Behavioral Phenotype of Sex Chromosome Aneuploidies: 48,XXYY, 48,XXXY, and 49,XXXXY

Jeannie Visootsak,1* Beth Rosner,2 Elisabeth Dykens,3 Nicole Tartaglia,4 and John M. Graham Jr.5

1Department of Human Genetics and Pediatrics, Emory University School of Medicine, Atlanta, Georgia
2Department of Psychiatry, Neuropsychiatric Institute, David Geffen School of Medicine at UCLA, Los Angeles, California
3John F Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, Tennessee
4M.I.N.D. Institute, UC Davis Medical Center, Sacramento, California
5Department of Pediatrics, Medical Genetics Institute, Steven Spielberg Pediatric Research Center, Cedars-Sinai Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California

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Sex chromosomal aneuploidy is the most common disorder of sex chromosomes in humans, with an incidence of 1 in 400 newborns. The addition of more than one extra X and/or Y chromosome to a normal male karyotype is less frequent and has its own distinctive physical and behavioral profile. This study examines the behavioral similarities and differences in individuals with 48,XXYY compared to 48,XXXY and 49,XXXXY. The participants include 11 males with 48,XXYY and 13 males with 48,XXXY and 49,XXXXY. Using the Vineland Adaptive Behavior, the Achenbach Child Behavior Checklist, and the Reiss Personality Profiles, parents are asked to characterize the behavior and personality of their boys with sex chromosome tetrasomy and pentasomy. Males with 48,XXYY have higher overall adaptive scales in daily living skills, socialization, and communication compared to males with 48,XXXY and 49,XXXXY. Both groups are at risk for maladaptive behavior, although 48,XXXY males are at a higher risk for internalizing and externalizing symptoms. 48,XXXY and 49,XXXXY function at a lower cognitive level and their behavior is often immature for their chronological age. Both groups display interests in helping others, but have a low tolerance for being rejected or teased. Specific recommendations and interventional strategies are provided for individuals with 48,XXYY, 48,XXXY, and 49,XXXXY. © 2007 Wiley-Liss, Inc.

Key words: sex chromosomal aneuploidies; 48,XXYY; 48,XXXY; 49,XXXXY; Klinefelter syndrome; tetrasomy; pentasomy; behavior

INTRODUCTION

Sex chromosome aneuploidies (SCAs) are the most frequently occurring chromosomal abnormalities with an incidence of 1 in 400 births [Linden et al., 1995]. SCAs involve the addition or deletion of an X or Y chromosome to a normal female or male chromosome karyotype, resulting in 47,XXX, 47,XXX, 47,XXY, 47,XXX, or 45,X abnormalities. The clinical and behavioral characteristics of these conditions are relatively well-described in the literature [Robinson et al., 1986, 1990; Graham et al., 1988; Visootsak et al., 2001; Simpson et al., 2003]. However, the addition of more than one extra sex chromosome is rare and relevant clinical information is limited. Few studies have compared behavioral profiles of individuals with 48,XXYY, 48,XXXY, and 49,XXXXY. Furthermore, behavioral characteristics of individuals with sex chromosome tetrasomy and pentasomy have been limited to case studies and usually lack standardized normative measures. This study is the first to investigate the effects of additional Xs and Y on behavioral features, and specific

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*Correspondence to: Jeannie Visootsak, M.D., 2165 N. Decatur Rd, Decatur, GA 30033. E-mail: jvisootsak@genetics.emory.edu
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recommendations are suggested for anticipatory guidance and treatment plans.

METHODS

Subjects with 48,XXYY, 48,XXXY, and 49,XXXXY were ascertained through national Klinefelter syndrome (KS) support group chapters (Klinefelter Syndrome and Associates, and American Association for Klinefelter Syndrome Information and Support). After approval by the Cedars-Sinai Medical Center Institutional Review Board, interested families were recruited through support group mailings and at the KS national meetings, as well as from referrals through university-based geneticists. Participant clinical histories and chromosomal karyotype reports were reviewed to confirm their diagnosis. Participants in this study consisted of 11 males with 48,XXYY (mean age \( \pm SD = 21.83 \pm 7.31 \)) and 13 males with 48,XXXY and 49,XXXXY (mean age \( \pm SD = 21.08 \pm 13.26 \)), with 8 from the 48,XXXY group and 5 from the 49,XXXXY group (Fig. 1).

Parents were invited to participate in a study on the behavioral and personality aspects of individuals with SCAs. Parents in each group completed the Vineland Adaptive Behavior Scales-Interview Edition [Sparrow et al., 1984]. This measure assesses three domains of adaptive functioning: communication, daily living skills, and socialization.

The Child Behavior Checklist [CBCL; Achenbach, 1991] asks parents to rate 112 problem behaviors on a three-point scale: (0) not true; (1) sometime true; (2) often true. The CBCL consists of an internalizing domain (withdrawn, anxious/depressed, and somatic complaints), externalizing domain (aggressive behavior and delinquent behavior), and three other subdomains (social problems, thought problems, and attention problems) that sum for a total score. The reliability and validity of this measure have been well established in persons with mental retardation.

The Reiss Personality Profiles of Fundamental Goals and Motivation Sensitivities for Persons with Mental Retardation [Reiss and Havercamp, 1998] consist of 100 statements that are rated on an informant on a 5-point scale (strongly disagree to strongly agree). This instrument allows researchers to assess personality motivation using normative groups of people, with or without mental retardation. The Reiss Profiles differ from other available instruments for people with mental retardation since they do not measure maladaptive behavior or psychopathology. Instead, they assess motivational strengths and styles.

RESULTS

Results from the Vineland Adaptive Behavior Scales are shown in Table I. On the Vineland Scales, males with 48,XXYY score higher than males with 48,XXXY and 49,XXXXY in daily living skills, communication, and socialization. Males with 48,XXYY show strengths in their adaptive daily living skills and weaknesses in their socialization and communication skills. It appears that communication and socialization skills are equally problematic. However, 48,XXXY and 49,XXXXY subjects show significant weaknesses in daily living skills compared to their socialization skills, but the communication domain has the lowest overall score (Fig. 2).

This is a cross-sectional study examining maladaptive behavior but does not assess how maladaptive behavior changes across age groups.

Results from the CBCL are shown in Table II. The CBCL total domain raw scores are converted to T-scores. Clinically significant T-scores are those above 64, as established by Achenbach [1991] using large epidemiological samples of children with and without identified problems. Males with 48,XXYY more often exceed the clinical cut-off of 64 compared to males with 48,XXXY and 49,XXXXY, with 3 out of 11 from the 48,XXYY and 3 out of 13 from the 48,XXXY and 49,XXXXY groups exceeding the clinically significant T-scores. Internalizing and externalizing behaviors are higher in males with 48,XXYY. Based on the subdomains, 48,XXYY group has increased risk for anxiety, withdrawal, somatic complaints, and attention problems. In the externalizing subdomain, increases are found in aggressive and delinquent behaviors. Significant difference is seen in the social subdomain with 48,XXYY having higher risk for social difficulty.
On the Reiss Personality Profiles (data available from authors), 48,XXYY subjects show elevated scores in anxiety, frustration, order, and vengeance domains compared to 48,XXXY and 49,XXXXY. Both groups had virtually identical scores in the activity level, food, help others, morality, pain, and sex domains.

**DISCUSSION**

KS was first described in 1942 [Klinefelter et al., 1942] in males with infertility, hypogonadism, gynecomastia, and increased excretion of follicle-stimulating hormone. It was initially thought to be an endocrine disorder, and the etiology of these findings was unknown until Bradbury et al. [1956] demonstrated that cells of buccal mucosal of males with KS contained an extra sex chromatin body. It was not until 1959 that KS was recognized to be a chromosomal disorder, in which the extra X chromosome results in the karyotype of 47,XXY [Barr et al., 1959; Jacobs and Strong, 1959]. Although 47,XXY is the most common chromosomal abnormality in individuals with SCAs, additional supernumerary Xs and/or Ys chromosome do exist.

Muldal and Ockey [1960] described the 48,XXYY karyotype as the “double male.” It is the most common variant of KS, representing 2.3% of patients with KS [Hasle et al., 1995]. The incidence ranges from 1 in 17,000 to 1 in 50,000 males [Sorensen et al., 1978; Nielsen and Wohlert, 1990]. Males with 48,XXYY are tall with an adult height over six feet, typically exceeding males with 47,XXY. They have eunuchoid habitus with long legs, small penis and testicles, hypergonadotropic hypogonadism, and gynecomastia. Peripheral vascular disease may cause leg ulcers and varicosities [Linden et al., 1995]. Their IQs range from 60 to 80, with 10% having an IQ above 80 [Sorensen et al., 1978]. Global developmental delay and severe expressive language disability are common. Behavioral features range from shyness to aggressiveness based on several reported case studies [Linden et al., 1995].

![Image of male with 49,XXXXY from childhood to adulthood. Note the change in physical appearance with age.](image-url)
The presence of more than one extra X chromosome results in individuals with either a 48,XXYY or 49,XXXXY karyotype. Individuals with these SCAs were initially described in 1959 and 1960 [Barr et al., 1959; Fraccaro et al., 1960]. Effects on physical and mental development increase with the number of extra Xs, and each X reduces the overall IQ by 15–16 points, with language most affected [Linden et al., 1995]. Height decreases and radioulnar synostosis becomes more frequent as the number of X chromosomes increases. Males with 48,XXYY have average to tall stature, with hypertelorism, flat nasal bridge, small penis and testicles, infertility, and gynecomastia (due to hypergonadotropic hypogonadism). Males with 48,XXXY have a coarse face with microcephaly, ocular hypertelorism, flat nasal bridge, and upslanting palpebral fissures. Bifid uvula and/or cleft palate may be present. Skeletal abnormalities including radioular synostosis, genu valgum, pes cavus, or clinodactyly may also be present. In addition, most have short stature with hypotonia and hyperextensible joints. Genitalia are underdeveloped with hypergonadotropic hypogonadism. Males with 49,XXXXY have a coarse face with microcephaly, ocular hypertelorism, flat nasal bridge, and upslanting palpebral fissures. Bifid uvula and/or cleft palate may be present. Skeletal abnormalities including radioulnar synostosis, genu valgum, pes cavus, or clinodactyly may also be present. In addition, most have short stature with hypotonia and hyperextensible joints. Genitalia are underdeveloped with hypergonadotropic hypogonadism. Males with 49,XXXXY have IQs between 40 and 60, and males with 49,XXXXY range between 20 to 60 [Linden et al., 1995]. Behavioral features consist of immaturity, passivity, with occasional irritability, temper tantrums, and outbursts [Linden et al., 1995].

The value of earlier studies on individuals with SCAs is questionable since the subjects were often recruited from biased ascertainment; such as, mental/penal settings, institutions for the individuals with mental retardation, and psychiatric hospitals. Recent prospective, unbiased studies have focused on individuals ascertained through prenatal screening and/or those who reside with their parents or independently. All of our participants reside at home with their parents at the time of the study.

This study is the first to characterize the similarities and differences in behavioral features seen across individuals with 48,XXYY compared to 48,XXXY and 49,XXXXY, and seeks to provide anticipatory guidance and strategies to improve outcome in life for males with these genetic conditions.

48,XXYY subjects have higher overall adaptive scales in daily living skills, socialization, and communication. Males with 48,XXYY and 49,XXXXY are lower functioning cognitively compared to 48,XXXY, since each X reduces the overall IQ by 15–16 points. This is also reflected in their weaknesses in daily living skills, socialization, and communication. Both groups have early language deficits that result in significant lower scores in the communication domain. Both groups are at risk for maladaptive behavior, although 48,XXYY males are at a higher risk for internalizing and externalizing problems. Problems in the 48,XXYY males range from anxiety and withdrawal to aggressive and delinquent behaviors. We hypothesize that males with 48,XXYY are more prone to these problems than 48,XXXY or 49,XXXXY males because their higher cognitive functioning provides more opportunities to interact in social settings. For this reason, they would be at an increased risk for encountering challenges in a more complex social settings due to their deficits in communicative and social skills. Furthermore, the most distinctive difference on the CBCL is the social contact domain between the two groups, with 48,XXYY males appearing particularly vulnerable to obstacles in social situations.

Similarities are recognized across the 48,XXYY and 48,XXXY/49,XXXXY groups in the following areas: activity level, help others, pain tolerance, morality, and rejection. Both groups demonstrate interests in helping others, but have a low tolerance for being rejected or teased. Reiss Profiles findings suggest that males with 48,XXYY are anxious and easily frustrated or impatient. They like orderliness, and they experience difficulties with transitions or changes.

### Table II. Child Behavior Checklist (CBCL): Mean, Range, SD, F- and P-Values

<table>
<thead>
<tr>
<th>CBCL</th>
<th>48,XXYY</th>
<th>48,XXXY/49,XXXXY</th>
<th>F-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing</td>
<td>16.09</td>
<td>11.62</td>
<td>1.49</td>
<td>0.235</td>
</tr>
<tr>
<td>Externalizing</td>
<td>19.27</td>
<td>13.25</td>
<td>2.85</td>
<td>0.105</td>
</tr>
<tr>
<td>Social problems</td>
<td>65.66</td>
<td>56.17</td>
<td>0.82</td>
<td>0.375</td>
</tr>
<tr>
<td><strong>Subdomains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious/depressed</td>
<td>6.55</td>
<td>5.00</td>
<td>0.55</td>
<td>0.466</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>5.45</td>
<td>3.62</td>
<td>2.64</td>
<td>0.118</td>
</tr>
<tr>
<td>Somatic</td>
<td>4.90</td>
<td>3.00</td>
<td>0.66</td>
<td>0.426</td>
</tr>
<tr>
<td>Social problems</td>
<td>9.09</td>
<td>6.08</td>
<td>7.95</td>
<td>0.010</td>
</tr>
<tr>
<td>Thought problems</td>
<td>2.64</td>
<td>2.08</td>
<td>0.31</td>
<td>0.585</td>
</tr>
<tr>
<td>Attention problems</td>
<td>9.50</td>
<td>7.00</td>
<td>3.70</td>
<td>0.068</td>
</tr>
<tr>
<td>Delinquent behavior</td>
<td>5.91</td>
<td>3.85</td>
<td>1.59</td>
<td>0.220</td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td>13.36</td>
<td>9.38</td>
<td>2.50</td>
<td>0.124</td>
</tr>
</tbody>
</table>
The results from this study are useful as guideposts for psychosocial interventions. Males with SCAs typically have global developmental delay in gross motor, fine motor, and speech and language [Graham et al., 1988, Samango-Sprouse, 2001]. Similar to males with 47,XXY, males with increased numbers of extra Xs or Ys are at risk for oral language and auditory processing problems that may place them at risk for learning deficits, emotional issues, school and/or social adjustment difficulties [Graham et al., 1988].

Parents and educators must be helped to understand the nature of the child's communication problems so as to minimize negative interactions, which may impact the child's development. Because these difficulties are chronic, it becomes extremely important that boys with tetrasomy and pentasomy receive early and ongoing speech and language therapy. Specific speech therapies should also address oral motor planning deficits and developmental apraxia. Attention should be directed toward vocabulary building and enhancing the ability to understand sentences and stories of increasing complexity [Graham et al., 1988]. They should be taught how to express their feelings and emotions in order to alleviate frustrations. They should also understand social cues when interacting with their peers in order to successfully adapt in a social environment. These goals may be accomplished through social skills training program.

A highly structured environment may be beneficial, especially in the 48,XXYY group since they prefer orderliness. Providing adequate warning prior to transitions is very important to lessen frustrations or tantrums. Since both groups have an interest in helping others, it may be valuable to assign household tasks to build self-confidence and develop competence in daily living skills. Additionally, supervised volunteer experiences may improve self-esteem and provide opportunities for positive social interactions.

In terms of educational intervention strategies, a comprehensive psychoeducational assessment is recommended to ascertain the child's strengths and challenges. An individualized educational plan (IEP) includes a language-based communication program is strongly recommended, since all males with SCAs have communicative problems. Occupational therapy and physical therapy are important to address decreased muscle tone and poor coordination in gross and fine motor skills. Exposure to peers with normal development is recommended, since it will facilitate the development of social skills and allow opportunities for individuals with SCAs to imitate and model appropriate behaviors.

The effects of supernumerary X and Y chromosomes strongly impact developmental and behavioral aspects throughout childhood and adolescence. Increasing numbers of X chromosomes affect physical and cognitive profiles more than behavioral characteristics. Since additional Y chromosomes are often accompanied by additional X chromosomes (48,XXXXY, 49,XXXXXY), it is difficult to pinpoint specific features in these phenotypes that are unique to either the X or Y chromosome [Linden et al., 1995]. Furthermore, relative to the general population, people with mental retardation are twice as likely to encounter significant psychopathology. It is recognized that individuals with mental retardation are at risk for maladaptive behaviors which may not be present in those without mental retardation [Dykens, 1999]. Certain behaviors may wax and wane with age. At present, researchers have yet to address how behavioral problems in males with 48,XXXXY, 48,XXXXY, and 49,XXXXXY change over the course of development. We hope this study will spark interest in additional unbiased prospective studies on polysomy X and/or Y group that will help provide a better understanding concerning the number of additional sex chromosomes and their influence on the behavioral phenotype and its treatment.

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