The Expanding Family of Fragile X Associated Disorders

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Outline

• *FMR1* gene
• Fragile X-associated disorders (FXDs):
  – Fragile X Syndrome
  – Fragile X-associated Primary Ovarian Insufficiency (FXPOI)
  – Fragile X-associated Tremor Ataxia Syndrome (FXTAS)
• Australian premutation carrier study
• FXTAS treatments
Treating FXDs: A Multidisciplinary Approach

Clinicians
• Neurologists
• Neuropsychiatrists
• Developmental Paediatricians
• Infertility Specialists
• Rehabilitation and geriatricians

Psychology, Nursing & Allied Health
• Detailed assessments
• Planning & implementing interventions
• Planning & implementing supports
• Family and Systems issues

Clinical Investigations
• Neuropsychologists
• Developmental assessments
• MRI
• Gait lab

Genetics & Laboratory
• Clinical Geneticists
• Molecular genetics
• Animal models
• Pharmacological treatments

Person with an FXD
Family with FXDs
Fragile X Mental Retardation 1 (FMR1) Gene

The FMR1 gene is located in the 5’ untranslated region of the long arm of the X chromosome and contains a DNA segment of CGG repeats.

**Normal Population:**
<45 CGG repeats

**Premutation Carriers:**
55-200 CGG repeats

**Full-mutation:**
>200 CGG repeats

Oostra & Willemsen (2009), Biochimica Et Biophysica Acta-General Subjects, 1790(6), 467-477
Fragile X-associated Disorders

- Fragile X-associated primary ovarian insufficiency (FXPOI)
  - 20-25% female carriers

- Fragile X-associated tremor ataxia syndrome (FXTAS)
  - 40-45% male carriers over 50 years
  - 8-12% female carriers over 40 years

- Fragile X syndrome (FXS)
  - 1 in 3600 males
  - 1 in 4000-6000 females

FMRP

Premutation:
(55–200 CGG repeats)

Full mutation:
(>200 CGG repeats)
Fragile X Syndrome

- Fragile X Syndrome - leading inherited cause of Intellectual Disability, most common genetic cause of Autism

- Caused by full mutation (>200 CGG repeats) of the FMR1 gene

- FXS affects about 1 in 3600 males and 1 in 4000-6000 females
  - >80% males with FXS have an IQ less than 70
  - Females IQ more variable

- Premutation carried in about 1 in 209 women and 1 in 430 men
  - Gene for FXS carried on the X Chromosome, both males (XY) and females (XX) have an X chromosome and can be affected
Fragile X Syndrome: Physical Features

- Large ears
- Long face or jaw
- Loose flexible joints
- Strabismus
- Soft smooth skin
- Flat feet
- High arched palate
- Macroorchidism

Fragile X Syndrome: Cognitive and behavioural features

- Verbal intelligence exceeds performance
- Speech & language development is almost always delayed
- 80% of males have ID, most in mild-moderate range
- 25% of females have ID
- In those without ID, other learning difficulties, attentional disorders are common

- Social anxiety
- Aversion of gaze
- Autism in about 30%
- Autistic Spectrum in about 30%
- Other:
  - Perseveration
  - Mannerisms, hand flapping
  - Poor eye contact, socially avoidant
  - Self injury, aggression
  - ADHD
Fragile X Syndrome: Differential Diagnosis

- Sotos Syndrome
- Prader-Willi Syndrome (PWS)
- Autism
- Attention deficit-hyperactivity disorder (ADHD)
- Fragile XE Syndrome (FRAXE)
Fragile X-associated Disorders

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Premutation: (55–200 CGG repeats)

Full mutation: (>200 CGG repeats)
Fragile X-associated Primary Ovarian Insufficiency (FXPOI)

**DEFINITION AND CAUSE:**
- Cessation of normal functioning of ovaries in women <age 40
- 20-25% Female Premutation carriers manifest FXPOI
- Paternal-parent-of origin effect on FXPOI
- Premutation carriers found in up to 13% of women with familial POI

**MANIFESTATIONS:**
- Possible reduced number of eggs/rate of loss increases over time
- Absent or irregular periods
- Symptoms of menopause e.g. Hot flashes and night sweats, early menopause and Sub-infertility or Infertility, thinning and drying of the vagina
- 5-10% of women may conceive after diagnosis of POI (Nelson et al., 2005)
Fragile X-associated Disorders

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Fragile X syndrome (FXS)
- 1 in 3600 males
- 1 in 4000-6000 females
Fragile X-associated Tremor Ataxia Syndrome (FXTAS)

- An “adult onset” neurodegenerative disorder
- Affects proportion of FMR1 premutation carriers (55-200 CGG repeats)

1 in 3000 men over age 50 will develop FXTAS

1/430 males at risk

1/209 females at risk

Penetrence increases with age

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## FXTAS: Neurological manifestations

<table>
<thead>
<tr>
<th>Central</th>
<th>Peripheral</th>
<th>Autonomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Tremor</td>
<td>- Neuropathy</td>
<td>- Orthostatic hypotension</td>
</tr>
<tr>
<td>- Gait ataxia</td>
<td>- Hearing loss</td>
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<td>- Parkinsonism</td>
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<td>- Cognitive Decline</td>
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<tr>
<td>- Behavioural &amp; Psychiatric</td>
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FXTAS Progression

- Tremor
- Ataxia/balance
- Cognitive
Neuropsychiatric profile

<table>
<thead>
<tr>
<th>Cognitive Deficits</th>
<th>Rates of Mental Disorders</th>
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<tr>
<td>• Executive functioning</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Working memory</td>
<td>• Anxiety</td>
</tr>
<tr>
<td>• Information processing</td>
<td>• Irritability</td>
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<tr>
<td>• Fine motor</td>
<td>• Agitation / Aggression</td>
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<td></td>
<td>• Disinhibition</td>
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<td>• Apathy</td>
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# Systematic review of cognitive features

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Global cognitive function</th>
<th>General intelligence</th>
<th>Memory</th>
<th>Executive function</th>
<th>Attention</th>
<th>Working memory</th>
<th>Language</th>
<th>Visuospatial</th>
<th>Information processing</th>
<th>Fine motor</th>
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- **FXTAS < Controls**
- **FXTAS = Controls**
- **Domain not examined**
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Neuroimaging: MRI

- High signal lesions in MCP & dentate nucleus on T2/FLAIR
- Increased white matter hyper-intensities
- Cerebral atrophy
- Decreased white matter integrity as measured by DTI in multiple white matter tracts
- Grey matter loss in multiple brain regions
- Reduced activation in lateral prefrontal cortex during a working memory task

FXTAS: Neuropathology\textsuperscript{1, 2}

- Ubiquitin positive intranuclear inclusions in neurons and astrocytes throughout the central and peripheral nervous systems
- Cerebral and cerebellar white matter disease
- Loss of axons, myelin and cerebellar Purkinje cells
- Spongiosis of MCP and white matter
- Larger CGG repeats = higher percentage inclusions

FXTAS: Molecular correlates

Larger *FMR1* CGG repeats
- ↑ relative risk for cognitive impairment
- ↓ response inhibition
- ↓ verbal fluency
- ↓ visuospatial working memory
- ↓ full scale and performance IQ

Increased *FMR1* mRNA
- ↑ psychiatric symptoms
- ↓ activation in brain regions associated with memory, working memory and social cognition

Decreased FMRP
- ↓ amygdala activation and social information processing
- ↓ full scale and performance IQ
FXTAS Case

- 58 year old male
  - Subtle balance problems 55+
  - Tremor 57+
  - No cognitive complaints
- Medical History
  - ex smoker (only 2 pack years)
  - no other vascular risk factors
  - ETOH 20g x 3 per week
- Family History
  - Negative for ID
  - Positive for IHD, PVD
  - obligate carrier daughter (in early 20s) identified

- Assessment:
  - History PTSD (full remission)
  - FSIQ= 80, VIQ= 84, PIQ= 81
  - Impaired on: Hayling (response inhibition); verbal fluency (COWAT); processing speed (trails A and B, Digit symbol coding); language (Boston Naming Test)

- Bloods:
  - Routine normal
  - 91 CGG repeats
  - mRNA= 3.57 x normal
Tremor 1

Handwriting (dominant hand only):

This is a sample of my best handwriting.

Signature. Date.

13.6.13

This is not a sample of my best handwriting.
Tremor 2
Gait
# FXTAS Diagnostic Criteria


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**Diagnostic categories (inclusion criteria = 55-200 CGG repeats):**

- **Definite:** One major radiological sign + one major clinical symptom
- **Probable:**
  - a) One major radiological sign + one minor clinical symptom, or
  - b) Two major clinical symptoms
- **Possible:** One minor radiological sign + one major clinical symptom
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FXTAS: Differential Diagnosis

• Vascular Dementia
• Corticobasal Degeneration
• Multiple System Atrophy
• Progressive Supranuclear Palsy
• Wilsons Disease
• HIV associated Dementia
• Huntingtons Disease
• Parkinsons Disease with Dementia
• Frontal variant Frontotemporal Dementia
• Motor Neuron Disease
• Essential Tremor
• Pseudodementia
When to Consider Testing for FMR1 Premutation?

• Males and females:
  – over 50 who present with tremor, ataxia +/- cognitive disorder
  – presenting with cognitive disorder in context of FHx of FXDs
  – with characteristic scan changes (with motor or cognitive symptoms).
  – with psychiatric disorder in context of FHx of FXDs

• Females:
  – with POI and cognitive disorder (+/- motor signs)
Neurodevelopmental: cognitive/behavioural

FXPOI

FXTAS

AGE
No Evidence for a Difference in Neuropsychological Profile among Carriers and Noncarriers of the FMR1 Premutation in Adults under the Age of 50

Jessica Ezzell Hunter, Emily Graves Allen, Ann Abramowitz, Michele Rusin, Mary Leslie, Gloria Novak, Debra Hamilton, Lisa Shubeck, Krista Charen, and Stephanie L. Sherman


Lifespan changes in working memory in fragile X premutation males.

Cornish KM, Kogan CS, Li L, Turk J, Jacquemont S, Hagerman RJ.

Neuroscience Laboratory for Research and Education in Developmental Disorders, McGill University,

Age-dependent cognitive changes in carriers of the fragile X syndrome

Cortex 44 (2008) 628–636


Selective spatial processing deficits in an at-risk subgroup of the fragile X premutation

Darren R. Hocking, Cary S. Kogan, Kim M. Cornish

Monash Institute for Brain Development and Repair (MIBDR), Monash University, School of Psychology and Psychiatry, Faculty of Medicine, Melbourne, Australia

School of Psychology, University of Ottawa, Ottawa, Canada
Neurodevelopmental profile?

FXPOI

Early markers?

FXTAS

AGE

10 20 30 40 50 60 70 80 90
Australian *FMR1* Premutation Carrier Study

**Females: Melbourne; Asymptomatic FMR1 Carriers**
- Questionnaire (medical and family history, self report psychiatric symptoms)
- Neuropsychological assessment
- Neuromotor assessment
- Oculomotor assessment
- Bloods

**Males: Sydney; Any FMR1 Premutation Carriers**
- Questionnaire (medical and family history, self report psychiatric symptoms)
- Informant questionnaire and interview
- Neuropsychological assessment
- Psychiatric diagnostic interview
- Neuromotor assessment
- Bloods
- Brain MRI
## Asymptomatic Female FRM1 Premutation Sample

<table>
<thead>
<tr>
<th></th>
<th>FMR1 PM-carriers (N = 35)</th>
<th>Controls (N = 35)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>M ± SD (range)</td>
<td>M ± SD (range)</td>
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<tr>
<td></td>
<td>41.14 ± 8.34 (22-55)</td>
<td>41.11 ± 8.64 (22-55)</td>
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<td><strong>FSIQ</strong></td>
<td>M ± SD (range)</td>
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<td>110.26 ± 10.94 (88-128)</td>
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<td><strong>VIQ</strong></td>
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<td>106.59 ± 13.90 (73-128)</td>
<td>108.11 ± 11.36 (84-136)</td>
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<td><strong>PIQ</strong></td>
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<td>110.86 ± 11.34 (87-133)</td>
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<td>65.7%</td>
<td>17.1%</td>
<td></td>
</tr>
<tr>
<td><strong>CGG-repeat length</strong></td>
<td></td>
<td></td>
<td>.001**</td>
</tr>
<tr>
<td></td>
<td>86 ± 15.07 (59-122)</td>
<td>26 ± 3.52 (20-42)</td>
<td></td>
</tr>
</tbody>
</table>
Psychiatric Status and Executive Control in Females

American Journal of Medical Genetics Part B: Neuropsychiatric Genetics

Full title: Impaired response inhibition is associated with self-reported symptoms of depression, anxiety and ADHD in female FMR1 premutation carriers

*Claudine M. Kraan¹, Darren R. Hocking, PhD¹, Nellie Georgiou-Karistianis¹, PhD, Sylvia A Metcalfe, PhD²,³, Alison D Archibald, PhD²,³,⁴, Joanne Fielding¹,⁸, Julian Trollor, MD⁵, John L. Bradshaw, PhD¹, Jonathan Cohen²,⁶,⁷ and **Kim M. Cornish, PhD¹

- PM-carriers significantly elevated on self-reported social anxiety and ADHD-PI symptoms.
- EF correlated with self-reported symptoms of anxiety, depression and ADHD-PI.
- But: independently of mental symptoms, female PM-carries still performed significantly worse than controls on a response inhibition test.
- And: PM-carriers with good EF did not have mental disorders.
Cognitive-motor interference during postural control indicates at-risk cerebellar profiles in females with the FMR1 premutation


- poorer proprioceptive awareness
- slower reaction time
- greater ML postural displacement on foam when performing a concurrent verbal fluency task
- motor paradigms may identify surrogate markers of future decline in female PM-carriers.
Oculomotor Function in Female Premutation Carriers (Submitted JNNP)

- Subset of 14 FMR1 premutation carriers and Controls
- Ocular motor and neuropsychological tests of response inhibition and working memory.
- Female PM-carriers:
  - poorer inhibitory control on both ocular motor and neuropsychological tasks
  - dissociation between performance for low repeat (61-80 CGG repeats) and moderate repeat (81-102 CGG repeats) PM-carriers, with only low repeat PM-carriers exhibiting a greater proportion of errors on the antisaccade task than controls.
- impaired inhibitory control may represent a sensitive risk biomarker in at least a subgroup of females with the FMR1 premutation
FMR1 Premutation Sample Characteristics (Males)

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=24)</th>
<th>Premutation carriers (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.D)</td>
<td>55.3 (14.6)</td>
<td>54.0 (14.9)</td>
</tr>
<tr>
<td>Range</td>
<td>26-77</td>
<td>26-80</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.D)</td>
<td>13.5 (3.4)</td>
<td>13.0 (3.4)</td>
</tr>
<tr>
<td>Range</td>
<td>9-20</td>
<td>9-21</td>
</tr>
<tr>
<td><strong>FMR1 CGG repeats</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.D)</td>
<td>29.9 (4.1)</td>
<td>89.6 (17.0)**</td>
</tr>
<tr>
<td>Range</td>
<td>20-44</td>
<td>72-134</td>
</tr>
<tr>
<td><strong>FMR1 mRNA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.D)</td>
<td>1.1 (0.2)</td>
<td>2.2 (1.1)**</td>
</tr>
<tr>
<td>Range</td>
<td>0.8-1.6</td>
<td>1.0-5.2</td>
</tr>
<tr>
<td><strong>Full scale IQ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.D)</td>
<td>113 (11)</td>
<td>106 (14)</td>
</tr>
<tr>
<td>Range</td>
<td>86-133</td>
<td>79-127</td>
</tr>
<tr>
<td><strong>Verbal IQ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.D)</td>
<td>112 (12)</td>
<td>106 (14)</td>
</tr>
<tr>
<td>Range</td>
<td>80-133</td>
<td>78-126</td>
</tr>
<tr>
<td><strong>Performance IQ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.D)</td>
<td>111 (12)</td>
<td>105 (14)</td>
</tr>
<tr>
<td>Range</td>
<td>81-127</td>
<td>81-136</td>
</tr>
<tr>
<td><strong>FXTAS Rating Scale Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.E)</td>
<td>15 (2)</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Range</td>
<td>5-36</td>
<td>2-90</td>
</tr>
</tbody>
</table>
Males: Psychiatric Profile

<table>
<thead>
<tr>
<th>Condition</th>
<th>Controls</th>
<th>Premutation carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 DSM-IV Dx</td>
<td>8.33%</td>
<td>31.82%</td>
</tr>
<tr>
<td>ADHD Highly Probable</td>
<td>29.17%</td>
<td>47.06%</td>
</tr>
<tr>
<td>Mild-Severe Depression</td>
<td>4.35%</td>
<td>8.70%</td>
</tr>
<tr>
<td>Mild-Severe Anxiety</td>
<td>13.04%</td>
<td>13.04%</td>
</tr>
<tr>
<td>Mild-Severe Stress</td>
<td>0%</td>
<td>17.39%</td>
</tr>
<tr>
<td>Self report cognitive complaints</td>
<td>34.78%</td>
<td>65.22%</td>
</tr>
</tbody>
</table>
MALES: FXTAS rating scale score V’S age

$R^2 = 0.697$

$p = 0.000$
Working memory: $p = .003$
Working memory: $p=.003$

Processing speed: $p=.003$
Working memory: $p = 0.003$

Processing speed: $p = 0.003$

Behaviour regulation: $p = 0.05$
Working memory: $p = 0.003$

Processing speed: $p = 0.003$

Behaviour regulation: $p = 0.05$

Response inhibition: $p = 0.001$
- Verbal memory, visual memory, visuospatial, attention, language all n.s
Falls risk\(^1\) and sway: Males

- Significantly increased falls risk among premutation carriers (\(p=0.035\))

<table>
<thead>
<tr>
<th></th>
<th>Sway on floor (eyes open)</th>
<th>Sway on floor (eyes closed)</th>
<th>Sway on foam (eyes open)</th>
<th>Sway on foam (eyes closed)</th>
<th>Falls risk</th>
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<tr>
<td>FMR1 CGG repeats</td>
<td>Correlation -.293</td>
<td>-.551</td>
<td>-.278</td>
<td>-.342</td>
<td>.376</td>
</tr>
<tr>
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<td>Sig .054</td>
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<td>.075</td>
<td>.041</td>
<td>.012</td>
</tr>
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<td>FMR1 mRNA</td>
<td>Correlation -.185</td>
<td>-.664</td>
<td>-.341</td>
<td>-.435</td>
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<td>.020</td>
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</tbody>
</table>

\(^1\) Lord SR et al. Physical Therapy 2003;83:237-252
Falls risk and sway

- Controlling for age and FXTAS ratings, significantly increased falls risk among premutation carriers ($p=0.035$)

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- Significant negative associations between $FMR1$ measures and sway

FXTAS Treatments & Trials

Pharmacological and other Treatments

- **Tremor** - Beta-blockers, e.g. Propranolol, primidone; DBS

- **Ataxia** – Normally non-responsive to medication, Amantadine helped some people with FXTAS

- **Parkinsonism** – Few patients mild/short-lived improvement with Carbidopa/levodopa

- **Other FXTAS Symptoms** – Dementia; Donepezil. Anxiety and Depression; Selective serotini reuptake inhibitors. Agitation and disinhibited behavior; Venlafaxine. Leg pain; Gabapentin

Clinical Trials

- Memantine
Conclusion

- FMR1 gene is involved in 3 distinct disorders:
  - FXS
  - FXTAS
  - FXPOI
- FXS and FXTAS are disorders with phenotypes
- FMR1 Premutation ? Neurodevelopmental trajectory
- Fertile grounds for further investigation
- Future holds promise for intervention and improved outcomes
Treating FXDs: A Multidisciplinary Approach

Clinicians
- Neurologists
- Neuropsychiatrists
- Developmental Paediatricians
- Infertility Specialists
- Rehabilitation and geriatricians

Psychology, Nursing & Allied Health
- Detailed assessments
- Planning & implementing interventions
- Planning & implementing supports
- Family and Systems issues

Clinical Investigations
- Neuropsychologists
- Developmental assessments
- MRI
- Gait lab

Genetics & Laboratory
- Clinical Geneticists
- Molecular genetics
- Animal models
- Pharmacological treatments

Person with an FXD
Family with FXDs
Acknowledgements

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UNSW:
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Miss Rachael Birch

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Dr Darren Hocking
Jo Fielding
John Bradshaw
Nellie Georgio-Karistianis
Robert Iansek
Claudine Kraan

GOLD:
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NeuRA:
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Chriselle Hickerton

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