

**Genetic Syndromes and Developmental Risk for Autism Spectrum and Attention
Deficit/Hyperactivity Disorders: Insights from Fragile X Syndrome**

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Abstract

Many genetic markers are associated with atypical developmental outcomes. In this article, we review evidence from studies on the most common inherited cause of intellectual disability, fragile X syndrome (FXS). We aim to highlight general developmental consequences as well as specific implications for autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD), including the complexity of characterizing ASD and ADHD symptoms in FXS. We address three issues: First, links among genes, brain, and cognition need to be situated in a developmental context, even in a monogenic disorder like FXS. Second, the comparatively early age of diagnosis of FXS offers the opportunity to study developmental trajectories of risk and resilience for a complex, behaviorally defined disorder highly associated with FXS but diagnosed later: ASD. Third, the high occurrence of both ASD and ADHD in FXS allows for a novel investigation of their comorbidity, with important caveats.

The increased availability of genetic testing has resulted in a growing cumulative frequency of diagnoses associating gene markers and generalized developmental delay (1), as well as more specific behaviorally defined difficulties, such as autism spectrum disorder (ASD; 2) and attention/hyperactivity disorder (ADHD; 3). Because specific genes can be mapped onto molecular, cellular, and systems neuroscience pathways, genetically identified syndromes have long offered the opportunity to study relationships among the genetic, neural, cognitive, and behavioral levels (4, 5). In this article, we highlight three additional opportunities afforded by studying genetic syndromes, as well as caveats and limits of each, because developmental psychologists should exercise both promise and caution in considering these issues.

First, despite exciting multilevel prospects, links between the brain and behavior can be studied only in a developmental context (6, 7). Second, diagnoses that occur prenatally or perinatally mean that genetic syndromes offer a unique opportunity to study risk for behavioral syndromes that are typically identified clinically later in childhood (e.g., ASD or ADHD). And third, genetic syndromes present a prospective longitudinal handle on risk for and resilience to comorbidity of ASD and ADHD.

We illustrate these three emerging research opportunities by examining fragile X syndrome (FXS) because of its history of research at many levels of description (genes, brain, and behavior) and recent developmental approaches that have offered important insights. We begin with a brief overview of the genetic, molecular, and systems neuroscience of the disorder to convey the excitement that has drawn geneticists, neuroscientists, and psychiatrists to study its manifestations at many levels. We then look at the literature on developmental trajectories of neural, cognitive, and behavioral risk in FXS. Our focus is on risk for ASD and ADHD, though other pathways of developmental risk (e.g., social anxiety that begins in childhood or adolescence) hold similar implications. Part of this focus includes

the need to discuss whether ASD and ADHD symptoms in individuals with FXS are indeed similar to those experienced by individuals diagnosed with ASD and ADHD who do not have FXS (idiopathic cases). Overall, our approach to genetic disorders like FXS offers a novel and fruitful avenue for researchers investigating pathways to risk and resilience in disorders that are typically diagnosed only behaviorally. We close with suggestions for work on predictors of resilience and positive outcomes, including questions for research in FXS, genetic syndromes, and neurodevelopmental disorders more broadly.

An Overview of Fragile X Syndrome:

Bridging the Gap Between Genotype and Phenotype

Fragile X syndrome is the most common single-gene cause of genetically inherited intellectual disability, occurring in approximately 1 in 2,500 males and females (8). The disorder results from a mutation on the *FMR1* gene that leads to a reduction of the fragile X mental retardation protein, FMRP. The FXS phenotype features marked sex differences: *FMR1* is located on the X chromosome and compared to males, impairment is more variable and less severe in females, for whom one of the two X chromosomes is inactivated randomly (9).

At the cellular level, FXS has been associated consistently with anatomical and functional changes related to the synaptic connections between neurons (see 10 for a review). Models of FXS in mice suggest that these changes may be transient and occur at specific times in development (11), stressing the importance of a developmental perspective. These temporal dynamics, combined with differing timings of environmental influences, may explain variation in the cognitive outcomes and developmental trajectories we discuss later.

Investigating FXS at the level of cognitive neuroscience has yielded links among genes, the brain, and behavior by identifying relationships among FMRP levels (a measure of

how complete *FMR1* gene inactivation is in FXS), brain activity, and specific cognitive impairments. For example, memory impairments, particularly working memory, correlate with FMRP levels in FXS as well as with abnormal brain activation in regions critical for memory functions (12). As another example, FMRP levels correlate with atypical activity in dorsostriatal brain networks in attention and impulse-control tasks (e.g. 13). Apart from attention and memory, links between the brain and behavior have also been proposed for social impairments in FXS. Associations may also exist among reduced FMRP levels, reduced amygdala volume, and atypical amygdala activation when individuals with FXS process emotions (14). These social findings may also be influenced by the high degrees of generalized and social anxiety that are characteristic of FXS (15).

While much of the early research on the FXS brain focused on school-age children and adults, recent structural imaging studies have taken advantage of early diagnosis (compared to disorders that are behaviorally defined) to study preschoolers and younger children with the syndrome (we return to these findings in the following section). Despite these links among FMRP, the brain, and cognition, for some behaviors (including autistic behaviors), severity was predicted by environmental factors (e.g., effectiveness of educational and therapeutic services), not FMRP (16). While we do not discuss these findings in detail, we mention them because they highlight the complexity of both gene and environmental influences, and they suggest possible protective factors against the risk of ASD.

Theme 1: Beyond Simple Brain-Behavior Links Through Longitudinal Insights

Many cognitive symptoms characterize FXS, including significant deficits in attention, working memory, and social-cognitive skills. Subtle behavioral and cognitive delays are evident as early as infancy, with parents becoming concerned about their children on average as early as 1 year, although clinical confirmation of first diagnosis often occurs

later (17). Diagnosing younger siblings of children with FXS can then occur earlier, even prenatally. In addition to these early signs, FXS presents a distinct cognitive profile from infancy: poor response inhibition (18), poor control of saccadic eye-movement (19), and prolonged visual attention to objects (i.e., sticky fixation; 20). Later in development, children and adolescents also display poor response inhibition (21) and atypical patterns of visual attention, including impairments in selective, sustained, and divided attention (22, 23). Finally, FXS in childhood affects executive function, with concomitant impairments to working memory (24), despite relative strengths in long-term memory and life skills (25).

In addition to these cross-sectional profiles, we have gained insights about changes in patterns of strengths and weaknesses over time from studying FXS longitudinally. To highlight these novel dimensions, we focus on attentional control because attention modifies how developing systems interact with their environment (e.g., 4), but we also refer to other cognitive domains for a broader perspective. The first insight describes atypical attentional biases that alter developmental trajectories from the outset for children with FXS (26-28). Although research tells us that boys with FXS have significant delays in attentional control, this is not a case of developmental arrest. Instead, longitudinal research has identified dynamic trajectories of delayed development. For example, a prospective longitudinal study of boys with FXS found improvements over time in attention and working memory, despite significant delays (28). Indeed, these longitudinal developmental advances in inhibitory control have since been measured in 3-year-olds with FXS (29). Following seminal studies of longitudinal changes in maladaptive behavioral symptoms (25, 30), researchers revealed dynamic trajectories of more specific cognitive abilities, including gaps in cognitive functioning that narrow and widen over adolescence, demonstrating strengths and weaknesses over time. The gap between typically developing individuals and those with FXS

widens for verbal comprehension, perceptual organization, and processing speed, but narrows for freedom from distractibility (31).

The second insight involves trajectories of brain development. Given the comparatively early age of diagnosis, recent structural imaging studies have targeted very young children with the syndrome (32-34). Complementing earlier cross-sectional studies demonstrating atypical neuroanatomy of key cognitive control areas (e.g. 35), this work has also tapped into the power of longitudinal designs. For example, in one study (33), researchers examined 1- to 3-year-old boys with FXS over two years to investigate brain maturation. Areas of the brain were identified that were either enlarged or reduced, and these differences held from the start to the end of the study, highlighting stable regional effects early in development. Other brain regions revealed initial volume similar to that of typically developing children, but these areas subsequently increased in size in children with FXS, again stressing the need for longitudinal and developmental perspectives when considering the atypical brain (6). These brain regions include those related to inattention and socialization, and have been implicated in ASD and ADHD. In general, these results underscore how abnormalities in different brain regions develop differently over time in children with FXS, reflecting the time-dependent effects of FMR1 silencing. Indeed, differing trajectories of brain growth can distinguish children with idiopathic ASD from children with FXS (34). These divergences and atypical trajectories in brain development would not have been detected in studies featuring only cross-sectional designs.

In addition to the aforementioned group-level differences in developmental trajectories, a final longitudinal insight expands on what clinicians working with individuals with FXS verify: striking individual differences in attention outcomes, with some individuals affected by inattention more seriously than others, despite equivalent IQs. Large longitudinal studies can dissect within-syndrome variability in FXS more easily to determine how this

predicts subsequent outcomes. For example, in one study, visual, auditory, and multimodal attention were measured in young boys with FXS; the boys were 4 to 10 years at the start of the study and were assessed again a year later (27). In addition, behavior was assessed through teacher questionnaires targeting dimensions relevant to ADHD symptoms. At an individual level, while visual attention was a significant longitudinal predictor of ADHD symptoms in the boys with FXS (27), auditory attention predicted later symptoms related to ASD (26). This finding suggests that auditory attention should also be investigated in idiopathic autism (i.e., cases where autism is the primary diagnosis, not secondary to a genetic syndrome such as FXS).

Theme 2: Charting Early Risk for Autism Spectrum Disorders: Promise and Caveats

In addition to highlighting the significance of longitudinal insights in understanding the profile of individuals with FXS specifically, FXS also serves as a model for understanding risk for behaviorally defined disorders, including ASD and ADHD. Roughly 33% to 67% of patients with FXS also meet the clinical diagnosis for ASD (36, 37). The risk is even greater for ADHD: 74% of individuals with FXS meet the criteria for a clinical ADHD diagnosis (38). Despite the high risk for these behaviorally defined disorders, as previously noted, variability in behavioral outcomes across individuals with FXS is the rule. Therefore, investigating what factors cause individual differences in ASD and ADHD symptoms is important theoretically and clinically. Why do many children with FXS have problems with social and cognitive control that are similar to those experienced by children diagnosed with ASD and ADHD, while others do not? One advantage of using FXS as a model for behaviorally defined disorders is the substantially earlier diagnosis (potentially 3 to 7 years earlier than for ASD and ADHD), making FXS ideal for assessing high risk early in development.

However, in investigating FXS as a model for ASD risk, several questions arise: Are the autistic traits in individuals with FXS the same as those in individuals with idiopathic ASD? Alternatively, do these behaviors represent the severe end of a continuum of cognitive and behavioral difficulties in individuals who are more affected by FXS (39)? Even if the symptoms appear the same, could ASD symptoms in individuals with FXS be manifestations of underlying cognitive or emotional mechanisms that differ from those that drive similar behaviors in idiopathic ASD? Separating these interpretations is not easy, yet we must do so to develop treatments that address the core impairments in ASD and FXS.

One way to address these questions focuses on whether autistic symptoms in ASD that co-occur with FXS differ from those in idiopathic ASD. According to some researchers, the low IQ associated with these individuals explains ASD behaviors in FXS (39). They found dissimilar autistic symptoms in those diagnosed with FXS and ASD, and in those with idiopathic ASD, and a negative association between autistic behaviors and IQ. However, other studies have reported few to no differences in autistic symptoms between these groups (e.g., 36).

Regarding whether low IQ explains ASD behaviors, in other longitudinal work, the greatest predictor of ASD symptoms in individuals with FXS was not overall cognitive delay or IQ, but adaptive socialization (40). In addition, other genetically identified syndromes (e.g., Williams syndrome) suggest a distinction between overall cognitive ability and social impairment, as individuals with this syndrome also have low IQ but are hypersocial. Indeed, in a recent meta-analysis, low IQ was characteristic of many genetically defined disorders, but ASD symptoms were not (2). This work highlights the importance of investigating profiles not just within a specific genetic disorder, but also across disorders to understand more fully behaviorally defined disorders such as ASD.

An alternative strategy of investigating ASD symptoms in individuals with FXS may be to avoid comparing individuals on symptoms alone, but rather investigating specific pathways or mechanisms behind the symptoms. For example, in one study (41), although social gaze avoidance in typically developed individuals was related to degree of autistic symptoms, in children and young adults with FXS, communication ability and not autistic symptoms predicted social gaze. These results again suggest that researchers should be cautious when comparing autistic symptoms between individuals with co-occurring FXS and ASD, and individuals with idiopathic ASD; while individuals with both disorders may have similar levels of a specific symptom (e.g., gaze avoidance), these behaviors may be caused by different underlying mechanisms. Researchers are now using FXS as a prospective model of risk for investigating emerging ASD symptoms in 9-month-olds with FXS well before ASD can be diagnosed (42). In a study (42), early negative affect predicted later symptoms of anxiety in these young children, but not ASD symptoms; in contrast, in previous studies, negative affect was related to ASD symptoms in infants at familial risk for ASD without FXS. This work not only highlights the importance of longitudinal designs (our first point), but also stresses how genetic disorders that are identified early, such as FXS, can aid in investigating both common and syndrome-unique pathways that lead to symptoms normally identified and studied later in childhood (our second point).

Theme 3. Charting Risk for Complex Outcomes:

High Likelihood of ASD and ADHD Symptoms

A parallel to the discussion of ASD emerges when considering the mechanisms responsible for high prevalence of hyperactivity and inattention in individuals with FXS (3). Similar to the argument made for ASD in individuals with FXS, the earlier age of diagnosis of FXS (compared to when ADHD is diagnosed) allows for prospective longitudinal analysis

of early markers of ADHD. Prospective studies of ADHD are limited: Investigating infants and young children at familial risk for ADHD in a manner similar to investigations of autism is difficult because of the age gap between siblings (familial risk is defined as having an older sibling with the diagnosis and children with ADHD are typically diagnosed at age 6 or 7). Although some research has investigated familial risk via parents' symptoms (43), prospective investigation of ADHD could also occur by studying young children with genetic syndromes like FXS (27).

In addition, with high risk comes the opportunity to study protective factors for the *co-occurrence* of ASD and ADHD. Only with the most recent revision of the Diagnostic and Statistical Manual of the American Psychiatric Association have comorbid diagnoses of idiopathic ASD and ADHD been allocated. Previously, children who were diagnosed with ASD could not be diagnosed with ADHD and vice versa. Since the new manual allows for a diagnosis of both ASD and ADHD in the same individual, the comorbidity of these disorders has become the focus of intensive study. Prospective longitudinal studies of familial risk (e.g., the British Autism Study of Infant Siblings, <http://www.basisnetwork.org/>) are often unbalanced in the context of investigating comorbidity because participants are identified by high risk for either ASD or ADHD, but not necessarily for both.

In contrast with studies of familial risk, because of the high risk for both ASD and ADHD, genetic syndromes offer the opportunity to study both risk for and resilience to the comorbidity of ASD and ADHD. In one study (44), boys with FCX and clinical ASD levels met the ADHD diagnosis more frequently than boys who did not meet the cutoff for ASD, suggesting a high comorbidity in FXS. In addition, parent surveys reveal that ASD rarely occurs in isolation in individuals with FXS, and is more likely to be accompanied by problems with attention, anxiety, and hyperactivity (45). Indeed, the high prevalence of anxiety in individuals with FXS (15) might at least in part drive the emergence of the social

difficulties and hyperactivity encountered by children and adolescents with FXS. However, since comorbidity is rarely investigated, both in FXS and in idiopathic ASD and ADHD, this possibility has not yet been tested.

Conclusion: Looking Ahead for a Developmental Psychology of Risk and Resilience

We have used fragile X syndrome as a case study in emphasizing three developmental implications of investigating cognition in genetic syndromes. First, a silenced gene cannot be mapped directly onto the resulting phenotype: In FXS, gene-phenotype links can be studied only in a developmental context because of complex effects relevant to many domains of cognition, starting with attention and changing over time. Longitudinal data show that even in seemingly simple monogenic disorders like FXS, the resulting phenotype displays significant variability across individuals. Second, because of increasingly early diagnoses, genetic syndromes present both a clinical imperative and a unique opportunity to study risk for behavioral syndromes clinically identified later in childhood (e.g., as ASD or ADHD); they also raise the question of how these symptoms resemble or differ from those in idiopathic cases without an identified genetic etiology. This is not unique to FXS, of course; for example, Williams and Down's syndromes are also characterized by high risk for ADHD symptoms and are also diagnosed early. Third, these diagnoses often co-occur with intellectual disability or symptoms of ASD or ADHD, offering a longitudinal handle on assessing risk for and resilience to comorbidity.

In conclusion, young children with genetic syndromes are at greater risk of poor outcomes than children who develop typically, but outcomes are variable: Some children have high ASD and ADHD symptoms, while others do not. This variability—coupled with our ability to diagnose genetic syndromes at younger ages—raises the opportunity of

studying predictors of positive outcomes to identify modifiable environmental factors for intervention.

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