

Presentation: Hyperactivity and impaired social interaction in fragile X premutation mice-310.6

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Carriers of *FMR1* premutation alleles have 55-200 CGG•CCG-repeats in the 5' untranslated region of the gene. These individuals are at risk of primary ovarian insufficiency (females). Males, and to a lesser extent females, are also at risk for fragile X associated tremor and ataxia syndrome. Recently, premutation carrier status has also been shown to be associated with autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) (Farzin et al, *Dev Behav Ped* 27:S137, 2006). In premutation carriers, *FMR1* mRNA levels are often higher than those with normal sized alleles. In contrast, full mutation alleles, which have >200 repeats, are silenced. This results in fragile X syndrome (FXS), the leading heritable cause of intellectual disability. This disorder is also associated with ASD and ADHD, although it is not known whether these symptoms involve the same mechanism as in premutation carriers. We have studied a knock-in (KI) mouse model of the FXS premutation with 120-140 CGG repeats; the KI mouse has increased *fmr1* mRNA levels and regionally selective decreases in concentration of FMRP (Entezam et al, *Gene* 395:125-134, 2007). We subjected wild type (WT) and KI mice to four behavioral tests: 1) Activity in the open field; 2) Social interaction; 3) Elevated zero maze; 4) Passive avoidance test. In comparison to WT mice, KI mice were hyperactive and exhibited less anxiety in both the open field and the zero maze. KI mice had impaired fear learning on the passive avoidance test, and they exhibited a reduction in social interactions. These data provide evidence of behavior associated with ASD and ADHD in the KI mouse model, attributes seen in patients with both the FXS premutation and full mutation.

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