Dimensions of Symptom Presentation and Scholarly Representation of Young Females with Fragile X Syndrome

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Abstract

Females with Fragile X Syndrome (FXS), an X-linked neurodevelopmental disorder, receive little representation in scientific literature. This has resulted in inadequate developmental norms. The primary aims of this systematic review are (a) to identify the primary dimensions of symptom presentation for females with FXS and (b) to provide quantitative evidence for their underrepresentation. Twenty-four articles were reviewed for information on symptom presentation, and the sample sizes for males in females in each study were recorded. The main dimensions of symptom presentation were Intellectual Ability (IA), Autistic Features (AF), and Anxiety and Other Comorbidities (AOC). Females with FXS have symptoms of varying severity within these dimensions. The observed representation of males and females was assessed using a chi-square test of independence, with expected values based on widely accepted prevalence estimates. The results revealed significant differences between the observed and the expected values, providing evidence for the underrepresentation of females with FXS. Future studies can test the reliability of the tri-dimensional model of FXS symptomology and use larger samples of females to create accurate developmental norms for this population.

Keywords: Females, Fragile X Syndrome, childhood, symptoms, development

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Fragile X Syndrome (FXS) is an X-linked neurodevelopmental disorder with a known single-gene permutation. The Fragile X Mental Retardation 1 (FMR1) gene contains a series of repeated cytosine-guanine-guanine trinucleotides (Hersh & Saul, 2011; Lee, Martin, Berry-Kravis, & Losh, 2016; Raspa, Wheeler, & Riley, 2017). A typical FMR1 gene has between 6 and 44 of these repeats, but the mutated gene has over 200. This repeat expansion causes methylation, which results in the reduction or absence of the Fragile X Mental Retardation Protein (FMRP), which is necessary for normal brain development (Grigsby, 2016; Hersh & Saul, 2011; Hessl et al., 2009; Lee et al., 2016; Raspa et al., 2017). FXS can severely disrupt functioning during childhood and cause significant distress for parents and caregivers.

Both males and females with FXS can have additional physical and psychiatric symptoms, but these tend to be more discreet in females (Hersh & Saul, 2011). Physical features can include a prominent jawbone, protruding ears, and a long, narrow face (Abrams et al., 2012; Hersh & Saul, 2011). Cognitive functioning is often suboptimal. Males tend to have mild to severe intellectual disability (ID), and females—although better than males—tend to function in the normal-to-borderline region (Hersh & Saul, 2011). Common comorbidities include Autism Spectrum Disorder (ASD), anxiety disorders, Attention-Deficit/Hyperactivity Disorder (ADHD), depression, and communication disorders (Gabis, Baruch, Jokel, & Raz, 2011; Hersh & Saul, 2011; Newman, Leader, Chen, & Mannion, 2015; Raspa et al., 2017). These impairing symptoms often benefit from behavioral therapy and medication; treatment can improve functioning, but, as with other neurodevelopmental disorders, symptoms are unlikely to fully remit.

Although FXS is a relatively rare condition, it profoundly affects FXS carriers by influencing family planning and other life decisions. Recent prevalence estimates suggest that the full FXS mutation is relatively rare, affecting about .014–.027% of males and .009–.014% of females (Grigsby, 2016; Hersh & Saul, 2011). However, the premutation form of the FMR1 gene—characterized by 50–200 trinucleotide repeats—exists in about .3% of males and about .6% of females (Maenner et al., 2013). The premutation is a concern only because of the strong likelihood that it will expand into a full mutation in subsequent generations, especially when the affected FMR1 gene passes from mother to son (Hersh & Saul, 2011). Although rare, an FXS diagnosis holds serious implications for individuals and families because, in some cases, a single diagnosis could mean that an entire family (including grandparents, aunts, uncles, and cousins) should consider genetic testing and genetic counseling when planning to have children.

Although FXS has received moderate attention in the scholarly literature, the possible sex differences in symptom presentation remain somewhat unclear. The consensus is that females typically function better than males. However, females are often underrepresented in FXS research studies (Hatton et al., 2009). According to the prevalence rates provided by Grigsby (2016) of .014% for males and .009% for females, females should constitute approximately 38.89% of FXS research participants. However, it is possible that a combination of selection bias (e.g., selecting participants from male-dominated groups) and under-detection may result in female underrepresentation in these studies. This is problematic because a small sample of females can reduce statistical power and increase Type II error rates, which can obscure sex differences in symptom presentation; this is also problematic because it could result in a conceptualization of FXS based primarily on the male phenotype, which could cause some females with FXS to remain undiagnosed. The primary aims of this literature review were (a) to

identify potential dimensions of symptom presentation (i.e., ID, ASD, and Anxiety) for females with FXS based on the existing literature and (b) to demonstrate the underrepresentation of females with FXS in research studies as a critical methodological flaw that challenges the validity of the existing research.

Method

Articles were selected and reviewed using a systematic methodology described by Postăvaru and Cramer (2016) in the *Sage Research Methods* database. This method was used to reduce researcher bias. In accordance with this methodology, the aims, objectives, search terms, and inclusion criteria were established before the article search and remained unaltered during the search process. The primary database used in this study was the American Psychological Association database *PsychINFO*, which deals primarily with psychological and brain sciences. Only one database was used so that the project would be more manageable for a single researcher working toward a strict deadline. The main search terms were *Fragile X*, *development*, *female OR girl*, and *childhood*. Articles that dealt exclusively with populations other than female children (ages 0 – 12) with FXS were excluded. This age group was selected to differentiate between symptoms presentations in childhood and adolescence. Differences in male and female representation were measured using the number of males and females in each sample as an estimate. I expected that females with FXS would constitute 38.89% of research participants. After these articles were reviewed, all the information relevant to the populations in question, including the samples sizes employed in each study, were included in a formal write-up.

The initial search results yielded 76 articles. After limiting the results to peer reviewed sources that dealt with childhood (ages 0 – 12), as defined by the database, 61 articles remained. After a systematic review of these articles, an additional 38 articles were excluded either because

they were inaccessible during the imposed timeframe for data collection (n = 3; including one untranslated article) or because they examined populations other than female children with FXS (n = 35), including articles that examined only males or adults. Twenty-three articles were included in the final write-up.

Results

As a previous review has demonstrated (i.e., Hersh & Saul, 2011), females with FXS exhibited a more diverse symptom presentation than males and had varying levels of impairment. In general, their symptoms could be categorized based on the disorders in which they most often occur: ID, ASD, and Anxiety. These dimensions formed the basis of a tri-dimensional model of symptom presentation in females with FXS. Symptoms of these disorders frequently co-occur, so significant overlap may exist among these dimensions. However, the degree of overlap is unclear. The environmental and biological factors that frequently attend individuals with FXS may combine to create these three dimensions, or the symptoms themselves may combine to produce other symptoms. As Cervantes and Matson (2015) demonstrated, individuals with comorbid ID and ASD possess an increased risk for developing anxiety. Although some females with FXS show little or no impairment in these areas (e.g., Hessl et al., 2009), those who do show impairment tend to have symptoms that fit within these dimensions. Additional research is needed to determine how these dimensions interact in individuals with FXS. A visual representation of this model can be found in Figure A1. It is worth noting, however, that many of these researcher articles had small samples of females with FXS.

Intellectual Disability Dimension

ID is a neurodevelopmental disorder characterized by deficits in intellectual and adaptive functioning, as measured by standardized testing and clinical judgement (American Psychiatric

Association [APA], 2013; Ditterline, Oakland, & McGoldrick, 2016). ID affects about 1–1.5% of individuals in the United States and is more common in males (Friedman, Gibson Parrish, & Fox, 2018). Hessl et al. (2009) demonstrated that about 27.2% of females with FXS qualify for mild (16.3%), moderate (8.7%), or severe (2.2%) ID when tested using gold standard measures of intellectual and adaptive functioning. An additional 21.7% fall in the borderline region. In that same study, which had a sample of 83 females with FXS, not one female qualified for a diagnosis of profound ID, while about 2.2% of males met those criteria (Hessl et al., 2009). Differences in FMRP levels likely explain the differences in ID prevalence between males and females with FXS. Some studies have demonstrated that decreased FMRP levels are associated with deficits in intellectual functioning, and decreased intellectual functioning is associated with deficits in adaptive functioning (Ditterline et al., 2016; Hahn, Brady, Warren, & Fleming, 2015; Hall, Burns, Lightbody, & Reiss, 2008; Hessl et al., 2009). In other words, decreased FMRP leads to deficits in intellectual and adaptive functioning.

Reduced FMRP and Intellectual Functioning. The methylation and subsequent silencing of the FMR1 gene can result in the reduction of FMRP in females with FXS, which can lead to abnormal brain development (Hall et al., 2008; Lee et al., 2016). Unlike males with the full FXS mutation, whose silenced FMR1 gene can cause the complete absence of FMRP, females with at least one viable copy of the FMR1 gene can have FMRP levels that approach normalcy (Hall et al., 2008; Kover, Pierpont, Kim, Brown, & Abbeduto, 2013). In individuals without the FXS mutation, about 90–100% of their cells produce FMRP, which can be measured using a blood test, but in females with FXS, these estimates are reduced to about 48–53%, which approximates the expected frequency of 50% (Hall et al., 2008; Kover et al., 2013). Biological sex serves as a protective factor for females with FXS because having a second X chromosome increases the

probability of having a viable FMR1 gene that can partially compensate for the mutation, allowing them to have higher FMRP levels than males with FXS, who have only one copy of the FMR1 gene.

Reduced FMRP levels seem to result in cognitive deficits in males and females with FXS. Although the exact function of FMRP remains a mystery, research suggests that aside from playing a role in normal brain development, FMRP may help regulate a metabotropic glutamate receptor commonly found in the dendrites of certain neurons (Halls et al., 2008; Hersh & Saul, 2011; Lee et al., 2016). A moderate positive correlation seems to exist between FMRP levels and intellectual functioning (Hall et al, 2008; Hessl et al., 2009). Additionally, Kover et al. (2013) found a positive association between FMRP levels and verbal ability, working memory, fluid reasoning, and overall intelligence in children and adolescents with FXS. Both male and female children with FXS tend to score lower on standardized IQ tests compared to the normally developing children with which the tests were normed (Hall et al., 2008; Hessl et al., 2008). However, it is worth noting that in one study that compared females with FXS to a group of females with other developmental disorders, females with FXS scored significantly higher on standardized IQ tests (Ballinger, Cordeiro, Chavez, Hagerman, & Hessl, 2014); this suggests that although reduced FMRP causes females with FXS to score lower than normally developing individuals, their cognitive functioning is still better than that of females with other developmental disabilities.

Intellectual Functioning and Adaptive Functioning. FMRP levels may influence adaptive functioning directly, but deficits in intellectual functioning may mediate this relationship. Adaptive functioning refers to the range of abilities that are required for daily living, specifically within the domains of conceptual, social, and practical skills (Ditterline et al.,

2016). One of the gold standard measures for adaptive behavior is the Vineland Adaptive Behavior scale, which has a standardized Adaptive Behavior Composite mean of 100 (*SD* = 15) and four subscales: communication, daily living skills, socialization, and motor skills (Ditterline et al., 2016; Roberts, Weisenfeld, Hatton, Heath, & Kaufmann, 2007). On average, females with FXS score an average of 76 on this measure, demonstrating that many experience deficits in adaptive functioning (Roberts et al., 2007). FMRP levels may indirectly influence adaptive functioning by affecting intellectual ability, which subsequently influences adaptive ability (Hessl et al., 2009). This is understandable, considering that females with FXS tend to show better adaptive functioning than their male counterparts who have reduced FMRP levels (Roberts et al., 2007). Other factors that influence adaptive functioning include the several domains of developmental age: gross and fine motor ability, expressive and receptive language, and visual reception (Rogers, Hepburn, & Wehner, 2003). These findings demonstrate that FMRP levels account, both directly and indirectly, for deficits in adaptive functioning in females with FXS.

Both males and females with FXS can experience declines in adaptive functioning between childhood and adolescence, which Hahn et al. (2015) describe as a slower growth rate than same-age peers. For females with FXS, communication—one of the Vineland subscales—was a notable area of decline (Klaiman et al., 2014). However, these declines are not inevitable. Hahn et al. (2015) has demonstrated three possible developmental trajectories for adaptive functioning in children with FXS: (a) steady declines, (b) steady increases followed by declines or plateaus, or (c) steady increases. Together, deficits in intellectual and adaptive functioning can cause enough impairment to warrant an ID diagnosis.

Autism Spectrum Dimension

Unlike the ID dimension of FXS symptomology, the ASD dimension is somewhat more

difficult to conceptualize, partially because the criteria for ASD are especially diverse. ASD is a neurodevelopmental disorder characterized by fixed interests, repetitive behaviors, and differences in social functioning (Xiao et al., 2014). In children with ASD, a few associated characteristics include avoidance of eye contact, atypical use of gestures, difficulties making friends, hypersensitivity to stimuli, or insistence on routines (APA, 2013). Prevalence estimates for ASD are around 1.47% for the general population, but that rate is significantly increased in children with FXS (Niu et al., 2017). Only about 22.6% of females with FXS meet full diagnostic criteria for ASD, but almost all exhibit at least one autistic behavior (Clifford et al., 2007; Lee et al., 2016; Niu et al., 2017). The literature demonstrated that females with FXS often exhibit deficits in social abilities—specifically with joint engagement, communication, and various challenging behaviors that are associated with ASD.

Social Deficits. Supported and coordinated joint engagement between child and caregiver are necessary social interactions that aid in the development of language, and they are particularly important in females with FXS, who tend to show language deficits from a very young age (Finestack, Sterling, & Abbeduto, 2013; Hahn et al., 2016; Hahn, Zimmer, Brady, Romine, & Fleming, 2014). Supported joint engagement refers to preliminary social interactions in which both the child and the caregiver interact with an object (e.g., a xylophone or music box), but the child does not acknowledge the caregiver's participation or input (Hahn et al., 2016). Over time, supported joint engagement evolves into coordinated joint engagement, in which the child acknowledges the caregiver's participation and input; the child might look at the caregiver and gesture for him or her to interact with the object (Hahn et al., 2016). By the time they are six months old, typical infants can engage in regular periods of supported joint engagement with brief intervals of coordinated joint engagement (Hahn et al., 2016). By about

13 months, coordinated joint engagement becomes the norm (Hahn et al., 2016). Children with FXS, including females, have difficulty establishing regular patterns of coordinated joint attention and continue to exhibit predominately supported joint engagement in the toddler period (Hahn et al., 2016). Similar deficits appear in toddlers with ASD, in whom low levels of overall joint engagement are associated with deficits in social communication (Adamson, Bakeman, Suma, & Robins, 2017; Gillespie-Lynch et al., 2012). Similarly, decreased levels of coordinated joint attention are associated with language delays in female toddlers with FXS Hahn et al. 2016; Hahn, Brady, Fleming, & Warren, 2016). Beginning in this stage, females with FXS follow a trajectory that differs from the norm.

In general, language delays and social problems are positively associated with ASD symptomology, especially within the domain of social communication (Roberts et al., 2007). One study that compared females with FXS to their sisters without the mutation revealed that females with FXS had higher levels of social problems and were more withdrawn (Mazzocco, Baumgardner, Freund, & Reiss, 1998). Aside from joint engagement abnormalities, children with FXS demonstrate irregularities with eye contact. Compared to typically developing children, children with FXS spend less time looking others in the eye, which is one of the hallmark features of ASD (APA, 2013; Farzin, Scaggs, Hervey, Berry-Kravis, & Hessl, 2011; Roberts et al., 2007; Senju & Johnson, 2009). Abnormal eye contact patterns in FXS are associated with increased autistic behaviors (Roberts et al., 2007). Females with FXS can display a wide variety of social problems related to ASD symptomology. As is the case with ID, the symptom severity within the ASD dimension exists on a spectrum.

Repetitive Behaviors and Other Concerns. Although children with FXS can exhibit a variety of repetitive movements, the present literature review did not reveal many examples of

such. Aside from deficits in adaptive functioning and social skills, ASD symptoms are associated with an increased prevalence of self-injurious behaviors, repetitive movements, and ADHD (Hatton et al., 2009; Newman et al., 2015; Roberts et al., 2007; Langthorne & McGill, 2012). Baranek et al. (2005) found that about 80% of children with FXS engage in leg stereotypies (i.e., repetitive leg movements), which is another characteristic of ASD. Langthorne and McGill (2012) found that when children with FXS engage in self-injurious behaviors, about 40% do so as a means of social escape (i.e., to avoid undesirable social situations). They may also present with motor or vocal tics (Gabis et al., 2011). Repetitive behaviors may help perpetuate social problems in children with FXS because abnormal actions or interests may lead to ostracism, but additional research is needed to test this possibility. Females with FXS can exhibit many symptoms that are similar to those found in ASD that may cause similar impairment.

Anxiety and Other Comorbidities Dimension

In addition to ID and ASD, females with FXS often receive a diagnosis of other disorders, such as ADHD, depression, enuresis, encopresis, or anxiety (Gabis et al., 2011). Compared to males, females with FXS are at greater risk of having both ADHD and depression (Newman et al., 2015). Anxiety disorders are characterized by excessive worry about *future* events that causes significant impairment (APA, 2013). Anxiety disorders do not have uniform etiologies and prevalence estimates; some are more heritable than others (APA, 2013). About 50% of children with FXS have a specific phobia, and about 31% have social anxiety (Gabis et al., 2011). In the general population, these disorders both have prevalence estimates of about 7% (APA, 2013). Social anxiety is associated with neurobiological factors, such as an increased behavioral inhibition response, while specific phobias are more associated with environmental factors (APA, 2013). This dimension of symptom presentation is a little more difficult to define.

Anxiety occurs frequently in females with FXS. Although not as debilitating as the ID and ASD symptoms, the *Anxiety and Other Comorbidities* symptoms cause significant impairment to females with FXS.

It is likely that the Anxiety and Other Comorbidities dimension, like the ID or ASD dimensions, results from a combination of biological and environmental factors. Some research has demonstrated that individuals with FXS or other developmental disabilities exhibit a reduced amygdala response toward fearful faces compared to typically developing individuals (Ballinger et al., 2014). This reduction may be associated with the increased risk for anxiety (Ballinger et al., 2014). Although this seems counterintuitive, Ballinger et al. (2014) argued that similar findings in twin studies demonstrated that *decreased* amygdala activity is associated with an increased risk for an anxiety disorder of genetic origin while *increased* amygdala activity is associated with an increased risk for an anxiety disorder of environmental origin. These findings may suggest that a relationship exists between FMRP levels and amygdala functioning, but additional research is necessary.

Overall Representation of Females

As Hatton et al. (2009) has noted, females with FXS are generally underrepresented in studies that examine children with FXS, and this literature review confirms that statement. Two articles contained only female participants (n = 8; n = 15), and two articles contained duplicate samples. After these were excluded, 19 articles remained, and their samples were included in the final analysis. Using the population estimates for FXS described by Grigsby (2016) of .014% for males and .009% for females, it was estimated that of the 1401 participants included in these journal articles, 856.15 (61.11%) would be male and 544.85 (38.89%) would be female. The actual values were 906 (68.33%) and 420 (31.67%), respectively. The representation of females

was 20.16% lower than expected. A chi-square analysis was calculated to test the fit between the expected and the observed values. The results revealed significant differences in the representation of males and females compared to the population estimates, $X^2(1) = 36.24$, $p < .001$. The differences are unlikely due to chance. Despite this significance, the phi coefficient demonstrated a relatively small effect, $\varphi = .16$. The median number of males and females in each study were 35 and 11, respectively, which also demonstrated that females with FXS tend to be underrepresented in research studies.

The underrepresentation of females in these studies, although relatively small, is potentially problematic because of the methodological flaws that accompany small sample sizes. Over half of the articles used in this study had fewer than 12 females (see Table A1). Aside from yielding poor external validity, small sample sizes can decrease statistical power and increase Type II error rates (Bradley & Brand, 2013). This is especially problematic when studying the differences between two populations because small sample sizes can make true differences difficult to detect. This may have been the case with Farzin et al. (2011), who found no significant differences between males ($n = 12$) and females ($n = 3$) in the amount of time spent looking others in the eyes. Although the literature suggests that males and females with FXS are different, the extent of those differences is somewhat unclear, which could lead to ineffective intervention strategies.

Discussion

The primary aims of this study were to identify the most common symptom presentations that cause developmental delays in young females with FXS and to demonstrate the underrepresentation of females with FXS in the scientific literature. In a sense, these two aims were mutually exclusive because demonstrating that females are indeed underrepresented would

inevitably limit the generalizability of any findings on symptom presentations. The existing literature demonstrates that females *have symptoms*, and these findings demonstrate a need to clarify the *extent of those symptoms*.

The present review provides evidence for a tri-dimensional model of symptom presentation, with affected individuals exhibiting different levels of severity (i.e., from severely impaired to normal) within each dimension. As shown in Figure 1, the three dimensions for symptom presentation are Intellectual Ability, Autistic Features, and Anxiety and Other Comorbidities. These names were selected because some of the most impairing symptoms in FXS are related to these three types of disorders. Considering that these symptom sets frequently co-occur in other psychiatric disorders (see APA 2013), significant overlap may exist among these dimensions, but additional research is needed to determine the extent of this overlap.

Within the Intellectual Ability dimension, females with FXS can range from severe ID to normal intellectual functioning, with average standardized IQ and adaptive behavior scores in the borderline region (Roberts et al., 2007). A significant proportion meet criteria for mild to severe ID (Hessl et al., 2009). Within the Autistic Features dimension, females with FXS can exhibit varying degrees of social problems, repetitive movement, and fixed interests (Baranek et al., 2005; Clifford et al., 2007; Klaiman et al., 2014). However, only about one in five receive an ASD diagnosis (Clifford et al., 2007). Within the Anxiety and Other Comorbidities dimension, females can display a range of anxious symptoms or other comorbidities such as depression and ADHD (Gabis et al., 2011; Newman et al., 2015). Further research is needed to establish the exact parameters and norms for these domains. This model could be useful because it emphasizes the symptoms that cause the most impairment in children with FXS, which are often what concern caregivers the most (Cross et al., 2016). In other words, this model honors the lived

experiences of the individuals who bear the financial and psychological burden of caring for children with FXS.

Aside from summarizing the common symptom presentations in females with FXS, the present review provided evidence of the underrepresentation of females with FXS in the scientific literature. The chi-square goodness of fit test demonstrated that fewer females with FXS than expected were included in these empirical studies—a difference that cannot likely be attributed to chance. Half of the articles in this study had fewer than 12 females, and these small samples may have resulted in decreased statistical power and increased Type II error rates, potentially masking the differences between males and females, but additional research on these sample sizes is necessary. Those studies that used larger sample sizes, and even some of those that used smaller sample sizes, revealed that significant differences existed between males and females, but further investigation into the extent of those differences is recommended. It is possible that current interventions for females with FXS are based on the symptom presentation that is most common in males.

Future empirical studies and metanalyses could use larger samples of both males and females to establish representative norms for both sexes. This would allow for more accurate comorbidity estimates and for tailored interventions that best address the problems faced by males and females with FXS. The tri-dimensional model of symptom presentation in females with FXS could be expanded to include both sexes, and standardized measure could be developed to quantify symptom severity in each. Because the present review examined only the early developmental period, it is possible that females are only underrepresented in this age group. Additional reviews and metanalyses that examine the representation of females with FXS in the scientific literature could use a larger sample of articles with multiple search terms to

achieve a more representative sample.

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Appendix

Table A1

Articles included in this study with their respective sample sizes.

Lee, M., Martin, G. E., Berry-Kravis, E., & Losh, M. (2016). A developmental, longitudinal investigation of autism phenotypic profiles in fragile X syndrome. *Journal of Neurodevelopmental Disorders*, 8doi:10.1186/s11689-016-9179-0	31	34	Hall S, Burns D, Lightbody A, Reiss A. Longitudinal changes in intellectual development in children with fragile X syndrome. *Journal Of Abnormal Child Psychology* [serial online]. August 2008;36(6):927-939. Available from: PsycINFO, Ipswich, MA. Accessed May 15, 2018.	90	55
Hahn, L. J., Zimmer, B. J., Brady, N. C., Romine, R. S., & Fleming, K. K. (2014). Role of maternal gesture use in speech use by children with fragile X syndrome. *American Journal of Speech-Language Pathology, 23*(2), 146-159. doi:10.1044/2013_AJSLP-13-0046	23	4	Ballinger, E. C., Cordeiro, L., Chavez, A. D., Hagerman, R. J., & Hessl, D. (2014). Emotion potentiated startle in fragile X syndrome. *Journal of Autism and Developmental Disorders, 44*(10), 2536-2546. doi:10.1007/s10803-014-2125-7	67	43
Hahn, L. J., Brady, N. C., Warren, S. F., & Fleming, K. K. (2015). Do children with fragile X syndrome show declines or plateaus in adaptive behavior? *American Journal on Intellectual and Developmental Disabilities, 120*(5), 412-432. doi:10.1352/1944-7558-120.5.412	44	11	Langthorne, P., & McGill, P. (2012). An indirect examination of the function of problem behavior associated with fragile X syndrome and Smith-Magenis syndrome. *Journal of Autism and Developmental Disorders, 42*(2), 201-209. doi:10.1007/s10803-011-1229-6	31	3
Klaiman, C., Quintin, E., Jo, B., Lightbody, A. A., Hazlett, H. C., Piven, J., & ... Reiss, A. L. (2014). Longitudinal profiles of adaptive behavior in fragile X syndrome. *Pediatrics, 134*(2), 315-324. doi:10.1542/peds.2013-3990	186	89	Baranek, G. T., Danko, C. D., Skinner, M. L., Bailey, D. J., Hatton, D. D., Roberts, J. E., & Mirrett, P. L. (2005). Video Analysis of Sensory-Motor Features in Infants with Fragile X Syndrome at 9-12 Months of Age. *Journal of Autism and Developmental Disorders, 35*(5), 645-656. doi:10.1007/s10803-005-0008-7	10	1
Sterling, A. M., Warren, S. F., Brady, N., & Fleming, K. (2013). Influences on maternal responsivity in mothers of children with fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities, 118*(4), 310-326. doi:10.1352/1944-7558-188.4.310	44	11	Farzin, F., Scaggs, F., Hervey, C., Berry-Kravis, E., & Hessl, D. (2011). Reliability of eye tracking and pupillometry measures in individuals with fragile X syndrome. *Journal of Autism and Developmental Disorders, 41*(11), 1515-1522. doi:10.1007/s10803-011-1176-2	12	3

Table A1 (cont.)

Greenberg, J., Seltzer, M., Baker, J., Smith, L., Warren, S. F., Brady, N., & Hong, J. (2012). Family environment and behavior problems in children, adolescents, and adults with fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities, 117*(4), 331-346. doi:10.1352/1944-7558-117.4.331	40	8	Gabis, L. V., Baruch, Y. K., Jokel, A., & Raz, R. (2011). Psychiatric and autistic comorbidity in fragile X syndrome across ages. *Journal of Child Neurology, 26*(8), 940-948. doi:10.1177/0883073810395937	23	5
Hessl, D., Nguyen, D. V., Green, C., Chavez, A., Tassone, F., Hagerman, R. J., & ... Hall, S. (2009). A solution to limitations of cognitive testing in children with intellectual disabilities: The case of fragile X syndrome. *Journal of Neurodevelopmental Disorders, 1*(1), 33-45. doi:10.1007/s11689-008-9001-8	134	83	Clifford, S., Dissanayake, C., Bui, Q. M., Huggins, R., Taylor, A. K., & Loesch, D. Z. (2007). Autism spectrum phenotype in males and females with fragile X full mutation and premutation. *Journal of Autism and Developmental Disorders, 37*(4), 738-747. doi:10.1007/s10803-006-0205-z	33	31
Kover, S. T., Pierpont, E. I., Kim, J., Brown, W. T., & Abbeduto, L. (2013). A neurodevelopmental perspective on the acquisition of nonverbal cognitive skills in adolescents with fragile X syndrome. *Developmental Neuropsychology, 38*(7), 445-460. doi:10.1080/87565641.2013.820305	37	16	Roberts, J. E., Weisenfeld, L. H., Hatton, D. D., Heath, M., & Kaufmann, W. E. (2007). Social approach and autistic behavior in children with fragile X syndrome. *Journal of Autism and Developmental Disorders, 37*(9), 1748-1760. doi:10.1007/s10803-006-0305-9	92	20
Finestack, L. H., Sterling, A. M., & Abbeduto, L. (2013). Discriminating Down Syndrome and Fragile X Syndrome based on language ability. *Journal of Child Language, 40*(1), 244-265. doi:10.1017/S0305000912000207	18	4			

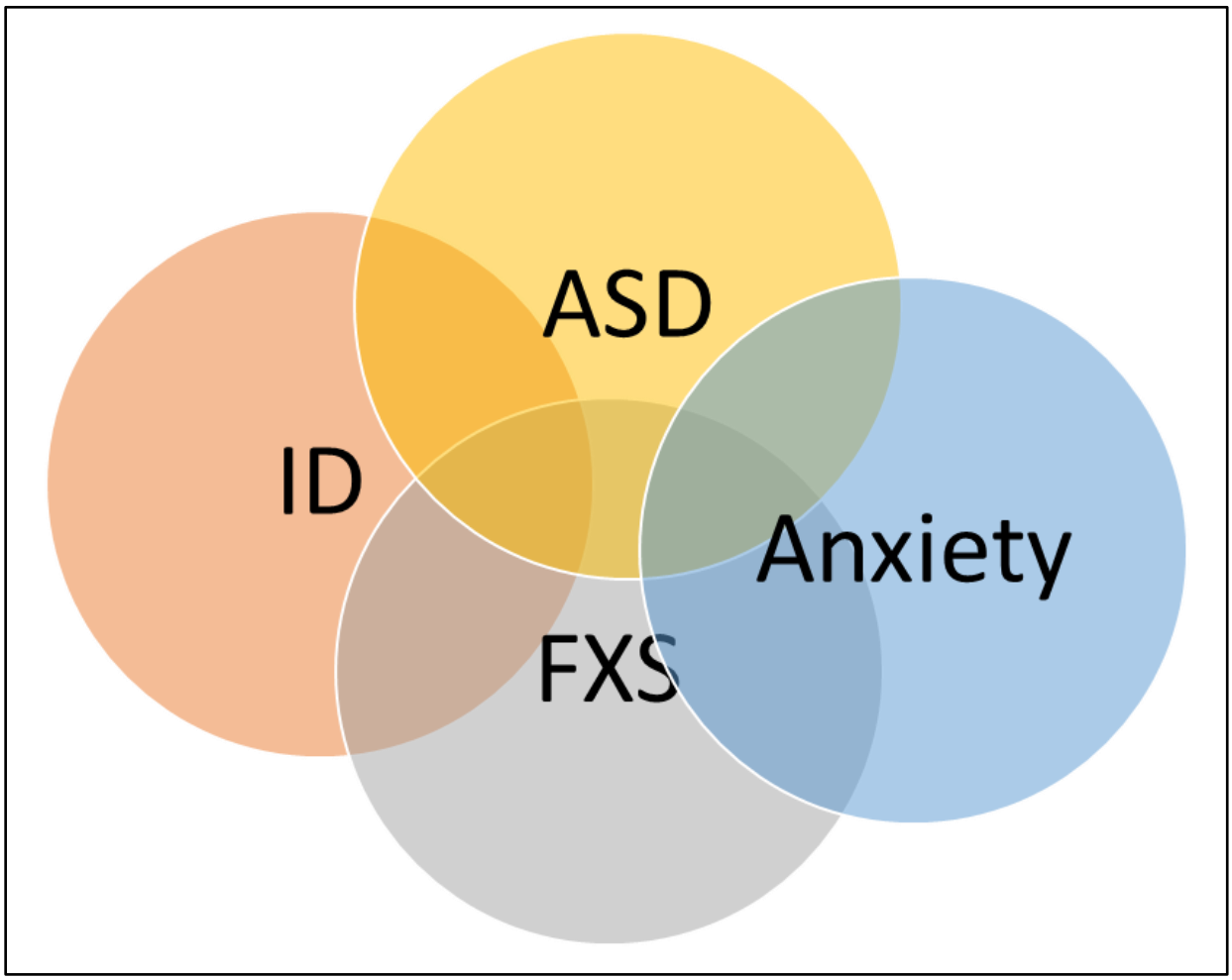

Figure A1. Dimensions of symptoms most frequently in females with Fragile X Syndrome (FXS). About 27% have Intellectual Disability (ID; Hessl et al., 2009), 22% have Autism Spectrum Disorder (ASD; Clifford et al., 2007), and about 50% have a specific phobia (Gabis et al., 2011).