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# Women with the *FMR1* premutation: a within-family observational sibling study

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## ABSTRACT

**Introduction** Understanding the relative risk of the *fragile X messenger ribonucleoprotein 1* (*FMR1)* premutation (PM) versus the risk of the PM and parenting a child with fragile X syndrome (FXS) is critical for PM carriers, their families and clinicians. For this study, we compared women with the PM with their biological sisters; some sisters also had the PM and some had normal-range cytosine–guanine–guanine (CGG) repeats. The sisters were further differentiated by whether they had a child with FXS.

**Methods** This study of 67 women from 30 families used multilevel modelling to probe the effects of the PM with or without parenting a child with FXS, with strong control for family-of-origin factors and background genetics.

**Results** Controlling for the false discovery rate, we found that mothers with the PM who had children with FXS were *similar* to their sisters who had the PM but did not have a child with FXS in health, sleep, social relationships, depressive symptoms and executive functioning, differing only in anxiety and stress. However, there were many *differences* when mothers with the PM who had children with FXS were compared with their sisters with normal-range CGGs, including greater fragile X-associated tremor/ataxia syndrome-type, depressive and anxiety symptoms, poorer sleep, greater negative support and greater stress.

**Conclusions** In this study, the effect of the PM was stronger than the effect of parenting a child with FXS. Thus, the PM phenotype should not be primarily attributed to the effect of parenting a child with FXS. Additionally, by comparing mothers who had the PM and children with FXS with their sisters without the PM, the findings confirmed the effect of this dual vulnerability and here the vulnerability emerged even with strong familial controls.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Most past studies of the *fragile X messenger ribonucleoprotein 1* (*FMR1)* premutation (PM) phenotype in women contrasted mothers with the PM who had children with fragile X syndrome (FXS) to unrelated women who neither had the PM nor had children with FXS and were not able to separate the effect of the PM from parenting a child with FXS. The present study compared sisters who were Concordant for the *FMR1* PM but differed in whether they had a child with FXS, making it possible to separate the genetic effect of the PM from the effect of parenting a child with FXS.

### WHAT THIS STUDY ADDS

⇒ Findings of the present study suggested that the effect of the PM was a considerably stronger factor than parenting a child with FXS in contributing to health and well-being, after controlling for family-of-origin contextual factors and background genetics.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The within-family approach of this study provided insights about a question that has been frequently asked but still not fully answered in past research, namely *what are the separate effects of the PM and parenting for a child with FXS,* with relevance for researchers, clinicians and families affected by *FMR1* expansions. The findings indicated that characteristics of women with the PM should not be primarily attributed to the effect of parenting their child with FXS, but rather primarily to the effect of the *FMR1* PM.

## INTRODUCTION

The *FMR1* gene (*fragile X messenger ribonucleoprotein 1),* located on the X-chromosome, plays a critical role in normal neurological development and functioning, and regulates the translation of approximately 30% of all transcripts in the synaptic proteome.[1] While 30 cytosine–guanine–guanine (CGG) repeats within the 5' untranslated region of *FMR1* is the modal number of repeats in the general population, expansions of over 200 CGG repeats result in fragile X syndrome (FXS), a neurodevelopmental disorder that is the most common genetic cause of intellectual disability and autism. Expansions of 55–200 CGG repeats result in the *FMR1* premutation (PM). CGG expansions in the *FMR1* gene are transmitted within a family across the generations. The transmission follows an X-linked pattern of inheritance; a mother with a PM has a 50% chance of passing her allele with

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normal range CGG repeats to each of her children, and a 50% chance of passing either a PM or full mutation (resulting in FXS) to each of her daughters and each of her sons, whereas a father with a PM will pass his PM only to all of his daughters. This results in a range of PM, full mutation and normal CGG repeat sizes among family members within and across generations.[2]

The focus of this study is on women with the PM and their biological sisters, some of whom have the PM and some of whom have normal-range CGG repeats. The sisters in the present study are further differentiated by their parenting status, contrasting those who have a child with FXS and those who do not. (Note that women with normal-range CGG repeats cannot have a child with FXS, regardless of their sister's or parent's *FMR1* status.) The within-family research design of the present study offers the opportunity to advance understanding about the effects of the PM versus the effect of parenting a child with FXS, with strong control for family-of-origin contextual factors, such as parenting style and socio-economic status during childhood and adolescence, and for background genetics, above and beyond variants in the *FMR1* gene.

Most women with the PM are identified via cascade testing only after a member of their family is diagnosed with FXS. Therefore, past studies of women with the PM have most often centred on mothers of children with FXS, comparing them to unrelated controls.[3–7] This research has produced strong and consistent evidence that mothers with the PM who had children with FXS have elevated cognitive, neuromotor, linguistic, reproductive and psychiatric symptoms compared with unrelated unaffected controls. However, most such studies cannot separate the effects of the PM from the effects of parenting a child with FXS. This is an important gap in current knowledge given the well-established research findings linking parenting a child with developmental disabilities, including FXS, with chronic parenting stress and risks to parents' mental and physical health.[8 9] Thus, an understanding of the relative risk associated with the PM alone versus a PM and parenting a child with FXS is critical for women with the PM, their families and clinicians.

A few studies evaluated the effects of the *FMR1* PM in women who did not have children with FXS, pointing to elevated health risk. Gossett *et al*[10] compared 24 women with the PM who did not have children with FXS with 26 community controls, and found that those with the PM reported significantly elevated psychiatric symptoms. Movaghar *et al*[11] used machine learning to analyse the electronic health records from a population-biobank that had been screened for CGG repeats (98 individuals with the PM, 55–125 CGG repeats, compared with 1001 age/sex matched controls). None of the individuals with the PM had a child with FXS or were aware of their own PM status. Those with the PM were not sicker overall; when all conditions in the health record were considered, there were no differences in number of conditions or number of medical encounters between those with the PM and controls. It was only with respect to PM-associated conditions that the greater burden of disease was observed, suggesting that the PM is associated with a unique pattern of health conditions, even in the absence of parenting a child with FXS. In a study focusing on neuromotor functioning, Mailick *et al*[12] compared women with the PM (n=35, 55–101 CGG repeats) who did not have children with FXS with matched controls (n=61) with respect to symptoms associated with fragile X-associated tremor/ataxia syndrome (FXTAS). Structured neurological assessments indicated that among women without any potentially confounding diagnoses, there was a statistically significant age-associated elevation in FXTAS-type signs in those with the PM. White *et al*[13] compared mothers with the PM who had children with FXS (n=51), women with the PM who did not have children (n=17), mothers with normal-range CGG repeats who did not have children (n=28) and mothers of typically developing children (n=44) with the goal of understanding whether women with the PM have elevated risk of mental health problems and autistic traits. Findings indicated that women with the PM reported significantly elevated autistic traits and anxiety, but this risk did not interact with maternal status, suggesting that the risk is specific to the presence of the PM and is not fully accounted for by stressful parenting.

### Past within-family *FMR1* premutation research

Research designs including members of the same family, such as case reports and case–control studies, have been used in past *FMR1* PM research to compare siblings. Case reports have most often described atypical genotype–phenotype associations in siblings within families with *FMR1* CGG expansions (eg, Basuta *et al*,[14] Martorell *et al*[15]). Case–control studies have used group designs to compare those who had *FMR1* PM CGG expansions and their siblings who constituted the control group (eg, Allen *et al*,[16] Hessl *et al*,[17] Jacquemont *et al*[18]), revealing increased health burden in those who had CGG expansions. However, in these case–control studies, within-family statistical analyses were not conducted, foregoing the opportunity to directly contrast siblings who grew up in the same family and who shared background genetics. Notably, evaluation of background genetics among PM carriers has increasingly been observed to contribute to the primary PM phenotype,[19–21] highlighting the importance of direct within-family comparison of siblings.

Only a few studies, including the present one, conducted within-family comparisons to directly contrast women with the *FMR1* PM and their sisters. In an early study, Franke *et al*[22] contrasted five groups of women: (1) 13 full mutation mothers of children with FXS, (2) 61 mothers with the PM who had children with FXS, (3) 17 women who had the PM who were sisters of women in the first two groups, but who did not have children with FXS, (4) 18 sisters of the first two groups without either the *FMR1* full mutation or the PM and without affected



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children and (5) 42 mothers who had children with autism who were not related to other groups. The goal of the Franke *et al* study was to determine whether participants' psychological problems were related to their *FMR1* mutation status or, alternatively, to the stress of raising a child with FXS. Among the many comparisons reported, findings indicated that mothers who had the PM and who had a child with FXS (Group 2), as well as their sisters who had the PM but did not have affected children (Group 3), were more likely to be diagnosed with social phobia than the control group of mothers of children with autism (Group 5), suggesting that this psychological problem could be attributed to the genetic effect of the PM rather than to the effect of parenting a child with a developmental disability.

### The present study

The present investigation shares a similar goal as the Franke *et al* study, namely to conduct within-family analyses to directly compare women with the PM and their sisters—some of whom had the PM and others who did not, and some of whom had children with FXS and some did not—with the aim of separating the genetic effects of the PM from the effects of parenting a child with FXS. By controlling for shared family factors, this research design offers a more accurate assessment of the effects of genetic variation than most prior group comparisons. However, unlike the Franke study, the present study used multilevel models to account for the nested structure of the data, where individual sisters were nested within families, rather than treating within-family data as independent observations.

Here, we make two parallel sets of comparisons. First, for our primary comparison, we contrast mothers with the PM who have children with FXS to their sisters who also carry the PM but whose children do not have FXS; these sisters are referred to as '*FMR1* Concordant'. Second, for a supplemental comparison, we contrast mothers with the PM who have children with FXS and their sisters with normal-range CGG repeats; these sisters are referred to as '*FMR1* Discordant'. Although a 'cleaner' approach for this supplemental comparison would have been between women with the PM who do not have children with FXS with their sisters who have normal-range CGGs, our study sample does not contain any such sister pairs. Nevertheless, this supplemental comparison of Discordant sisters provides within-family data that parallels most of the extant literature that has focused on the effect of the PM and parenting a child with FXS versus unrelated controls who neither have the PM nor a child with FXS, but in the present study we control for family background genetics and contextual factors.

We conduct these comparisons for PM-associated conditions (FXTAS-type symptoms, mental health symptoms and executive functioning difficulties). In addition, we conduct comparisons focused on broader health and social characteristics (general health, sleep quality, social relationships and perceived stress), all of which have been identified as elevated among PM carriers in previous research.[8 11 23] Using a within-family approach, we predicted that sisters with both the PM and a child with FXS will have more severe PM-associated conditions, worse health, more compromised social relationships and greater perceived stress compared with their sisters who have normal-range CGG repeats as well as compared with their sisters who also carry the PM but do not have a child with FXS.

## MATERIALS AND METHODS

### Participants

Participants in the present study were a subset of the sample members included in an ongoing longitudinal study of mothers with the PM who had sons and daughters with FXS aged 12 and older, referred to here as the 'main study'.[24] The data for the present analysis were collected in 2019–2020. At that time, they were asked to provide contact information for each of their full biological siblings, who subsequently were invited to participate in this within-family study. Approximately half of the main study participants (n=53, 44.2%) had at least one sibling who participated in the within-family study. Data were collected from all of these siblings regardless of their PM status, sex or whether they had children with FXS. We compared main study participants who had at least one brother or sister participating in the sibling study with main study participants whose siblings did not participate. There were no significant differences between these groups with respect to demographic characteristics, PM-associated conditions and broader health and social characteristics. However, those with at least one participating sibling had a significantly greater number of brothers and sisters than those who did not have any siblings participating (3.83 vs 3.02, t=2.74, p<0.01).

Mothers in the main study and their siblings were asked to report their *FMR1* testing history and results. All but five participants were aware of their PM status and provided the requested information, which was further verified by medical records and/or molecular assays conducted by the Rush University Medical Center Molecular Diagnostics Laboratory under the direction of EMB-K. DNA was isolated from buccal samples using standard methods. *FMR1* genotyping to determine CGG repeat length was conducted with the Asuragen AmplideX Kit.[25 26]

Due to sex differences associated with the *FMR1* PM (ie, the risk of giving birth to a child with FXS, higher rates of anxiety and reproductive symptoms), the present study focused on sisters. Therefore, we excluded from the analysis 18 main study participants who had only brothers participating in the sibling study. We also excluded five main study participants whose sisters in the sibling study also had children with FXS because these sisters did not fit into the present study's design. After excluding these main study participants and their siblings, the present analysis included 67 women from 30 families who ranged in age from 31 to 75, with an average age of 58 at the time



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of data collection. CGG repeats did not differ between the *FMR1* Concordant sisters (mean for mothers with the PM who had a child with FXS=91.9; mean for their sisters with the PM who did not have a child with FXS=91.0). However, the CGG repeats differed significantly between the *FMR1* Discordant sisters (mean for mothers with the PM who had a child with FXS=93.2; mean for mothers with normal-range CGGs=30.8, p<0.001). The children with FXS in these families averaged 30.3 years of age when the data for the present study were collected. Note that when we refer to 'children with FXS', the term 'child' is used in the intergenerational sense rather than implying chronological age.

The within-family analyses among *FMR1* Concordant sisters compared 19 women with the PM who had children with FXS (all of whom were main study participants) with 25 of their sisters who similarly had the PM but did not have children with FXS. Analysis of the *FMR1* Discordant sisters compared 11 women with the PM (also all main study participants) who had children with FXS with 12 of their sisters who had normal-range CGGs.

At the time of data collection, 76.3% of the children with FXS were coresiding with their mothers, 76.7% had intellectual disabilities and 28.6% had co-occurring autism (28.6%). Regarding their levels of maladaptive behaviour, none had severe behaviour problems, 6.7% had moderate levels, 20.0% had marginal levels and most were classified as having normal levels of behaviour problems on the SIB-R (Scales of Independent Behavior-Revised).[27] Regarding their functional levels, they averaged 21.7 on the W-ADL scale, with a range of 4–34 on this measure (Waisman-Activities of Daily Living,[28] which corresponds to a moderate level of intellectual disability). Coresidence was most strongly associated with mothers' characteristics (correlations with anxiety symptoms=−0.386, p<0.05; depressive symptoms=−0.406, p<0.01; FXTAS-type symptoms=−0.535, p<0.01; number of medications prescribed by their physician=−0.475, p<0.01).

## Measures

Identical measures were collected from the main study participants and from their sisters. Data were collected via telephone interviews and self-administered questionnaires.

### Measures of premutation-associated conditions

Three domains of PM-associated conditions were measured: (1) FXTAS-type symptoms, (2) mental health symptoms and (3) executive functioning symptoms. We did not include menopausal symptoms related to fragile X-associated premature ovarian insufficiency because 10% of the current sample were premenopausal.

FXTAS-type symptoms were assessed via responses to a measure included in the Chonchaiya *et al*[29] study of daughters who had the PM whose fathers had FXTAS. The 14 items covered four domains (tremor, neuropathy, memory, balance), with questions such as 'Do you have tremor (shakiness) of the hands?', 'Any problems with burning or pain in the legs?', 'Do you have problems with memory?' and 'Have you had any problems with your balance?' Items were rated as 0=no problems, 1=have problems but not clinically diagnosed or treated with medication for this symptom, and 2=have clinically diagnosed problems or treated with medication for this symptom, and summed into a total score.

Depressive symptoms were measured using the 20-item *Center for Epidemiologic Studies Depression Scale*.[30] Participants rated how many days over the past week they experienced depressive symptoms (eg, depressed mood, feelings of loneliness, lack of positive affect) on a 4-point scale from 0 (never) to 3 (5–7 days). Cronbach alpha for this sample was 0.93. Anxiety symptoms were measured by the 9-item anxiety subscale of the *Profile of Mood States*.[31] Symptoms such as feeling tense, shaky, uneasy, nervous as experienced over the previous week were rated from 0 (not at all) to 4 (extremely). Cronbach alpha for this sample was 0.90.

Participants completed the *Behavior Rating Inventory of Executive Function-Adult Version* (BRIEF-A[32]), which assesses executive functioning limitations. Participants indicated the extent to which they experienced each of 75 items in the past month on a scale from 1 (never) to 3 (often), and converted to T-scores. The reliability and validity of the BRIEF-A was well established.[32 33]

### Measures of broader health and social domains

Participants rated their *health* as 1=poor, 2=fair, 3=good, 4=very good and 5=excellent. Considerable previous research has provided evidence of the validity of such health ratings in predicting health and mortality.[34] Additionally, participants provided a listing of the medications prescribed by their physician that they were currently taking; a *count of the medications* was analysed.

Participants' sleep quality over the past month was assessed using the 19-item *Pittsburgh Sleep Quality Index* (PSQI).[35] The PSQI measures sleep quality, latency, duration, efficiency, disturbance, medication use, daytime dysfunction, with scores ranging from 0 (no difficulty) to 3 (severe difficulty). A PSQI score greater than five is considered indicative of poor sleep quality, based on its high sensitivity and specificity in identifying patients with sleep issues. The PSQI has demonstrated strong reliability and validity.[36 37]

Three measures of social relationships were included—amount of positive support, amount of negative support and emotional closeness to siblings. Using a modified version of the 'convoy model',[38] participants were first asked to list up to 10 persons in their social network who were important to them, and to indicate whether each individual provided them with six types of positive support (each coded as yes=1 or no=0): someone in whom they could confide; a source of reassurance when feeling uncertain; someone to talk with when upset, nervous or depressed; someone who made them feel respected; someone who would provide care if the respondent was



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ill; and someone the respondent could talk about her health. *Total positive support* was obtained by summing the availability of the six types of positive support from all members in the network.

In addition to positive support, we included two items measuring the extent to which the participant was the recipient of 'negative support'. For each person in the social network, participants were asked to indicate whether (yes=1 or no=0) the network member made excessive demands on her or made the participant feel uncomfortable talking about the details of her day-to-day life. *Total negative support* was the sum of the two types of negative support across all members in the network.

Participants rated their *emotional closeness to each sibling* on a scale from 1 = 'not at all close' to 7 = 'very close'. Responses were averaged across all siblings.

Two measures of stress were included—perceived stress and negative life events. Notably, the *Perceived Stress Scale* does not focus on parenting stress, but rather is a measure of general stress, indicating the degree to which participants found their lives to be unpredictable, uncontrollable and overloading.[39 40] We used a measure of general stress, rather than a measure specifically focused on parenting stress, because it could be administered to all participants, regardless of parental status. Each item was rated on a 5-point scale ranging from 0=*never* to 4=*very often*. Cronbach alpha for this sample was 0.92. Participants also reported whether they had directly experienced 11 negative life events in the past 12 months using a modified version of Abidin's[41] *Life Stress Scale* (eg, marital dissolution, finances, substance abuse, deaths, health problems and caring for an ageing parent). A count of *negative life events* was analysed.

### Plan for data analysis

We employed multilevel modelling to account for the nested structure of the data, where individual sisters were nested within families. The main study participants, all of whom were mothers with the PM who had children with FXS, were specified as the reference category in the models, allowing for two sets of within-family contrasts—between *FMR1* Concordant sisters, which was the primary comparison motivating the present study, and between *FMR1* Discordant sisters, which provided a supplemental comparison. To control for within-family age variation, each sister's age was centred at the family mean and included as a covariate in the models. Analyses were conducted using Stata V.19.[42] Outcomes were treated as continuous variables, with the exception of two binary outcomes—marital status and employment status—for which logistic multilevel models were applied. Fully 94% of participants had complete data on the measures analysed for the present study. For variables where there was missing data, the case was dropped from that analysis. Sample sizes for analyses where there was any missing data are indicated in tables 1–3, and in the online supplemental tables.

As noted, for our primary comparison, we predicted that sisters who have the PM and a child with FXS will have poorer outcomes as compared with their sisters who also carry the PM but do not have a child with FXS. Additionally, we expected that sisters who have the PM and a child with FXS will have poorer outcomes than their sisters who have normal-range CGG repeats and no child with FXS, although this comparison is limited in that it cannot separate the effect of the PM from the effect

**Table 1** Within-family comparisons and multilevel model analyses comparing *FMR1* Concordant sisters and Discordant sisters: demographic characteristics*

| | (A) *FMR1* Concordant sisters | | | (B) *FMR1* Discordant sisters | | |
|---|---|---|---|---|---|---|
| | Mean (*SD*) for premutation sisters who had children with FXS (n=19) | Mean (*SD*) for premutation sisters who did not have children with FXS (n=25) | Coefficients (SE) (95% CI) | Mean (*SD*) for premutation sisters who had children with FXS (n=11) | Mean (*SD*) for sisters with normal-range CGGs who did not have children with FXS (n=12) | Coefficients (SE) (95% CI) |
| Age | 58.2 (6.5) | 58.0 (10.3) | 0.27 (1.73) (–3.12 to 3.67) | 55.6 (5.5) | 59.7 (10.2) | 2.83 (2.28) (–1.63 to 7.30) |
| Years of schooling | 16.4 (2.6) | 16.4 (3.5) | –0.14 (0.63) (–1.38 to 1.09) | 15.1 (2.7) | 14.5 (1.9) | –1.18 (0.84) (–2.82 to 0.46) |
| Marital status (% married) | 78.9 | 64.0 | –1.27 (0.69) (–2.61 to 0.07) | 100.0 | 75.0 | –0.63 (0.87) (–2.33 to 1.07) |
| Employment (% currently working) | 78.9 | 58.3 (n=24) | –1.81 (0.95) (–3.67 to 0.04) | 90.9 | 58.3 | –1.40 (1.16) (–3.67 to 0.86) |
| Number of children | 2.0 (1.0) | 1.4 (1.8) | –0.47 (0.30) (–1.05 to 0.12) | 1.8 (0.9) | 1.6 (1.6) | –0.38 (0.40) (–1.16 to 0.40) |

*Sample size of a cell is indicated if it is different from the full sample size.
*FMR1*, *fragile X messenger ribonucleoprotein 1*; FXS, fragile X syndrome.



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**Table 2** Within-family comparisons and multilevel model analyses comparing *FMR1* Concordant sisters and Discordant sisters: premutation-associated conditions†

| | (A) *FMR1* Concordant sisters | | | | (B) *FMR1* Discordant sisters | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean (*SD*) for premutation sisters who had children with FXS (n=19) | Mean (*SD*) for premutation sisters who did not have children with FXS (n=25) | Coefficients (SE) (95% CI) | Effect size‡ | Mean (*SD*) for premutation sisters who had children with FXS (n=11) | Mean (*SD*) for sisters with normal-range CGGs who did not have children with FXS (n=12) | Coefficients (SE) (95% CI) | Effect size‡ |
| FXTAS-type symptoms | 3.4 (3.6) | 2.2 (2.5) | −1.69 (0.81)* (−3.28 to −0.10) | −0.58 | 5.1 (4.5) | 1.3 (1.8) | −2.77 (1.05)**†§ (−4.83 to −0.71) | −0.94 |
| Anxiety symptoms | 9.0 (4.3) | 6.2 (6.5) | −2.90 (1.34)*§ (−5.53 to −0.28) | −0.62 | 11.0 (7.4) | 2.8 (3.7) (n=11) | −7.15 (1.82)***§ (−10.72 to −3.57) | −1.52 |
| Depressive symptoms | 10.9 (7.1) | 9.0 (10.3) | −1.54 (2.05) (−5.55 to 2.47) | −0.22 | 12.3 (13.0) | 2.8 (3.1) (n=11) | −9.19 (2.81)***§ (−14.70 to −3.68) | −1.29 |
| Executive functioning limitations | 58.1 (12.8) (n=18) | 53.2 (13.1) (n=24) | −3.88 (3.03) (−9.81 to 2.05) | −0.35 | 56.5 (11.3) | 47.7 (5.6) (n=10) | −8.06 (4.07)* (−16.1 to −0.07) | −0.74 |

*p<0.05, **p<0.01, ***p<0.001, based on one-tail tests.
†Sample size of a cell is indicated if it is different from the full sample size.
‡The effect size, Cohen's *d*, was calculated by dividing the regression coefficient by the square root of the residual variance from each multilevel model. Effect sizes (Cohen's d) are categorised as medium (≥0.5) or large (≥0.8).
§This coefficient remained significant after adjusting for multiple comparisons using the Benjamini-Hochberg procedure, setting the false discovery rate at 0.05.
*FMR1*, *fragile X messenger ribonucleoprotein 1*; FXS, fragile X syndrome; FXTAS, fragile X-associated tremor/ataxia syndrome.



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**Table 3** Within-family comparisons and multilevel model analyses comparing *FMR1* Concordant sisters and Discordant sisters: broader health and social characteristics†

| | (A) *FMR1* Concordant sisters | | | | (B) *FMR1* Discordant sisters | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean (*SD*) for premutation sisters who had children with FXS (n=19) | Mean (*SD*) for premutation sisters who did not have children with FXS (n=25) | Coefficients (SE) (95% CI) | Effect size‡ | Mean (*SD*) for premutation sisters who had children with FXS (n=11) | Mean (*SD*) for sisters with normal-range CGGs who did not have children with FXS (n=12) | Coefficients (SE) (95% CI) | Effect size‡ |
| Self-rated health | 3.5 (1.0) | 4.0 (1.0) | 0.34 (0.23) (–0.11 to 0.78) | 0.42 | 3.7 (0.9) | 3.9 (1.2) | 0.39 (0.30) (–0.20 to 0.98) | 0.49 |
| Number of medications | 1.8 (1.7) | 2.1 (2.2) | 0.15 (0.53) (–0.89 to 1.20) | 0.08 | 2.5 (2.7) | 2.8 (2.6) | 0.31 (0.70) (–1.06 to 1.69) | 0.17 |
| Sleep quality | 6.3 (3.6) | 5.2 (4.0) | –0.72 (0.75) (–2.19 to 0.75) | –0.28 | 6.5 (4.1) | 3.3 (2.1) | –3.13 (1.00)**§ (–5.10 to –1.16) | –1.21 |
| Emotional closeness to siblings | 5.0 (1.3) | 5.2 (1.3) | 0.17 (0.24) (–0.31 to 0.65) | 0.21 | 4.7 (1.3) | 5.3 (1.3) | 0.54 (0.33)* (–0.10 to 1.19) | 0.66 |
| Amount of positive support | 30.9 (15.4) | 33.1 (15.4) | 0.78 (3.37) (–5.82 to 7.38) | 0.07 | 32.5 (14.5) | 38.8 (13.6) | 8.45 (4.44)* (–0.26 to 17.16) | 0.72 |
| Amount of negative support | 1.0 (1.6) | 0.6 (1.1) | –0.45 (0.32) (–1.07 to 0.18) | –0.38 | 1.0 (1.3) | 0.1 (0.3) | –0.95 (0.41)*§ (–1.75 to –0.15) | –0.80 |
| Number of negative life events | 1.1 (1.4) | 1.0 (0.9) | 0.17 (0.28) (–0.37 to 0.72) | 0.17 | 0.4 (0.7) | 0.5 (0.7) (n=11) | –0.20 (0.37) (–0.92 to 0.52) | –0.19 |
| Perceived stress | 18.9 (7.1) | 13.4 (6.7) | –4.22 (1.63)**§ (–7.42 to –1.02) | –0.73 | 16.3 (8.0) | 8.0 (5.7) (n=11) | –8.77 (2.22)***§ (–13.11 to –4.42) | –1.52 |

*p<0.05, **p<0.01, ***p<0.001, based on one-tail tests.
†Sample size of a cell is indicated if it is different from the full sample size.
‡The effect size, Cohen's *d*, was calculated by dividing the regression coefficient by the square root of the residual variance from each multilevel model. Effect sizes (Cohen's d) are categorised as medium (≥0.5) or large (≥0.8).
§This coefficient remained significant after adjusting for multiple comparisons using the Benjamini-Hochberg procedure, setting the false discovery rate at 0.05.
*FMR1*, *fragile X messenger ribonucleoprotein 1*; FXS, fragile X syndrome.



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of parenting a child with FXS. Given the directionality of these predictions, we used one-tailed tests of statistical significance for the comparisons. We set the level of statistical significance at p<0.05. We controlled false discovery rate (FDR) across the 24 hypothesised comparisons using the Benjamini-Hochberg procedure,[43] setting the FDR level at 0.05. The results of the FDR procedure are described in the text and noted in the tables.

Comparisons of Concordant siblings had 80% power to detect medium sized effects (*d*=0.5), whereas comparisons of Discordant siblings had 80% power to detect only large sized effects (*d*=0.8). Effect sizes, based on Cohen's *d*, were calculated by dividing the regression coefficient by the square root of the residual variance from each multilevel model and are reported in tables 2 and 3.

## RESULTS

### Within-family demographic characteristics

Descriptions of within-family demographic characteristics are presented in table 1. Panel A focuses on sisters who are Concordant for the *FMR1* PM but differ in whether they had a child with FXS, while Panel B focuses on sisters who are Discordant for the *FMR1* PM, such that sisters who have the PM and a child with FXS are compared with their sisters who have normal-range CGG repeats. Within each panel, means are presented for each group, followed by the coefficients for the within-family comparisons generated by the multilevel models. No hypotheses were posed for these descriptive comparisons; when comparisons were implemented (using two-tailed tests of statistical significance), no significant differences were found. The within-family pattern of similarity on demographic characteristics, for both Concordant and Discordant sisters, reflects strong control for family-of-origin contextual effects and background genetic influences.

### Premutation-associated conditions

#### *FMR1* Concordant sisters

As shown in table 2A, sisters with the PM who had children with FXS had significantly greater severity of FXTAS-type symptoms (p=0.019, with medium sized effects); this comparison was no longer significant after implementing the FDR adjustment procedure. Sisters with the PM also significantly greater anxiety than their sisters who did not have children with FXS (p=0.015, with medium sized effects; this comparison remained significant after FDR adjustment). However, there were no significant differences between Concordant sisters in depressive or executive functioning symptoms.

#### *FMR1* Discordant sisters

Next, we compared sisters who were Discordant for the *FMR1* PM and who were also Discordant for having a child with FXS, with respect to PM-associated conditions. As shown in table 2B, sisters with the PM who had a child with FXS had significantly worse functioning with respect to all PM-associated conditions measured in this study compared with their sisters who had normal-range CGGs. The sisters with the PM had more severe FXTAS-type symptoms (p=0.004, with large effect size), significantly worse anxiety and depressive symptoms (p<0.001, reflecting large effect sizes), and greater executive functioning limitations (p=0.024, with medium effect sizes), than their sisters who had normal-range CGGs. The first three of the comparisons in Panel B remained significant after implementing the FDR adjustment procedure, but the executive functioning comparison was no longer significant after adjustment. This pervasive pattern of differences reflects the dual effects of the PM as well as the effects of parenting a child with FXS.

These sets of comparisons of PM-associated characteristics between *FMR1* Concordant sisters and between *FMR1* Discordant sisters were based on one-tailed statistical tests, guided by our directional hypotheses. When two-tailed tests were implemented as sensitivity analyses, all coefficients reported in table 2 where one-tailed tests had been implemented remained statistically significant (see online supplemental table S1).

### Broader health and social characteristics

#### *FMR1* Concordant sisters

As shown in table 3A, sisters who were Concordant for PM status did not differ with respect to either self-rated health or for the number of prescription medications taken at the time of data collection. They also did not differ in their sleep quality, although both groups were above the cut-off of a score of 5 on the PSQI, signifying poor sleep quality. Regarding the three indicators of social relationships, these siblings did not differ in their ratings of emotional closeness to their other siblings, their total amount of positive support from the members of their social support network or the amount of 'negative support' from these friends and family members. Additionally, the sisters did not differ in their experience of negative life events during the past year. However, sisters who were parenting a child with FXS had significantly greater perceived stress than those who did not have a child with FXS (p=0.005, a medium effect size; this comparison remained significant after FDR adjustment).

#### *FMR1* Discordant sisters

As shown in table 3B, *FMR1* Discordant sisters did not differ in either self-rated health or their number of medications. However, they differed significantly in their sleep quality, with sisters with the PM who were parenting a child with FXS having significantly poorer sleep quality, exceeding the cut-off on the PSQI, as compared with those who had neither risk factor (p=0.01; this was a large sized effect that remained significant after implementing the FDR adjustment procedure). Regarding social relationships, sisters with the PM who were parenting a child with FXS reported significantly less emotional closeness to the siblings in their family (p=0.049) and significantly less positive social support from friends and family (p=0.029), both reflecting medium sized effects, although these two comparisons were no longer significant after



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FDR adjustment. However, sisters with the PM who were parenting a child with FXS reported significantly greater 'negative support' (p=0.01, a large sized effect that remained significant after FDR adjustment) than their sisters with normal-range CGGs. Finally, although sisters with the PM who had a child with FXS did not differ in the number of negative life events they experienced in the past year, they had substantially greater perceived stress than their sisters with normal-range CGGs (p<0.001, a large sized effect; this comparison remained significant after implementing FDR adjustment).

These sets of comparisons of broader health and social characteristics between *FMR1* Concordant sisters and between *FMR1* Discordant sisters were based on one-tailed statistical tests, as guided by our directional hypotheses. When two-tailed tests were implemented as sensitivity analyses, support was provided for all of the patterns observed in table 3, although the coefficients for two variables (emotional closeness to siblings and amount of positive support) became trends. The other statistically significant coefficients remained statistically significant in the sensitivity analysis (see online supplemental table S2).

## DISCUSSION

Most past studies of the *FMR1* PM phenotype in women contrasted mothers with the PM who had children with FXS to unrelated women who neither had the PM nor had children with FXS. A few studies included family members of women with the PM as controls. However, to the best of our knowledge, this is only the second study of the *FMR1* PM phenotype to directly conduct within-family comparisons among sisters. This approach offered three advances.

First, the within-family research design provided strong control for family-of-origin contextual factors, such as parenting style and socio-economic status during childhood and adolescence, as well as background genetics, above and beyond variants in the *FMR1* gene. The sibling relationship constitutes the longest-lasting family tie, beginning with the birth of the younger sibling and ending with the death of one member of the sibling pair. Siblings share a common family heritage. Sisters share approximately 50% of their DNA and hence have a similar (though not identical) genetic background.[44] Second, by comparing sisters who were concordant for the *FMR1* PM but differed in whether they had a child with FXS, the present study separated the genetic effect of the PM from the effect of parenting for a child with FXS. Third, by comparing sisters who were Discordant for the *FMR1* PM, it was possible to assess whether between-group differences observed in prior case-control research conducted between unrelated women would also be observed when comparisons were made within the same family.

The current study revealed that sisters from the same family, regardless of PM status and regardless of whether they were parenting a child with FXS, did not differ in self-rated health, number of medications taken and their exposure to negative life events. These aspects of similarity suggest that the PM and stressful parenting do not have *pervasive* negative effects across all aspects of life when the study design includes within-family control.

However, many differences between sisters were observed in the present study, taking into account FDR adjustment for multiple comparisons. The sisters who were PM carriers and parented a child with FXS had greater vulnerability in some PM-associated conditions (particularly anxiety symptoms), as compared with their *FMR1* Concordant sisters who did not have a child with FXS—but they did not differ in others (depressive symptoms and executive functioning). In contrast, when comparisons were made with their sisters who had normal-range CGGs, statistically significant greater vulnerability in all PM-associated characteristics measured in this study were confirmed (although executive functioning limitations did not survive FDR adjustment), consistent with prior research using non-relative controls.[4 7 13] By conducting both types of within-family contrasts, we were able to observe elevated risk in PM-associated conditions as well as where stressful parenting exacerbated this risk even further.

When we probed broader health and social characteristics, no differences emerged between *FMR1* Concordant sisters on any characteristic except for perceived stress, with mothers of children with FXS experiencing greater stress. In contrast, *FMR1* Discordant sister pairs differed significantly from one another on many health and social characteristics; mothers of children with FXS reported particularly poor sleep quality, received a greater amount of negative support and experienced greater stress, again taking into account FDR adjustment and mirroring the patterns in past between-group comparisons.

### Implications

This study offers implications for the medical community, clinical care, patients, families and health policy. Women who had the PM, who for many years were believed to be clinically unaffected, have been shown to have many significant health risks. The present study suggests that these health risks are largely separate from the effects of parenting a child with FXS. Millions of people globally carry the *FMR1* PM, most of whom are not diagnosed.[2 45] Thus, greater availability of population-level PM carrier testing should be an important public health priority. The genetic risk of the PM is understood, testing is reliable and the family-wide ripple effects are extensive.

Additionally, although not the primary focus of the present study, we note that there was substantial heterogeneity among the children with FXS whose mothers had the PM. A child characteristic that was particularly associated with mothers' outcomes was whether their child continued to coreside in the parental home, with mothers whose child lived elsewhere having greater anxiety, depressive and FXTAS-type symptoms and a greater number of medications. Future research should



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probe the direction of effects between co-residence and these indicators of maternal well-being in order to further elucidate the clinical implications of this association.

### Limitations

The implications of this study's findings are limited by small sized samples, especially among Discordant sisters. Our power calculations estimated 80% power to detect medium to large effects (d≥0.5), which were borne out by most of the statistically significant results and by FDR adjustment for multiple comparisons. However, while the study design ensures adequate power to detect effects of moderate magnitude, power to detect smaller effects—which have both practical and theoretical relevance in this area of research—was limited. Consequently, the risk of Type II error is elevated for small effects, and non-significant findings cannot be interpreted as evidence of their absence. Rather, small effect sizes may still be meaningful in complex psychosocial and genetic contexts. Future studies with larger samples will be necessary to more precisely estimate and test small effects.

It is challenging to isolate symptoms in PM carriers stemming directly from the PM itself, in part due to variations in the living environments and lifetime exposures of *FMR1* Concordant sisters, including the effects of caregiving burden for those who had a child with FXS, and especially when data are collected in midlife as in the present study. Further, even for sisters, polygenic mechanisms may be contributing to between-sibling variation, including variants in other genes and even epigenetics with variation in methylation patterns.

Additionally, an ideal comparison among *FMR1* Discordant sisters would have contrasted sisters who had the PM *who did not have a child with FXS* with their sisters who had normal-range CGGs (and similarly no child with FXS). Unfortunately, the current data set did not include any of these types of sister pairs; this offers an important opportunity for future research. Nevertheless, the Discordant sister analysis provides valuable data because of the within-family research design—thus offering an advance in the understanding of within-family variation in families variously affected by *FMR1* CGG expansions.

There was little racial and ethnic diversity (almost all were white non-Hispanic) and they were highly educated. All participants volunteered for the present study. The data were obtained by self-report, and therefore in future research broader data sources including objective testing and clinical assessments, as well as formal psychiatric diagnostic testing, should be a priority. A limitation of self-report data is awareness of PM carrier status, with all participants except for five aware of their status and this might have influenced their responses.

## CONCLUSIONS

In conclusion, the within-family approach of this study provided a unique opportunity to address a question that has been frequently asked but still not fully answered in past research, namely *what are the separate effects of the PM and parenting for a child with FXS?* The present study provided insights about this question with respect to both PM-associated conditions and broader health and social characteristics, with relevance for researchers, clinicians and families affected by *FMR1* expansions. Although tempered by the study's limitations, findings suggested that the effect of the PM was a considerably stronger factor than parenting a child with FXS in contributing to their health and well-being, controlling for family-of-origin contextual factors and background genetics. Thus, characteristics of women with the PM should not be primarily attributed to the effect of parenting their child with FXS. Yet it is important that by comparing sisters who were Discordant for the *FMR1* PM, the findings confirmed the dual vulnerability conferred by genetics and parenting a child with FXS that has been extensively reported in past research, but here the vulnerability emerged even with strong familial controls.

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