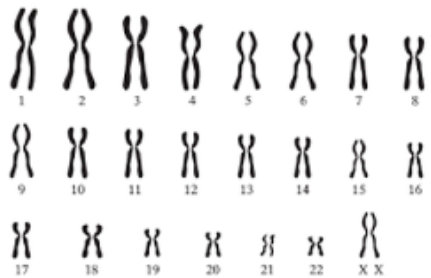

Recent gains in understanding genetic aetiologies due to advances in technology & analysis
1
Chromosome analysis
2
Single gene analysis

Refresher – chromosomes & genes

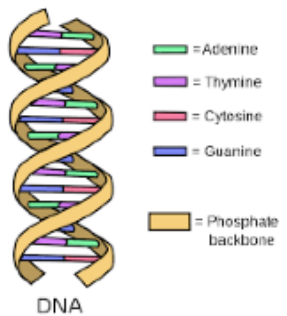
Cell



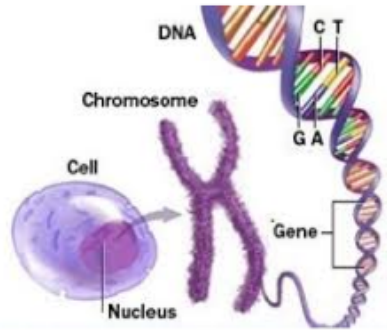
Chromosome



DNA



Single genes



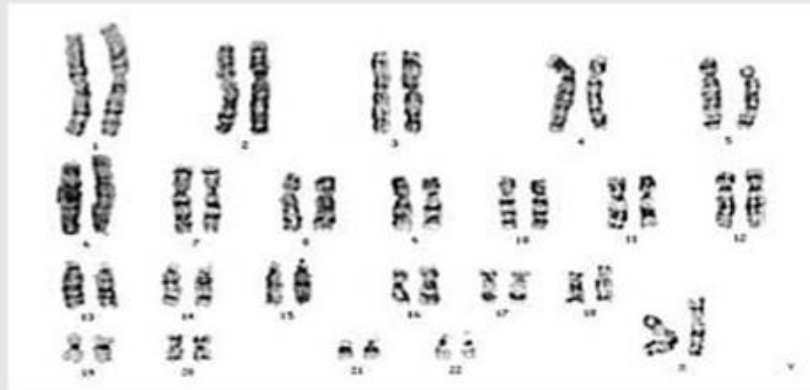
Hundreds to thousands of genes arranged on each chromosome
Each gene has its own unique position like a street address (16p11.2)

Detecting chromosomal changes

Outdated and early genetic methods - karyotype 1959

Trisomy 21

Cri du chat
6p deletion

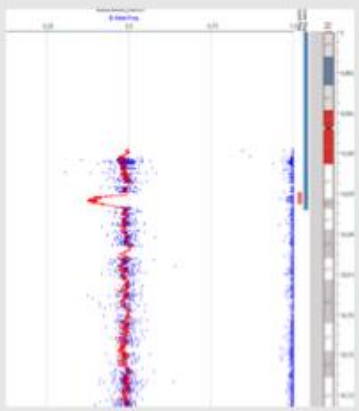


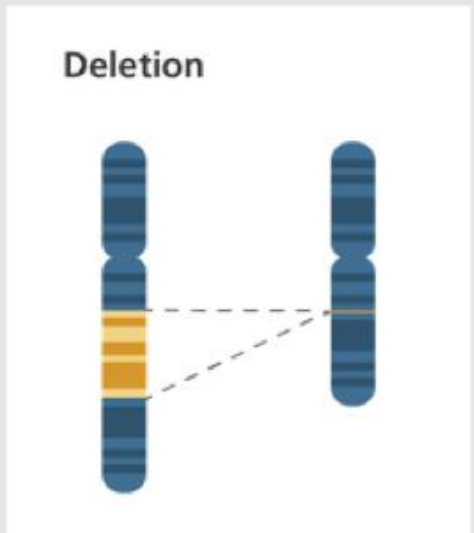
Karyotype: number & appearance of chromosomes

Detecting chromosomal changes

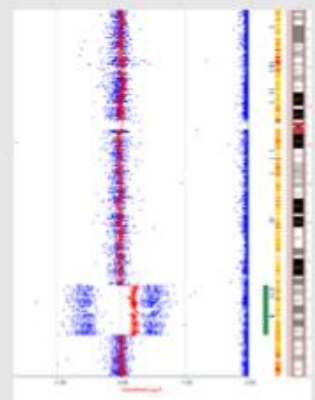
Chromosomal microarray karyotyping - modern day approach

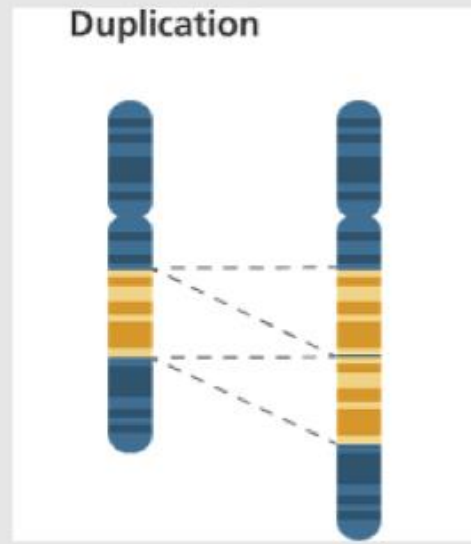
Deletion

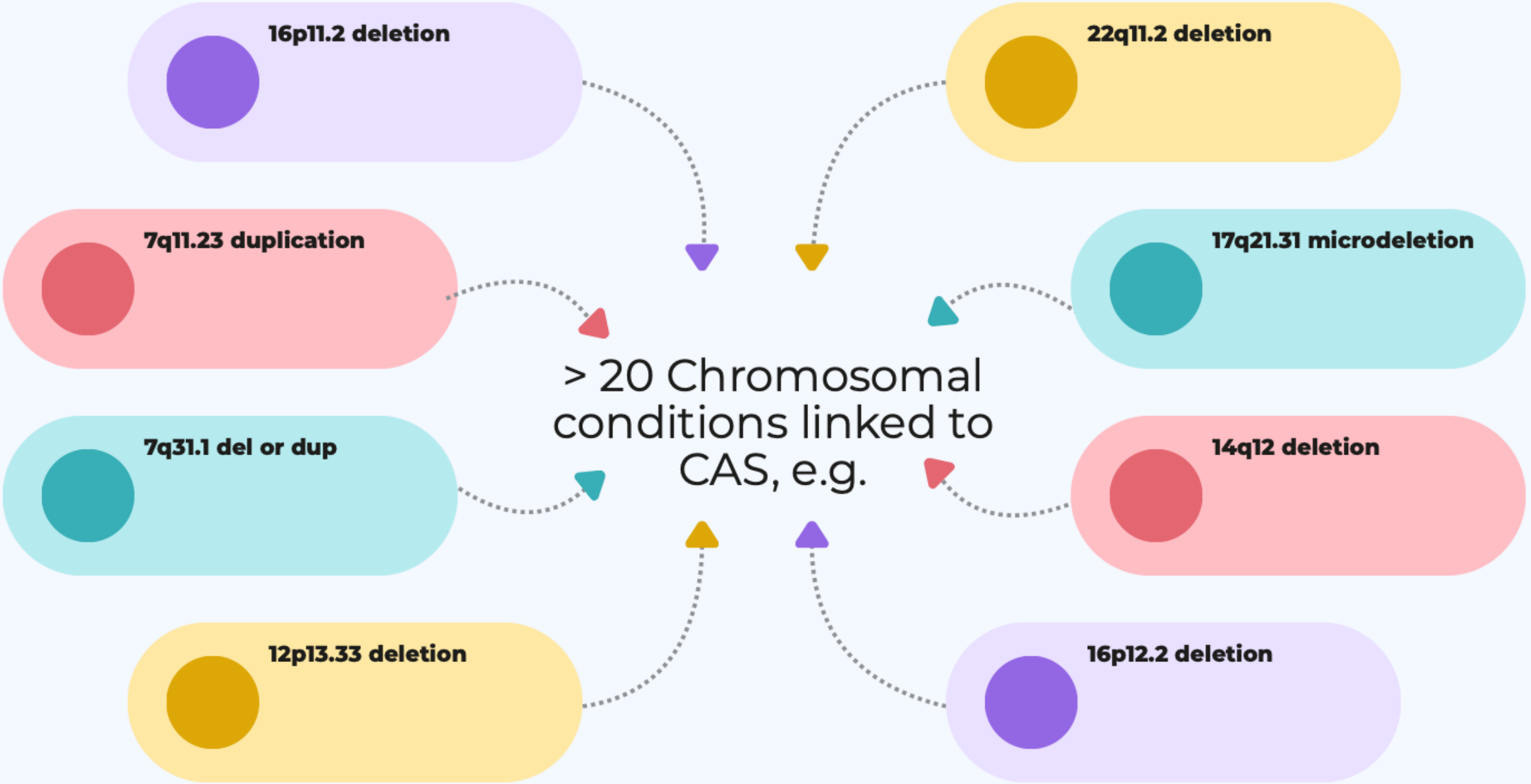




Duplication

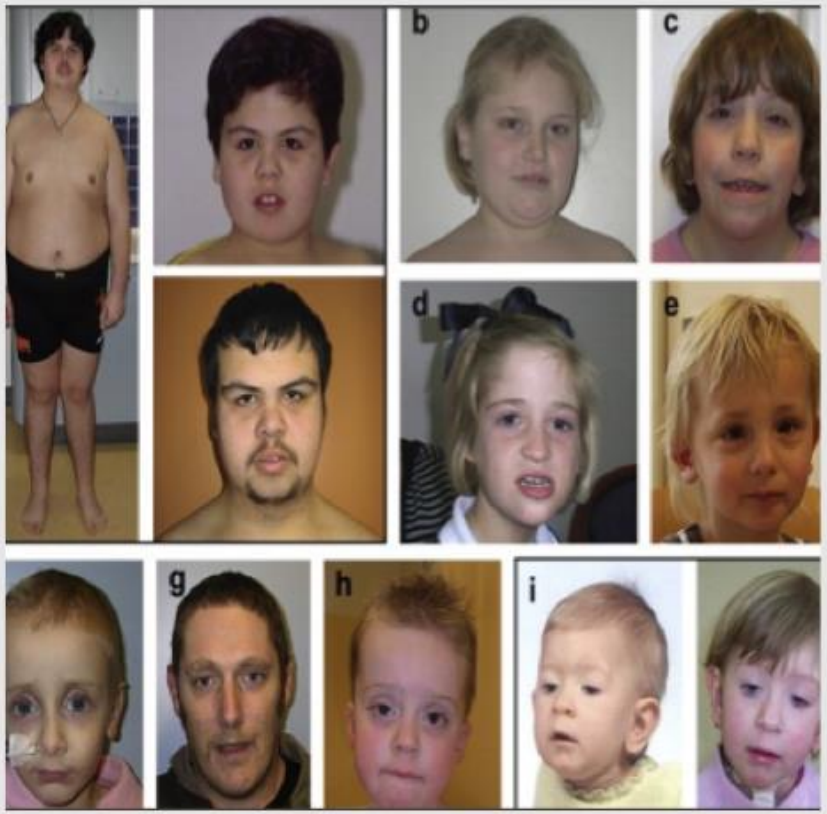





16p11.2 deletion
22q11.2 deletion
7q11.23 duplication
17q21.31 microdeletion
> 20 Chromosomal conditions linked to CAS, e.g.
7q31.1 del or dup
14q12 deletion
12p13.33 deletion
16p12.2 deletion

16p11.2 deletion

Phenotype



Prevalence of 1/5,000-10,000
Autism spectrum disorder (ASD)*
Mild-mod intellectual impairment
Mild-mod language impairment
Epilepsy (20%)
Macrocephaly (large head)
Obesity
Childhood apraxia of speech

*16p11.2 deletion explains 1/150 cases with ASD

Miller et al., 2015 Gen Rev

16p11.2 deletion

Phenotype

7;7 year old Australian male
CAS
Mild-moderate expressive & receptive language impairment
Low average non-verbal IQ
Mainstream school
Hearing WNL

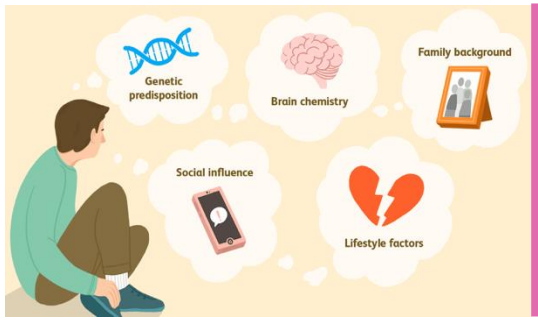
Detecting chromosomal changes in childhood apraxia of speech
How does this help in the clinic?

Dear Speech Pathology,

Thankyou for seeing 3;5 year old male with 17q21.31 microdeletion.

Family are keen for support with communication development.

Kind regards,



Why?

Prognosis?

Therapies?

Detecting chromosomal changes in childhood apraxia of speech
How does this help in the clinic?

Early speech development in Koolen de Vries syndrome limited by oral praxis and hypotonia - PubMed

PubMed.gov

17q21.31 microdeletion speech language

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> Eur J Hum Genet. 2018 Jan;26(1):75-84. doi: 10.1038/s41431-017-0035-9. Epub 2017 Dec 11.

Early speech development in Koolen de Vries syndrome limited by oral praxis and hypotonia

FULL TEXT LINKS

PMC FREE Full text

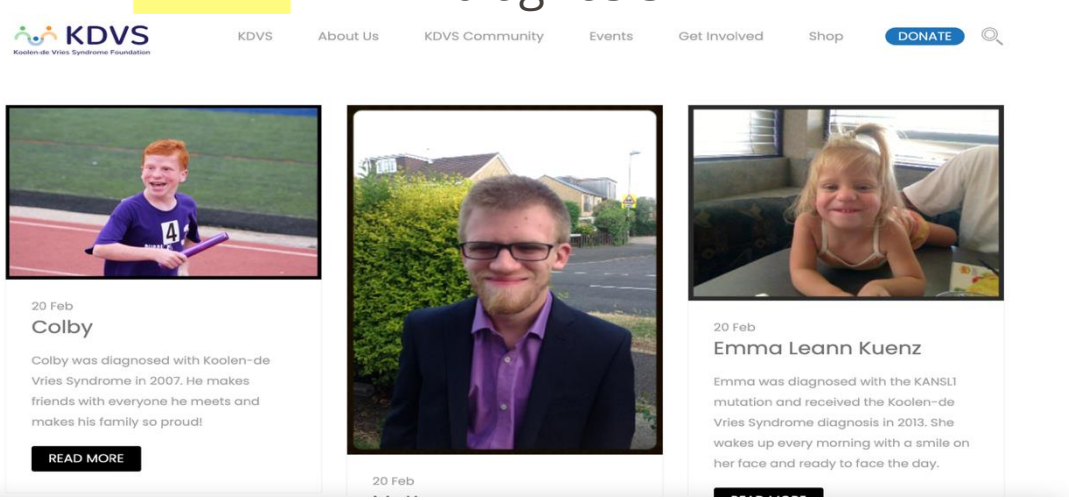
ACTIONS

Abstract

Communication disorder is common in Koolen de Vries syndrome (KdVS), yet its specific symptomatology has not been examined, limiting prognostic counselling and application of targeted therapies. Here we examine the communication phenotype associated with KdVS. Twenty-nine participants (12 males, 4 with KANSL1 variants, 25 with 17q21.31 microdeletion), aged 1.0-27.0 years were assessed for oral-motor, speech, language, literacy, and social functioning. Early history included hypotonia and feeding difficulties. Speech and language development was delayed and atypical from onset of first words (2; 5-3; 5 years of age on average). Speech was characterised by apraxia (100%) and dysarthria (93%), with stuttering in some (17%). Speech therapy and multi-modal communication (e.g., sign-language) was critical in preschool. Receptive and expressive language abilities were typically commensurate (79%), both being severely affected relative to peers. Children were sociable with a desire to communicate, although some (36%) had pragmatic impairments in domains, where higher-level language was required. A common phenotype was identified, including an overriding 'double hit' of oral hypotonia and apraxia in infancy and preschool, associated with severely delayed speech development. Remarkably however, speech prognosis was positive; apraxia resolved, and although dysarthria persisted, children were intelligible by mid-to-late childhood. In contrast, language and literacy deficits persisted, and pragmatic deficits were apparent. Children with KdVS require early, intensive, speech motor and language therapy, with targeted literacy and social language interventions as developmentally appropriate. Greater understanding of the linguistic phenotype may help unravel the relevance of KANSL1 to child speech and language development.

Bert de Vries,David Koolen

diagnosis



Support group - quality of life & wellbeing


Recent gains in understanding genetic aetiologies due to advances in technology & analysis
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Chromosome analysis
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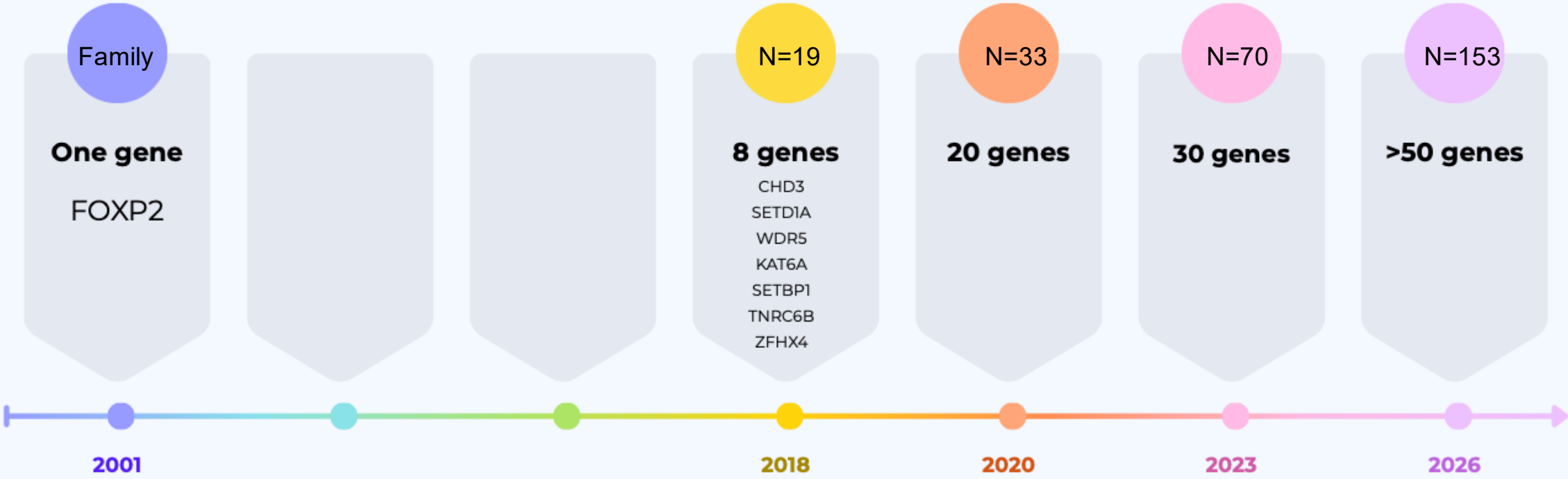
Single gene analysis

Single genes for childhood apraxia of speech 2001-2026




Simon Fisher


Else Eising


Australian team

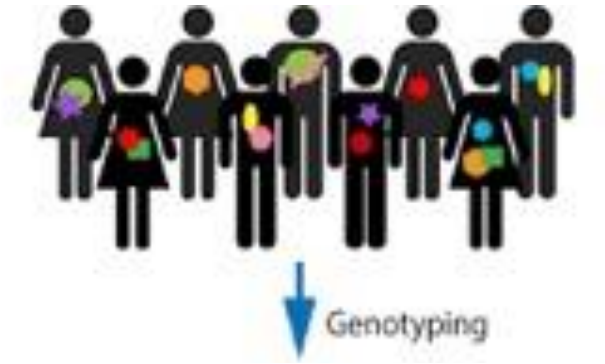

Australian team


Australian team

Also work and further genes identified in the US by Beate Peter, presented next! and Marisa Mitchell

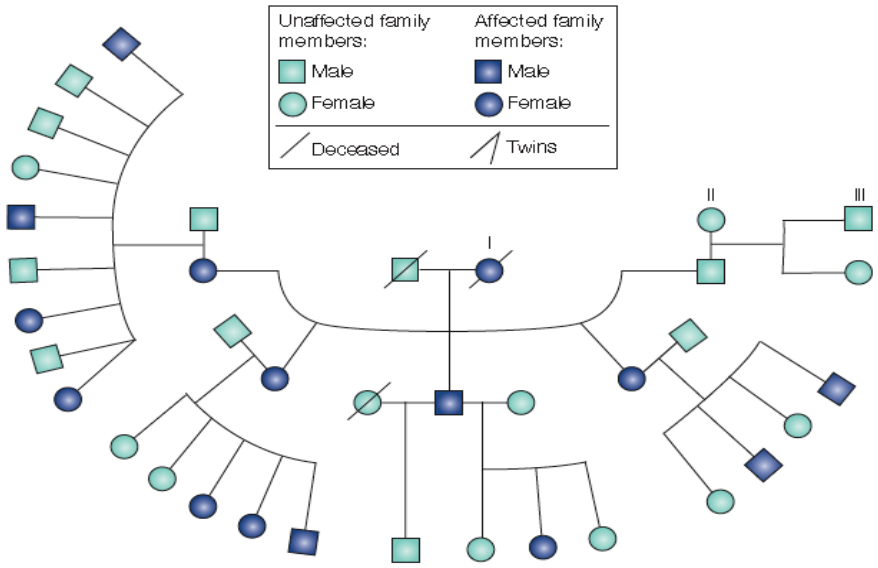
Childhood apraxia of speech is genetically heterogeneous – (as for all neurodevelopmental disorders)

Group of children with CAS

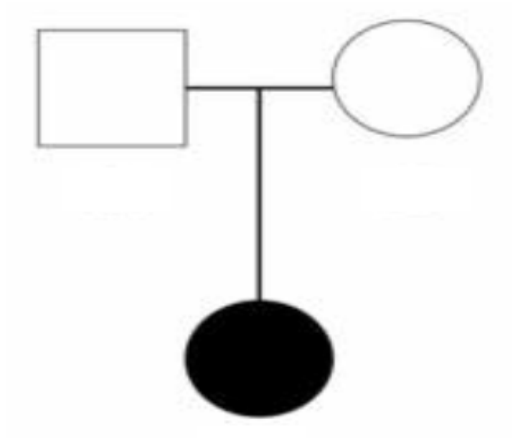


Genetic does NOT always mean inherited

More often sporadic – than inherited

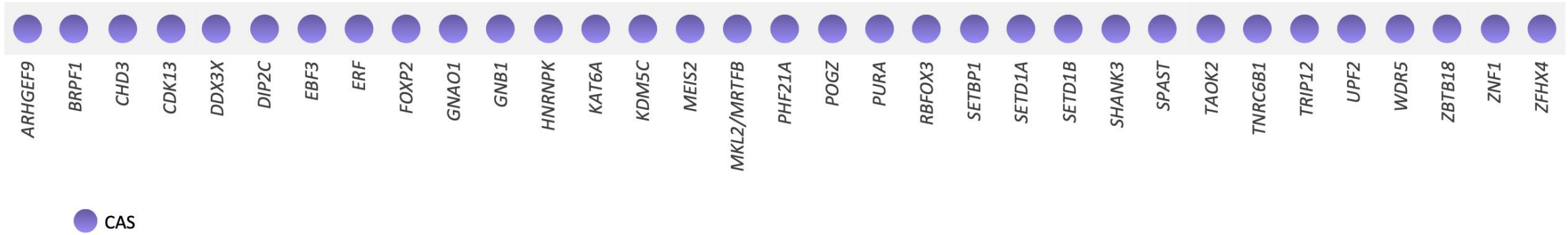


Inherited model
– multi generational



Sporadic – ‘de novo’ (occurring for the first time in the family)

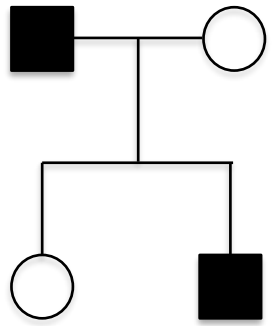
Broadening phenotype of known neurodevelopmental disorders (IQ>70 for CAS cases)



CAS candidate genes and co-occurring conditions (> seen in general population)

CACNA1A-related condition

- Paternal history speech delay, subclinical autism traits
- First words at age 2 years
- Mild delays in receptive language & academic skills
- Motor milestones slightly delayed; walked at 16 months
- Some autism traits noted
- Staring spells, EEG normal
- No dysmorphism noted
- c.3829C>T; p.(Arg1277*) (ClinVar 8506)



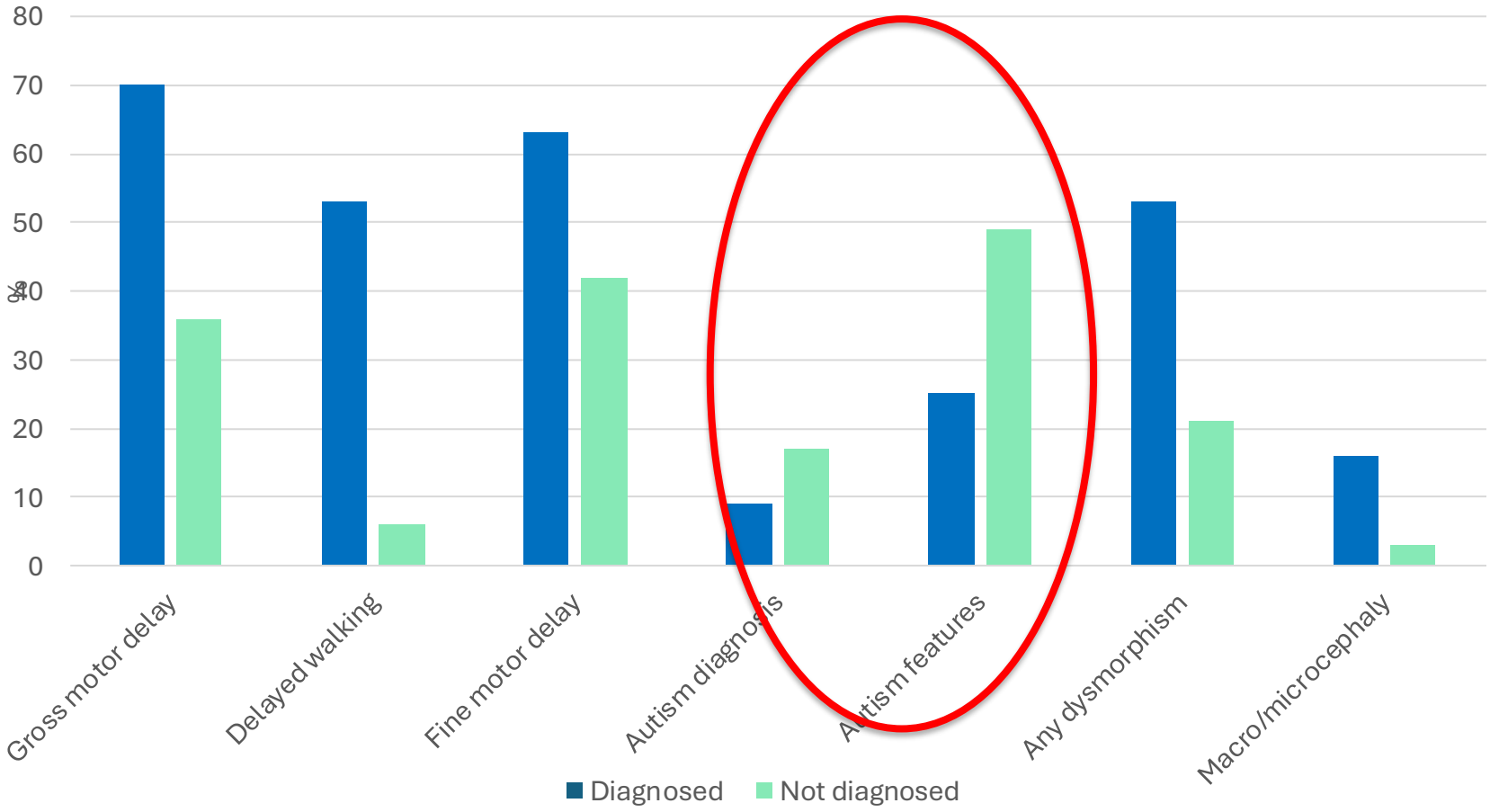
ESHG www.nature.com/ejhg

ARTICLE OPEN

Childhood motor speech disorders: who to prioritise for genetic testing

Halianna Van Niel[1,13], Mariana Lauretta[1,2,13], Emma Baker[1,2], Lorraine O'Donnell[1,2], Charlotte Boulton[1,2], Celia Brenchley[1,2], David Coman[3,4], Evyenia Michellis[1], Himanshu Goel[5], Geoff Thompson[6], Richard Webster[7], Georgia Paxton[2,8], Zornitza Stark[9], Ingrid E. Scheffer[8,10], Michael S. Hildebrand[8,10,11], David J. Amor[2,8,9,14] and Angela T. Morgan[1,2,4,12,14]

Can we predict who will receive a single gene diagnosis?



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Check for updates

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Single genes for apraxia - translating research into the clinic
Value of genetic testing in the clinic?

www.nature.com/ejhg

ESHG

ARTICLE OPEN

Check for updates

The value of genomic testing in severe childhood speech disorders

Yan Meng[1], Stephanie Best[1,2,3,4], David J. Amor[1,5,6], Ruth Braden[5], Angela T. Morgan[1,5,6,7] and Ilias Goranitis[1,2,5,7]

Marginal utilities & willingness to pay - general public N=950

	Marginal WTP (AU$)[c]
Number of children who receive genetic diagnosis	45
Knowledge gained from a genomic diagnosis (some knowledge)	1478
Knowledge gained from a genomic diagnosis (a lot of knowledge)	3092
Chance of improving the process of the child's medical care now	90
Time between now and when your child does the test	−201
Cost of testing to you	
Allowing access to educational support services	1140
Enabling access to relevant genetic-based family support groups	520

Marginal utilities & willingness to pay – apraxia families N=54

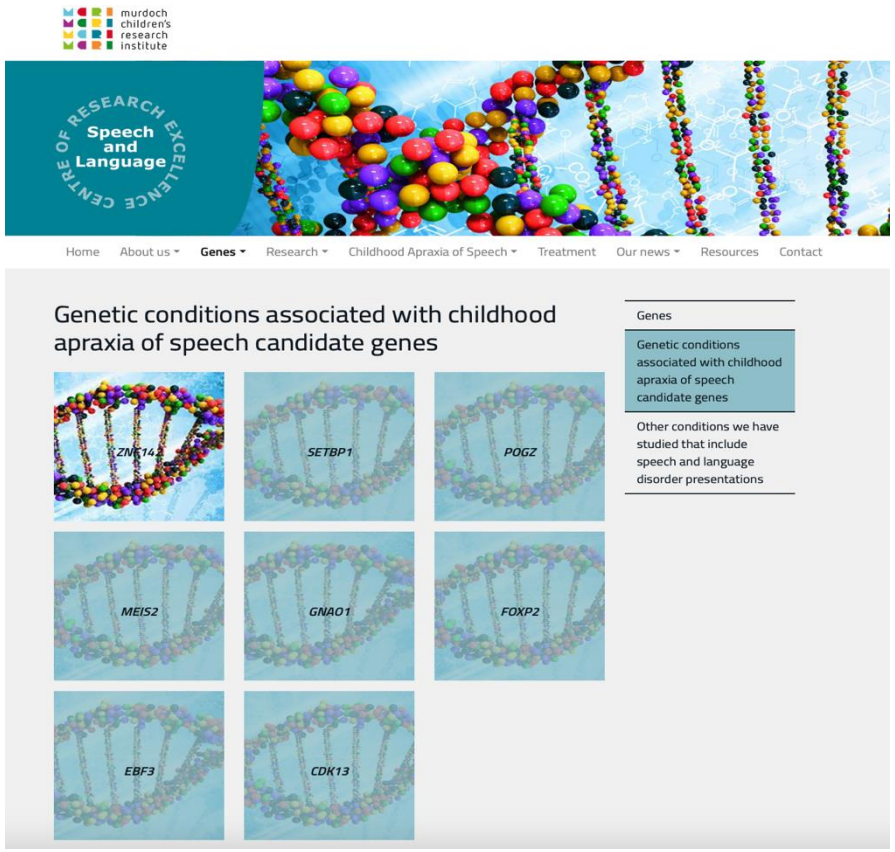
	Marginal WTP (AU$)
Number of children who receive genetic diagnosis	49
Knowledge gained from a genomic diagnosis (some knowledge)	2352
Knowledge gained from a genomic diagnosis (a lot of knowledge)	4207
Chance of improving the process of the child's medical care now	93
Time between now and when your child does the test	−169
Cost of testing to you	
Allowing access to educational support services	3094
Enabling access to relevant genetic-based family support groups	658

3

1

2

Genetics in the clinic – impacts for clinical practice?
Supporting families, consumer groups



Frequently asked questions

- What are the associated health or developmental conditions seen in children with *SETBP1* haploinsufficiency disorder?
- At what age to children with *SETBP1* haploinsufficiency disorder begin speaking?
- When children start speaking – what are the main features of their speech?
- How does speech develop over time?
- Do the children attend mainstream schools?
- What are the best-evidenced speech and language therapies?
- What happens to communication during adolescence and into early adulthood?
- What do children with *SETBP1* haploinsufficiency disorder sound like across the lifespan?
- Further information and support


Lottie Morison


Olivia van Reyk


Ruth Braden


Miya St. John


Elana Forbes


Sarah Horton

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David Amor, Clinical Geneticist, University of Melbourne, VCGS, MCRI
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Ingrid Scheffer, Neurologist, UoM
Karen van Hulst, Leenke Haaften, David Koolen, Bert de Vries RUMC
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Else Eising, MPI
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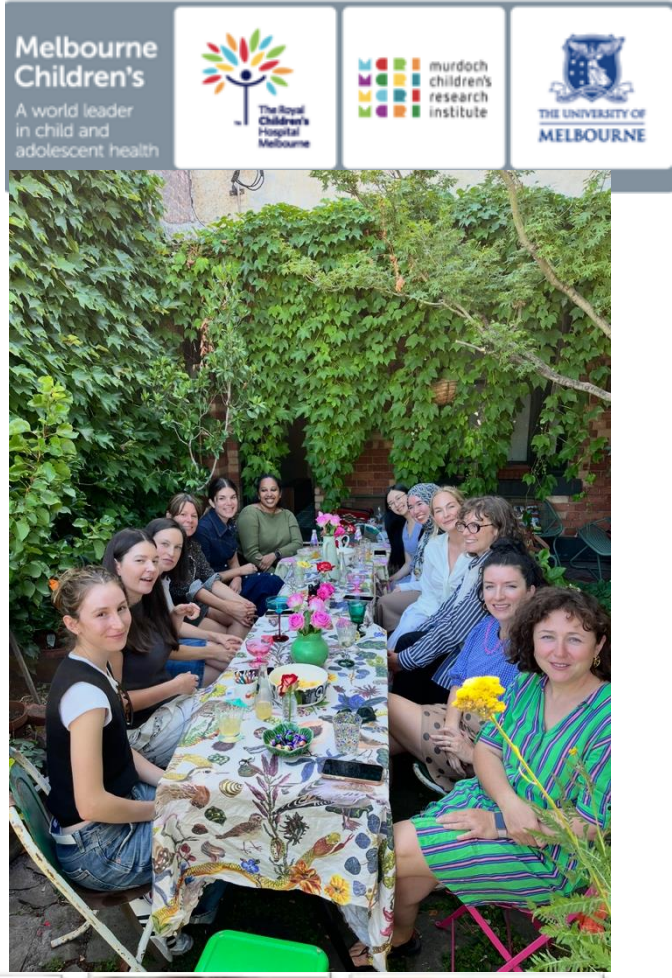
Sheena Reilly, Speech Pathologist, Griffith University
Stephanie Best, Peter Mac
Anna Jarmolowicz, UoM
Ilias Goranitis, Health economist, University of Melbourne, MCRI

MCRI, RCH speech and language genetics team
Olivia van Reyk, Speech pathologist
Lottie Morison, Speech pathologist
Mariana Lauretta, Speech pathologist
Elana Forbes, Psychologist
Miya St. John, Speech pathologist
Sarah Horton, Speech pathologist
Dr. Ruth Braden, Speech pathologist
Dr. Emma Baker, Psychologist
Bronwyn Parry-Fielder, Speech pathologist

Sincere thanks to individuals & families who have taken part in this research




David Amor
Clinical genetics

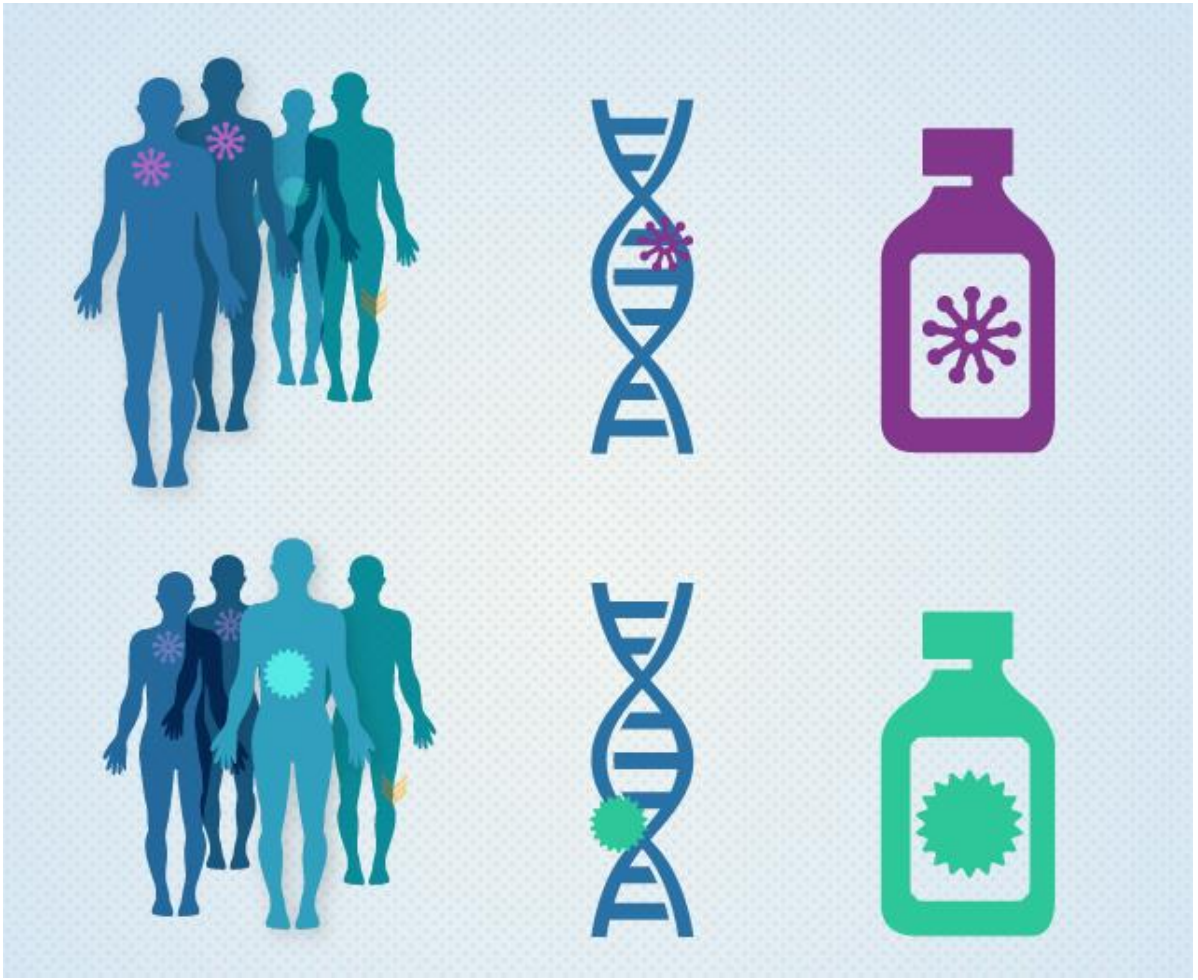

Ingrid Scheffer
Neurology


Fred Liegeois
Neuroscience


Simon Fisher
Biology


Michael Hildebrand
Molecular genetics

Precision or personalized medicine – biologically targeted therapies



Unique therapies that treat an individual's (speech) disorder based on the specific genetic abnormalities of their condition

Towards precision medicine, biologically targeted therapies
Replicating genetic variants & trialing drug therapies

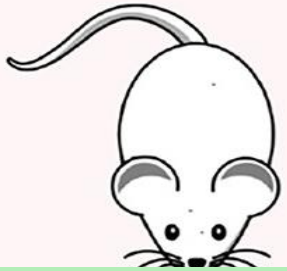
Cell cultures

SETBP1 variant

Pros:
- Derivable from patient iPS cells
- Readily available
- Easy to manipulate
- High throughout

Cons:
- Lacks brain cytoarchitecture
- Lacks 3D microenvironment
- Missing many cell types

Animal models



SETBP1 variant

Pros:
- Intact brain structure
- 3D microenvironment
- Behavioral testing

Cons:
- May not generalize to patients
- Low throughput

Brain organoids

SETBP1 variant

Pros:
- Human origin
- Derivable from patient iPS cells
- Brain-like cytoarchitecture
- 3D microenvironment

Cons:
- Limited maturity & size
- Missing certain cell types
- Neural activity not well defined