Assessing Psychiatric Trait Burden in FXS Families: The Potential Benefits of Whole Family Intervention

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Background: Fragile X Syndrome (FXS) is the most common single gene disorder and leading cause of intellectual and cognitive disability (Hunter 2021). It is highly associated with comorbid disorders such as autism and anxiety. Research that focuses on women with FXS premutation has been significantly underrepresented within the field of behavioral phenotypes. many studies on mental health outcomes are limited to women with a premutation who are mothers of children with FXS, thus; findings are confounded by the impact of elevated maternal stress on mental health (Hunter 2021, White 2021). Yet, familial factors are highly implicated in anxiety, with several studies associating maternal anxiety disorders with children's behavioral inhibition and anxiety (Hunter 2021). Behavioral studies affirm that children begin to model the anxious responses they observe in parents. Also, maternal anxiety may also result in parental over-involvement and reduced child encouragement, each associated with elevated child anxiety symptoms (Potter, 2022). Genetic factors are also implicated, as both behavioral inhibition and anxiety disorders are considered highly heritable, and distinct patterns of temperament have been defined in disorders such as FXS (Hunter 2021, Potter 2022). Elevated anxiety is often reported to be one of the most impairing comorbidities associated with FXS and is well documented in children and adults alike (Hunter 2021, Tassanakijpanich 2021). Studies have shown that mothers of children with FXS show more signs of compromised psychological well-being than mothers of children with Down Syndrome and a strong association between child behavior and maternal stress and depression has been found in this population (Adams 2018). Currently, studies show that parents do not have access or are not frequently recommended services to help alleviate or garner coping skills related to parental stress (Potter, 2022).

Methods: Of the 21 FXS probands identified 16 pedigrees were able to be made based off sibling groups and completed family medical history (FOH) and fragile X genetic testing and Family history forms. Pedigrees were curated using Quickped online Pedigree creator (https://magnusdv.shinyapps.io/quickped). Pedigree charts were then downloaded and edited in Adobe Acrobat to attribute predetermined genetic and medical history to family members based on completed forms.

We identified 19 FXS probands for whom had a confirmed FXS diagnosis, along with psychosocial data on four previously identified FXS- associated comorbid psychosocial disorders: sex, autism spectrum disorder (ASD), anxiety disorder, and attention deficit hyperactivity disorder (ADHD). Ranking the psychosocial disorders from the most (Autism) to least (ADHD) discriminating, we assessed the proportion of cases with multiple comorbid psychosocial disorders in relation to FXS diagnosis and sex independently and in combination.
From the 19 identified probands, we collected data on 16 mothers of probands with confirmed FXS diagnosis. Four previously identified psychosocial disorders with high-transmittance risk were identified: anxiety disorder, depressive disorder, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD). Ranking the psychosocial disorders from most (Anxiety) to least (OCD) discriminating, we assessed the proportion of mothers with multiple comorbid psychosocial disorders independently and in combination with each other.

Additional analysis was completed in looking at specific case-study examples of mothers with high trait burden or low trait burden and the current outcome of trait burden on their FXS proband.

Results: Of the 19 FXS probands 26% were female. None of the female probands received a positive ASD diagnosis. Additionally, ADHD was more common in the female population (4/5) than anxiety (2/5). Only 10% of the female probands had 2 diagnoses, whereas 20% of the female probands had at least 1 psychosocial comorbid diagnosis. 5% of the female FXS subjects had no formal diagnosis.
74% of the FXS probands were male. 42% of the male subjects had a positive ASD diagnosis with 26% of that population having one additional psychosocial diagnosis (anxiety or ADHD). Of the ASD positive males, 16% were negative for additional psychosocial disorders (anxiety and ADHD). 32% of the males did not have a diagnosis of

ASD. Of those 32%, 16% had at least one additional psychosocial disorder, whereas 16% had no other comorbid diagnosis.
Out of the 16 identified mothers of FXS probands 25% of them did not have anxiety. Interestingly, the entirety of the 25% also did not have depression. ADHD or OCD. Mothers with positive anxiety (75%) had at least one other diagnosis (depression, ADHD and/ or OCD). Only 6% of mothers positively reported all 4 psychosocial disorders.

Conclusions: Given small samples in the current study and that we did not measure trait burden risk intergenerationally, it is difficult to conclude the effects of inherited psychiatric disorder risk between mothers and children with FXS. Additionally, fathers and grandparents psychiatric disorder risk were not analyzed. Given the associations had no proven statistical significance, self-reported maternal psychiatric disorders could be associated with raising a child with a developmental disability as prior literature suggested (Scherer et al., 2019). Given FXS is also highly associated with anxiety, ADHD, mood instability and aggression it is likely that appropriate assessment of these symptoms in children can be challenging as it is in many subjects with intellectual impairment outside of FXS (Wadell, 2013). This study is limited by small size and lack subject diversity, future studies should include larger and more diverse samples to increase generalizability. Lastly, there needs to be greater focus on the statistical relationship between inherited psychiatric disorder risk across generations. Out of the results of an intergenerational risk ratio study, there needs to be greater focus on the intervention strategies that address anxiety (and other psychiatric disorders) within mothers (and potentially fathers) of children affected by FXS where genetic liability (i.e., premutation) may coalesce.

Figures:

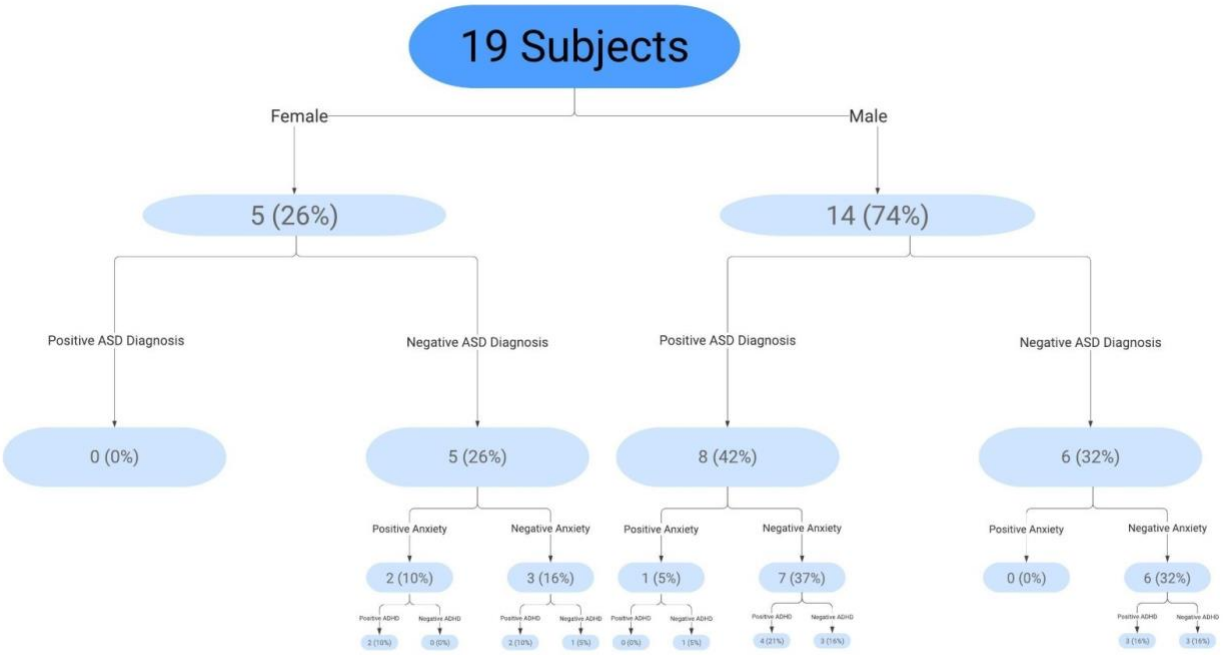

Figure 1: Flowchart of the yield FXS probands diagnosed with four key psychiatric disorders.

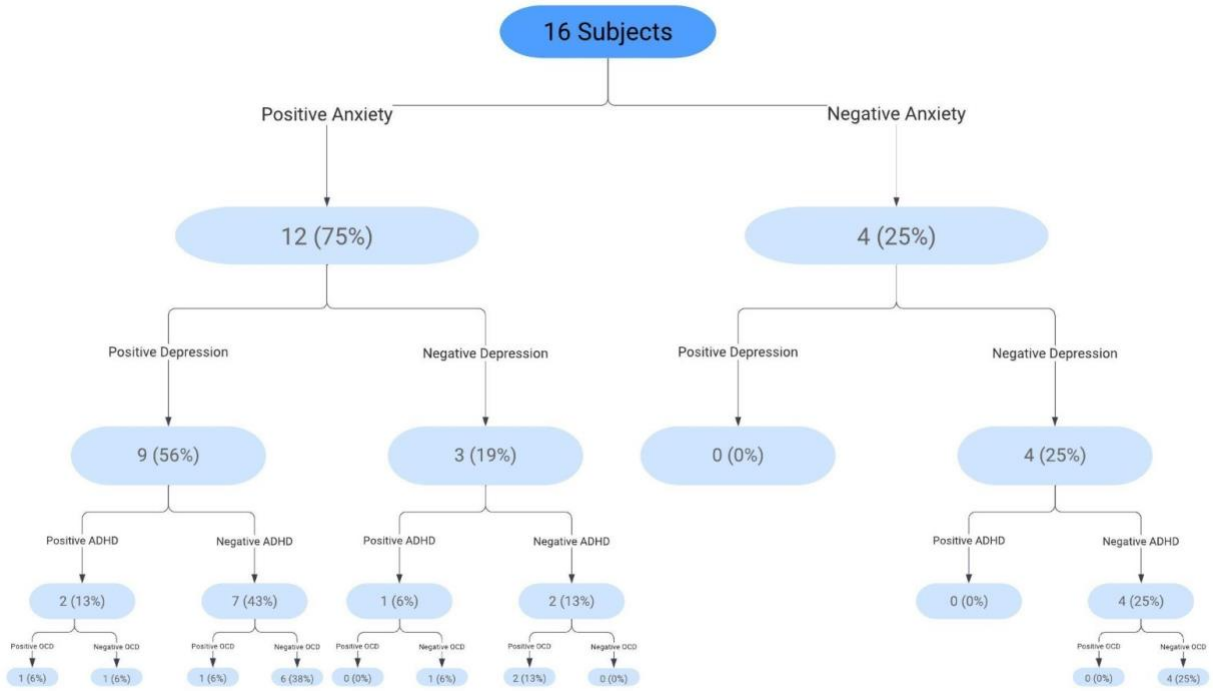

Figure 2: Flowchart of the yield of mothers of children with FXS with diagnosis of 4 key psychiatric disorders.

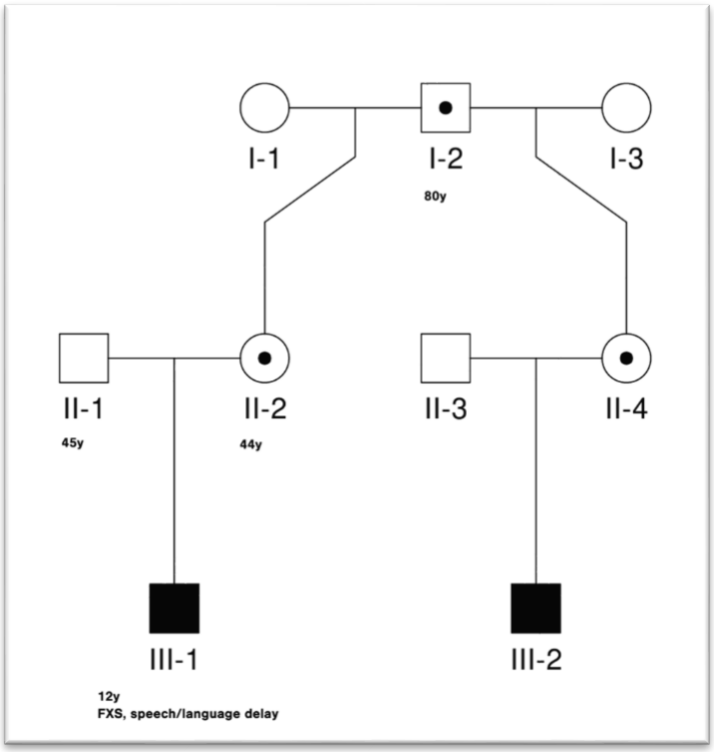

Figure 3: UNC0227 (III-1) family pedigree.

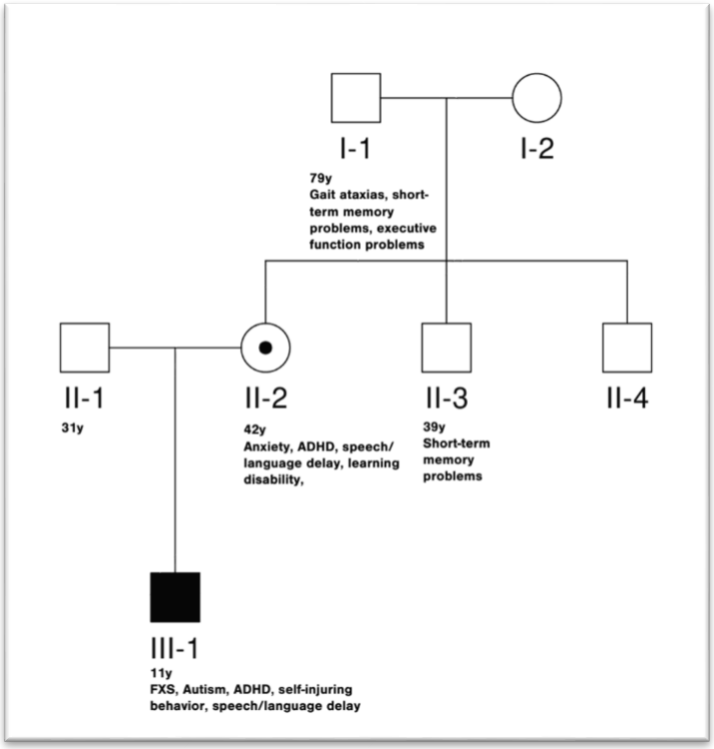

Figure 4: UNC0239 (III-1) family pedigree.

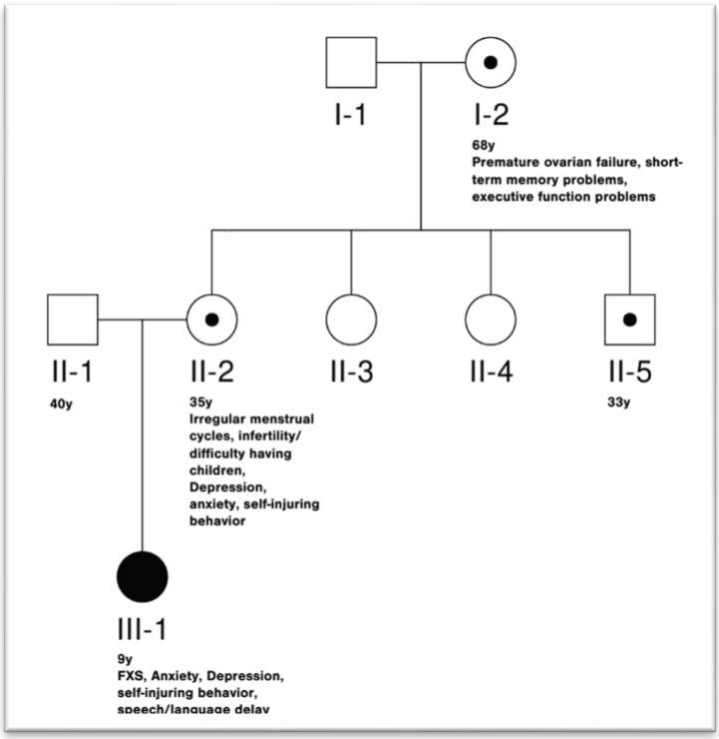

Figure 5: UNC0244 (III-1) family pedigree.

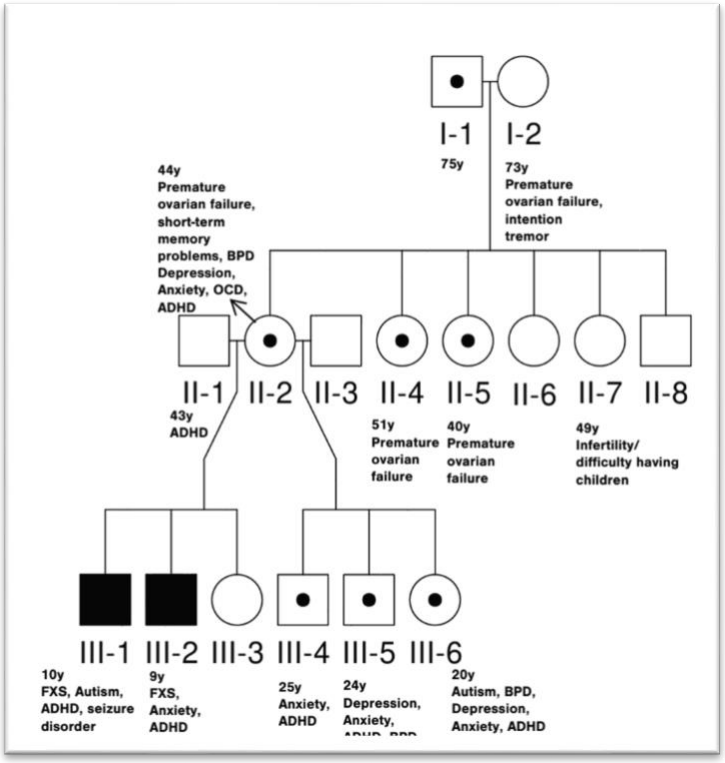

Figure 6: UNC0243 (III-1) family pedigree.

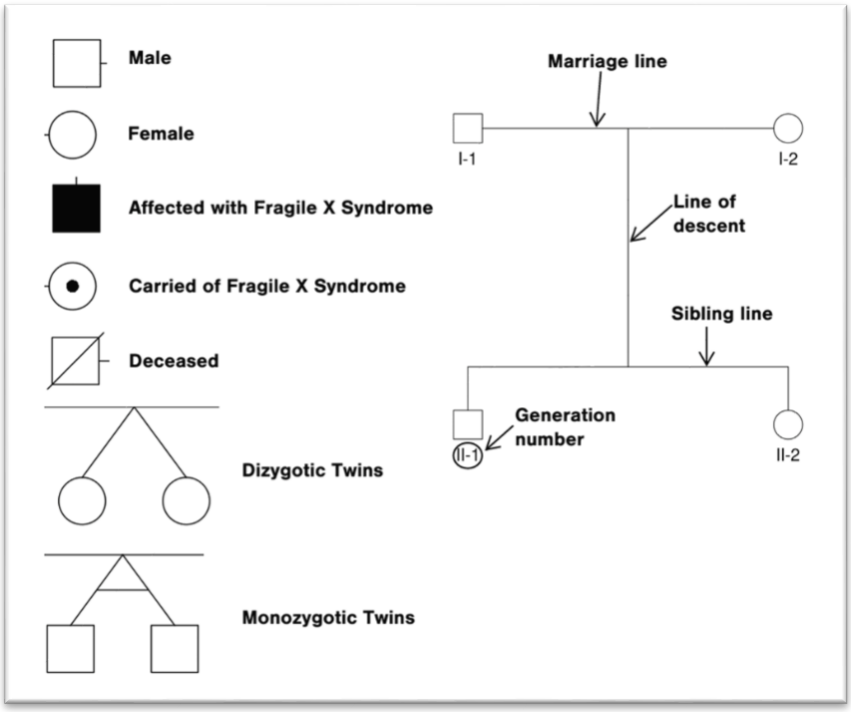

Figure 7: Pedigree Key