

## Abstract 25

### PSYCHOPATHOLOGY IN PREMUTATION CARRIERS: SHOULD THIS BE ADDED TO FRAGILE X-ASSOCIATED DISORDERS?

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*Introduction:* Several reports have described mood and anxiety disorders in premutation carriers using standardized assessments. Inclusions are present in the limbic system including the amygdala in patients with FXTAS, so we know that RNA toxicity is impacting the structures in the CNS important for mood and anxiety disorders. Perhaps the premutation is causing toxicity in these structures, even before the onset of FXTAS in some individuals. This study assesses the prevalence of mood and anxiety disorders in carriers with and without FXTAS compared to population controls.

*Methods:* Structured Clinical Interview for DSM-IV (SCID) was conducted on 85 individuals with the fragile X pre-mutation (obtained through families and through the clinic), 47 with the fragile X-associated tremor/ataxia syndrome (FXTAS; 33 male, 14 female, mean age 66) and 38 without FXTAS (16 male, 22 female, mean age 52). Lifetime prevalence for mood and anxiety disorders among carriers with and without FXTAS was compared to available age-specific population estimates from the National Co-morbidity Survey Replication (NCS-R).

*Results:* Among subjects with FXTAS, 30 cases (65%) met lifetime DSM-IV-TR criteria for mood disorder; 24 cases (52%) met lifetime DSM-IV-TR criteria for anxiety disorder. Among the non-FXTAS subjects, there were 15 cases (42%) of lifetime mood disorder and 18 cases (47%) of lifetime anxiety disorder. When compared to age-specific NCS-R data, the lifetime prevalence of any mood disorder, major depressive disorder, any anxiety disorder, panic disorder, specific phobia, and PTSD were significantly higher in the subjects with FXTAS. The lifetime rates of social phobia in individuals with the premutation without FXTAS were significantly higher than NCS-R data.

*Conclusions:* This sample of carriers of the fragile X premutation had a notably high lifetime risk of mood and anxiety disorders. Mood and anxiety disorders may be part of the clinical phenotype of the fragile X premutation and therefore should be recognized as a fragile X-associated condition even without FXTAS. The RNA toxicity may have an impact on the limbic system throughout development into adulthood in addition to the neurodegenerative progression of FXTAS.