

## Pathogenesis of FXTAS

**PI: Paul Hagerman, MD, PhD**  
**UC Davis School of Medicine**  
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Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurological disorder that affects some adults (mainly men; but some women) over fifty years of age who are carriers of premutation forms (55 to 200 CGG repeats) of the fragile X gene. The major features of FXTAS are **tremor** with activity (e.g., writing) and balance or walking difficulties (**ataxia**). Associated features include parkinsonism, memory loss and/or changes in behavior, and loss of sensation or pain/tingling in the feet or hands (**neuropathy**).

Although FXTAS and fragile X syndrome are caused by the same (*FMR1*) gene, the two are entirely separate disorders. Fragile X syndrome occurs when the gene shuts off for large expansions (>200 CGG repeats, full mutation), so there is no mRNA and therefore no *FMR1* protein (FMRP). By contrast, FXTAS is the result of *too much* gene activity (high mRNA levels) in the premutation range. The elevated *FMR1* mRNA in premutation carriers, now thought to be responsible for FXTAS, was discovered in 2000 by Dr. Flora Tassone in our lab.

Studies in both humans and animals point to the increased RNA levels as being responsible for the neurological problems of FXTAS; that is, the CGG-repeat containing RNA is directly toxic to brain cells. However, the reason that the *FMR1* RNA causes cell damage and the neurological disease is not understood.

Dr. Claudia Greco, a neuropathologist at UC Davis, discovered small spherical particles, termed "**inclusions**," in the nuclei of brain cells from FXTAS patients in 2002; such inclusions are now considered a pathologic hallmark of FXTAS. The Hagerman laboratory has recently been able to induce cultured human brain cells to form similar inclusions in the cell nuclei when the expanded CGG-repeat RNA is present, even if the portion of the gene coding for the *FMR1* protein is removed.

Over the past two years, Christine Iwahashi and others in the lab have developed procedures to isolate these inclusions and to find out what is in them – the *FMR1* mRNA is there as well as at least thirty proteins, many of which we have now identified.

One of these proteins, lamin A/C (A and C are two related forms of the same protein), is of particular interest, since mutations in this same gene cause a form of neuropathy (Tingling or loss of feeling in the feet or legs due to disease or loss of the long nerve fibers in the spinal column and the peripheral nerves of the arms and legs.) that is quite similar to the neuropathy found in FXTAS patients. Following up on this possible link, Dr. Dolores Garcia-Arocena, a postdoctoral fellow in the lab, made the striking discovery that expression of the expanded CGG repeat causes a breakdown in the organization of lamin A/C in the nucleus of the affected cell. Thus, lamin A/C may hold a key to FXTAS. If we can gain a better understanding of how the expanded CGG repeat causes lamin A/C dysregulation, and how such dysregulation leads to abnormal cell function, we will have identified potential targets for therapy, the principal objective of our research on FXTAS.

To approach this objective, Dr. Garcia-Arocena will further characterize the means by which the expanded CGG repeat, as mRNA, leads to altered lamin A/C function in the cell culture model systems. She will also investigate how such alterations contribute to abnormal cell function.