

Abstract 41

ROLE OF THE FRAGILE X MENTAL RETARDATION PROTEIN AND BRN-3 DURING NEURONAL MORPHOGENESIS IN THE HABENULO-INTERPEDUNCULAR CIRCUIT IN FRAGILE X SYNDROME MODELS

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Fragile X Syndrome (FXS) is a monogenetic disorder that is the most common form of inherited mental retardation. The clinical phenotype of FXS is broad, including mild to severe mental retardation, autistic behaviours, hyperactivity, poor motor co-ordination, tremor ataxia, epilepsy, and sleep problems. The causative mutation in FXS is a CGG (cytosine-guanine-guanine) expansion of the untranslated region of the X-linked *fmr1* gene. Whereas there has been a concerted research effort to understand the role of FMRP in synaptic plasticity in the adult brain, we currently understand very little about the role of FMRP in early embryonic development. We have found by yeast two hybrid analysis a novel interaction between FMRP and a member of the POU family of transcription factors Brn-3, a protein that is critical for the normal development of the nervous system, promoting both, neuronal survival and neurite outgrowth. Our studies in the mouse and zebrafish models demonstrate physical interactions between FMRP and Brn-3 in the habenula-interpeduncular nucleus circuitry, where the two proteins are present in a complex *in vivo*. The habenulo-interpeduncular system is implicated in a wide range of cerebral functions including modulating motor behaviours, learning conditional avoidance responses, spatial learning and attention, sleep, and circadian rhythms. Interestingly, these functions have many commonalities with the clinical phenotype of FXS. Furthermore, by applying a multi-scale morpho-topological approach using *in vivo* microscopy we studied the migration, acquisition of neuronal morphology, branching and wiring during habenular-IPN circuit formation in the mouse and zebrafish and show that the interaction between the corresponding genes indicates that FMRP and Brn-3 function together to regulate the habenula neurons function, development and behaviour in fragile X syndrome.