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Fragile X Syndrome, IDD, and Dementia

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What follows is a brief characterization of Fragile X spectrum disorders with a particular emphasis on conditions which are most germane to our consideration of possible connections between FXS and dementia- Fragile X Syndrome (FXS) and Fragile X Associated Tremor and Ataxia Syndrome (FXTAS).

Fragile X Spectrum Disorders

Fragile X is associated with a group of conditions that reflect changes in the FMR1 gene (Fragile X Messenger Ribonucleoprotein-1), located on the X chromosome. The fragile X gene occurs in every cell in the body but is abundant within nerve cells. Variations in the expression of FMR1 have been linked to neurological conditions, medical issues, cognitive, behavioral, sensory, social, and neuropsychiatric problems. The FMR1 gene produces an important regulatory RNA-binding protein called the FMRP which is important for brain development and function. The FMR1 gene can undergo changes, when inherited, which affects the pattern of DNA consisting of the repeated sequence of cytosine-guanine-cytosine, referred to as C-G-G.

Typically, for individuals who are unaffected, CGG repeats less than 40 and up to 54 times. Premutation “carriers” have 55–200 CGG repeats, which signifies that they do not exhibit signs of FXS but can transmit an expanded version of the gene resulting in offspring with FXS. Someone with FXS has a full mutation of the FMR-1 gene with more than 200 CGG repeats.

FXS is caused when a full mutation silences or “shuts down” the FMR1 gene. This process called “methylation,” results in a failure to produce the Fragile Messenger Ribonucleotide Protein (FMRP). The absence of FMRP in individuals with FXS is thought to result in the FXS phenotype of cognitive impairment, behavioral and social difficulties. Although other variations of the FMRI gene including premutation and mosaicism do not typically result in FXS, they may be associated with milder forms of cognitive dysfunction, learning problems, or medical conditions.

Fragile X Gene Variation	Associated condition	Description
Normal	**unaffected**	< 40-5 CGG repetitions
Premutation	**Fragile X -associated Tremor and Ataxia (FXTAS)** **Fragile X-associated primary ovarian insufficiency (FXPOI):**	55-200 CGG repetitions Late onset (>50) neurodegenerative condition which involves movement disorder, executive dysfunction and possible dementia. A condition affecting ovarian function that can lead to infertility and early menopause in some female premutation carriers
Mosaic	Possible mild cognitive, learning, adaptive, and social behavior but less affected than individuals with full mutation	Combination of genes that are premutation and those that are fully mutation
Full Mutation	**Fragile X syndrome (FXS)**	>200 CGG repetitions Most common inherited genetic cause of Intellectual Disability

1.What is the connection between the ID specific condition of Fragile X Syndrome (FXS) and dementia? Is the person aging with FXS at increased risk for dementia?

Fragile X Syndrome (FXS)

Fragile X syndrome (FXS), also known as Martin-Bell Syndrome, is a specific genetic condition that occurs with ID; it is considered the leading heritable cause of intellectual disability and is significantly associated with autism. Moreover, it has multisystemic implications impacting not only cognitive, behavioral, sensory, and social functioning but involving possible neuropsychiatric challenges and physical symptoms, including ocular, gastric, and connective tissue problems.

FXS has been associated with structural and functional brain abnormalities, including abnormal protein deposition and synaptic dysfunction. The question remains if this may predispose individuals with FXS to neurodegenerative conditions like dementia. Earlier reports distinguished between individuals with FXS who demonstrate early life intellectual and developmental problems and those with premutation of the FMR-1 gene who are carriers, do not themselves exhibit early life cognitive disturbance, but are at risk for Fragile X-associated tremor and ataxia syndrome (FXTAS). In recent years, studies have shown that individuals with

FXS may face an elevated risk of developing dementia as they age, particularly in the form of Alzheimer's disease. The exact mechanisms underlying this increased risk remain a subject of ongoing research.

Aging with FXS: Although the impact of FXS upon childhood is well documented, the natural history of the condition in persons aging with FXS is less well studied or understood. Early reports indicated that individuals with FXS displayed intellectual, behavioral, and social difficulties in childhood, but were unlikely to be at higher risk for developing FXTAS. AD or other forms of dementia in later life.

More recent biomedical research has raised an interesting association between FXS and AD revealing that both FXS and AD share anomalies of AP deposition. Recent research has identified genetic links between FXS and dementia-related genes, such as the APP gene implicated in Alzheimer's disease. These genetic overlaps may contribute to the increased susceptibility of individuals with FXS to dementia. Lizarazo and colleagues (2022) propose a conceptual framework involving overlaps among amyloid- peptide (A), A precursor protein (APP), and FMRP.

As individuals with FXS age, the cumulative effects of cognitive and neurological deficits may exacerbate the risk of dementia. Several studies have documented a decline in measured IQ scores over time from childhood through adolescence. Hagerman et al. (2017) identified the aging trajectory for persons with FXS but did not find a heightened incidence of FXTAS or dementia but did see heightened incidence of Parkinson’s Disease, and possible parkinsonism associated with long-term use of antipsychotics, and hyperarousal and sensitivity to environment, which may persist into adulthood and take the form of neuropsychiatric problems.

Aging and Fragile X-associated tremors and ataxia syndrome (FXTAS).

FXTAS is a late-onset neurodegenerative disorder found among adult carriers of Fragile X gene premutation, characterized by progressive intention tremor, ataxia, cognitive decline, executive dysfunction, and generalized brain atrophy. These symptoms may influence intelligence, working memory, remote recall, information-processing speed, and temporal sequencing. Impaired executive function may lead to psychiatric and behavioral disorders as noted by increased anxiety, irritability, agitation, hostility, obsessive-compulsiveness, apathy, and depression. The condition may progress to dementia.

Aging and FXTAS: The risk for FXTAS appears to begin among FMR1 carrier (premutation) men in their 50’s and increases with age, with an estimated 75% of male carriers in their 80s presenting with fragile X-associated tremor/ataxia syndrome (FXTAS). Although female carriers can also develop FXTAS, they are less likely to be cognitively affected and present with a lower incidence of dementia than their male counterparts. Additionally, individuals with FXTAS may have features of parkinsonism, peripheral neuropathy, lower limb muscle weakness, and autonomic dysfunction.

3. What best practices address intervention and support for older adults with FXS who have been diagnosed with dementia?

Considerations for discussion:

Lifestyle and Health Factors Individuals with FXS often have comorbid conditions and behavioral issues that can affect overall health and potentially increase the risk of dementia. The heightened risk of Parkinson's disease, other movement disorders, and hypertension place the aging individual with FXS at heightened risk for cognitive and adaptive decline. This suggests there is value in addressing known medical conditions found among individuals who age with FXS such as obesity, movement disorder, and hypertension.

Value of Genetic Testing

Given the range of conditions associated with variation in the Fragile X gene, it would be valuable to screen for FXAS and Fragile X premutation, especially in families with a history of ID, Parkinson's Disease or others movement disorder of unknown etiology.

DNA testing can determine how many copies of the CGG repeat a person will have. Currently, there are two tests (PCR and Southern Blot) that need to be performed to determine whether someone has FXS, and to determine whether family members have a potential to transmit the expanded FMR1 gene to their children.

Differential Diagnosis

FXTAS is sometimes misdiagnosed as Parkinson's Disease, Alzheimer's disease, or stroke. It would be helpful to consider FXTAS among individuals who manifest unexplained movement disorder, unexplained personality, or neurological changes.
Symptoms such as impulsivity, short-term memory loss, depression, mood instability, or irritability may be attributed to the aging process and not recognized as possible symptoms of FXTAS.

Neuropsychological Testing

Males with FXS may develop progressive problems (age >40) in performing tasks that require the working memory. Phonological memory (or verbal working memory) deteriorates has been noted with age in males, while visual-spatial memory is not found to decline (Cornish et al.,2009).

Previous neuropsychological studies that have compared the profiles of individuals with FXTAS who develop dementia and those individuals with Alzheimer's have shown that people with FXTAS-linked dementia display cognitive and functional decline on an order like individuals with Alzheimer's Disease. However, the patterns of decline are distinct. pattern of a mixed cortical-

subcortical decline because of the involvement of the hippocampal and frontal lobes (cortical0 and cerebellar region and white matter (Seritan et al, 2008)

Developing a research agenda

- Given some preliminary reports that the IQ scores of individuals with FXS decline with age, monitoring the trajectory of intelligence and adaptive skills over time.
- Given the limited research on aging with FXS, studies of individuals aging with FXS and longitudinal studies of individuals with FXS are needed.
- Further research is needed on the co-occurrence of FXS and AD, FXTAS and AD and FX and FXTAS
- Knowledge of the proteins that are regulated by FMRP has led to the identification of multiple targets for therapeutic intervention; this continues to be a valuable target for research (Ranjan et al, 2023)
- The relationship between Fragile X Syndrome and dementia is an evolving field of study. There appears to be a common molecular pathway that underlies APP deposition in both FXS and AD. The precise mechanisms underlying this association remain speculative. Further research into FXS and its relationship to dementia promises to expand our understanding of neurodegenerative disorders and may pave the way for innovative treatments and interventions in the future (Ranjan et al., 2023).

Understanding the connection between FXS and dementia is vital for early intervention and support. While there is currently no cure for either condition, early diagnosis and targeted interventions can help manage symptoms and improve the quality of life for affected individuals. Additionally, ongoing research into the molecular and genetic mechanisms underlying this association may pave the way for future treatments and interventions aimed at reducing the risk of dementia in those with FXS.

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Resource Websites

https://fragilex.org
What is Fragile X Syndrome (FXS)? | CDC
FXTAS Clinics | NFXF (fragilex.org)

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