

# Prenatal Testing

## Reproductive carrier screening

Dr Michael Gattas  
Sat 16<sup>th</sup> Nov 2024

## Disclosures

- I work two days a week at Genetic Health Queensland
  - RBWH at Herston
  - Senior Medical Officer since 1996
- I work three days a week in private practice since 2004
  - Brisbane Genetics at Greenslopes Private Hospital
  - Wellspring Genetics



## Overview

- Current tests available
- A case history
  - Family history of SMA
- Expanded carrier test
- Tricky Issues
  - SMA
  - Fragile X

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## Current tests

- SMA (CNV), CF (SNV) and Fragile X (triplet repeat)
  - Medicare funded for women and their reproductive partner
- Expanded carrier tests
  - Beacon (SNP/Sonic)
  - Horizon (QML/Healius)
  - Genomics for Life - NIPT paternity testing
  - Prepair (VCGS pathology) – couples, saliva
  - Blueprint Genetics (Aust Clinical Laboratories)

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## Mackenzie Casella

### BACKGROUND

#### A dedication to Mackenzie

In May 2018 Federal Budget, the Australian Government announced \$500 million towards genomic research the Australian Health Care Mission, starting with a \$20 million study of reproductive genetic carrier screening called Mackenzie's Mission.

Mackenzie's Mission offered screening to up to 50,000 couples across Australia for about 100 autosomal recessive genetic conditions, allowing prospective parents to gain information about their likelihood of having a child with any of these genetic conditions.

The Mission used research already aimed at determining the evidence for making free reproductive genetic carrier screening available to all couples in Australia who wish to have it. The study ended in 2020.

Mackenzie's Mission is funded by the Medical Research Future Fund, part of a government-led Australian Genomics



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## 1,283 genes, \$1,500 per couple or 59 cents per gene

Panel 1: Mackenzie's Mission, Reproductive Carrier Screening

### Mackenzie's Mission, Reproductive Carrier Screening (Version 0.109)

Level 2: Screening

Panel types: Victorian Clinical Genetics Services, Rare Diseases, New South Wales Health Pathology, PathWest

#### Description

This panel has been developed for Mackenzie's Mission, a reproductive carrier screening project that will offer testing to 50,000 couples.

OnWise used to select genes are: the condition should be life-limiting or disabling, with childhood onset, such that couples would be likely to take steps to avoid having an affected child prior to sex for which early diagnosis and intervention would substantially change outcome (PACD: 10070200).

The panel is managed by Mackenzie's Mission.

#### 8 reviewers

Alison Young (Victorian Clinical Genetics Services)

South Hylbert (University of New South Wales)

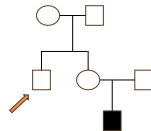
Shawn Kohn (New South Wales Health Pathology Newcastle)

Teresa Phan (Victorian Clinical Genetics Services)

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## Case history – 34 yr old male

- Please see Don for genetic counselling. His nephew was recently diagnosed with SMA at 18 months of age. After d/w his sister he is now seeking a genetic test. I hope you can discuss with him further.
- He has no current partner but is interested in raising a family in the foreseeable future.



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## SMA and neonatal screening

In June 2022, the Queensland Government announced that **from the end of May 2023**, the NBS program in Queensland will include testing for two additional conditions, spinal muscular atrophy (SMA) and severe combined immunodeficiency (SCID). In 2021, participation in NBS in Queensland was approximately 99%.

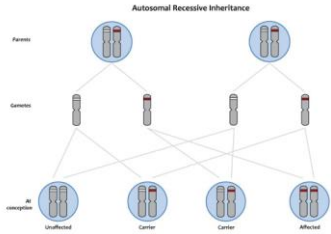


Queensland Health

<https://www.health.qld.gov.au/our-lifestyle>

Newborn screening | Report of the Chief Health Officer ...

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MBS item number

Category 6 - PATHOLOGY SERVICES

Group PF - Genetics

Item 73451

Testing of the reproductive partner of a patient who has been found to be a carrier of a pathogenic or likely pathogenic variant in the CFTR or SMN1 gene identified by testing under item 73451, for the purpose of determining the couple's reproductive risk of cystic fibrosis or **SpinaMuscular Atrophy**.

One test per condition per allele

Fee: \$400.00 Benefit: 75% = \$300.00 65% = \$260.00  
(See para 25.2.16 of explanatory notes to this Category)

➔ Previous Item 73451 ➔ Next Item 73453 ➔

Expanded carrier test

| Gene   | Condition Name                                                      | Inheritance | Ethnicity                           | Carrier Frequency | Detection Rate | Carrier Prevalence | Residual Risk    |
|--------|---------------------------------------------------------------------|-------------|-------------------------------------|-------------------|----------------|--------------------|------------------|
| CD44   | Familial C28 Deficiency                                             | AR          | General Population                  | <1 in 500         | 99%            | 1 in 49,900        | <1 in 10 million |
| CDAN1  | Charcot-Marie-Tooth congenital axonal type 1A                       | AR          | General Population                  | <1 in 500         | 99%            | 1 in 49,900        | <1 in 10 million |
| CDCA7  | Neurodegenerative syndrome with early-onset intellectual disability | AR          | General Population                  | <1 in 500         | 99%            | 1 in 49,900        | <1 in 10 million |
| CDH2   | Usher syndrome type 1D                                              | AR          | General Population                  | 1 in 2,880        | 99%            | 1 in 2,880         | 1 in 7,344       |
| CEP350 | Juvenile amyotrophic lateral sclerosis                              | AR          | General Population                  | <1 in 500         | 99%            | 1 in 49,900        | <1 in 10 million |
| CEP350 | CEP350-related disorders                                            | AR          | General Population                  | <1 in 500         | 99%            | 1 in 49,900        | <1 in 10 million |
| CEP350 | CEP350-related Charcot-Marie-Tooth                                  | AR          | General Population                  | 1 in 190          | 99%            | 1 in 1,900         | 1 in 7,600       |
| CERKL  | Retinitis pigmentosa 35                                             | AR          | General Population                  | 1 in 148          | 98%            | 1 in 2,280         | 1 in 4,360,792   |
| CERS3  | Compensatory cleft lip                                              | AR          | General Population                  | <1 in 500         | 99%            | 1 in 49,900        | <1 in 10 million |
| CFTR   | Cystic fibrosis                                                     | AR          | General Population                  | 1 in 32           | 99%            | 1 in 3,200         | 1 in 796,800     |
|        |                                                                     |             | African/African American Population | 1 in 61           | 99%            | 1 in 6,000         | 1 in 1,644,244   |
|        |                                                                     |             | Asymptomatic Jewish Population      | 1 in 24           | 99%            | 1 in 2,400         | 1 in 220,896     |
|        |                                                                     |             | Consanguineous Population           | 1 in 25           | 99%            | 1 in 2,400         | 1 in 240,300     |
| CHAT   | Congenital myasthenic syndrome 8                                    | AR          | General Population                  | 1 in 84           | 99%            | 1 in 840           | 1 in 1,470,756   |
|        |                                                                     |             | Latino Population                   | 1 in 66           | 99%            | 1 in 660           | 1 in 1,320,430   |
| CHAT   | CHAT                                                                | AR          | General Population                  | 1 in 107          | 99%            | 1 in 10,600        | <1 in 10 million |
| CHN    | Chondrodysplasia                                                    | AR          | General Population                  | 1 in 25,000       | 99%            | 1 in 499,900       | 1 in 1,999,604   |

FINAL RESULTS

TEST PERFORMED

Carrier Couple Identified

Monash Beacon Expanded Female Carrier Screening Panel v2.1

Condition and Gene

Inheritance

De Wit, Ashleigh

McCaig, Timothy

INTERPRETATION:

Notes and Recommendations:

- Both partners are carriers for mutations in the CHCHD7 gene; this means that there is a 1 in 4 risk of having a child affected by Smith-Lemli-Opitz syndrome.
- In total, their results are consistent with the female partner being positive for variants in 2 genes, and the male partner being positive for variants in 3 genes. A negative result reduces, but does not eliminate, the chance to be a carrier for any condition included in this screen. Please see the supplemental table for details.

## Tricky issues (the fine print)

### Reproductive Carrier Screening

| CONDITION                     | CARRIER RISK | RESULT                                           |
|-------------------------------|--------------|--------------------------------------------------|
| Cystic fibrosis (CF)          | Low risk     | No CFTR variants detected                        |
| Fragile X syndrome (FXS)      | Low risk     | Normal range allele(s) detected<br>FMR1: 10-26.5 |
| Spinal muscular atrophy (SMA) | Low risk     | At least two copies of the SMN1 gene detected    |

### INTERPRETATION

CF This individual is unlikely to be a carrier of CF. Residual risk varies with ethnicity and family history.

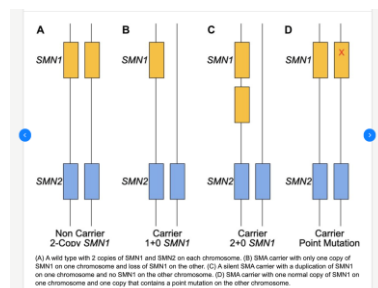
FXS This individual is unlikely to be a carrier of FXS. Residual risk varies with ethnicity and family history.

SMA This individual is unlikely to be a carrier of SMA. Residual risk varies with ethnicity and family history.

### RECOMMENDATION

This individual is unlikely to be a carrier for CF, FXS or SMA. Carrier status for rare disease-causing variants in these genes has not been excluded. This report should be interpreted in conjunction with the reproductive partner carrier screen result, if performed.

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## Fragile X pre-mutations

Fragile X (FMR1 triplet repeat expansion) Result:

Number of Trinucleotide repeats (CGG) 29 & 30

Fragile X Interpretation:

NO FMR1 REPEAT EXPANSION DETECTED

Triplet primed PCR (TP-PCR) analysis showed two unexpanded FMR1 CGG repeat alleles within the normal range.

This patient is not a carrier for fragile X syndrome caused by a triplet repeat expansion.

Reference ranges of CGG trinucleotide repeat allele sizes

|               |            |
|---------------|------------|
| Normal        | : 5 - 44   |
| Intermediate  | : 45 - 54  |
| Pre-mutation  | : 55 - 200 |
| Full mutation | : > 200    |

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Genetics  
inMedicine

ORIGINAL RESEARCH ARTICLE

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### Fragile X full mutation expansions are inhibited by one or more AGG interruptions in premutation carriers

Sarah L. Nolin, PhD<sup>1</sup>, Anne Glicksman, MS<sup>1</sup>, Nicole Ensales, BS<sup>1</sup>, Carl Dobkin, PhD<sup>1</sup>, W. Ted Brown, MD, PhD<sup>1</sup>, Ru Cao, PhD<sup>2</sup>, Eliot Blatt<sup>2</sup>, Sachin Sah, MS<sup>2</sup>, Gary J. Latham, PhD<sup>2</sup> and Andrew G. Hadd, PhD<sup>2</sup>

**Purpose:** Fragile X CGG repeat alleles often contain one or more AGG interruptions that influence allele stability and risk of a full mutation transmission from parent to child. We have examined transmission of maternal and paternal alleles with 45-90 repeats to quantify the effect of AGG interruptions on fragile X repeat instability.

**Methods:** A novel FMR1 polymerase chain reaction assay was used to determine CGG repeat length and AGG interruptions for 1,040 alleles from 705 families.

**AGGs:** Two contractions in maternal transmission were accompanied by loss of AGGs, suggesting a mechanism for generating alleles that lack AGG interruptions. Maternal age was examined as a factor in full mutation expansions using prenatal samples to minimize ascertainment bias, and a possible effect was observed though it was not statistically significant ( $P=0.06$ ).

**Conclusion:** These results strengthen the association of AGG repeats with CGG repeat stability and provide more accurate risk estimates of full mutation expansions for women with 45-90 repeat alleles.

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Table 1 Full mutation expansions by maternal repeat size

| Maternal repeat size | No. full mutation/<br>total transmissions | %   |
|----------------------|-------------------------------------------|-----|
| 45–49                | 0/98                                      | 0   |
| 50–54                | 0/102                                     | 0   |
| 55–59                | 1/197                                     | 0.5 |
| 60–64                | 2/115                                     | 1.7 |
| 65–69                | 6/85                                      | 7   |
| 70–74                | 18/84                                     | 21  |
| 75–79                | 47/99                                     | 47  |
| 80–84                | 60/96                                     | 62  |

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Table 2 Unstable transmissions and full mutation expansions sorted by repeat size and number of AGG

| Maternal repeat size | No. AGGs | Total transmissions | Unstable transmissions* | %   | No. full mutations | %  |
|----------------------|----------|---------------------|-------------------------|-----|--------------------|----|
| 45–49                | 0        | 3                   | 4                       | 90  | 0                  | 0  |
|                      | 1        | 83                  | 6                       | 19  | 0                  | 0  |
|                      | 2        | 37                  | 3                       | 5   | 0                  | 0  |
|                      | 3        | 5                   | 0                       | 0   | 0                  | 0  |
|                      | 4        | 5                   | 0                       | 0   | 0                  | 0  |
| 50–54                | 0        | 9                   | 9                       | 100 | 0                  | 0  |
|                      | 1        | 49                  | 11                      | 22  | 0                  | 0  |
|                      | 2        | 47                  | 5                       | 12  | 0                  | 0  |
|                      | 3        | 2                   | 0                       | 0   | 0                  | 0  |
|                      | 4        | 1                   | 0                       | 0   | 0                  | 0  |
| 55–59                | 0        | 30                  | 29                      | 97  | 1                  | 3  |
|                      | 1        | 95                  | 50                      | 53  | 0                  | 0  |
|                      | 2        | 64                  | 9                       | 9   | 0                  | 0  |
|                      | 3        | 5                   | 0                       | 0   | 0                  | 0  |
| 60–64                | 0        | 37                  | 36                      | 97  | 2                  | 5  |
|                      | 1        | 39                  | 33                      | 85  | 0                  | 0  |
|                      | 2        | 39                  | 20                      | 53  | 0                  | 0  |
|                      | 3        | 5                   | 1                       | 20  | 0                  | 0  |
| 65–69                | 0        | 35                  | 35                      | 100 | 4                  | 11 |
|                      | 1        | 28                  | 25                      | 89  | 0                  | 0  |
|                      | 2        | 20                  | 14                      | 70  | 0                  | 0  |
|                      | 3        | 2                   | 0                       | 0   | 0                  | 0  |
| 70–74                | 0        | 29                  | 29                      | 100 | 15                 | 52 |
|                      | 1        | 43                  | 40                      | 94  | 3                  | 7  |
|                      | 2        | 13                  | 13                      | 93  | 0                  | 0  |
| 75–79                | 0        | 43                  | 43                      | 100 | 32                 | 75 |
|                      | 1        | 42                  | 42                      | 100 | 14                 | 33 |
|                      | 2        | 16                  | 16                      | 100 | 1                  | 7  |
| 80–84                | 0        | 31                  | 31                      | 100 | 27                 | 87 |
|                      | 1        | 45                  | 45                      | 100 | 30                 | 67 |
|                      | 2        | 23                  | 23                      | 100 | 5                  | 22 |
| 85–90                | 0        | 8                   | 8                       | 100 | 7                  | 88 |
|                      | 1        | 30                  | 30                      | 100 | 21                 | 70 |
|                      | 2        | 4                   | 4                       | 100 | 3                  | 75 |

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| Molecular Genetics                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MG FRAXA AGG Interrups Final Report                                                                                                                                                                                                                                                                                                                                                                     |
| Accession #: MG-24-05380                                                                                                                                                                                                                                                                                                                                                                                |
| Collection date: 23/06/2024 09:00                                                                                                                                                                                                                                                                                                                                                                       |
| Received date: 18/07/2024 09:30                                                                                                                                                                                                                                                                                                                                                                         |
| Specimen type: DNA (From peripheral blood)                                                                                                                                                                                                                                                                                                                                                              |
| External Reference: 370104-001 (Pathology Queensland Reference Number)                                                                                                                                                                                                                                                                                                                                  |
| Clinical indication: FRAX premutation carrier, 20, 58 yrs (SNP). Currently pregnant, amnio done, results pending. Testing to inform FND for future preg.                                                                                                                                                                                                                                                |
| Test requested: FRAX - AGG interrupt analysis by genotyping PCR                                                                                                                                                                                                                                                                                                                                         |
| Results:                                                                                                                                                                                                                                                                                                                                                                                                |
| Allele 1, 58 repeats: (CGG) <sup>58</sup> AGG (CGG) <sup>58</sup> AGG (CGG) <sup>58</sup>                                                                                                                                                                                                                                                                                                               |
| Allele 2, 30 repeats: (CGG) <sup>10</sup> AGG (CGG) <sup>9</sup>                                                                                                                                                                                                                                                                                                                                        |
| Interpretation:                                                                                                                                                                                                                                                                                                                                                                                         |
| This individual is a carrier of a premutation-sized allele of 58 triplet repeats which has a low risk of expansion to a full mutation in one generation.                                                                                                                                                                                                                                                |
| This allele contains 2 AGG interrupts, with the longest uninterrupted region of 38 triplet repeats. From alleles between 50-59 repeats with two AGG interrupts, there are no reports of a full mutation expansion upon maternal transmission and 3% (5 out of 145) have unstable transmissions with a median repeat change of 1 repeat, ranging from -2 to 1 repeat (Bustin et al 2015, PMD: 25219937). |
| The second allele for this individual is within the normal size range with 1 AGG interrupt.                                                                                                                                                                                                                                                                                                             |
| Conclusion:                                                                                                                                                                                                                                                                                                                                                                                             |
| This result confirms the carrier status of this individual for a premutation-sized allele.                                                                                                                                                                                                                                                                                                              |

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Thank You and Any Questions?

• Dr Michael Gattas  
• Sat 16<sup>th</sup> Nov 2024



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