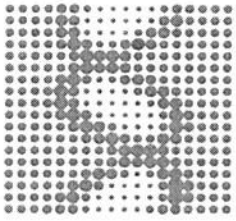
Berlin, 4.-7. September 2011

15th International MR Workshop



MPIMG

15th International Workshop on Fragile X and Other Early-Onset Cognitive Disorders

September 4 – 7, 2011,
Harnack-House
Ihnestr. 16,
14195 Berlin, Germany

http://www.mrworkshop-berlin.de/

P_08-049

FMR1 intron 1 methylation predicts FMRP expression in blood of female carriers of expanded FMR1 alleles.

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The Fragile X Syndrome (FXS) is caused by loss of the Fragile X mental retardation (FMR1) gene product (FMRP) through promoter hypermethylation, which is usually associated with CGG expansion to full mutation size (FM >200 CGGs). Methylation sensitive Southern blot is the current 'gold standard' for the molecular diagnosis of FXS. For females it provides the activation ratio, which is the proportion of unmethylated alleles on the active X chromosome. Here we examined the relationship of FMRP expression to methylation patterns of two fragile X-related epigenetic elements (FREE) analysed using matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) and the activation ratio determined using Southern blot. We showed that the differential methylation of the FREE2 sequences within FMR1 intron 1 was related to depletion of FMRP expression. We also showed that, using the combined cohort of 12 females with premutation (PM - 55-200 CGGs) and 22 females with FM alleles, that FREE2 methylation analysis was superior to activation ratio as a predictor of the proportion of FMRP positive cells in blood. Due to the high-throughput and minimal DNA requirements of MALDI-TOF MS these findings have implications for routine FXS testing and population screening.

P_08-050

FMR1 premutations may be associated with a wider spectrum of phenotypes

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The fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder caused by expansions of 55-200 CGG repeats in the 5'UTR of the FMR1 gene. These FMR1 premutation expansions have relatively high frequency in the general population. To estimate the frequency of FMR1 premutations among Portuguese males with non-familial, late-onset movement disorders of unknown etiology, we assessed CGG repeat size in males with disease onset after the age of 50 and negative or unknown family history for late-onset movement disorders, who were sent for SCA, HD, or PD genetic testing at a reference laboratory. The selected patients had a primary clinical diagnosis based on one of the following cardinal features of FXTAS: ataxia, tremor, or cognitive decline. The frequency of FMR1 premutations was 1.9% (1/54) in our group of patients with ataxia as the primary clinical feature, and 1.2% (1/86) in the larger movement disorders group. Premutation-transmitting females presented a history of psychiatric symptoms, suggesting that, given the wide phenotypical expression of the premutation, neuropsychiatric evaluation was necessary in fragile X family members. We are now clinically evaluating fragile X premutation-associated conditions in premutation carriers and non-carriers from fragile X families. These preliminary results will be presented.