Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)
*an older face of the fragile X gene*

Fragile X Association of Australia

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Adult-onset problems among premutation carriers of the fragile X gene
Mothers of children with fragile X syndrome complained of specific problems with their own (carrier) fathers

- Frequent falls/ balance problems
- Difficulty writing, eating
- Memory loss
- Numbness/tingling in hands legs
- Loss of bladder/bowel control
Fragile X-associated tremor/ataxia syndrome (FXTAS)

Case DR: Premutation carrier with 89 CGG repeats, identified through two grandchildren with fragile X syndrome.

First identified case of a carrier grandfather with progressive neurological dysfunction

Core features

Tremor – Onset in right hand at age 54, left hand within two years; writing illegible at 58 yr; retired early as an electrician at 58 yr.

Ataxia – Progressive difficulty with balance and gait; frequent falls
Core clinical features of FXTAS

Non-resting tremor
Gait ataxia

Associated forms of clinical involvement
- Peripheral neuropathy
- Cognitive decline
- Autonomic dysfunction
- Anxiety, mood instability
- Parkinsonism
Prior diagnoses for individuals with FXTAS

Sixty-two patients FXTAS and family history of fragile X syndrome (55 men, 7 women; age of onset, 60.2 ± 7.1 years)

56 sought medical help – 98 prior diagnoses

Hall et al. (2005) Neurol 65:299
Penetrance of FXTAS in families with known fragile X syndrome

- Approximately 40% of male premutation carriers (>50 yr) have combined tremor and ataxia
- Penetrance of clinical features increases with age
  - males: 17% (50s); 38% (60s); 47% (70s); 75% (80s)
  - far lower in females  
  Jacquemont et al. (2004)

- Multiple screening studies find the premutation in 2 – 5% of unexplained ataxia cases over 50 yr
  
  Jacquemont et al. (2006)
Women with FXTAS have less severe involvement than men

- FXTAS is less frequent in women: 16% vs >50% (Jacquemont et al 2004; Coffey et al 2008; Rodriquez-Revenga et al 2009)

- Less severe white matter disease; less severe brain atrophy; less frequent MCP sign (Adams et al 2007)

- Less frequent (rare) dementia (Seritan et al 2010; Schneider et al 2014)

- When dementia does occur in women it is associated with Alzheimer changes in brain pathology (Tassone et al 2012)
Why wasn’t FXTAS identified earlier?

None of the first ~100 cases we identified was associated with the fragile X gene by adult neurologists.

The fragile X scientific community did not accept that the neurodegenerative features were due to the premutation.

Instead... "normal "aging
- essential tremor
- various cerebellar atrophies
- multiple system atrophy
- atypical Parkinson’s disease
- Alzheimer's disease
- etc.

A second discovery: *The fragile X gene is too active in the premutation range*

<table>
<thead>
<tr>
<th>Typical (CGG) &lt; 45</th>
<th>Premutation (CGG) 55 - 200</th>
<th>Full mutation (CGG) &gt; 200</th>
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<tbody>
<tr>
<td>mRNA</td>
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<td>FMRP</td>
<td>Clinical</td>
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<td>Typical</td>
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<td>Primary Ovarian Insufficiency (POI)</td>
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<td>Neurodevelopmental problems</td>
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The *RNA itself* may be the cause of the premutation-specific disorders — concept of “RNA toxicity”
FXTAS is an inclusion disorder

- Ubiquitin-positive
- Distinct from nucleoli in neuronal nuclei
- Never observed in oligodendroglia

Ubiquitin immunostaining of cortical neurons and astrocytes

Greco
The expressed CGG repeat stimulates formation of inclusions

Mouse *Fmr1* gene with ~100 CGG repeats (Willemsen et al., 2003)

Fly with ~90 CGG repeats placed in an unrelated reporter gene (Jin et al., 2003)
FXTAS inclusions point to a role of DNA damage repair in FXTAS

DNA damage and repair:
- We also see γH2AX induction following DOX-induced expression of an expanded CGG repeat in stably-transfected SK cells Hoem et al. (2011) Hum Mol Genet 20:2161-70.

We hypothesize that unrepaired damage at/near the CGG repeat element, caused by R-loop induced damage, leads to inclusion formation.

Partial reversibility of FXTAS inclusions in the premutation mouse

Hukema et al, 2015.

Mice engineered to have premutation CGG repeat (~100 CGG)
Gene can be turned on / off with an antibiotic (doxycycline)

Weeks CGG-repeat gene on (green)
Start (3 wks) → 8 12 weeks gene off (yellow)

CGG-repeat reporter gene
On                                     Off

Mouse brain
Stopping expression after eight weeks in FXTAS mouse:

substantial reversal of inclusion size and number

But no reversal seen if the gene was turned off after 12 weeks

Need early diagnosis and treatment
Current and Recent Collaborators

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