

Older male fragile X premutation carriers are at risk to develop fragile X-associated tremor/ataxia syndrome (FXTAS), characterized by tremor, ataxia (balance and walking problems), symptoms of Parkinsons disease, and sometimes nerve disease and/or psychiatric and cognitive problems. MRI scans from individuals with FXTAS often show evidence of damage in brain white matter, especially in a structure called the middle cerebellar peduncle (MCP), and general loss of brain substance. The MRI and clinical findings in FXTAS suggest that the white matter, which contains the tracts, or axons, that connect brain cells, is the area of the brain where damage in FXTAS occurs earliest and is most evident. This is consistent with the current idea that the premutation promotes toxicity to axons in brain and nerves. Diffusion tensor imaging (DTI) is a new, highly sensitive MRI technique for evaluation of brain white matter axon integrity and can detect damaged white matter before a routine MRI. Thus DTI would likely be a valuable way to identify and track early disruption of axon integrity in brain white matter of premutation carriers.

Not all premutation carrier males develop FXTAS. At present there is no way to determine who will develop symptoms, when symptoms will occur, or how rapidly symptoms will progress. FXTAS symptoms are far less frequent and severe in female premutation carriers. DTI measures might predict disease onset and progression in males and even identify rare females at-risk for FXTAS symptoms.

Through this project, we will study DTI scans from three age-matched groups of males over age 50: premutation carriers with FXTAS symptoms, premutation carriers without FXTAS symptoms, and non-carrier controls with no neurological symptoms. Severity and location of abnormalities on the DTI scans will be compared to the amount and type of clinical symptoms in the participant, determined through use of a standardized neurological scale to quantify FXTAS symptoms.

From this data we expect to find out if the DTI scan can show us damage to white matter in a male carrier before symptoms or abnormalities on routine MRI develop, whether the degree of abnormality of DTI is predictive of the amount of symptoms, and whether the pattern of abnormal DTI measures in different brain areas (eg. MCP vs. other) is able to predict the subject's symptoms (eg. tremor vs parkinsonism).

With basic information from this pilot study, it is expected that the project can expand to evaluate involvement in specific brain pathways, correlate DTI changes with CGG repeat size, and evaluate changes in white matter integrity in younger carriers and women. DTI studies have the potential to help determine when axon damage first begins in individuals with the premutation, identify patterns of involvement in specific pathways, and predict risk for developing symptoms of FXTAS for individual carriers. Thus, it is hoped that through this and future studies, DTI measures can be identified to serve as predictors of disease course in FXTAS and even as potential measures of outcome for future preventative and therapeutic trials in FXTAS.