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Outline

• Introduction to Developmental Neuropsychiatry
• *Example 1: Fragile X Syndrome*
• *Example 2: Fragile X-associated disorders (FXDs):*
  • Genetic testing in Developmental Disorders
  • New horizons in treatment
  • Neuropsychiatric approach
• Conclusion
Behavioural phenotype

• ‘phenotype’ of a genetic syndrome:
  – the set of physical characteristics produced by a genetic abnormality, or genotype; eg Down syndrome.

• ‘behavioural phenotype’:
  – a characteristic pattern of motor, cognitive, linguistic and/or social abnormalities which is consistently associated with a biological disorder (SSBP)
Example 1: Fragile X Syndrome

- [http://www.fragilex.org](http://www.fragilex.org)
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

Full-mutation:
>200 CGG repeats

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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

Premutation: (55–200 CGG repeats)

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

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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: Phenotype

- 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 Phenotype

- 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)
Example 2: Other Fragile X related Disorders
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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
• Premature 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-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

Penetrance increases with age\(^1\)

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Fragile X Tremor Ataxia Syndrome: Phenotype
FXTAS: Neurological manifestations

Central
- Tremor
- Gait ataxia
- Parkinsonism
- Cognitive Decline
- Behavioural & Psychiatric

Peripheral
- Neuropathy
- Hearing loss

Autonomic
- Orthostatic hypotension
FXTAS Progression

- Tremor
- Ataxia/balance
- Cognitive
### Cognitive and Behavioural Phenotype

**Cognitive Deficits**
- Executive functioning
- Working memory
- Information processing
- Fine motor

**Rates of Mental Disorders**
- Depression
- Anxiety
- Irritability
- Agitation / Aggression
- Disinhibition
- Apathy

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# Systematic review of cognitive features

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<thead>
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<th>General intelligence</th>
<th>Memory</th>
<th>Executive function</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

- 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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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)
## 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>
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<th>FMR1 PM-carriers (N = 35)</th>
<th>Controls (N = 35)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>M ± SD (range)</strong></td>
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<tr>
<td>Age (years)</td>
<td>41.14 ± 8.34 (22-55)</td>
<td>41.11 ± 8.64 (22-55)</td>
<td>.989</td>
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<tr>
<td>FSIQ</td>
<td>110.26 ± 10.94 (88-128)</td>
<td>111.91 ± 9.54 (79-129)</td>
<td>.506</td>
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<tr>
<td>VIQ</td>
<td>106.59 ± 13.90 (73-128)</td>
<td>108.11 ± 11.36 (84-136)</td>
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<tr>
<td>PIQ</td>
<td>110.86 ± 11.34 (87-133)</td>
<td>113.89 ± 11.15 (79-133)</td>
<td>.260</td>
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<tr>
<td>SE disadvantage</td>
<td>8.6%</td>
<td>14.3%</td>
<td>.869ᵇ</td>
</tr>
<tr>
<td>psychotropic meds</td>
<td>14.3%</td>
<td>5.7%</td>
<td>.232ᵇ</td>
</tr>
<tr>
<td>Child special needs</td>
<td>65.7%</td>
<td>17.1%</td>
<td>.001**ᵇ</td>
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<tr>
<td>CGG-repeat length</td>
<td>86 ± 15.07 (59-122)</td>
<td>26 ± 3.52 (20-42)</td>
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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, Joanne Fielding¹, 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.
• 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 (accepted 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></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

$R^2 = .697$

$p = .000$
Working memory: $p = .003$

Response inhibition: $p = .001$

- Verbal memory, visual memory, visuospatial, attention, language all n.s
Falls risk\(^1\) and sway

- Controlling for age and FXTAS ratings, significantly increased falls risk among premutation carriers (\(p=.035\))

<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>
</tr>
</thead>
<tbody>
<tr>
<td>FMR1 CGG repeats</td>
<td>Correlation: -.293</td>
<td>-.551</td>
<td>-.278</td>
<td>-.342</td>
<td>.376</td>
</tr>
<tr>
<td></td>
<td>Sig: .054</td>
<td>.001</td>
<td>.075</td>
<td>.041</td>
<td>.012</td>
</tr>
<tr>
<td>FMR1 mRNA</td>
<td>Correlation: -.185</td>
<td>-.664</td>
<td>-.341</td>
<td>-.435</td>
<td>.350</td>
</tr>
<tr>
<td></td>
<td>Sig: .229</td>
<td>.000</td>
<td>.027</td>
<td>.008</td>
<td>.020</td>
</tr>
</tbody>
</table>

- Significant negative associations between \(FMR1\) measures and sway

New Approaches in Genetic Screening in People with ID/DD
Protocols for genetic screening in People with ID/DD

- Chromosomal microarray (CMA)\(^3\) now standard for screening

- Previous standard:
  - G-banded karyotyping\(^1\)
  - FISH\(^2\)

- FISH still standard for recognizable chromosomal syndromes e.g. trisomy 21, 13, Turner syndrome, or Klinefelter syndrome

\(^1\)G-banded karyotyping allows visualization and analysis of chromosomes for chromosomal rearrangements, including genomic gains and losses.

\(^2\)FISH: fluorescence *in situ* hybridization, visualises the presence or absence of specific DNA sequences on denatured chromosomal DNA using fluorescent probes that bind to parts which are similar in sequence

\(^3\)CMA similar to karyotyping but much higher ‘resolution’.
Approach to Genetic Screening in People with ID/DD

- Initial screening
  - ID; Developmental Delay; ASDs; Multiple Congenital anomalies
  - Prevalence of ID 2-3%; ASDs higher
  - Most lack sufficient physical/behavioural identifiers

- Adults with ID; ASDs
  - Settings which justify
  - Benefits
  - Risks

- Genetic counselling
Risks of Genetic Screening in People with ID/DD

• Stress, inconvenience

• Genetics:
  – variants of uncertain clinical significance (VOUS)
  – Identification of variants with implications for untested family members

• Assessment of Pathogenicity of a CNV variant:
New Horizons in Treatment for Developmental Disorders
Fragile X Trials

• Animal models:
  – metabotropic glutamate receptor (mGluR) blockers
  – gamma amino-butyric acid (GABA) agonists

• Humans:
  – AFQ056 (mavoglurant), Novartis mGluR5 antagonist
  – RO4917523, Roche mGluR5 antagonist
  – Arbaclofen: GABA-B receptor agonist
  – Others: donepezil, acamprosate
FXTAS Treatments & Trials

• Memantine trial: for cognitive/neurological

• As 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 serotonin reuptake inhibitors. Agitation and disinhibited behaviour; Venlafaxine. Leg pain; Gabapentin
Down syndrome

• Ts65Dn Mouse Model
  – Trisomy portion of Ch 16
  – DS like phenotype but no AD pathology
  – Learning deficits, craniofacial effects, motor dysfunction, cardiac anomaly, age-related cholinergic loss, hippocampal dependent learning tasks
• Deficiency in hippocampal neurogenesis rescued
  – GABA\textsubscript{A} receptor antagonists improve learning and memory
  – NMDA receptor antagonist memantine- improves leaning and memory in mice, ambiguous results in people with DS
Tuberous Sclerosis Complex (TSC)

- Animal models with either germ-line mutations in TSC1 or TSC2 gene
- Learning impairments, altered social behaviours
- Aberrant regulatory function of mTOR complex (mTORC1/mTORC2)
- Rapamycin (Sirolimus) and everolimus inhibit mTORC1
  - Impact on soft tissue tumours, seizures, skin lesions (topical)
  - Being trialled for cognitive/neuropsychiatric impact
- Other drugs with effect on mGluR5 also of interest (Lithium, fenobam)
Treating Developmental Disorders of Genetic Origin: A Multidisciplinary ‘Neuropsychiatric’ Approach
Treating Developmental Disorders of Genetic Origin: A Multidisciplinary ‘Neuropsychiatric’ Approach

Clinicians
- Clinical geneticists
- 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
- Molecular genetics
- Animal models
- Pharmacological treatments

Person with specific ID/DD
A Family

Department of Developmental Disability Neuropsychiatry
(02) 9931 9160  dddn@unsw.edu.au  3dn.unsw.edu.au  www.facebook.com/3dn.unsw
Conclusion

• Developmental neuropsychiatry is expanding its frontiers
• Rich clinical and research potential
• Expanded awareness of related conditions (eg FXPOI, FXTAS)
• Animal models are available for many disorders
• Drug trials in animals suggest future hope for drugs which may change the developmental trajectory associated with key disorders
• The neuropsychiatrist has a key role to play in a multidisciplinary approach to developmental disorders
Other Resources

• Websites:
  – Genetics education resources
    https://www.genome.gov/10000464
  – Specific genetic disorders:
    http://www.genome.gov/10001204
    http://omim.org/
  – Clinical trials
    http://www.clinicaltrials.gov/ct2/home
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NeuRA:
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