Research Gaps in Fragile X Syndrome: An Updated Literature Review to Inform Clinical and Public Health Practice

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Abstract

Objective—The phenotypic impact of fragile X syndrome (FXS) has been well-documented since the discovery of the *FMR1* gene 30 years ago. However, gaps remain in clinical and public health research. The purpose of this literature review was to determine the extent to which these gaps have been addressed and identify targeted areas of future research.

Methods—We conducted an electronic search of several scientific databases using a variety of key words. The search focused on five areas identified as research gaps by an earlier review: (1) diagnosis, (2) phenotypic presentation, (3) familial impact, (4) interventions and treatments, and (5) lifespan perspectives. Inclusion criteria included publication between 2014 and 2020, focus on human subjects, and publication in English. A total of 480 articles were identified, 365 were reviewed, and 112 are summarized in this review.

Results—Results are organized into the following categories: (1) FXS phenotype and subtypes (FXS subtypes, medical profile, cognitive/developmental profile, social and behavioral profile); (2) Needs of adults; (3) Public health needs (clinical diagnosis and newborn screening, healthcare needs and access); (4) Treatment (treatment priorities, pharmacological treatments, behavioral and educational interventions); (5) Families (economic burden, mother-child relationship).

Conclusion—Despite the progress in many areas of FXS research, work remains to address gaps in clinical and public health knowledge. We pose three main areas of focused research, including early detection and diagnosis, determinants of health, and development and implementation of targeted interventions.

Keywords

Fragile X syndrome; clinical phenotype; public health needs; treatment; family needs

INTRODUCTION

Fragile X syndrome (FXS) is the leading known single-gene cause of intellectual and developmental disabilities. Expansions of trinucleotide repeats (CGG) on the 5'untranslated

region of the fragile X messenger ribonucleoprotein 1 gene (*FMR1*) gene, located on the X chromosome, impact the production of fragile X messenger ribonucleoprotein (FMRP) which is crucial for brain development. Individuals with more than 200 CGG repeats have the full mutation, or FXS, whereas those with 55 to 200 repeats are carriers of FXS, also referred to as having the *FMR1* premutation. Typically, males are more severely affected given the protective factor of a second X chromosome in females.

The phenotypic impact of FXS has been well-documented since the discovery of the *FMR1* gene 30 years ago, including our own public health literature review which summarized research between 1991 and 2014[1]. The goal of the previous review was to identify what was known about FXS in the areas of development, social-emotional well-being, medical needs, treatment options, and the impact on the family. Five gaps were identified as areas in need of further research: (1) identification of FXS subtypes; (2) needs of adults with FXS; (3) public health needs, such as access to health care services; (4) efficacy of educational, behavioral, and pharmacological treatments; and (5) impact on families of individuals with FXS.

The purpose of this updated literature review is to examine the progress made in addressing these gaps and to summarize recent research. These updated findings can be used to inform both future research initiatives and clinical and behavioral health services for individuals with FXS and their families.

METHODS

A list of search terms can be found in Table 1. We limited our search to articles published since our earlier review (2014-2021) with samples of human subjects. Language was limited to English. The following databases were searched: PubMed, CINAHL, EBSCOhost, PsycINFO, and Web of Science.

Articles were reviewed using Covidence[2], a systematic review management program designed to organize complex literature reviews. Results were uploaded into Covidence and screened by the study team to remove articles that were not applicable (e.g., animal models, individuals with *FMR1* premutation) or were covered in the previous literature review. The remaining studies were double coded for inclusion based on relevance. Any discrepancies between reviewers were discussed and resolved. A total of 112 articles were included in the current review. Figure 1 depicts the PRISMA[3] flow diagram for this review.

RESULTS

Results from the systemic review are organized based on the research gaps identified in the previous literature review.

FXS Phenotype and Subtypes

Medical Profile.—Classic clinical features of FXS include an elongated face, broad forehead, prominent ears, and flat feet. Hyper flexibility of joints and connective tissue problems are also common. New evidence suggests that as adults, individuals with FXS may be at increased risk for a number of other medical problems, such as obesity,

hypertension, and gastrointestinal disorders. Additionally, seizures are a common co-morbid feature. Females with FXS have a less severe presentation given the presence of a second unaffected X-chromosome.[4] A review of neuroanatomical studies of individuals with FXS have shown dendritic spine abnormalities and changes in brain structure and EEG studies show alterations in gamma waves which correlate with clinical symptomology.[5]

Cognitive/Developmental Profile.—Our earlier paper[1] provides a detailed overview of the cognitive development of individuals with FXS. A recent review furthers this work by summarizing what is known about executive function in FXS.[6] Verbal and non-verbal working memory is impaired in individuals with FXS across the lifespan, although performance on tasks was dependent on cognitive load. Challenges with inhibitory control, cognitive flexibility, and processing speed emerge early in childhood and persist into adulthood. Attention is one of the core deficits in FXS, with impairments in both auditory and visual sustained attention when compared with chronologically age-matched and mental age-matched peers. In a study of infants with FXS, delays in overall development were seen as early as 6 months when compared with typically developing peers.[7]

Language development in FXS is well studied. Recent work adds to the knowledge base in receptive, expressive, and pragmatic development. Children with FXS show signs of receptive and expressive language delays as early as 12 months.[8] Early use of consonants during babbling and intentional communication, including the use of gestures, is predictive of later expressive language.[9] By the time of preschool, though, children with FXS have the ability to repair a breakdown in communication (e.g., when there is a miscommunication with a conversational partner), indicating well-developed language and social skills. In addition, maternal language plays a role in language development. Maternal commenting is associated with receptive but not expressive vocabulary from early childhood into adolescence.[10] Maternal pragmatic language is associated with receptive and expressive vocabulary in adolescents and young adults.[11] Although receptive language ability is lower in children and adolescents with FXS than those who are typically developing, it is a relative strength when compared with ability levels of those with autism spectrum disorder (ASD) or Down syndrome.[12,13]

Children with FXS continue to make improvements in their functional skills into middle childhood, at which point cognitive development begins to slow. However, those with lower nonverbal developmental scores or more ASD symptoms had different growth patterns and less overall skill attainment when examining raw scores.[14] Over time, males with higher adaptive behavior age-equivalent scores in early childhood had fewer aberrant behaviors at age 10.[15] When compared with typically developing children, those with FXS show plateaus or declines in their adaptive behavior over time suggesting that those with FXS overall have a lower rate of skill attainment.[16] Cross-sectional studies have found similar patterns when comparing young children with FXS to their same-aged peers.[17] Another study, though, showed adaptive skills, in particular standard scores for communication and social ability, improved over time.[18]

Social and Behavioral Profile.—In a recent review of behavioral concerns, prevalence estimates across studies for individuals with FXS were 48.8% for self-injury, 35.8% for

aggression, and 24.5% for destruction, with males significantly more likely than females to engage in any type of challenging behavior.[19] When compared with males with mixed-etiology intellectual disability, males with FXS had higher rates of self-injury and specific forms of aggression, such as scratching or biting other.[20,21] Functional analysis of these behaviors has shown that social or environmental factors, including gaining attention or access to preferred objects or escaping from social demands, reinforce and maintain these challenging behaviors.[22]

Other behavior problems include restrictive and repetitive behaviors and sensory issues. Cross-sectional studies across the lifespan show peaks in sensory-motor behaviors between 2 and 12 years of age, and in restricted and repetitive behaviors between 7 and 12 years of age.[23] Restricted interests, such as being strongly attached to one specific object and fascination with one subject or activity, were rated as moderate to severe.[24] Studies differ, however, on whether restricted and repetitive behaviors are related to IQ.[23,24] Recent work exploring sensory processing indicate that hypersensitivity to visual, auditory, or tactile stimuli may be the underlying issue in behavioral challenges in individuals with FXS.[25,26]

Social avoidance is a key characteristic which emerges in males as early as infancy, with increases into middle childhood, but steadying in later years.[27] During observational assessments, eye contact avoidance, in particular, was evident in adolescent and young adult males, especially in those with more ASD symptoms. Alternate measurement techniques of social avoidance have been developed, including caregiver-completed assessment scales,[28] other observational rating scales,[29] and eye-tracking techniques.[30]

FXS Subtypes.—One of the gaps we identified in our earlier paper was lack of information regarding subtypes of the FXS phenotype. Since then, our understanding of the FXS phenotype has continued to grow, with increased focus on genotype-phenotype associations and neuroanatomical correlates of clinical features. Mosaicism (i.e., variation in CGG repeats across different cell types) and methylation status (i.e., variation in FMRP levels across different cell types) are now well-known molecular indicators of phenotypic impact.[31,32] Research uncovering novel mutations and mosaic genetic presentations on the *FMR1* gene have helped to identify disruptions on specific exons and untranslated regional variations, which have implications for the function of FMRP and the variable phenotypic expression seen in FXS.[33,34] Studies have explored how FMRP acts as a regulator and impacts clinical features in individuals with FXS.[35,36] In one, as FMRP levels decreased below 70% of the mean for unaffected individuals, individuals with FXS had declining IQ scores. An average FMRP level of 35% below the mean was needed for individuals with FXS to reach an IQ of 85, or one standard deviation below average.[37] Given the role FMRP plays in cognitive functioning, studies have suggested it as a therapeutic target.[38] However, challenges remain in accurately measuring FMRP in different sample types (e.g., blood versus buccal cells).[35]

Work on identifying phenotypic subgroups in FXS has continued to emerge. One study examined how best to diagnose ASD in individuals with FXS using FX-specific versions of the Social Communication Questionnaire and the Social Responsiveness Scale.[39] Additional studies have examined behavioral differences in those with FXS only compared with those

with FXS and ASD. In keeping with earlier work, individuals with FXS and ASD show more severe behavioral problems, challenges with receptive and expressive language and social interaction, and greater cognitive impairment.[40-42] A second subgroup, those with both the FXS and Prader-Willi phenotype, is marked by obesity, hyperphagia, and delayed puberty, with about half also diagnosed with ASD.[43]

Needs of Adults with FXS

A second gap in the literature we identified in our earlier review was a lack of understanding of the needs of young adults, middle-aged adults, and seniors living with FXS. Individuals with FXS live, on average, to 87 years of age,[44] underscoring the importance of understanding the trajectory of adult needs in this population.

Over the last several years there have been a handful of studies describing the phenotype of adults, although mostly in young to middle adulthood. Receptive language skills continued to be a relative strength in adults when compared with expressive ability.[45] In a large-scale survey study, young adults ages 18 to 21 years had more ASD symptoms than middle aged adults. Eye contact continues to be a deficit for adults with FXS.[46] Despite these challenges, adolescents and adults with FXS were more likely to engage in hobbies, spend time with friends or neighbors, and have a mutual friend when compared with those with ASD.[47]

Positive findings also emerge when functional and behavioral skills are examined into adulthood. Although some studies have found plateaus or even declines in functional skills, a longitudinal study of adolescents and adults showed some growth in adaptive behavior over time. Behavior and internalizing problems were inversely related to age. Maternal criticism was a significant predictor of behavior problems and externalizing problems.[48] IQ[48-50] and executive function[50] have been shown to be strongly associated with functional skills.

Public Health Needs

Another major gap in knowledge previously identified was the public health needs of individuals with FXS. These needs were categorized into (1) clinical diagnosis and newborn screening and (2) health care needs and access.

Clinical Diagnosis and Newborn Screening.—Traditionally, diagnosis of FXS is done clinically after the onset of symptoms.[51] However, this process can be long and arduous for families, with a mean age of diagnosis around 32 months and fewer than 20% of children receiving a diagnosis within the first year of seeking medical attention.[52] There have been efforts to decrease the diagnostic odyssey and improve the process for receiving a clinical diagnosis, including carrier screening of women prior to or during pregnancy[53-55] preimplantation genetic testing, [56,57] and newborn screening.

Newborn screening for FXS in both males and females is supported by the majority of developmental and behavioral pediatricians. However, voluntary screening is preferred over mandatory.[58] Voluntary screening in hospitals shortly after birth is possible, but challenging. In a multi-site U.S. study of 28,000 newborns, two-thirds of parents were willing to have their child screened, but educational materials were essential in supporting informed

decision-making.[59] A smaller-scale study in Australia found higher rates of consent, with 94% agreeing to screening.[60] More recently, a statewide, voluntary newborn screening study conducted in North Carolina was implemented as a partnership between public health staff and researchers. One of the main considerations was how to best recruit families.[61-63] Barriers to full-scale newborn screening for FXS include public health burden to conduct the screening; the need for inexpensive, high-throughput screening methodologies; lack of demonstrated treatment for asymptomatic children; and insufficient capacity for long-term follow-up.[64,65]

Healthcare Needs and Access.—Indirect and direct healthcare costs are sizable for individuals with FXS. Using Medicare/Medicaid administrative claims data, annual all-cause healthcare costs ranged from $2222 to $9702, with higher costs in the Medicaid cohort. Main cost drivers included medical procedures, both routine (e.g., office visits, immunizations) and non-routine (e.g., lab tests, therapies, anesthesia), followed by hospitalizations in a subset of individuals, and finally medications.[66] Studies in Europe also have found high healthcare and caregiver burden costs, with non-healthcare costs (e.g., informal care) being the main contributor.[67,68] Direct and indirect healthcare costs are higher for those with FXS and their families than those without FXS. [69,70]

In a survey study of over 600 caregivers of individuals with FXS, 20% reported having difficulty accessing specialty services and nearly 40% indicated their child's primary care provider was not knowledgeable about FXS.[71] Parent-reported data of preventive care services have shown that 92% of individuals with FXS met immunization guidelines and 75% met dental care guidelines, but only 55% met influenza vaccination guidelines, and just 24% met physical activity guidelines.[72]

Treatments for FXS

At the time of our 2017 literature review, a noted gap was lack of research to explore the impact of symptom-based pharmaceuticals and behavior-based interventions. In the intervening years, however, there have been extensive studies focused on identifying treatment priorities, pharmacological treatments, clinical trial, and educational and behavioral interventions.

Treatment Priorities.—Stakeholder involvement from the beginning of treatment development is considered best practice.[73] As such, understanding the perspectives of parents and individuals with FXS has been a key goal over the last few years. In a study of treatment targets, 439 family members of at least one individual with FXS indicated medications to address anxiety, learning, and behaviors such as tantrums and aggression were their top priorities.[74] Similarly, Cross and colleagues[75] found behavior and self-care to be the most important targets for treatment for caregivers across age groups. Parents are generally supportive of pharmacological clinical trials, yet there may be concerns about safety and long-term implications for their child in the decision process.[76] Concerns about side effects, swallowing tablets, blood tests, financial costs and travel can be barriers to participation in clinical trials,[77] as are misunderstanding of the objectives of

pharmacological clinical trials,[76] and the likelihood that their child will experience a direct benefit.[78]

Pharmacologic Treatment.—Psychotropic medications are used by more than two-thirds of adolescents and adults with FXS, while a quarter are likely to use non-psychotropic medications.[79] Once on a medication, individuals with FXS were more likely to stay on medication over a 3-year period. Those with more autism symptoms, behavioral challenges, and greater family incomes were more likely to use psychotropic medications. In a review of psychopharmacologic management in FXS, Eckert and colleagues[80] analyzed the use of medications to address irritability, aggression, agitation, and self-injury in 415 individuals with FXS. The most commonly utilized medications identified were the antipsychotics aripiprazole and risperidone (used by 37% and 27% respectively), with the majority of users experiencing no side effects from these medications. Psychopharmacological management tended to be accessed more often by older males who had more significant impairments. A retrospective analysis of the use of risperidone in conjunction with other non-antipsychotic medications to target irritability in 32 male patients with FXS found a 33% responder rate,[81] leading to a conclusion that monoantipsychotic treatment with risperidone is limited in FXS.

Clinical Trials.—Clinical trials of gamma-aminobutyric acid (GABA) modulators, including ganaxolone (a $GABA_A$ receptor agonist) and arbaclofen (a $GABA_B$ receptor agonist), and amino-terminal tripeptide of insulin-like growth factor 1 (i.e., trofinetide), have been used to target the core pathophysiology of FXS. A randomized, double-blind, placebo-controlled trial of ganaxolone [82] in children with FXS did not meet primary (i.e., Clinical Global Impression-Improvement scale) or secondary (e.g., Pediatric Anxiety Rating Scale-Revised) study end points. However, post hoc analyses showed a trend in reducing anxiety, hyperactivity, and social avoidance for a subset of participants who entered the study with higher anxiety or lower IQ scores. A Phase 3 trial of arbaclofen [83] demonstrated positive change in children who were on the highest dose (10 TID), with lower irritability and parenting stress scores; scores for social avoidance and hyperactivity trended towards statistical significance. More recently, a Phase 2 trial of trofinetide demonstrated benefit, with individuals in the treatment group having lower clinician- and parent-reported symptom scores on three core efficacy measures [84].

Other trials targeting cognition and/or behavior have found moderate success. A small study of individuals with FXS who received between 2.5 and 10.0 mg of donepezil, an acetylcholinesterase inhibitor, did not demonstrate change on cognitive or behavioral outcomes [85]. However, after 12 weeks of treatment, improvements were seen on direct versus averted gaze as measured by functional magnetic resonance imaging. In a randomized, double-blind, placebo-controlled trial of sertraline [86], a selective serotonin reuptake inhibiter (SSRI), children with FXS made improvements in secondary endpoints, including improved motor and visual perception skills and social participation. Two case series of individuals with FXS examined the use of metformin, typically used to treat to treat type 2 diabetes, obesity, or glucose intolerance [87,88]. Results showed improvements in behavior and language development. Finally, cannabinoids have been used to reduce anxiety and aberrant behavior, and improve language skills and overall quality of life.[89,90].

Behavioral and Educational Interventions.—In 2015, Moskowitz and Jones[91] published a systematic review of 31 behavioral intervention studies. Findings suggest behavioral approaches are promising for addressing a variety of disruptive behaviors or functional outcomes in individuals with FXS. In a 12-week trial of a telehealth delivered function-based behavior analytic intervention, rates of problem behavior decreased significantly in 8 out of 10 children with FXS ages 2 to 10 years.[92] In another intervention study, 20 boys with FXS, ages 8-18 years, were randomized to receive discrete trial instruction plus relaxation training administered at one of two prescribed doses over a 2-day period.[93] Levels of social gaze behavior increased significantly across blocks of training trials for six boys (60%) who received the high-dose behavioral treatment and for three boys (30%) who received the low-dose behavioral treatment. Therapeutic physical exercise[94] and specific diet[95] have also been used to address behavioral or socio-emotional challenges in FXS. Both of these studies suggest diet and exercise may be helpful for individuals with FXS but each approach requires further study.

A series of studies evaluated the use of Cogmed, a validated computer-based training designed to improve working memory and executive functioning in children with FXS. Results from the first study demonstrated the feasibility of a 5-week Cogmed training. [96] A follow up study indicated significant improvement in working memory, some domains of executive function, as well as parent and teacher reported behaviors during the treatment period, with many changes maintained at follow-up after 3 months without training.[97] In a subsequent "deep dive" into the data, those with a higher IQ or mental age at baseline showed greater gains.[98]

Communication is a significant challenge for many individuals with FXS and frustration with communication failures is likely a major contributor to problematic behaviors. In 2015, a multiple baseline study of a delayed video feedback intervention for a mother and her 31-month-old son showed that the behavior support strategies used increased appropriate requesting and reduced the frequency of the child's self-injurious behavior.[99] Two pilot studies of a parent-mediated language intervention found that mothers were able to increase their use of strategies to help focus their child's attention and communicative acts.[100,101] A follow-up randomized trial found that mothers in the treatment group used these strategies at post-treatment significantly more often than mothers of children in the comparison group. When compared with those in the control group, children in the treatment group were more likely to show increased duration of engagement, use more utterances that maintained the topic of the story, and use prompted inferential language.[102] Similar results were found in sample of younger boys and their mothers.[103] A combined pharmacologic and language treatment study used a randomized, double-blind trial design and assigned families to the same parent-mediated language intervention plus lovastatin (10-40 mg/day) or an intervention group plus placebo.[104] Both groups demonstrated improvements in all primary outcome measures, including direct assessment and parent report measures, further supporting the efficacy of the language intervention but not providing evidence for the benefit of the addition of medication.

For a subsample of individuals with FXS, verbal expressive language does not develop with enough capacity for efficient communication. For these individuals, augmentative

or alternative communication (AAC) techniques may be beneficial to provide an avenue for communicating their wants and needs. Schladant and Dowling recently conducted a qualitative study to explore parental acceptance, use, and engagement of AAC in four FXS affected mother-child dyads. The investigation exposed three main systemic gaps that may limit the successful integration of AAC in the home including (a) failure to consider unique aspects of the family context, (b) limitations of AAC technologies, and (c) inadequate knowledge of FXS and AAC among practitioners.[105]

Families

The initial public health literature review identified several gaps regarding the impact on families of individuals with FXS given the complex nature of the *FMR1* gene expansions. Families of individuals with FXS are unique; in the majority of cases there is more than one family member affected. Given the hereditary patterns of *FMR1* expansions, biological mothers of children with FXS nearly always have an *FMR1* premutation or may have a full mutation themselves. Given the high penetrance of symptoms among those with a premutation, mothers of children with FXS are at high risk for fragile X associated physical or mental health issues.[106] In addition, many families have a second child with FXS before the first is diagnosed, and/or choose to have additional children even after knowing the risk for FXS. Some families will have multiple members across generations with fragile-X associated disorders.

Mothers of children with FXS frequently reported behaviors such as defiance, tantrums, inattention, stereotypy, aggression, and social inappropriateness in their children, and describe these as having a major negative impact on family life.[41] Relative to other neurogenetic conditions (e.g., Williams syndrome), parents of children with FXS were more likely to indicate restrictions on the family and a less positive perspective of parenting as a result of their child's behavioral or psychiatric conditions.[107] Challenging behaviors of children over time negatively impacted maternal mental health, which in turn influenced the quality of the mother-child relationship.[108] Similar results were found in another study, with child challenging behavior serving as a predictor of changes in maternal depression over time.[109] Moreover, high levels of child challenging behavior was related to increased feelings of maternal closeness toward the child over time.

In a study exploring expressed emotion, mothers with FXS were described as having high levels of worry and emotional over-involvement.[110] This increased anxiety may have a negative impact on the outcomes of the child; lower closeness in the mother–child relationship and higher maternal distress was found to be associated with higher levels of withdrawal. In females with FXS, the closeness of the mother-child relationship predicted greater fluid and crystallized intelligence.[36] Maternal responsivity, one factor in the mother-child relationship, has also been found to be an important predictor of outcomes for individuals with FXS. Sustained maternal responsivity has a significant positive impact on the trajectories of communication and to a lesser extent, other adaptive behavior domains through middle childhood, with many effects remaining significant after controlling for autism symptoms and developmental level.[111, 112]

Family resources and social supports are important predictors of quality of life, well-being, and overall impact of the diagnosis;[113] however, little research has explored strategies to improve access to these necessary supportive resources. How and when the diagnosis is obtained and shared with family members remains another important topic for future exploration.[114, 115]

DISCUSSION

The primary goal of this updated review was to assess progress made in addressing identified research gaps in the FXS literature. Although progress has been made in the past few years, there is still work to be done to fill these gaps. Here we summarize the three main areas of that remain in need of more focused clinical and public health research.

Early Detection and Diagnosis

The American Academy of Pediatrics (AAP) provides guidance to pediatricians for the evaluation and referral to genetic testing for children with intellectual disability with unknown etiology.[116] Similarly, for children diagnosed with ASD, there are recommendations for fragile X testing.[117] However, children with FXS are typically diagnosed around 3 years of age, after clinical onset of symptoms.[118] Thus, early emergence of symptoms in infants and toddlers with FXS has not been well described. Without universal screening for FXS, it is likely that children with FXS are underdiagnosed. This makes it challenging to determine the timing and degree of symptom onset and delays access to early intervention or genetic services. Early detection and diagnosis of FXS is critical to ensuring optimal health and wellbeing. Additional work remains on determining how best to identify and diagnosis young children with FXS, such as through newborn screening or routine developmental surveillance. Further work is needed to understand the early phenotype of infants and toddlers with FXS. Finally, research documenting the impact of early intervention services on child and family outcomes will provide evidence on best practices to supporting development.

Examining Determinants of Health

There are many factors that impact health outcomes for all individuals, including personal, genetic, and environmental/social factors. Although the literature to date has provided a wealth of knowledge about the FXS phenotype, there is still much to learn. Given the wide variation in individuals with FXS, it is important to better understand personal or individual determinants of health. Studies are needed to document individual differences in FXS, such as phenotypic variation within males and females, and identify subgroups of FXS beyond simply classifying those with FXS only or those with FXS and comorbid ASD. Moreover, longitudinal studies into adulthood are needed to determine the lifelong impact of FXS on individuals. For example, little is known about the physical and mental health needs of adults with FXS. This information is helpful not only for further understanding the wide variation in functioning in individuals with FXS but importantly for determining inclusion/exclusion criteria for clinical trials and the potential impact of therapeutics.

Despite being a single-gene disorder, there is much to learn about the genetics of FXS. Genotype-phenotype association studies, in particular, are needed to understand how molecular and biochemical functioning have differential impact on individuals with FXS. For example, recent work has shed light on the relationship between FMRP and cognitive and behavioral functioning. But more studies are needed to understand how the transcription of the *FMR1* gene and downstream regulation impact the daily life of individuals with FXS. Additional research is needed on the extent to which cell or methylation mosaicism contributes to development and functioning, and how behavioral characteristics cluster together and are related to molecular indicators.

There is a significant lack of knowledge regarding the environmental and social determinants of health in individuals with FXS. Only a handful of studies have examined the access to health care services and the educational needs of individuals with FXS. Critically, there remains a lack of information about the potential differential needs and access to health care for those from minority backgrounds. Racial inequalities for individuals with intellectual and developmental disabilities have been described for other conditions but are lacking in FXS. More information is needed to understand the community and social factors and their impact on individuals with FXS. These could include studies on access to leisure activities and the quality of friendships for individuals of all ages with FXS. Finally, research on employment and housing of adults with FXS would provide additional insights into the impact of aging.

Developing and Implementing Pharmacological and Other Interventions

It is clear that a large focus over the past 6 years has been on the development of targeted therapeutics and identification of appropriate outcome measures for use in clinical trials. Advances in understanding molecular pathways have paved the way for promising new treatments. However, there is more work to do in understanding the molecular biology and systemic function of FMRP.[119,120]. A deeper understanding of the expression of *FMR1* and the role FMRP plays in regulation of cellular activity will provide new insights into potential pharmacological treatment targets. Moreover, many outcome measures still require additional evaluation to determine their sensitivity to change, a quality necessary for being able to assess the efficacy of a given treatment.

Research into effective educational and behavioral interventions also is needed. The handful of studies conducted to date provide a foundation on acceptable, feasible, and efficacious approaches. However, many are focused on small samples and target very specific skills or behaviors. Next steps should include large scale replication studies to build the evidence base and demonstrate scale-up of implementation. In addition, continued development and testing of new interventions that address broad areas of development are needed to complement targeted interventions. Ideally, the field will create a variety of intervention approaches to support individuals with FXS and their families.

Conclusion

Despite significant progress made in addressing clinical and public health research gaps identified in our earlier review, much work remains for the FXS field. Early diagnosis and

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understanding of the FXS phenotype, from infancy through adulthood, will provide insights in variation in individuals with *FMR1* mutations. Detailing the impact of personal, genetic, family, social and environmental factors on individuals with FXS will advance not only our understanding but enable more targeted treatment approaches. With additional research, clinicians and other professionals will be well poised to meet the needs of individuals with FXS and their families.

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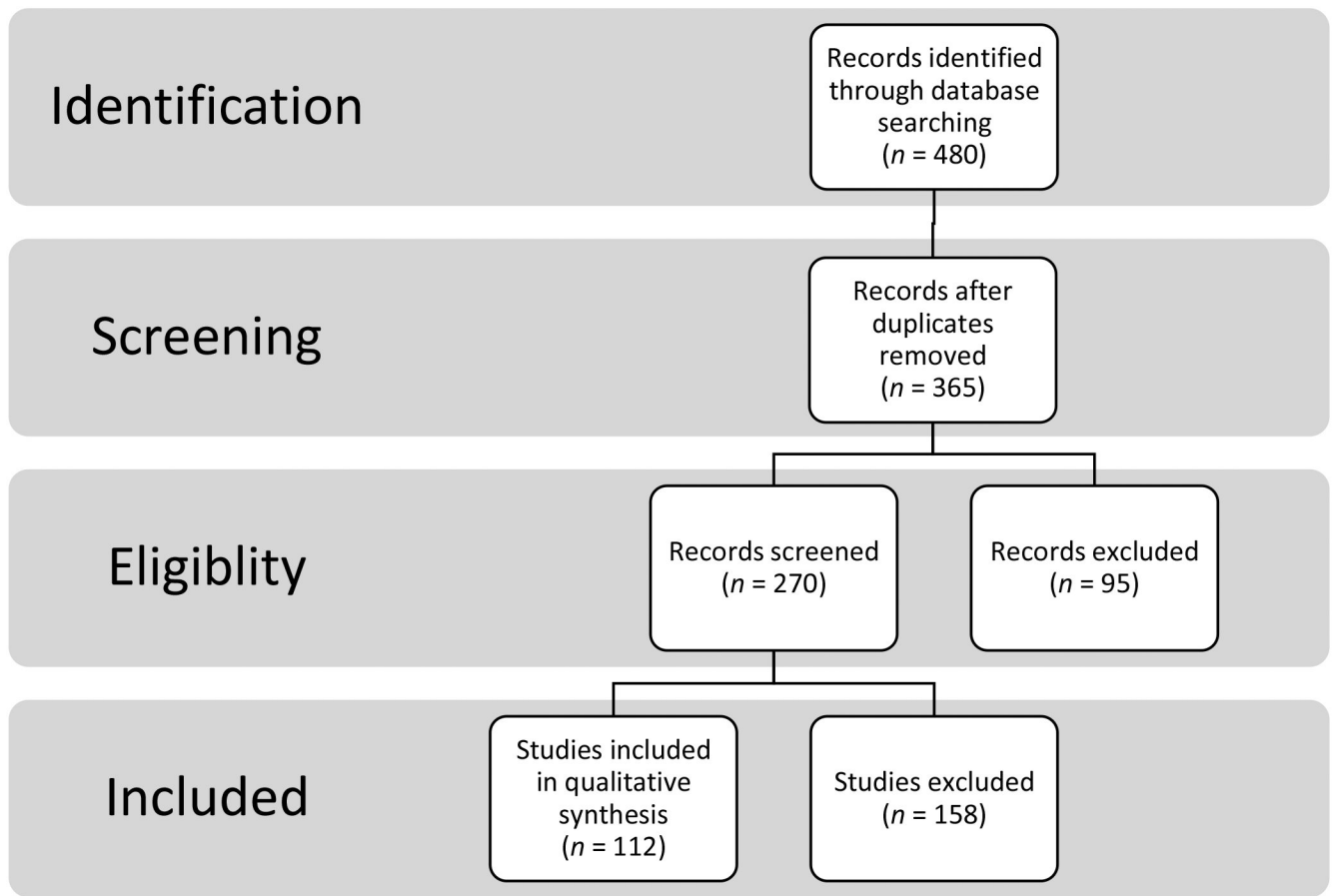
Figure 1.
PRISMA flowchart

Table 1

Search Terms and Inclusion/Exclusion Criteria by Topic Area

Topic Area	Search Terms
Diagnosis	(Fragile X syndrome) or (fragile X) or (FMR1) or (carrier) AND (Diagnosis) or (PCR) or (Southern blot) or (genetic testing) or (cascade testing) or (screening)
Phenotype	(Fragile X syndrome) or (fragile X) or (FMR1) AND (Phenotype) or (clinical presentation) or (clinical description) or (neurocognitive) or (cognitive) or (behavior) or (social-emotional) or (language) or (communication)
Familial Impact	(Fragile X syndrome) or (fragile X) or (FMR1) AND (Family adaptation) or (family impact) or (family outcomes) or (burden) or (cost of care)
Interventions & Treatments	(Fragile X syndrome) or (fragile X) or (FMR1) AND (Treatment) or (intervention) or (pharmacological) or (educational) or (behavioral) or (medication) or (clinical trial)
Lifespan	(Fragile X syndrome) or (fragile X) or (FMR1) AND (Life span) or (adolescent) or (adult) or (services) or (transition to adulthood)