

FXTAS Update

The Identification of FXTAS in Rare Carrier Females

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We have just published an article about the fragile X-associated tremor/ ataxia syndrome (FXTAS) in 5 females who are carriers of the premutation and a copy of this paper can be found on the web site for the NFXF under tremor or gait problems at www.fragilex.org. It is rare that this disorder of tremor (shaking of the hands with activities) and ataxia (unsteadiness in walking) occurs in older female premutation carriers. FXTAS is a disorder that can be seen in a subgroup of older mainly male carriers of the premutation. It can start anytime from the 50s to the 80s with either tremor or ataxia and it is usually gradually progressive. It can be misdiagnosed as atypical Parkinson's disease, cerebellar tremor or Multiple System Atrophy. Many individuals have relatively stable symptoms for years, whereas others can experience increasing problems with activities of daily living including handwriting, dressing, eating and eventually walking. Typically some degree of brain atrophy and white matter changes can be seen on MRI brain imaging. Changes in the white matter in the cerebellum can be characteristic of FXTAS, although these changes are only seen in about half of the carriers affected by FXTAS.

All previous papers about FXTAS have reported involvement only in older male carriers. In our California study regarding the prevalence of FXTAS among carriers in the California Northern and Southern Fragile X Associations female carriers were not significantly affected with tremor and ataxia compared to controls (Jacquemont et al 2004 JAMA). However, we have subsequently found symptoms of tremor and ataxia in 5 older female carriers who have come from all parts of the US. Their symptoms range from mild to severe and beginning as early as 42 years to as late as 82 years. None of the females with FXTAS had dementia, which sometimes can occur in males with FXTAS. Only one female had the characteristic cerebellar white matter findings. The female who developed tremor and ataxia in her 80s passed away at 85 and postmortem studies demonstrated the presence of inclusions in a small number of her neurons and astrocytes which has been reported in males with FXTAS (Greco et al 2002). We believe that the inclusions are formed because of too much messenger RNA of the FMR1 gene which gradually leads to inclusion formation and is associated with increased cell death of the neurons later in life leading to the symptoms of FXTAS (reviewed in Hagerman and Hagerman 2004 AJHG). We are now studying how to prevent the neurological damage which occurs in FXTAS. Many of the symptoms of FXTAS respond to a variety of medications (Jacquemont et al 2004 AJMR) and research on treatment is needed.

We have strong evidence from prevalence studies that females are rarely affected by FXTAS (Jacquemont et al 2004; Berry-Kravis et al 2003). They are likely protected because of the additional X chromosome without the premutation and perhaps because of hormone effects. We have studied one grandmother with the premutation who passed away in her late 60s because of breast cancer and she did not have neurological symptoms. On post mortem examination her brain did **not** have inclusions so it is likely

that inclusion formation is rarer in females than in males with the premutation. We also expect that background genetic effects (other genes that are carried by individuals besides the FMR1 gene) influence whether or not a carrier will develop FXTAS later in life and this is currently being studied. For the female carriers who are reading this, it is very unlikely that you will later experience FXTAS. However, if you do have neurological symptoms you need to discuss the possibility of FXTAS with your doctor so further medical workup is considered. If you have symptoms of tremor and/or ataxia and you are a premutation carrier you can contact Louise Gane at 916-703-0238 or Jen Cogswell at 916-703-0331 or Randi Hagerman at 916-703-0247 or Paul Hagerman at pjhagerman@ucdavis.edu for further questions, discussion and information.