

Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)

Paul J Hagerman, M.D., Ph.D.

Professor, Department of Biological Chemistry, UC Davis School of Medicine
and

Randi J Hagerman, M.D.

Medical Director, M.I.N.D. Institute and Tsakopoulos-Vismara Professor, Department of
Pediatrics, UC Davis Medical Center

EDITOR'S NOTE: In this article the exciting discovery of Fragile X Tremor Ataxia Syndrome is detailed. While obviously significant to older male carriers, this discovery also provides exciting opportunities to identify yet undiagnosed daughters and grandchildren who may carry or have fragile X syndrome. It is sure to interest, and bring to the fragile X community, a specialty of medicine previously uninvolved (adult neurology) and, according to the authors, provides a powerful new key to understanding the FMR1 gene and fragile X syndrome.

Carriers of premutation (CGG) expansions of the fragile X gene are generally thought to be spared most of the problems associated with the full mutation; however, a newly identified neurological disorder, involving progressively severe tremor and difficulty with walking and balance, appears to specifically affect some older premutation carriers, generally grandfathers of children with fragile X syndrome. Although this neurological disorder occurs by a completely separate mechanism from fragile X syndrome – and affects different individuals, it is caused by the same gene, and therefore opens a new portal for understanding how the fragile X gene works.

Over the past several years, we have become aware of many grandfathers (premutation carriers; 55 to 200 CGG repeats) of children with fragile X syndrome who, in their fifties or sixties, begin to suffer from a progressive neurological disorder. The initial appearance of the disorder may involve difficulty with writing, use of eating utensils, or pouring water (*tremor*); or may involve problems with balance, with frequent falls (*ataxia*). These initial symptoms generally progress slowly over years, or even decades, until carrying out many of the tasks of daily living, and walking without assistance, become difficult or impossible. Other features of this disorder may include loss of sensation in the feet or lower legs, difficulties with short-term memory, impotence, moodiness, anxiety and/or irritability. This disorder has been named the “**Fragile X-associated Tremor/Ataxia Syndrome**” (FXTAS).

Recent studies from several groups have firmly established the association between FXTAS and the fragile X mental retardation 1 (*FMRI*) gene. Surprisingly, the disorder appears to be largely limited to carriers of premutation (CGG) expansions, since the characteristic neurological and radiological findings have not been reported for individuals in the full mutation range (> 200 CGG repeats). Thus, children with fragile X syndrome would appear to be spared from FXTAS later in life. FXTAS is an enigma: it appears among individuals who are generally

clinically normal throughout childhood and early to mid adulthood, and who have normal or near normal levels of *FMRI* protein (FMRP) in both blood and brain cells. Furthermore, unlike fragile X syndrome, FXTAS mainly affects male carriers.

One important clue to the origin of FXTAS is the presence of elevated *FMRI* messenger RNA (mRNA) – the only consistent biochemical abnormality - in premutation carriers [see: NFXF Quarterly, Fall 2001]. Exactly how the elevated mRNA levels could lead to FXTAS is unclear at present; however, studies of a different neuromuscular disorder, myotonic dystrophy, may provide at least a partial answer. Myotonic dystrophy is the most common form of muscular dystrophy in adults; patients have very large expansions – often numbering in the thousands - of a CTG repeat in the gene (designated *DMPK*) responsible for that disorder. When the *DMPK* gene is transcribed into mRNA, the CTG repeat becomes CUG (the base, T, is replaced by a similar base, U, in RNA). There are proteins in the cell that normally bind to the unexpanded CUG repeat. However, when the repeat becomes dramatically expanded, the CUG-binding proteins bind excessively, causing their depletion in the cell. Since the CUG-binding proteins are no longer available to carry out their other functions, the muscle becomes dystrophic. In other words, the abnormal mRNA is *itself* causing the problem by hogging all of the CUG-binding protein.

Although no proof exists that the expanded CGG repeat in the *FMRI* mRNA is the culprit in FXTAS, those individuals with excess mRNA appear to be selectively vulnerable, whereas those who produce no mRNA (individuals with fragile X syndrome) do not appear to be affected by FXTAS. Thus, at this point, myotonic dystrophy remains a useful model for attempting to understand the basis of FXTAS, and provides a useful framework for further molecular studies of FXTAS; e.g., a search for CGG-binding proteins and their function(s) in the cell. Such investigations are currently underway.

In the meantime, recognition of FXTAS is of extreme importance for at least three reasons. First, every case of FXTAS seen in adult neurology clinics has been misdiagnosed, since adult neurologists are generally unaware of fragile X syndrome. Neurologists who treat adults with movement disorders generally have not made the connection between the neurological syndrome (FXTAS) in older adults and a neurodevelopmental disorder in their grandchildren (fragile X syndrome) – basically a two-generation disconnect. In some cases, individuals with FXTAS have seen eight or nine neurologists, and have been branded with various descriptive diagnoses, such as “atypical Parkinson disease”, “multiple system atrophy”, “olivopontocerebellar atrophy”, etc. Thus, the recognition of FXTAS among neurologists will allow them to more effectively tailor (symptomatic) treatment approaches to FXTAS patients.

Second, the existence of FXTAS provides us with a powerful new key to understanding the *FMRI* gene, and fragile X syndrome. The proteins we think are binding to the CGG repeat – and which therefore regulate the translation of the mRNA into FMRP – may provide us with “tracks” back to the cellular processes where FMRP is required. Identification of these processes may give us more targets for treating fragile X syndrome. In addition, the existence of FXTAS may provide the answer to the currently unanswered question as to why the *FMRI* gene becomes silenced in the first place – the event that leads to fragile X syndrome. Indeed, the presence of a “toxic” mRNA may lead the cell to shut down (silence) the *FMRI* gene to avoid a more serious disorder when the CGG element exceeds ~ 200 repeats. Although this suggestion is highly speculative at present, it provides a new way of thinking about the fundamental processes that lead to gene silencing, and how those processes may be bypassed.

Third, FXTAS does not occur in all older male premutation carriers. In an ongoing population study in California, we have found that FXTAS occurs in approximately 20 to 30% of male carriers; similar results have been obtained in the Netherlands by Arie Smits and in Australia by the Partington's. The fact that some carriers develop FXTAS and others appear to be protected suggests that additional factors may be playing a role in disease formation – another clue to the origin of this disorder.

Finally, we wish to acknowledge the grandfathers of fragile X children have bequeathed their brains to our fragile X research program. These donations are truly gifts that are helping us to understand the cause of the cell death that creates the symptoms of FXTAS, and more broadly, to understand the basis for the altered gene expression in fragile X syndrome. Dr. Claudia Greco, the neuropathologist on our research team at UC Davis, has discovered the presence of small particles (termed “inclusions”) in the nuclei of some neurons in FXTAS patients. The inclusions, present in all brains examined to date of men who have died of FXTAS, contain some of the *FMR1* message as well as many additional proteins. We believe that these inclusions hold important clues as to the origins of both FXTAS and fragile X syndrome, and our research team is actively attempting to identify all of the proteins within the inclusions.

Perspectives

The identification of FXTAS has given those who suffer from this neurological disorder a better understanding of the basis for their difficulties. There is now available a variety of symptomatic treatments available for tremor, cognitive deficits, and the anxiety that often accompanies these symptoms. Recognition of this clinical entity will allow researchers and neurologists to develop better treatments and eventually to find a cure for FXTAS. From the molecular perspective, FXTAS provides us with another approach to understanding fragile X syndrome; it is our hope that the study of both FXTAS and fragile X syndrome (two faces of the same gene) will provide effective treatments for both conditions.

The identification and characterization of FXTAS has benefited enormously from the support of the many families who have agreed to participate in the ongoing studies of FXTAS and fragile X syndrome; and, for FXTAS, by agreeing to donate the brain tissue samples that have made it possible for us to establish the nature of the disorder.

Anyone wishing further information regarding our FXTAS and fragile X syndrome research should contact us at pjhagerman@ucdavis.edu (PJH) or (916) 734-6348 (RJH).