**Title**: Depression, Anxiety, and Stress in *FMR*1 premutation carriers with children affected by fragile X

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**Introduction**: The diathesis-stress theory is a well-established model explaining how genetic vulnerability and environmental stressors may contribute to the development of mental disorders. Previous literature supports that individuals with a genetic vulnerability and high number of stressful life events are at greater risk than would be expected if these risk factors were simply additive, highlighting the need for increased attention to this population in mental health research (Colodro-Conde et al., 2018).

One such relevant population consists of carriers of the *fragile X messenger ribonucleoprotein* 1 (*FMR*1) gene, who have a genetic vulnerability to developing psychiatric disorders; this vulnerability appears to have a nonlinear relationship with repeat size, with the highest rates of mental disorders observed among women with mid-range repeats (Gossett et al., 2016; Hessel et al., 2005; Roberts et al., 2008; Loesch et al., 2014). Additionally, the challenges associated with caregiving for a child with fragile X can cause high levels of parenting stress (Backes et al., 2001). However, no known studies have examined the effects of this gene-environment interaction in *FMR*1 premutation carriers' caregiving for children with fragile X. The present study addressed this gap by examining whether previous reports of elevated mental health symptoms, particularly among carriers with mid-range repeats, are sustained when child challenging behaviors are matched across groups.

**Method**: Data from 53 fragile X caregivers with the *FMR*1 premutation and 53 neurogenetic disorder caregivers without the premutation were drawn from the Purdue Early Phenotype Study (PEPS) — an online survey administered to families of children with neurogenetic conditions — and the WellBeing of CAregiverS via Telehealth project (Project WellCAST) — a multi-phase clinical trial designed to support the mental health of rare disorder caregivers through self-guided resources, peer coaching, and various therapies. Participants in both groups were matched on challenging child behaviors — measured by the Child Behavior Checklist 1.5-5 (CBCL; Achenbach & Rescorla 2000) and the Aberrant Behavior Checklist-Community (ABC-C; Aman & Singh 1994) — along with child age. The Depression Anxiety and Stress Scale 21-items (DASS-21; Lovibond & Lovibond 1995) was used to measure severity of caregiver depression, anxiety, and stress. Participants with the *FMR*1 premutation were also asked to report CGG repeat size.

**Results**: To determine if fragile X caregivers with the *FMR*1 premutation experience elevated levels of depression, anxiety, and stress relative to other caregivers matched on child challenging behaviors, we conducted a series of Wilcoxon ranked sum tests to compare scores on the DASS-21 and its subscales — depression, anxiety, and stress — between the two groups. Results showed no significant difference between the groups on the DASS-21 total score (W = 1387.5, *p* = 0.544) or the depression (W = 1376, *p* = 0.573), anxiety (W=1442.5, *p* = 0.405), and stress (W = 1396.5, p = 0.522) subscale scores.

The Wilcoxon ranked sum test was then used to compare scores on the DASS-21 and its subscales between *FMR*1 premutation carriers with mid-range (65-99) and high-range (100-200) CGG repeat sizes to determine if the previously identified nonlinear relationship is present in this population. The results showed no significant difference regarding the DASS-21 total score (W = 230, p = 0.059) or the depression (W = 220, p = 0.10) and stress (W = 224.5, p = 0.08) subscale scores. However, participants with mid-range repeat sizes had significantly higher scores on the anxiety subscale (W = 244.5, p = 0.023).

Preliminary descriptive statistics suggested higher standardized CBCL and ABC-C scores among the mid-range repeat sizes (Mean Z-score = 0.086, SD = 0.97) than the high-range repeat sizes (M = -0.19, SD = 1.04). Final analyses will use linear regressions to compare scores on the DASS-21 and its subscales between carriers with mid-range and high-range repeat sizes, while controlling for challenging child behavior.

**Discussion:**

Contrary to some past literature, no significant difference in anxiety, depression, and stress was found between caregivers with and without the *FMR*1 premutation who were matched on child challenging behaviors. While anxiety was significantly higher in premutation carriers with mid-range repeat sizes than with high-range repeat sizes, there was also no significant difference in depression and stress between the two groups. However, child challenging behaviors differed across CGG repeat subgroups, necessitating future work to better understand these associations. It is possible that modest sample size and sampling characteristics unique to these participant groups explain differences from past work; for example, future research could explore other genetic moderators such as X-inactivation, as a previous study found the relationship between CGG repeat size and psychological symptoms in premutation women is only present when X activation is skewed toward >50% active premutation alleles (Hessel et al., 2005). This work contributes to the growing literature seeking to characterize association between the genetic vulnerability and environmental stress among premutation carriers, which can inform both the etiology of symptoms and the development of personalized treatments.

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