Title: Health, Mental Health, and Cognitive Profiles of Mosaic versus Non-Mosaic FMR1 Premutation Carriers

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Introduction: As part of an ongoing study, 100 women who were diagnosed as having the FMR1 premutation (mean age = 58 years) were studied with respect to their health and mental health. In this analysis, we explored the correlates of CGG repeat mosaicism on the expanded allele.

Method: Premutation carriers provided buccal swabs from which DNA was extracted and the FMR1 CGG genotyping was performed (Asuragen kit) in the laboratory of Dr. Elizabeth Berry-Kravis. Premutation carriers were categorized based on their longer allele into three groups: Group 1: premutation non-mosaic (n=45); Group 2: premutation mosaic (n=41), and Group 3: premutation/full mutation mosaic (n=14). The premutation mosaic mothers (Group 2) had at least two populations of cells in the premutation range on their longer allele. The premutation/full mutation mosaic mothers (Group 3) had a very small population of cells in the full mutation range on their expanded allele, in addition to their predominant premutation CGG expansion. Although participants were aware of their status as premutation carriers, they were not informed about their mosaicism status.

Results: Unexpectedly, premutation/full mutation mosaic (Group 3) had better health and mental health than the other two groups. Specifically, premutation carriers with full mutation mosaicism were significantly less likely to have any limitations in activities of daily living, higher positive self-rated health, lower negative self-rated health, lower severity of menopause symptoms, lower likelihood of having been prescribed psychotropic medications, and at a trend level, fewer diagnosed health conditions, less anxiety, higher levels of positive affect, lower levels of negative affect, and better executive functioning. To probe the better health, mental health, and cognitive profile, we delved into the specific symptoms and diagnosed conditions using machine learning approaches and we focused on how premutation/full mutation mosaic (Group 3) differed from each of the other two groups based on the results of the ANOVAs. A direct comparison between premutation/full mutation mosaics (Group 3) and premutation non-mosaic (Group 1) classified the groups with AUROC of 0.73, and a direct comparison between premutation/full mutation mosaics (Group 3) and premutation mosaics (Group 2) classified the groups with AUROC of 0.74.

Discussion: Although only 14 premutation carriers in the present sample also had a small population of full mutation cells, their profile of comparatively better health, mental health, and cognitive abilities was unexpected. These preliminary findings should motivate confirmation in additional research on larger samples. Additionally, there is a need for more extensive phenotyping to deepen our understanding of the clinical correlates of mosaicism in premutation carriers and to probe possible mechanisms.

References/Citations:
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