INTRODUCTION TO FRAGILE X SYNDROME

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FRAGILE X SYNDROME

Ann Genovese MD – child & adolescent psychiatrist

TOPICS

- 1. FXS subtypes
- 2. Neurobiology of FXS
- 3. Developmental impacts
- 4. Neuropsychiatric conditions
- 5. Treatment considerations
- 6. Research

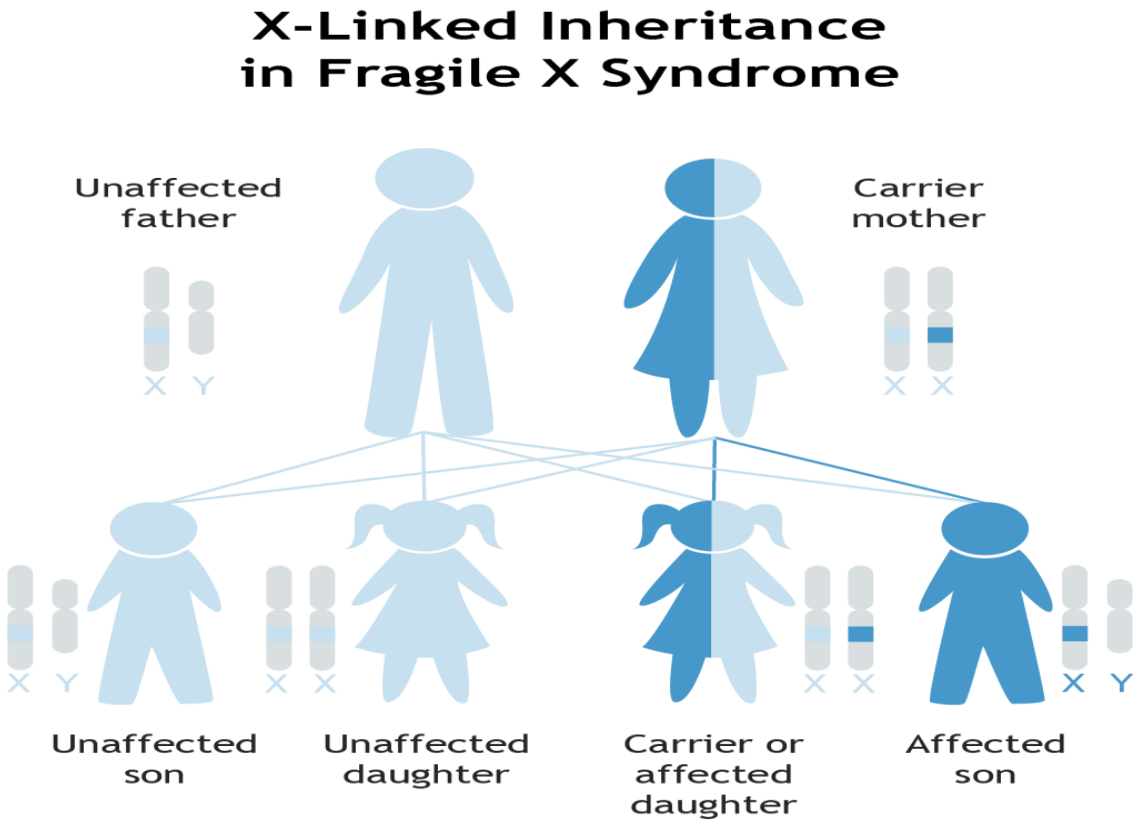
- REFERENCE

Hagerman et al (**2018**). Fragile X-Associated Neuropsychiatric Disorders (FXAND). *Frontiers in Psychiatry* 9:564.

FRAGILE X SPECTRUM

"Fragile X Spectrum" includes the wide range of overlapping characteristics in affected individuals with gene mutations of the FMR1, or Fragile X messenger ribonucleoprotein 1, referred to as the FMR1 protein or FMRP

GENETIC INHERITANCE IN FXS



- FXS and Fragile X premutation syndromes are associated with CGG trinucleotide repeats in the FMRI gene, with expansion size increasing across generations
- FXS is caused by the full mutation (> 200 CGG repeats in the FMR1 gene) leading to absence of the FMR1 protein, and premutation disorders (55 to 200 CGG repeats) with an elevation of FMR1 mRNA and reduced levels of the FMRI protein

FRAGILE X SYNDROME SUBTYPES

- FXS – the full mutation, discovered in 1969
- FXPOI — Fragile X associated Primary Ovarian Insufficiency: increased incidence of infertility and early menopause (prior to the age of 40) in female carriers
- FXTAS - Fragile X associated Tremor Ataxia Syndrome: a neurodegenerative condition impacting older male carriers, with typical onset in late 50's
- FXAND – Fragile X Associated Neuropsychiatric Disorder: psychiatric problems, most commonly anxiety, depression, attention deficit hyperactivity disorder (ADHD)

NEUROBIOLOGY

- In the full mutation, methylation of FMR1 occurs during fetal development, causing silencing of gene transcription, resulting in the *absence* of the FMR protein (FMRP) whereas premutation syndromes are associated with *reduced* levels of FMRP
- FMRP plays a critical role in brain development, regulating synaptic plasticity, which is the ability of neurons to modify the strength of their connections, a process involved in the functioning of brain networks and reorganization or repair after damage

NEUROBIOLOGY

- FMRP also affects Brain Derived Neurotropic Factor (BDNF) levels in the hippocampus (area of brain involved in learning and memory), in both early and late stages of brain development
- BDNF plays an important role in neuronal survival and growth, is a neurotransmitter modulator, and supports neuronal plasticity, essential for learning and memory
- Premutation leads to elevations of *FMR1* mRNA, causing toxicity to brain neurons via oxidative stress, and mitochondrial dysfunction

COGNITIVE AND LEARNING CONCERNS

- FXS is the most common known *inherited* cause of intellectual developmental disability (IDD), and the second most common *overall* cause of IDD second to Down Syndrome
- Inheritance is X-linked, therefore males with FXS are more impacted than females, due to the protective factor of females having one normal FMR1 allele on their second X chromosome

COGNITIVE AND LEARNING CONCERNS

- Most males with Fragile X syndrome have mild or moderate intellectual disability
- Methylation mosaicism is associated with better cognitive functioning relative to the fully methylated full mutation
- Intelligence (IQ) scores in FXTAS tend to decline with age due to neurodegenerative changes in the CNS

DEVELOPMENTAL DELAYS

- Developmental delays associated with FXS include
  - Cognitive (problem-solving and memory) skills
  - Social (interpersonal relatedness) and emotional self-regulation skills
  - Speech and language (reciprocal communication) skills
  - Fine and gross motor (coordination) skills

PERSONALITY AND OTHER STRENGTHS IN FXS

- Disposition characteristics often include:
  - Very sociable and friendly – "an empathetic nature"
  - Excellent imitation skills – "a gift for mimicry"
  - Strong visual and long-term memory
  - Especially nice, likes helping others
  - Wonderful sense of humor

AUTISM

- Autism Spectrum Disorder (ASD)
  - Occurs in about 50% of males and 20% of females with FXS
  - Autistic features can be relatively mild, particularly in affected females
  - Among the identifiable genetic causes of autism, FXS accounts for up to 6%

BEHAVIORAL FEATURES

- Behavioral characteristics may include:
  - Sensory challenges (fabrics or clothing, loud noises, crowds, food textures, etc.)
  - Aggressive or self-injurious behaviors, such as hand biting
  - Repetitive behaviors, such as hand-flapping
  - Poor eye contact (gaze avoidance)
  - Sleep problems

PSYCHIATRIC PROBLEMS - ANXIETY

- Anxiety is the most common emotional problem in FXS
  - Affects about 70%, often begins in childhood
  - May be related to sensory differences
  - Extreme shyness is common
- Most common types of anxiety disorders are:
  - Specific Phobia
  - Social Anxiety Disorder
  - Generalized Anxiety Disorder
  - Obsessive-Compulsive Disorder

PSYCHIATRIC PROBLEMS – MAJOR DEPRESSIVE DISORDER (MDD)

- MDD occurs in about 40% of premutation carriers, and 65% of patients with FXTAS
- Age of onset for depression in the premutation is later than in the general population
- Among female premutation carriers, mothers of children with FXS have a higher risk of developing postpartum depression than those who do not have children with FXS
- In FXTAS, depressive symptoms typically onset before motor symptoms, suggesting that depression could represent a prodrome in those who later develop FXTAS

CHRONIC PAIN, FATIGUE, INSOMNIA & IMMUNE FUNCTIONING IN PREMUTATION CARRIERS

- Elevated risk for musculoskeletal pain, back pain, general muscle pain, peripheral neuropathy, fibromyalgia & chronic fatigue
- Sleep problems are common and are likely related to a GABA deficit
- Autoimmune disorders affect up to 45% of female carriers, and often exacerbate neuropsychiatric problems

PSYCHIATRIC PROBLEMS – ADHD & LINKS TO SUBSTANCE ABUSE

- ADHD affects 45% of boys, 15% of girls with premutation, and 30% of male carriers
- ADHD itself associated with an increased risk of developing substance use
- ADHD, anxiety and/or depression may lead to self-medicating with substances
- Studies find alcohol and drug misuse is more common in carriers c/w controls
- Substance abuse increases the likelihood of developing FXTAS

TREATMENT CONSIDERATIONS

- Diagnosing premutation in FXAND helps identify the need to treat oxidative stress and mitochondrial dysfunction associated with the premutation
- Exercise can reduce depression and anxiety and improve brain functioning by stimulating neurogenesis and improving mitochondrial function
- Avoidance of excessive alcohol, opioids, exposure to pesticides, and isoflurane (an anesthetic) is recommended, as these can worsen neuroinflammation, white matter disease and brain atrophy, increasing the risk of FXTAS
- Marijuana (THC) has a high risk of causing psychosis, particularly in carriers

MANAGEMENT OF BEHAVIORAL ISSUES IN FXS

- Behavioral interventions are first line therapy
- ADHD medications can help with many behavioral issues
- Standard treatments are usually effective for depression and anxiety
  - These include psychotherapy, antianxiety medications and antidepressants
- Mood stabilizers and other meds can help with irritability and aggression
  - These include antipsychotics, antiseizure medications and others

INVESTIGATIONAL THERAPIES – CLINICAL TRIALS

- Zynerba Pharmaceuticals is recruiting males and females ages 3-22 with Fragile X syndrome for a Phase 3 clinical trial (RECONNECT) of Zygel*
- Zygel is a synthetic CBD, formulated as a clear gel that can be applied to the skin
- A phase 2/3 clinical trial demonstrated that Zygel may lessen behavioral abnormalities in children with the FXS full mutation
- Effectiveness was demonstrated with the Social Avoidance subscale of the Aberrant Behavior Checklist – Community FXS (ABC-C), which measures behaviors in FXS, including social avoidance, irritability, hyperactivity, and inappropriate speech

* Berry-Kravis E, Hagerman R, Budimirovic D, et al. A randomized, controlled trial of ZYN002 cannabidiol transdermal gel in children and adolescents with fragile X syndrome (CONNECT-FX). *Journal of neurodevelopmental disorders*, *14*(1), 56 (2022)

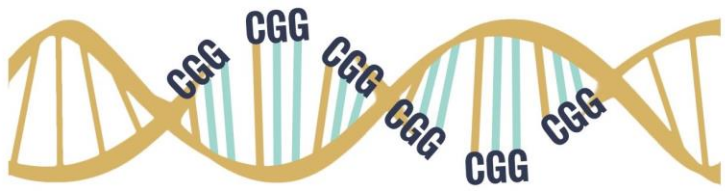
INVESTIGATIONAL THERAPIES – NOW RECRUITING

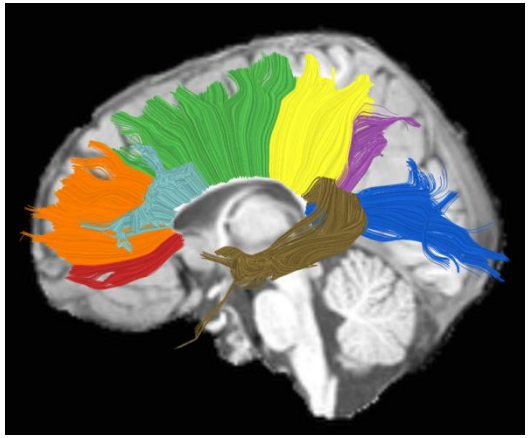
- Shionogi (Osaka, Japan) and Tetra Therapeutics Inc. (Grand Rapids, Michigan), have been granted the FDA Rare Pediatric Disease Designation for zatolmilast (BPN14770), an investigational treatment for FXS
- Zatolmilast modulates a signaling molecule called cyclic AMP (cAMP), which promotes the maturation of synaptic connections between neurons
- In a Phase 2 trial that included 30 adult males with FXS, zatolmilast was associated with improved cognition, language skills and daily functioning*
- Phase 3 trials are currently underway for males with FXS between ages 9 - 45

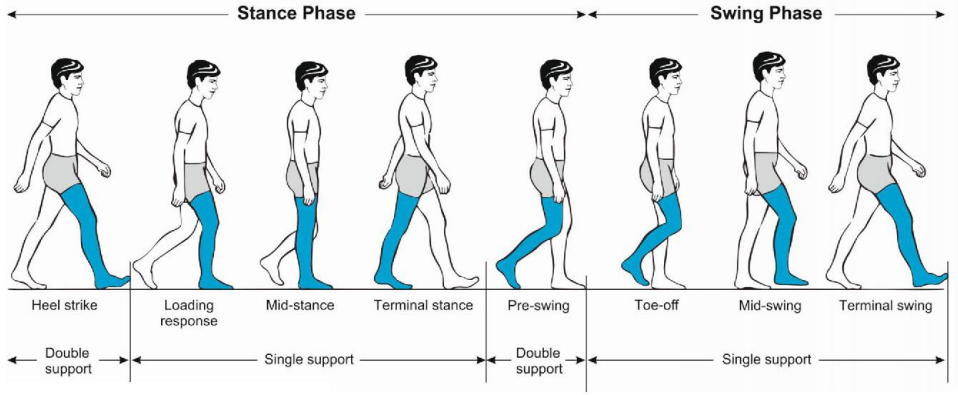
*Berry-Kravis EM, Harnett MD, Reines SA, et al. Inhibition of phosphodiesterase-4D in adults with fragile X syndrome: a randomized, placebo-controlled, phase 2 clinical trial. *Nat Med* 27, 862–870 (2021).

PROGRESS IN FXS

- Investigators have made significant progress in identifying the genetic, molecular, and cellular underpinnings of FXS, improving our ability to make accurate clinical diagnoses.
- Our growing understanding of FXS and Fragile X premutation syndromes across the life span gained from clinician, patient and caregiver perspectives, with contributions from research, will help create more effective treatments, services, and care.







Fragile X gene related conditions and services

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Professor, Clinical Child Psychology
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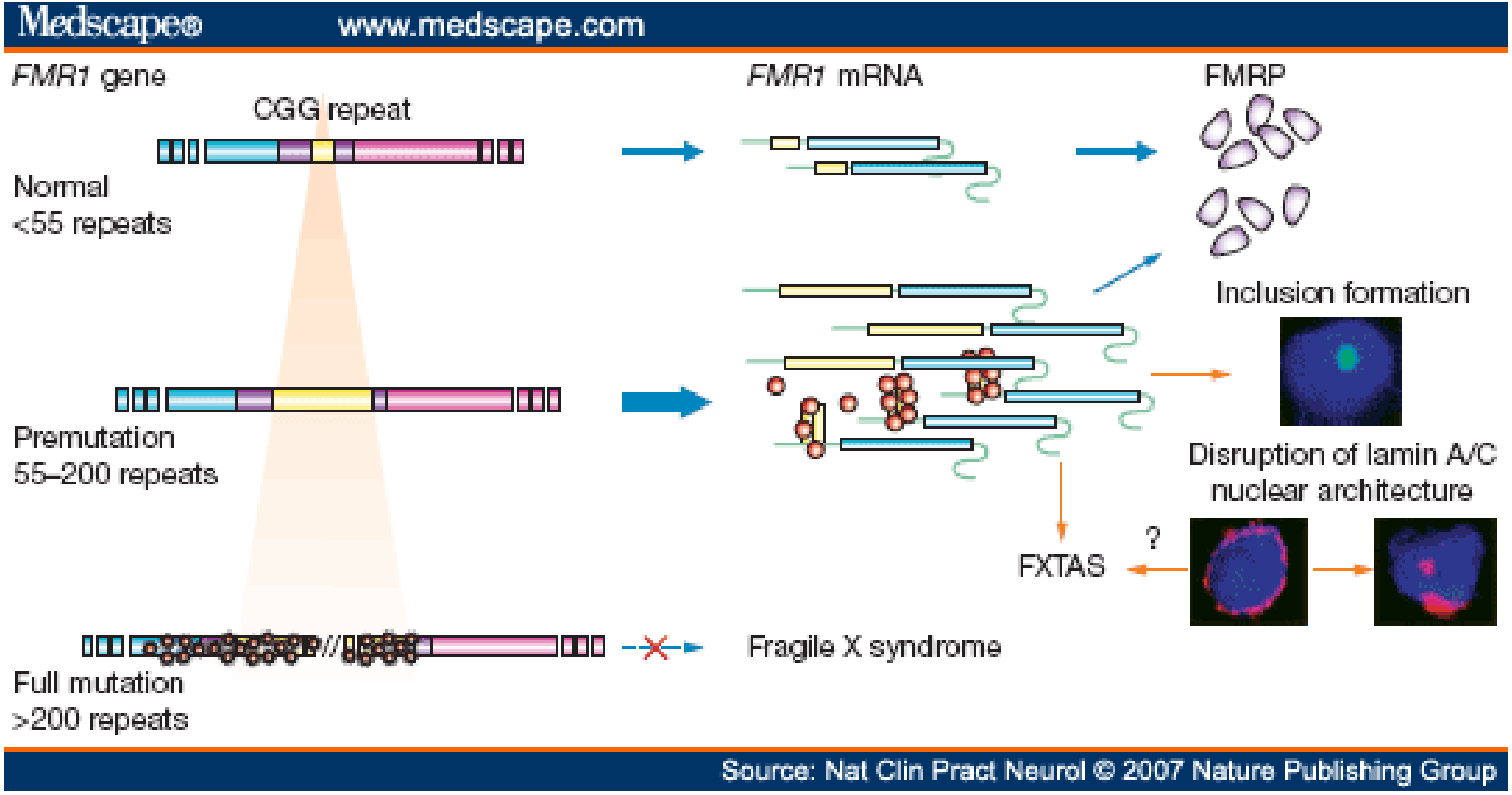
KU LIFE SPAN INSTITUTE
The University of Kansas

Fragile X gene (*FMR1*) disorders



The development of Fragile X-associated tremor/ataxia syndrome, or FXTAS

- Approximately 1:130 females and 1:800 males carry an *FMR1* premutation
- 40% of male premutation carriers suffer from FXTAS by age 50 years; 75% by age 80
- Female premutation carriers also may develop FXTAS, but the ratios are significantly lower (~15-20%)
- FXTAS is underdiagnosed, and often misdiagnosed as Parkinson's, ataxia, dementia and/or cerebrovascular disease (e.g., 4% of patients ever see a movement disorder specialist; Hall & Hagerman, 2018)

The FXTAS Complex

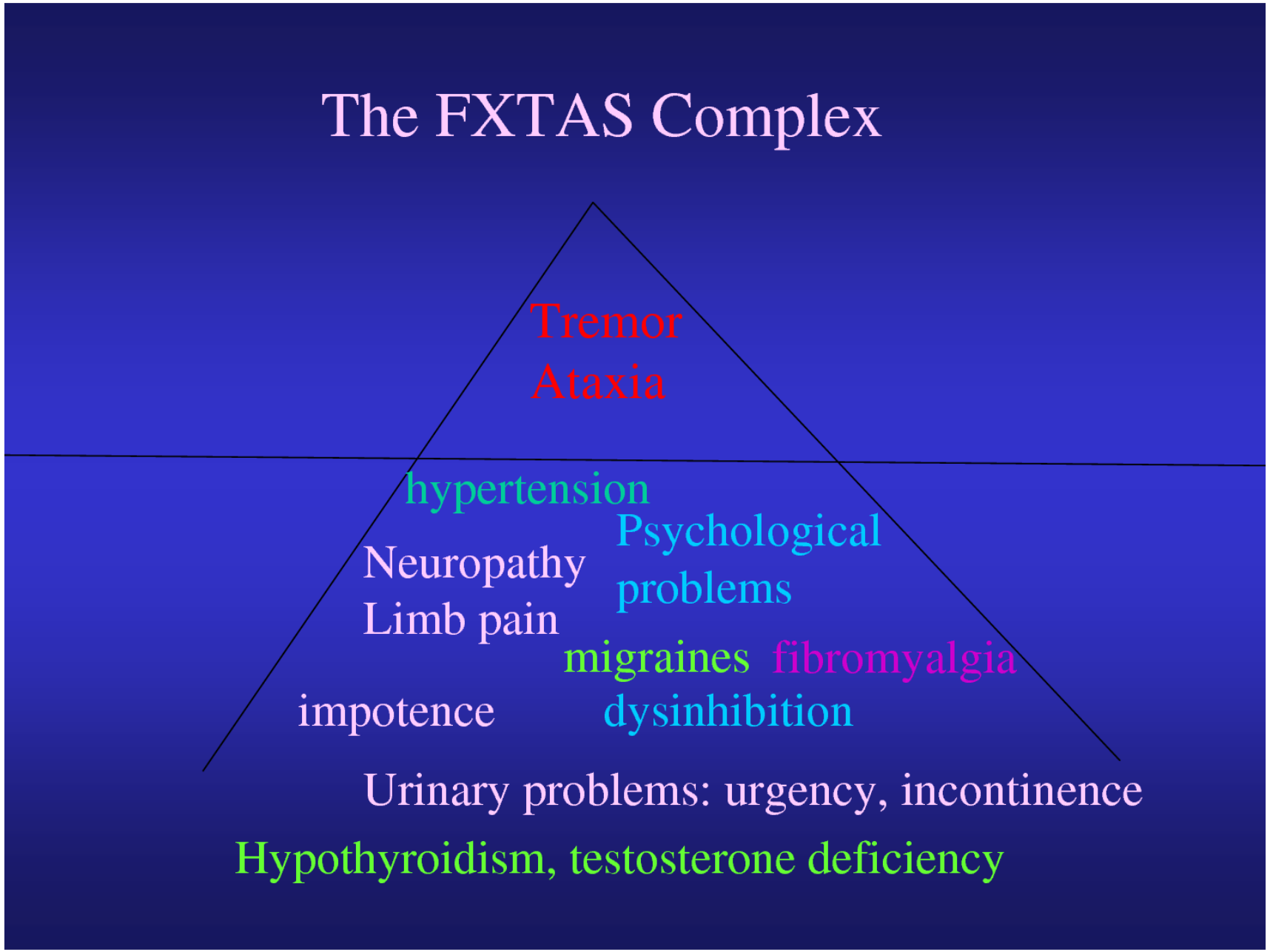


Table 1. Diagnostic Criteria for FXTAS

Molecular	***FMR1* CGG Repeat Size 55–200**
Clinical	
Major signs	Intention tremor
	Gait ataxia
Minor signs	Parkinsonism
	Moderate to severe short term memory deficits
	Executive function deficits
Radiological	
Major signs	MRI white matter lesions in the middle cerebellar peduncle (MCP sign)
Minor signs	MRI white matter lesions in cerebral white matter
	Moderate to severe generalized atrophy
Diagnostic Categories	
Definite	Presence of one major radiological sign plus one major clinical symptom
Probable	Presence of either one major radiological sign plus one minor clinical symptom or has two major clinical symptoms
Possible	Presence of one minor radiological sign plus one major clinical symptom

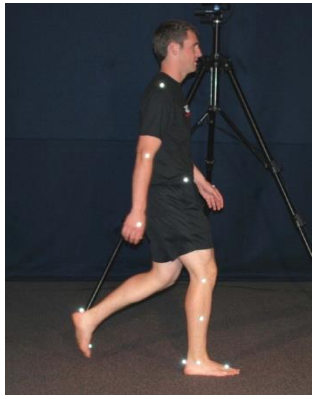
Abbreviations: *FMR1*, fragile X mental retardation 1; FXTAS, Fragile X-associated tremor/ataxia syndrome; MCP, middle cerebellar peduncles; MRI, magnetic resonance imaging

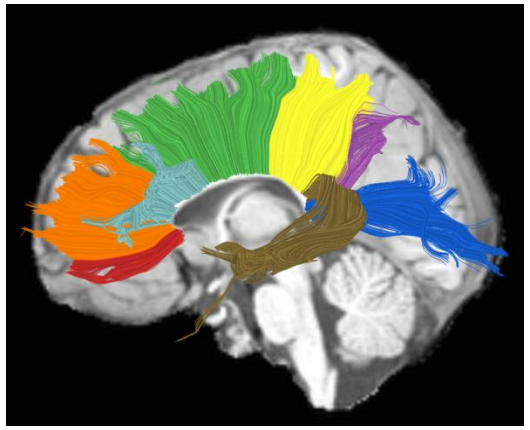
Adapted from Jacquemont et al, 2003.[2]

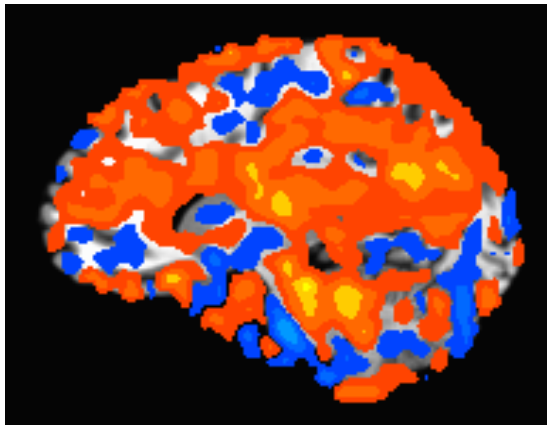
Hall & O'Keefe, 2013

Research on the FMR1 gene at KU/KUMC

There is a strong need to identify objective markers that will tell us who will develop FXTAS, who has FXTAS, and how FXTAS is evolving in different individuals

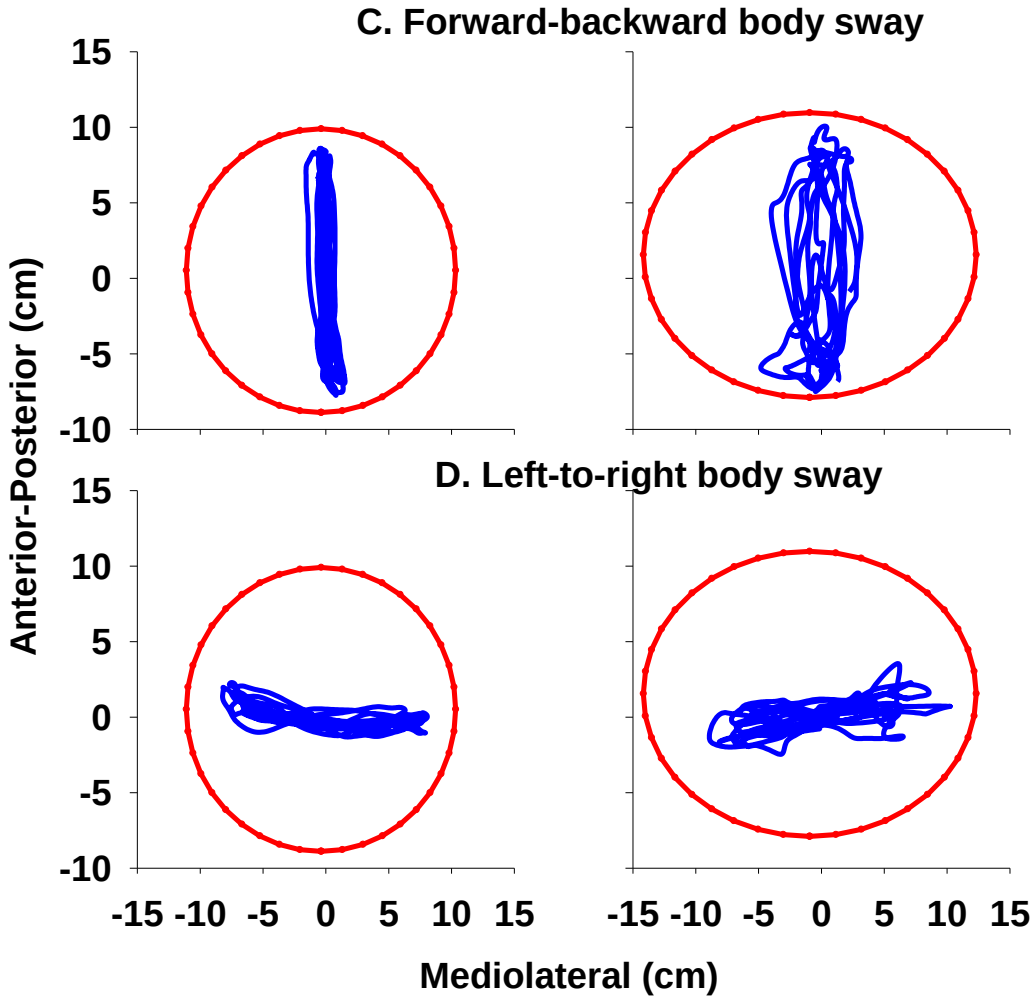




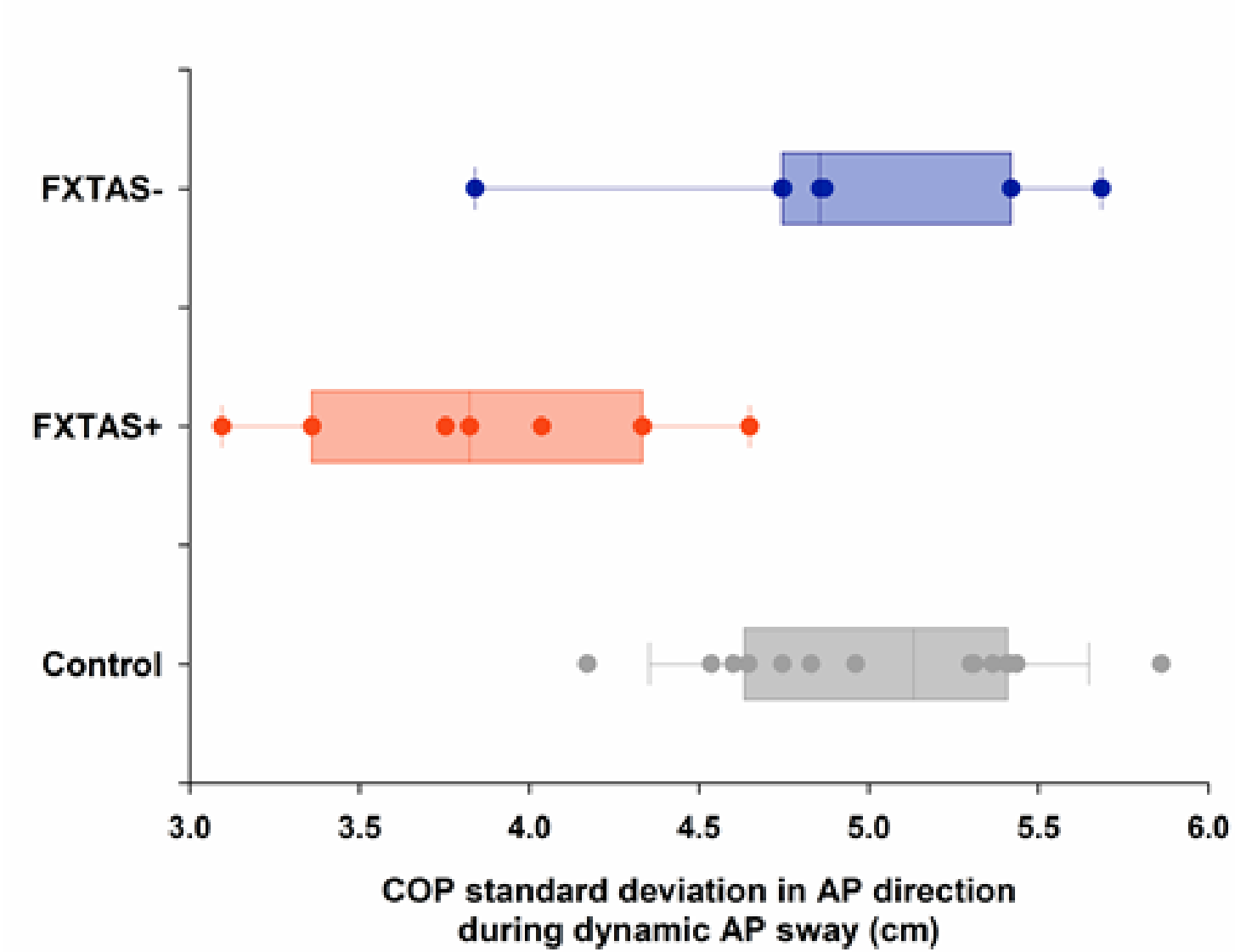


Precise characterization of postural stability

Individuals with FMR1 premutations show postural sway issues during static and dynamic stances (Wang et al., 2019)

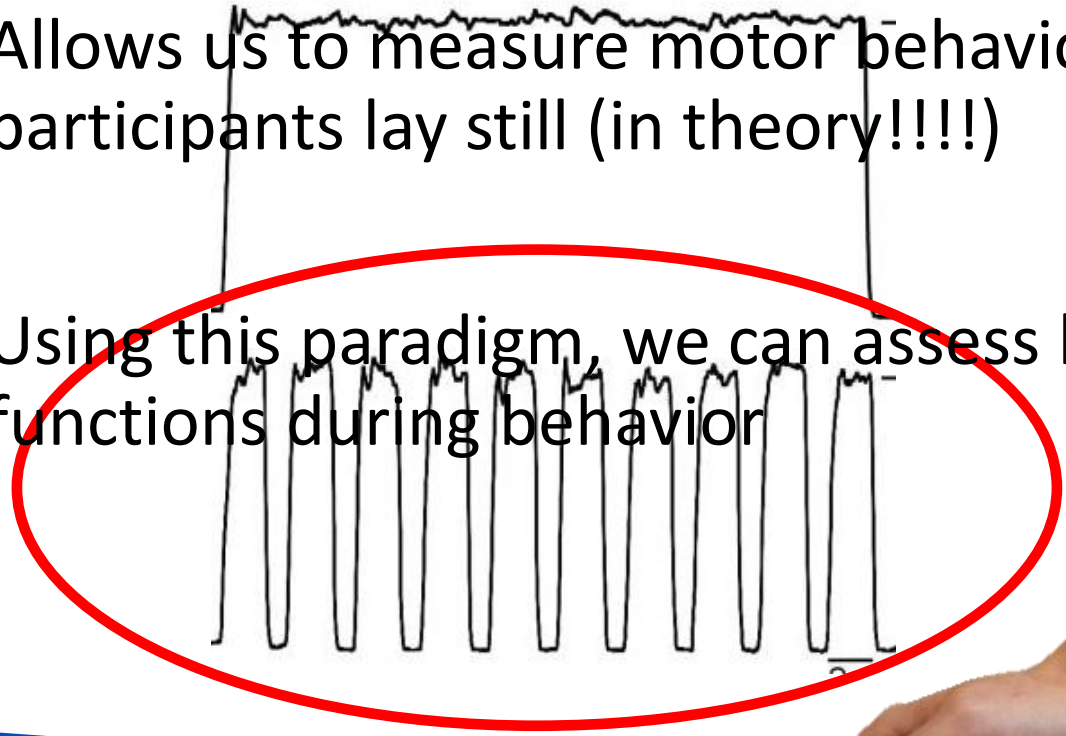


Reduced ability to sway along anterior-posterior axis differentiates premutation carriers with and without FXTAS



fMRI studies of visuomotor control

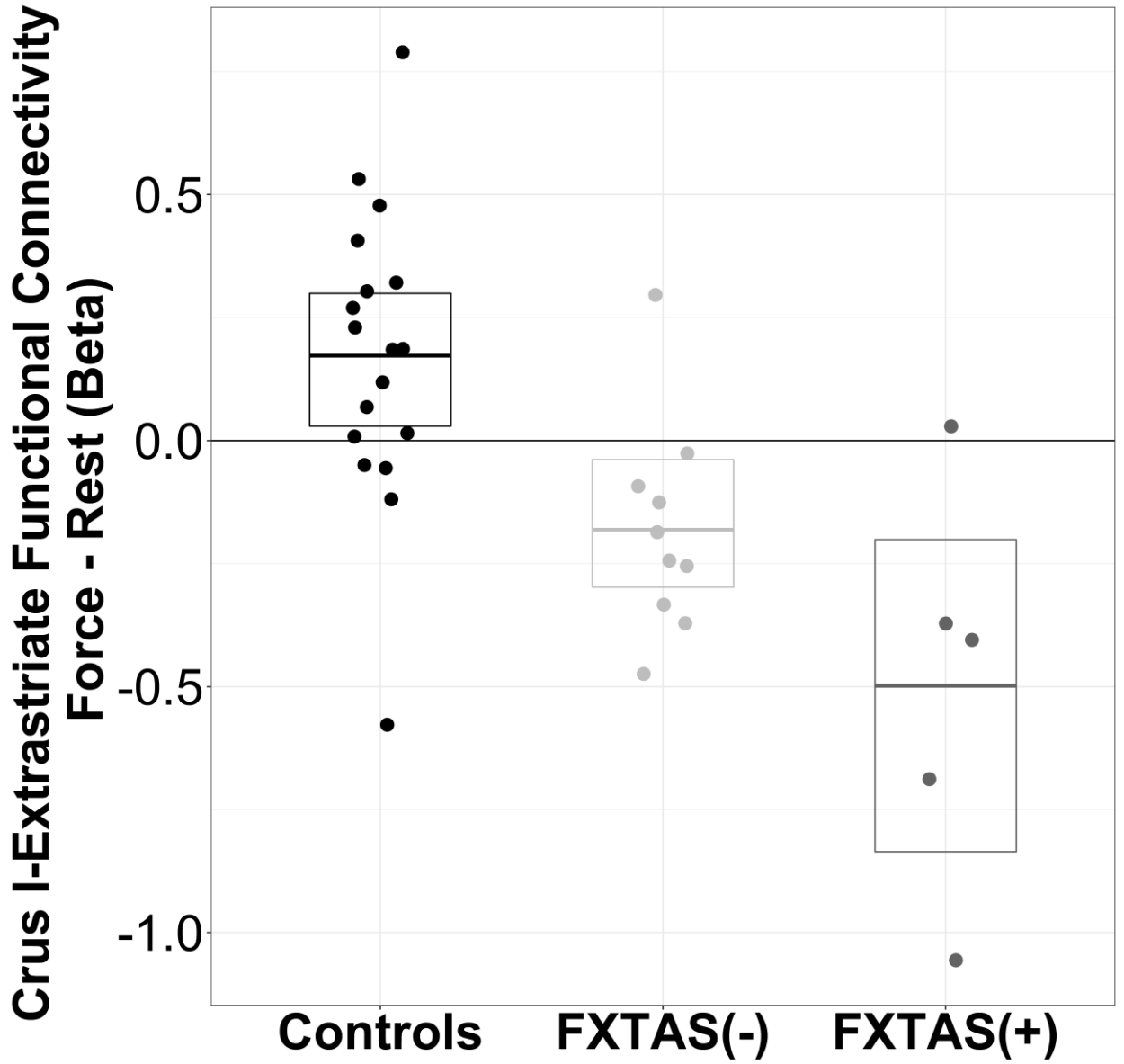
- Allows us to measure motor behavior while participants lay still (in theory!!!!)
- Using this paradigm, we can assess brain functions during behavior



Custom fiber-optic transducer

Neuroimaging Solutions, Inc.

Cerebellar – visual cortex functional connectivity is reduced in FXTAS



Current studies of FXTAS at KU/KUMC

KU THE UNIVERSITY OF KANSAS

Wakarusa Research Facility
1315 Wakarusa Drive
Lawrence, KS 66049

We are interested in understanding how the brain changes during aging, and whether it is affected by premutations of the fragile X gene, FMR1. We are seeking people **with FMR1 premutations** and people **WITHOUT FMR1 premutations** ages 50-80 years to participate in this study. Participants will be compensated for their time.

What's next?
Contact us at the phone number or email listed below or scan the QR code with your phone to visit our website.

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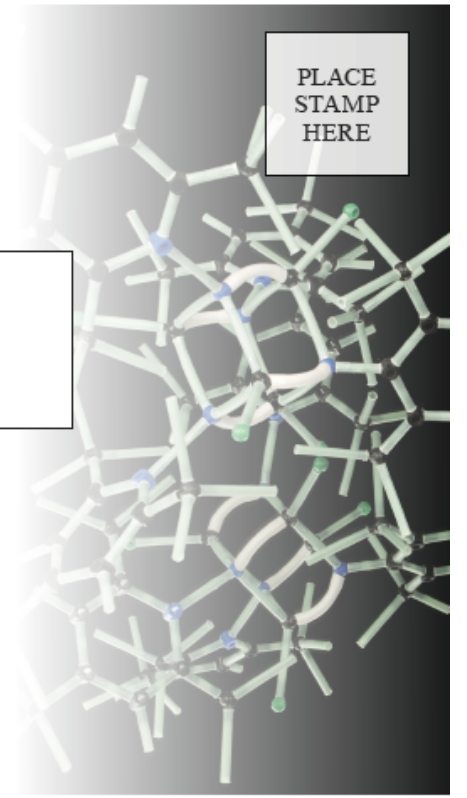

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FRAGILE X RESOURCES

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KU Clinical Contacts
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Dr. Michael Slogic
https://www.kansashealthsystem.com/care/specialties/child-health-development

913-588-1227

KUMC Psychiatry
Dr. Ann Genovese
https://www.kumc.edu/agenovese.html

KUMC Neurology – Landon Center on Aging
Dr. Dubinsky
https://www.kumc.edu/rdubinsk.html

Participate in Research
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Family Support and more information

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