ARTICLE

Is It All the X: Familial Learning Dysfunction and the Impact of Behavioral Aspects of the Phenotypic Presentation of XXY?

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The behavioral phenotype of children with XXY has not been extensively studied until recently and this research has been confounded by insufficient study populations and ascertainment biases. The aim of the study was to expand the behavioral aspect of the XXY phenotype as well as investigate the role of existing familial learning disabilities (FLD) on behavioral problems. Behavioral phenotype of XXY includes social anxiety, ADHD, social communication, and atypical peer interactions. The Child Behavior Checklist (CBCL), Social Responsiveness Scale (SRS), and Gilliam Autism Rating Scale (GARS) were completed by the parents of 54 boys with XXY who had not received hormonal replacement prior to participation. Our findings suggest fewer behavioral deficits and lower severity in the general 47,XXY population than previously published and found significant differences between the groups with a positive FLD on the behavioral assessments. Findings demonstrate that boys with FLD exhibit an increased incidence and severity of behavioral problems. Our study expands on the findings of Samango-Sprouse et al. [Samango-Sprouse et al. (2012b) J Intellect Disabil Res] and the significant influence that FLD has on not only neurodevelopment, but also behavioral deficits. Our study suggests that part of the XXY phenotypic profile may be modulated by FLD. Further study is underway to examine the interaction between the many salient factors effecting behavioral and neurodevelopmental progression in XXY and variant forms.

KEY WORDS: Klinefelter syndrome; XXY; behavior; language-based learning disabilities; genetics

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INTRODUCTION

47,XXY or Klinefelter syndrome (KS) is the most common X and Y Chromosomal Variation occurring 1 in 400 to 1 in 1,000 live male births [Nielsen and Wohlert, 1991; Bojesen et al., 2003; Morris et al., 2008]. KS is characterized by small testicular size, aspermatogenisis, and tall stature with eunochoid body type [Klinefelter et al., 1942]. Further studies of KS revealed endocrine insufficiencies resulting in delayed onset of puberty, reduced phallic and testicular size, low fertility, and deficient androgen production [Lahlou et al., 2004; Ross et al., 2005; Simpson et al., 2005; Zeger et al., 2008; Samango-Sprouse et al., 2012a].

With the advent of chromosomes and karyotyping, the etiology of KS was determined as an additional X chromosome to the male complement of XY [Bradbury et al., 1956]. This finding

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afforded the opportunity of prospective population studies through newborn screening as well as a variety of research investigations at different ages on boys with 47,XXY. Since the 1970s, several commonalities regarding the neurocognitive and neurodevelopmental profile were identified in individuals with XXY, including language-based learning disabilities, developmental dyspraxia with neuromotor dysfunction and speech and language abnormalities, reading disorders, and frontal dysfunction [Robinson et al., 1979, 1990; Bender et al., 1986, 1995, 2001; Simpson et al., 2003; Giedd et al., 2007; Bryant et al., 2011; Samango-Sprouse et al., 2012a].

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Further exploration of the phenotypic presentation of XXY, using MRI brain imaging, revealed decreased gray and white brain matter consistent with deficits in executive function (EF) and frontal function. These deficits include cognitive flexibility, working memory, planning, inhibition, and ADHD [Barkley, 1997; Giedd et al., 2007; Lee et al., 2011; Savic, 2012]. The differences in brain morphology provide additional empirical evidence linking brain, behavior, and neurogenetic disorder. It also augmented our understanding of the degree of variability of this very common but largely undiagnosed neurogenetic disorder.

Behavioral aspects of the phenotypic profile have had fewer studies conducted until recently. Early studies described boys with XXY as timid, aggressive, disruptive, and as having low self-esteem and social immaturity [Bancroft et al., 1982; Mandoki and Sumner, 1991]. Social anxiety, ADHD, social communication, and atypical peer interactions comprise some of the features of XXY newly described [Ross et al., 2005; Bishop et al., 2010; van Rijn et al., 2011; Savic, 2012; Stochholm et al., 2012; Tartaglia et al., 2012]. ADHD has been reported as a major behavioral deficit in boys with 47,XXY with an incidence ranging from 34% to 63% [Giedd et al., 2007; Bruining et al., 2010; Ross et al., 2012; Tartaglia et al., 2012]. These articles expanded our understanding of the phenotypic presentation of XXY; however, the findings may be confounded to some extent because the presence or absence of ADHD in extended family members was not documented in these studies.

The importance of familial learning disabilities (FLD) and the impact of these existing disorders on the XXY phenotype warrant further investigation and may provide additional insight into brain and behavioral interaction in XXY. Studies on ADHD, dyslexia, and anxiety disorders have documented a familial component to these disorders and higher incidence of the disorders in the offspring of those individuals with them [Scarborough, 1990; Beidel and Turner, 1997; Pennington and Lefly, 2001; van der Leij et al., 2001; Eley et al., 2003, 2007; Snowling et al., 2003; Torppa et al., 2006, 2007, 2011; Puolakanaho et al., 2007; van Bergen et al., 2011, 2012; Brown et al., 2012; Zavos et al., 2012].

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The familial component of the neurocognitive and neurobehavioral facets in XXY have not been well investigated; however, a recent study by Samango-Sprouse et al. [2012a] reported that boys with 47,XXY with positive family histories of language-based learning disabilities and/or dyslexia exhibit more severe neurodevelopmental deficits across multiple domains of speech, language, and neuromotor. Thus, it is important that sufficient attention be given to the effects of FLD on the behavioral as well as the neurodevelopmental phenotype present in XXY. Research literature for the last 50 years has commented on the variability of the phenotypic profile of the boy with XXY and it seems plausible and even likely that positive family history of learning disorders maybe a contributing factor to the neurodevelopmental profile of XXY. Subsequently, the query must be considered—how much of ADHD in XXY is familial and how much is due to presence of the additional X? These same questions could be posed for the presence of dyslexia or other learning disorders in the family history. This is a complex issue, determining the genetics of FLD and their impact on the behavioral and phenotypic presentation of XXY, but necessary if we are to understand the impact of an additional X on a child's life.

We hypothesized that some of the variability of XXY and the variant forms

may be explained by the presence of existing dysfunction in the family. More importantly we believe that the presence of these FLD compound the neurodevelopmental performance of the child with X and Y chromosomal variations to a significant degree.

METHODS

In this retrospective study, 54 boys with 47,XXY were referred by their physicians, parents and ancillary health care providers throughout the country for a comprehensive neurodevelopmental assessment at the Neurodevelopmental Diagnostic Center for Young Children in Davidsonville, MD. The respective diagnoses were confirmed through karyotype analysis and documented in the children's medical records. The majority of the boys with XXY were diagnosed prenatally and those diagnosed postnatally were identified prior to 2 years of age. None of the children had received testosterone replacement therapy prior to the study. In order to minimize ascertainment bias, scholarship monies were provided for travel and fees for those families in need of neurodevelopmental assessments after 2005. Consent for each evaluation was granted by each parent. Children were referred to early intervention programs when necessary. Many of the children in each group received supplementary private speech and language, physical, and occupational therapies coupled with their school based services.

Neurobehavioral Testing

The Child Behavior Checklist (CBCL), the Social Responsiveness Scale (SRS), and the Gilliam Autism Rating Scale (GARS) were completed by the parents of all participants. The CBCL is a parent-reported questionnaire consisting of two forms: one for 1.5–5 years of age and one for 6–18 years of age. Parents completed the questionnaire in accordance with their child's chronological age. The questionnaire contains items covering emotional and behavioral issues present in the past 6 months using a three point scale of "not true (as far as you know)," "somewhat or sometimes true," "very true or often true." Scores in the borderline and clinical ranges of the CBCL reflect behaviors that are moderately to very deviant in comparison to the scores from a normative peer sample [Achenbach and Ruffle, 2000].

The SRS is a 65-item, Likert scale, parent completed questionnaire used to identify children with social behavior, social communication and social deficits [Constantino and Gruber, 2005]. Parents completed the School-Age Form for ages 4–18. Scores are broken down into four categories: within normal limits, mild, moderate, and severe. Children in the mild range exhibit deficiencies with slight impacts on social interactions. Children in the moderate range exhibit deficiencies with significant impacts on daily social interactions. And children in the severe range exhibit deficiencies with pointedly impacts on daily social interactions [Constantino and Gruber, 2005].

The GARS is a 42 itemed assessment used to help identify children with autism from other children with clinical behavioral issues. The norms were based off of children previously diagnosed with Autism, and thus provide a more accurate and reliable instrument to measure behavioral attributes of those with Autism. Scores are cast into three possible ranges: "not likely," "possible," and "very likely." The GARS is broken down into three 14-item subscales (Stereotype Behaviors, Communication, and Social Interaction) all of which are factored into the child's overall Autism Quotient (AQ). AQ scores of 69 or less deem a child "unlikely" of having Autism, scores ranging from 70 to 84 indicate a "possible" Autistic phenotype, and scores of 85 or higher are "very likely" [Gilliam, 1995, 2006].

On the CBCL, *T*-scores of 65–69 comprise the borderline range and scores of 70 or above comprise the clinical range. On the SRS, *T*-scores of 60–65 comprise the mild range, 66–75 comprise the moderate range and *T*-scores of 76 or above comprise the severe range.

Statistical Analysis

The data were summarized by the number in each group, the median, the interquartile range (IQR or 25–75th centiles), and the *P*-value from the Wilcoxon rank sum test. When applicable, scores were categorized, using the pre-defined cut-points mentioned above, into groups based on behavior scores and compared across two groups using the Pearson's chi-squared test. The scales were bifurcated so the children were clustered between 4 and 10 years of age and then again between 11 and 17 years of age.

Family History

Families were categorized as having a FLD if either parent or a sibling had been diagnosed with dyslexia, with difficulties in fluency, comprehension, decoding, or ADHD, if there was sibling with an Individual Education Plan (IEP) because of learning disabilities, ADHD, or developmental delay.

RESULTS

Demographics of both groups are similar and reflect increased parental age with many holding advanced educational degrees (Table I). Analysis of the SRS and CBCL questionnaires revealed significant results across selected domains for 47,XXY. The presence of FLD had a significant influence on the severity and frequency of behavioral issues.

On the SRS, the mean age of the 47,XXY boys in the younger subset was 85 months. Of these 30 boys, 60% were within normal limits, 10% in the mild range, 17% in the moderate range, and 13% in the clinical range. There was a significant correlation between positive family history and SRS scores on multiple domains of the questionnaire, including Social Awareness ($P = 0.02$), Social Communication ($P = 0.02$) and Social Motivation ($P = 0.03$; Table II). When comparing the Total *T*-Scores of the SRS between groups (with and without positive family history) there was significance at $P = 0.03$. Of the boys in the severe range 100% had

TABLE I. Patient Characteristics of the Study Population

47,XXY (N = 48)			
Patient background		Parental background	
Mean birth weight	3.1 kg	Mothers	Fathers
Delivery	Vaginal, 23 Cesarean, 10	Mean age = 37 years Range 24–45 years	Mean age = 39 years Range 25–48 years
Race	Caucasian, 42 Hispanic, 1 African-American, 1 Other, 4	81% college degree	88% college degree

positive family histories, 60% of the moderate range presented positive family histories as well as 33.33% of the mild range.

In the older subset of boys (mean chronological age of 145 months), there were significant differences between the group with FLD and those without in the domains of Social Cognition ($P = 0.01$), Social Motivation ($P = 0.02$), and Autistic Mannerisms ($P = 0.01$). Total *T*-Scores of the SRS were significantly different between those with a positive family history and those without ($P = 0.05$) and also when subsequently grouped by scale, within normal limits, mild/moderate, and severe ($P = 0.02$; Table III). Fifty percent of boys with XXY had scores within normal limits with 8.33% in the mild range, 16.67% in the moderate range, and 25% in the severe range. Of the 50% that scored outside of normal limits, 91.67% had positive family histories.

On the preschool CBCL, the boys with 47,XXY scored in the clinical range with an incidence of 12.5% or more on six categories: emotionally reactive, withdrawn, internalizing problems, total problems, affective problems, anxiety problems, and pervasive developmental problems. When comparing the positive family history group to the no family history group, significant differences were found in the sleep problems domain ($P = 0.02$) within the internal emotional syndromes; and the domains of anxiety problems ($P = 0.01$), and pervasive developmental problems ($P = 0.02$) within the external emotional syndromes (Table IV).

On the Internalizing Problems domain of the CBCL for over 5 years of age, we found a low incidence of scores in the clinical range for the vast majority of the areas evaluated. The category with the highest incidence in the clinical range was internalizing problems with 19%, and 88% were within normal range. Within the Internalizing domain, we had the highest occurrence of clinical range in Social and Attention categories, with 28% and 12.5%, respectively. Significant differences were found between the two groups on the domains of thought problems ($P = 0.01$) and attention problems ($P = 0.03$).

There were similar findings in the externalizing domain of the CBCL for older children with very low incidence of scores in the clinical range. There was a 12.5% incidence of affective problems in XXY. Significant differences between the two groups were found in the domains of attention deficit/hyperactivity problems ($P = 0.03$), oppositional defiant problems ($P = 0.05$), and sluggish cognitive problems ($P = 0.01$) as well as in the overall externalizing problems category ($P = 0.04$).

The most significant incidence of scores in the clinical range was in the School Domain. For the activities, social, and total competence categories 16% of the 47,XXY were in the clinical range and 31% scored as clinical in the School category. When comparing the total problems between the two groups, significant differences were identified at $P = 0.01$ (Table V).

There was a significant difference between those boys with positive family history and negative history on the GARS scale on the AQ domain ($P = 0.05$; Table VI). For the social interaction and communication domains 13.95% of all boys with 47,XXY scored within the "very likely" range, and 16.28% for the stereotyped behaviors domain.

TABLE II. SRS[a] Scores in Boys (<10 Years Old) With 47,XXY by Family History of Learning Dysfunction

	Family history of LD		
	No (n = 14)	Yes (n = 16)	
	Median (IQR)[b]	Median (IQR)	*P*-value[c]
Child's age, months	99 (66–109)	72 (60–100)	0.29
Social responsiveness scale			
Social awareness	46 (39–52)	52 (49–70)	0.02
Social communication	48 (40–57)	63 (50–80)	0.02
Social motivation	49 (45–55)	61 (49–70)	0.03
Total *T*-score	49 (42–57)	65 (47–75)	0.03

[a]Social responsiveness scale.
[b]The interquartile range.
[c]From Wilcoxon rank-sum test.

DISCUSSION

The goal of this study was to further explore the behavioral aspects of the XXY phenotype as well as investigate the role of positive family

TABLE III. Comparison of SRS[a] in Boys (10–18 Years) With 47,XXY by Family History of Learning Dysfunction (LD)

	Family history of LD				
	No		Yes		
	N	Median (IQR)[b]	N	Median (IQR)	*P* value[c]
Child's age, months	10	133 (124–137)	14	148 (135–168)	0.04
Social responsiveness scale					
Social cognition	10	47 (39–55)	14	70 (59–81)	0.01
Social communication	10	46 (44–57)	14	67 (60–77)	0.02
Autistic mannerisms	10	50 (40–63)	14	73 (67–80)	0.01
Total *T*-score (continuous)	10	48 (43–59)	14	71 (59–79)	0.02
Total *T*-score (grouped)		%		%	
≤59 (normal)	8	80.0	4	28.6	0.05
60–75 (mild/moderate)	1	10.0	5	35.7	
76+ (severe)	1	10.0	5	35.7	

[a]Social responsiveness scale.
[b]The interquartile range.
[c]From Wilcoxon rank-sum test.

histories on the severity and incidence of behavioral problems. This retrospective study reveals the significant impact of FLD on the behavioral phenotype of children with XXY. Our findings offer insights into the interplay between FLD and the development of social language, presence or absence of Autistic phenotype and ADHD.

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TABLE IV. Pre-School CBCL[a] Scores in Boys With 47,XXY Syndrome by Family History of LD

	Family history of LD				
	No		Yes		
	N	Median (IQR)[b]	N	Median (IQR)	*P* value[c]
Child's age, months	19	36 (25–56)	5	57 (50–58)	0.10
Internal emotional syndromes					
Sleep problems	13	50 (50–56)	5	64 (59–64)	0.02
External emotional syndromes					
Anxiety problems	19	50 (50–54)	5	78 (54–84)	0.01
Pervasive developmental problems	19	51 (50–57)	5	82 (59–84)	0.02

[a]Child behavior checklist.
[b]The interquartile range.
[c]From Wilcoxon rank-sum test.

Some of the variability of the XXY phenotype may originate with the salient feature of FLD which includes ADHD and dyslexia. Language-based learning disabilities associated with XXY affect 70–80% of children with 47,XXY [Bender et al., 1986; Nielsen and Wohlert, 1991; Bender et al., 1993; Geschwind et al., 2000]. Our results demonstrate a significant and additional global effect on the behavioral aspect of neurodevelopmental function in 47,XXY when FLD exists. The variability of the phenotypic and behavioral presentation XXY is complex and effected by many factors. Our findings support that FLD is yet another contributing influence to the social, behavioral, as well as neurodevelopmental features of XXY [Samango-Sprouse et al., 2012].

Differences in neurocognitive abilities and behavioral phenotypes also arise between the populations who are prenatal and postnatal diagnosed. Prenatally diagnosed children with 47,XXY typically receive treatment and services earlier than children diagnosed postnatally and have been shown to exhibit fewer behavioral issues and less severe cognitive deficits [Simpson et al., 2003; Girardin et al., 2009; Ross et al., 2012]. We now postulate that FLD compound the effects of 47,XXY on behavioral presentation and subsequently these boys may be more compromised in multiple domains of development within the prenatal population.

Our study augments our understanding of the complexities of neurodevelopmental progression in this common but rarely diagnosed disorder. We are beginning to identify the numerous factors that may contribute to the evolution of brain function and neurocognitive development in 47,XXY, which include skewed X inactivation, early hormonal replacement, and prenatal or postnatal diagnosis. Differences in neurocognitive abilities and behavioral phenotypes arise between the populations with prenatal and postnatal diagnoses. FLD may explain some of the variance between prenatal and postnatal populations in XXY.

Our findings on the SRS and GARS indicate that the majority of

TABLE V. CBCL[a] (>5 Years) in Boys With 47,XXY by Family History of LD

	Family history of LD				
	No		Yes		
	N	Median (IQR)[b]	N	Median (IQR)	*P* value[c]
Child's age, months	12	121 (99–136)	19	119 (97–163)	0.36
Internal emotional syndromes					
Thought problems	12	51 (50–56)	18	60 (54–64)	0.01
Attention problems	12	51 (50–57)	18	61 (53–65)	0.03
Externalizing problems	12	48 (33–53)	18	56 (50–60)	0.04
Total problems	12	46 (41–56)	18	58 (56–65)	0.01
External emotional syndromes					
Attention deficit/hyperactivity problems	12	50 (50–52)	18	56 (50–60)	0.03
Oppositional defiant problems	12	52 (50–57)	18	57 (55–62)	0.05
Sluggish cognitive problems	12	50 (50–56)	18	60 (55–68)	0.01

[a]Child behavior checklist.
[b]The interquartile range.
[c]From Wilcoxon rank-sum test.

the children with 47,XXY do not exhibit the characteristics of the Autistic phenotype. Less than 15% of our 47,XXY cohort exhibited an Autistic phenotype on the GARS or SRS, which is similar to the findings by Ross et al. [2012], but 100% of the boys with Autistic like phenotype had FLD. The presence of FLD is highly associated with the incidence of autistic like phenotype in XXY based on our investigation. This is an intriguing finding because it suggests that if there is FLD, it may confound the behavioral development of the boy with XXY in a significant manner. Our study supports Samango-Sprouse's recent article that boys with XXY and FLD exhibit more severe neurodevelopmental deficits across multiple domains of speech, language, and neuromotor [2012]. The critical and yet unanswered questions are what aspects of FLD lead to this ASD profile in XXY? Many questions arise such as could the parent with FLD actually have mild Broader Autistic Phenotype (BAP) that has not been appreciated [Piven et al., 1997]. Is there a synergistic effect that occurs with the additional X and the presence of FLD that is not apparent yet but results in this Autistic like phenotype? Our study has amplified our understanding of the effect of FLD but the mechanics of this effect is not well understood and warrants further thoughtful study.

Previous research by Ross et al. [2012] and Tartaglia et al. [2012] demonstrate increased incidence of ADHD of 42% and 34%, respectively and boys with XXY who were prenatally diagnosed were significantly less likely to have ADHD in both cohorts. Our findings support these results as well as a novel dimension.

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In our study regardless of age, ADHD had an incidence of about 12.5% and FLD was highly associated with the clinical indication of ADHD on the CBCL ($P = 0.03$) in the prenatal population. Future investigations of co-morbid conditions of ADHD and XXY is necessary and it may be beneficial to consider both the time of diagnosis and FLD in order to identify the true effect of the additional X and the presence of ADHD.

TABLE VI. Comparison of GARS[a] in Boys With 47,XXY by Family History of LD

	Family history of LD		
	No (n = 22)	Yes (n = 21)	*P* value[b]
GARS-2			
Autism quotient			
≤69 (not likely)	18 (81.8)	12 (57.2)	0.05
70–84 (possible)	1 (4.6)	7 (33.3)	
85+ (very likely)	3 (13.6)	2 (9.5)	

[a]Gilliam Autism rating scale.
[b]From Pearson's chi-squared for difference in grouped score by family history of LD.

On all three behavioral assessments, the general social problems categories possessed the highest degree of abnormalities in XXY. Social interactions are highly associated with language skills, particularly the understanding of pragmatic language and social language. Social language includes many facets of communication that are subtle and inferential, which can be extremely challenging for all children with language based learning disorders [Winner, 2007]. Our study supports findings of previous research studies that social interactions and social language are a major challenge for the boy with XXY regardless of the time of diagnosis [Winner, 2007]. Focused attention on the development of social language skills should be implemented from preschool years throughout adulthood for boys with XXY to address these deficits.

Our findings, coupled with previous research studies, are beginning to reveal increased vulnerability in subset of boys with 47,XXY. We hypothesize that the boy with 47,XXY who is diagnosed later in life with FLD, without hormonal replacement during infancy, is at significantly increased risk for complex phenotypic presentation of XXY. Our understanding of the effect of the additional X on the behavioral aspect of neurodevelopmental progression and brain function will be enhanced with greater understanding of the interaction between multiple factors of skewed X inactivation, timing of the diagnosis, FLD, as well as hormonal treatment. This knowledge will augment our ability to provide targeted treatment and more syndrome specific care of the child with XXY to optimize his neurodevelopmental outcome. Future research studies on XXY should include a detailed history of FLD because the presence of dyslexia, ADHD, and broader phenotype of ASD could confound research findings otherwise deficits may be mistakenly attributed solely to the 47,XXY.

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