Evidence of a Distinct Behavioral Phenotype in Young Boys With Fragile X Syndrome and Autism

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Objective: How does the behavioral expression of autism in fragile X syndrome (FXS + Aut) compare with idiopathic autism (iAut)? Although social impairments and restricted, repetitive behaviors are common to these variants of autism, closer examination of these symptom domains may reveal meaningful similarities and differences. To this end, the specific behaviors comprising the social and repetitive behavioral domains in young children with FXS + Aut and iAut were profiled. **Method:** Twenty-three male subjects 3 to 5 years old with FXS + Aut were matched by age to a group of 38 boys with iAut. Repetitive behavior was assessed using the Repetitive Behavior Scales-Revised. Social behavior was evaluated using Autism Diagnostic Observation Schedule social item severity scores. **Results:** Rates of stereotypy, self-injury, and sameness behaviors did not differ between groups, whereas compulsive and ritual behavior scores were significantly lower for subjects with FXS + Aut compared with those with iAut. Those with FXS + Aut scored significantly lower (less severe) than the iAut group on five Autism Diagnostic Observation Schedule measurements of social behavior: gaze integration, quality of social overtures, social smile, facial expressions, and response to joint attention. **Conclusions:** The behavioral phenotype of FXS + Aut and iAut are most similar with respect to lower-order (motoric) restricted, repetitive behaviors and social approach, but differ in more complex forms of restricted, repetitive behaviors and some social response behaviors. These findings highlight the phenotypic heterogeneity of autism overall and its unique presentation in an etiologically distinct condition. J. Am. Acad. Child Adolesc. Psychiatry; 2012; 51(12):1324-1332. **Key Words:** fragile X syndrome, autism, repetitive behavior, behavioral phenotype.

Fragile X syndrome (FXS) is the most common known inherited cause of intellectual disability.[1] The behavioral phenotype of FXS includes many classically "autistic" features, including motor stereotypies and self-injurious behavior, perseverative behavior, social avoidance, poor eye contact, and odd or delayed speech.[2–7] Because of the phenotypic overlap with idiopathic autism (iAut), FXS is increasingly considered a subtype of autism or itself one of the "autisms."[8,9] Approximately one third of boys with FXS meet the *DSM-IV* criteria for autism, with nearly a third more meeting the criteria for a pervasive developmental disorder.[5,7]

If the FXS phenotype includes many classically autistic features, what differentiates children with FXS who receive a diagnosis of autism? It has been suggested that an excess repetitive behavior may account for many of the autistic symptoms associated with FXS.[10–12] For example, the stereotypical manipulation of objects differentiates children with FXS and autism (FXS + Aut) from those without an autism diagnosis.[13,14] This is notable given that repetitive object manipulation is among the earliest distinct markers of iAut.[15] However, other forms of repetitive behavior, such as compulsivity or self-injurious behavior, are increased in children with FXS regardless of the presence of autism.[16,17] Separate lines of research have identified key differences in social behaviors between those with FXS with and without autism.[6,7] Social avoidance and failure to recognize social cues may drive a diagnosis of autism in FXS, although impairments in this domain are expressed on a continuum in FXS regardless of the comorbid condition.[18,19] Because social avoidance and anxiety are common to children with FXS generally, it may not reliably distinguish those with from those without autism.[20] Minor degrees of difference in social performance may determine

whether a given individual falls just above or below the level of clinical significance on autism assessments.[6,20,21] As of yet, the precise constellation of repetitive and social behaviors constituting autism in FXS remains unclear.

Studies comparing individuals with FXS with and without autism have only partly informed the phenotype of FXS + Aut. By definition, autistic behaviors are more severe in those with FXS + Aut than in those with FXS without autism. There are comparatively fewer direct comparisons between FXS + Aut and iAut. Bailey et al.[22] found that FXS + Aut is characterized by a similar but generally milder profile of autistic symptoms compared with iAut. Others have found that children with FXS + Aut closely resemble those with iAut on total and symptom domain scores taken from the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule (ADOS).[7,23] It is worth noting that most group comparisons use summary-level diagnostic measurements. This approach generally lacks the precision necessary to identify specific behavioral differences. Studies comparing discrete social behaviors between groups have found that those with FXS + Aut show significantly less impairment on measurements of social smiling, shared enjoyment, and amount and quality of social interactions.[6,11] Kau et al.[11] concluded that, given their intermediate profile of social impairments, children with FXS + Aut likely receive an autism diagnosis because of high rates of repetitive behavior and limited communication ability. This view has been supported in part by recent findings showing significantly higher rates of repetitive behavior in adolescents and adults with FXS + Aut compared with individuals with iAut.[24]

Autism is highly heterogeneous, but its association with FXS affords the opportunity to refine a behavioral phenotype against a stable genetic background. A fine-grained examination of the FXS + Aut phenotype would clarify this specific variant of autism and inform studies seeking to establish gene-brain-behavior relations.[25,26] In the present study, the authors aimed to characterize the constituent features of repetitive and social behaviors in young boys with FXS + Aut and compare and contrast those patterns of behavior with a comparison group of young boys with iAut. Because the expression of autistic behaviors are known to change over time, the present study focused on a single age cohort (3–5 years old) to control for the effects of age on behavior.[14,27]

METHOD

Participants

Participants were part of a collaborative imaging study of FXS.[28,29] Children with FXS were recruited through regional and national FXS organizations and research registries maintained by Stanford University or the University of North Carolina (UNC). A comparison group of children with iAut were recruited through the University of North Carolina's Division Treatment and Education of Autistic and Related Communication-Handicapped Children and Stanford area clinics. Exclusion criteria for the parent study included evidence of tuberous sclerosis, history of CNS injury (e.g., cerebral palsy, significant pregnancy complications or perinatal/postnatal trauma, drug exposure), prematurity (<34 weeks), low birth weight (<2,000 g), seizures, and significant motor or sensory impairments. For the present study sample, children 3 to 5 years old with a complete Repetitive Behavior Scales–Revised (RBS-R)[30] and an Autism Diagnostic Observation Schedule–Generic (ADOS-G)[31] classification of autism and Autism Diagnostic Interview–Revised[32] scores consistent with this classification were included, yielding a total cross-sectional sample of 23 boys with FXS + Aut (mean age = 4 years, standard deviation [SD] = 0.8 year) and 38 with iAut (mean age = 4.2 years, SD = 1 year). Full-mutation FXS (>200 CGG repeats) was confirmed with the standard Southern blot technique and testing for fragile X protein (FMRP) expression by calculating the percentage of peripheral lymphocytes containing FMRP.[33] Participants in the iAut group were excluded for evidence of FXS. Participants meeting the ADOS criteria for "autism spectrum" were not included in the iAut or FXS + Aut group. Study approval was acquired from University of North Carolina and Stanford University institutional review boards and written informed consent was obtained from the parents or custodial guardians of each participant.

Measurements

The RBS-R is a 43-item parent-rated measurement of discrete types of repetitive behavior and yields total and subscale scores.[30] The RBS-R is comprised of six subscales: Stereotyped Behavior, Self-Injurious Behavior, Compulsive Behavior, Ritualistic Behavior, Sameness Behavior, and Restricted Behavior. The RBS-R has been independently validated for use in young children with autism.[34]

The ADOS is a standardized observational measurement of behaviors associated with autism. It includes different semistructured activities and presses intended to assess communicative, social, and play behaviors.[31] Individual items from the social domain of the ADOS were used to compare performances on specific social behaviors in a manner similar to the recent work by Hall et al.[6] To examine whether social avoidance or anxiety rather than social indifference drives social deficits in