Title: Stressful Parenting Interacts with Low Zone CGG Repeat Length: Gene by Environment Interaction

Authors: Jinkuk Hong¹, Leann Smith DaWalt¹, Jan Greenberg¹, Murray Brilliant², Marsha Mailick¹

¹ Waisman Center, Univ. of Wisconsin-Madison; ² Marshfield Clinic Research Institute

Introduction: With its known association with brain development and function, the FMR1 gene has been studied extensively, primarily with respect to fragile X syndrome and premutation CGG expansions. Yet, very little is known about phenotypic characteristics of the lower end of the spectrum of CGG repeats (“Low Zone”), defined as fewer than normal numbers of CGG repeats (23 or fewer). In this study, we examined differences in phenotypic outcomes between those in the Low Zone and those with normal numbers of CGG repeats. We also tested if the associations varied by stress exposure, here measured by stressful parenting, defined as parenting children with developmental (e.g., ASD, DS, ADHD) or mental health (e.g., bipolar disorder, anxiety, depression) conditions.

Method: Participants (n=389) were drawn from the population-based Marshfield Personalized Medicine Research Project (PMRP) and were unaware of their FMR1 CGG status. All were mothers of at least one biological or adopted child and were divided into two groups based on their CGG repeat number: 93 (24%) who were homozygous for the Low Zone (i.e., both alleles in the Low Zone range) and 296 (76%) who were homozygous for normal CGGs (i.e., both alleles in the normal range -- 24 – 40 CGG repeats). Their mean age was 57.9 years old (s. d. = 15.4, ranging from 28 to 98). One-third of participants (33.2%) experienced stressful parenting, and there was no significant difference in the percentage who reported stressful parenting between the Low Zone group and the normal group. The cognitive outcome variables included two BRIEF-A indexes – Behavioral Regulation Index (BRIEF) and Metacognition Index (MI). Physical health outcome included functional limitations and menopause symptoms. Mental health outcomes included depression measured by CES-D and anxiety measured by POMS Anxiety scale.

Result: Overall, stressful parenting was associated with poorer outcomes on all measures. Furthermore, the Low Zone group reported more severe menopausal symptoms than the normal group (b = 1.05, s.e. = .52, p < .05). There was a significant gene by environment interaction effect for depressive symptoms (b = 4.3, s.e. = 2.0, p < .05; see Figure 1) and trend-level interactions for the BRIEF-MI (b = 4.4, s.e. = 2.6, p < .10) and anxiety (b = 2.5, s.e. = 1.3, p < .06). Among those who did not experience stressful parenting, mothers in the Low Zone group were significantly better off than those in the normal group, i.e., better executive functioning and lower levels of depression than those with normal numbers of CGGs. However, the negative effects of stressful parenting were much greater for the Low Zone mothers such that differences between those who experienced stressful parenting and those who did not were much more pronounced than the normal group with respect to the BRIEF-MI, depression, and anxiety.

Discussion: This is one of few studies that explored the phenotypic characteristics of females with low numbers of CGG repeats and its possible interaction with stress exposure. We examined if stressful parenting had differential consequences – for cognitive function, physical and mental health – for mothers in the Low Zone compared with peers with normal numbers of CGG repeats. In line with a previous study with a different sample (Maillick et al., 2017), findings of this study provided evidence that the impact of stress exposure on phenotypic outcomes may vary by genotype. Mothers with Low Zone alleles were better off in the absence of parenting stress, but were worse off if they experienced stressful parenting. These interactions reflected a pattern of differential susceptibility (Belsky et al. 2007). Further studies are needed to replicate these results and to expand phenotypic characteristics of lower numbers of FMR1 CGG repeats.

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References/Citations:
