

## Abstract 27

### THE ROLE OF PREMUTATION AND GREY ZONE FMR1 ALLELES IN THE ORIGIN OF PARKINSONISM

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The neurological changes in Fragile X Associated Tremor/Ataxia Syndrome (FXTAS) are linked to the excessive FMR1 mRNA, which becomes toxic through a 'gain-of-function'. Since we found that levels of this mRNA are elevated in carriers of the intermediate size (GZ) alleles, as well as premutation (PM) alleles, we discuss possible role of these alleles in the origin of movement disorders. We screened 207 older males with parkinsonism from two Australian states: Victoria and Tasmania, for PM and GZ alleles, and the frequencies were compared with the population-based data obtained from 578 Guthrie spots from consecutive Tasmanian male newborns. There was a significant excess of PM ( $P=.005$ ), and GZ carriers, both in the total patients' sample ( $P=.031$ ), and in Tasmanian patients only ( $P=.034$ ), compared with normative data. In order to get better insight into pathomechanisms involved in a possible link between these small CGG expansion alleles and neurological involvement, we conducted clinical and molecular investigations in the identified carriers. Clinical investigation included neurological, neuropsychological and MRI testing, and molecular assays comprised the levels of FMR1, and ASFMR1 (antisense) transcripts and of protein product (FMRP) assessed in lymphoblasts. Both clinical and molecular results were correlated with apoptosis. The finding of an elevation of both ASFMR1 transcripts and the apoptotic markers in carriers of PM and GZ alleles, and of their relationship with the rate of cell survival, provide evidence for the cytotoxic effect of mRNA in lymphoblasts, and suggest that this toxicity applies to the whole range of small CGG expansions. The relationship between the molecular findings and specific neuropsychological measures provides confirmatory evidence for a significant role of small expansions in the origin of neurodegeneration, as well as potential biomarkers for the associated brain pathology.

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