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FXTAS - RECENT DEVELOPMENTS

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Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) is a late-adult-onset neurodegenerative disorder that affects individuals who carry a premutation CGG-repeat expansion (55-200 CGG repeats) in the 5' untranslated portion of the fragile X mental retardation 1 (*FMR1*) gene. Affected individuals display cognitive decline, progressive intention tremor, gait ataxia, neuropathy, psychiatric symptoms, and Parkinsonism; the severity of both clinical and neuropathological phenotypes is positively correlated with the extent of the CGG expansion. Overexpression of the expanded CGG-repeat mRNA results in direct cellular toxicity that is believed to form the pathogenic basis for FXTAS. This RNA-based "gain-of-function" mechanism is entirely different from the mechanism underlying fragile X syndrome, which is due to transcriptional silencing and consequent loss of *FMR1* protein. Clinical research on FXTAS has focused on quantitative approaches to further characterize the syndrome; whereas much of the research on the molecular/genetic aspects of the disorder have focused on understanding the link between the pathogenic *FMR1* mRNA, the proteins that are likely to mediate its toxic effects, and further details of molecular pathogenesis. One emerging element in the disease model is that cellular dysregulation is likely to be occurring much earlier than had been supposed, and that these early, non-degenerative cellular changes may underlie both developmental and early-mid-adult clinical involvement in some who carry premutation forms of the *FMR1* gene.