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The Cognitive Phenotype in Klinefelter Syndrome: A Review of the Literature Including Genetic and Hormonal Factors

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Abstract

Klinefelter syndrome (KS) or 47,XXY occurs in ~1 in 650 males. Individuals with KS often present with physical characteristics including tall stature, hypogonadism, and fertility problems. In addition to medical findings, the presence of the extra X chromosome can lead to characteristic cognitive and language deficits of varying severity. While a small, but significant downward shift in mean overall IQ has been reported, the general cognitive abilities of patients with KS are not typically in the intellectual disability range. Most studies support that males with KS have an increased risk of language disorders and reading disabilities. Results of other studies investigating the relationship between verbal and nonverbal/spatial cognitive abilities have been mixed, with differing results based on the age and ascertainment method of the cohort studied. Executive function deficits have been identified in children and adults with KS, however, the research in this area is limited and further investigation of the neuropsychological profile is needed. In this article, we review the strengths and weaknesses of previous cognitive and neuropsychological studies in males with KS in childhood and adulthood, provide historical perspective of these studies, and review what is known about how hormonal and genetic factors influence cognitive features in 47,XXY/KS.

Keywords

attention; language; intelligence; XXY; Klinefelter syndrome

Introduction

Klinefelter syndrome (KS) (47,XXY) occurs in ~1 in 650 males, and is associated with a physical phenotype that can include tall stature, hypogonadism, and fertility problems. Although there have been many studies investigating the medical aspects of males with KS, it is also known that the presence of the extra X chromosome can lead to characteristic cognitive and language deficits of varying severity.

The literature on cognitive and psychological features of individuals with KS has developed over three phases. The first set of literature followed the original description of the condition by Dr. Klinefelter in 1942 and the 1959 discovery by Dr. Patricia Jacobs that the clinical phenotype was due to the presence of an extra X chromosome [Klinefelter et al., 1942;

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Jacobs and Strong, 1959]. Increased rates of intellectual disability and other mental health problems were described in multiple studies, usually in samples ascertained in mental health hospitals or long-term care facilities for individuals with developmental disabilities [Eriksson, 1972; Johnston et al., 1974; Singh et al., 1974; Bourgeois and Benezech, 1977]. This literature soon received criticism due to recognition of the ascertainment bias, especially as additional genetic studies demonstrated the high prevalence of 47,XXY in the population [Jacobs et al., 1971; Hamerton et al., 1975; Lin et al., 1976]. However, it is important to keep in mind that these papers emerged during the period when chromosomes were first able to be visualized and when chromosome studies were being introduced to clinical medicine, and there was significant research interest in identifying medical and psychological correlates to chromosomal differences. Also, in this era important questions in psychology research related to the “nature versus nurture” debate, and these early studies on populations affected by cognitive and psychiatric disorders were among the first to show a direct association between psychological factors and genetic differences that could be directly tested.

The next set of studies on males with KS were designed in response to these initial biased studies, and included newborn screening of large populations to identify neonates with 47,XXY, and then prospective follow-up of these children through adolescence and young adulthood. These studies took place in many sites around the world, including Denver, Edinburgh, Toronto, and other sites, and the investigators met frequently to discuss findings in their cohorts and to pool results [Netley, 1986; Ratcliffe et al., 1990; Robinson et al., 1990]. These prospective studies form the basis of our current knowledge on developmental, cognitive, and behavioral characteristics in males with KS, and demonstrated that cognitive outcomes in males with KS were much better than the original literature suggested. The strengths of these studies include the selection of subjects from birth cohorts, prospective design and long-term follow-up. Many of the studies also used sibling controls which were valuable in controlling for socioeconomic status (SES), parenting styles, and other environmental factors. However, it is important to point out that while significant important literature resulted from these studies, the cohorts were still relatively small, with frequent psychological assessment and follow-up through their lives. For example, the Denver study consisted of a cohort of 15 patients with KS, the Toronto study included results on 31 patients, and the Edinburgh study included results on 19 patients. Thus, relative to the prevalence of KS in the general population, these results are based on repeated studies on relatively small sample sizes.

A third group of studies have emerged after the completion of the prospective studies, and describe more specific aspects of the psychological characteristics in males with KS including neuropsychological studies and studies correlating cognitive outcomes to various genetic factors [DeLisi et al., 1994; Boone et al., 2001; Zitzmann et al., 2004; Zinn et al., 2005; van Rijn et al., 2006; Ross et al., 2008]. Patients from these studies are generally recruited through clinical samples or advocacy groups, and thus ascertainment bias is again a weakness of these studies and the results do not represent the entire spectrum of outcomes seen in KS. It is now clear that many individuals with KS are not significantly affected by cognitive or psychological problems, and a large percentage of males with KS are highly successful in their academic achievements, personal lives and careers. However, there is a neuropsychological phenotype related to the presence of the extra X chromosome that can include cognitive, language, and other psychological impairments. The subgroup that is most affected by these problems is important to study in order to develop clinical recommendations and educational interventions, and perhaps to help us identify the genes on the X chromosome associated with the psychological features of males with KS.

In this article, we review the literature on cognitive and neuropsychological studies in males with KS in childhood and adulthood, and discuss what is known about how hormonal and genetic factors influence cognitive features of 47,XXY/KS.

Cognitive Outcomes

Contrary to other genetic syndromes that arise from chromosomal trisomy (e.g., Down syndrome, Trisomy 18), the general cognitive ability of patients with KS is not typically in the intellectual disability range. Early studies performed on this clinical population usually included a measure of general cognitive ability (IQ), thus, there are now numerous studies that have reported cognitive outcome data, both in cross-sectional as well as longitudinal samples.

In general, most studies have shown that the mean cognitive ability in patients with KS falls in the average to low average range, with statistically significant discrepancies shown relative to the population mean or sibling/control groups [Netley and Rovet, 1982b; Pennington et al., 1982; Graham et al., 1988; Ratcliffe et al., 1994; Rovet et al., 1996; Geschwind et al., 1998]. These studies have generally shown a normal distribution of scores, but with a small downward shift of the curve (see Fig. 1) which is thought to be driven by deficits in the verbal conceptual domain, rather than the nonverbal reasoning or spatial domain. Although the overall cognitive ability standard score [i.e., Full Scale IQ (FSIQ)] in these studies is usually in the 90's, the average magnitude of the difference between Verbal IQ (VIQ) and Performance IQ (PIQ) has been as little as a few standard score points in some studies to as much as one standard deviation difference in others. The reasons for this variability are not entirely clear; however, each study varies in sample size, method of ascertainment, as well as previous treatment and parental SES.

Regarding the effects of SES, the effect of environmental and background genetic factors in the eventual cognitive outcome of patients with KS should not be underestimated.

For example, Samango-Sprouse followed a cohort of 60 children with XXY from age 2 through age 7 who were prenatally ascertained but came from an upper middle class SES population (i.e., 90% of these parents had a college or graduate degree). These parents proceeded with the pregnancy despite finding out that their child had XXY syndrome, and thus a high level of concern and resource investment can be assumed. The developmental and psychometric evaluations showed that these children with KS manifested many of the physical and developmental delays characteristic of this population (i.e., truncal hypotonia, sensory defensiveness, expressive speech, and language delays), but yet, the mean IQ for the sample was 110, which is in the high average range [Samango-Sprouse, 2001].

The studies of children with KS highlight a few important points: patients with KS do not generally have general intellectual deficiency; they also do not represent a lower group in a bimodal distribution. Some patients with KS have above average or superior cognitive ability, although, as the diagram in Figure 1 would suggest, the percentage of those attaining those levels of functioning is slightly lower than in the general population.

As previously mentioned, a few larger cohorts of children with KS were identified a few decades ago via perinatal genetic screenings. Although the sample sizes were limited, the studies helped to eliminate some of the ascertainment bias confound (albeit some bias still exists in terms of who decided to participate in the study, etc) and the longitudinal design revealed some interesting patterns.

In the Denver longitudinal cohort, Pennington et al. reported cognitive scores for 15 children with KS: the mean VIQ score was 89.2 while the PIQ was around 100 on the Wechsler

Preschool and Primary Scale of Intelligence when the children with KS were 4–5 years of age [Pennington et al., 1982]. The decrement in verbal-conceptual skills was quite apparent even at this early age. A subset of these children (n = 14) was followed into adolescence (age 14–17) and their cognitive skills measured using the Wechsler Intelligence Scale of Children-Revised. This time the mean VIQ was 97.9 and the mean PIQ was 99.5, a nonsignificant difference [Bender et al., 1989]. A subgroup of 11 participants from this same cohort were then tested as adults [Bender et al., 2001], and some small differences again emerged with Wechsler Adult Intelligence Scale-Revised mean Vocabulary and Information subtests scaled scores being lower (7.64 and 7.09, respectively) than Object Assembly and Picture Completion subtests (8.55 and 10.3).

Although one might argue that the comparison is not perfect due to the attrition over time, these data seem to suggest that differences in verbal-conceptual and nonverbal reasoning skills diminish over time, with the former no longer being such an area of deficit. One possible explanation posited by the Denver cohort investigators is that the language deficits that continued to be apparent as these children got older (i.e., lexical retrieval efficiency, verbal memory, speed of verbal processing) were not captured by the cognitive tests at older ages; this is in contrast to the more basic expressive vocabulary and language deficits that manifest at earlier ages that do influence performance on measures of Verbal IQ.

Interestingly, a recent study by Ross et al. showed no discrepancy between verbal and nonverbal reasoning skills even at young ages [Ross et al., 2008]. In one of the largest cohorts investigated to date, Ross et al. reported on the cognitive functioning of 50 children with KS ages 4 through 17, using the differential ability scales (DAS). This measure is similar to the Wechsler IQ test series, and in fact has a high correlation with the latter. In this study, scores were reported for younger and older subgroups, based on a median age split (at 10 years of age). The DAS verbal and nonverbal cluster standard scores were 90.6 and 90.9, respectively, in the younger group, and 84.4 and 84.6 in the older group, indicating no disparity between verbal and nonverbal reasoning ability at either age range. This is contrary to previous findings of relative verbal conceptual deficits at least in younger ages reported by other investigators.

It should be noted that not all of the longitudinal studies showed this elimination of the VIQ-PIQ discrepancy. In the Toronto cohort, the difference between these two conceptual domains in a group of children (n = 28) tested at regular intervals from age 6 through age 20 remained stable over time [Rovet et al., 1996].

Researchers have also reported on the cognitive outcome of cross-sectional samples of adult patients with KS. A study by Boone et al. described three subgroups of adult patients with KS, all with overall cognitive abilities in the average range (FSIQ range = 95.25–101.25) [Boone et al., 2001]. Interestingly, one group had a significant VIQ decrement relative to PIQ, while another had the opposite pattern. The third group showed no difference between verbal conceptual and nonverbal reasoning skills. Older age was significantly correlated with the increase in VIQ relative to PIQ. The authors hypothesized that the relative PIQ decrement might materialize in young adulthood as a result of hormonal abnormalities detected during puberty. Others have speculated that the pattern in this group may reflect increased language processing ability related to the androgen treatment in these older males. It could also be the case that the PIQ decline in older patients with KS could be due to a faster than normal deterioration in nonverbal processing skills than what is typically observed during the aging process.

Another study of adults with KS in Denmark reported cognitive ability scores for 34 adults with KS who were identified based on a screening of consecutive admissions to a Male

Hypogonadism Study Section at a hospital in Copenhagen [Nielsen and Pelsen, 1987]. The results of the cognitive testing showed that this cohort had normal FSIQ scores (Mean = 102.8, SD = 11.2), and no discrepancy between VIQ and PIQ (101.9 versus 103.4, respectively). Interestingly, other aspects of these patients' psychosocial functioning were also assessed. The participants with KS reported fewer friends, few or no leisure interests, poor relations with siblings or parents, and little energy and initiative. A higher proportion, compared to a control group of patients with 46,XY who had been identified with hypogonadism, was also classified as being unskilled laborers. These findings, along with others that document psychiatric and social difficulties in this population, highlight an important point: adaptive functioning is not only dependent on general cognitive functioning, but also on the ability to use these skills purposefully in order to adapt to the dynamic social and work demands of everyday life.

These findings, along with others that document psychiatric and social difficulties in this population, highlight an important point: adaptive functioning is not only dependent on general cognitive functioning, but also on the ability to use these skills purposefully in order to adapt to the dynamic social and work demands of everyday life.

Overall, there is significant variability in the cognitive outcome of children and adults with KS. A small, but significant downward shift in overall IQ has been reported, but, on average these patients are not intellectually disabled. The language (and later academic) deficits that are seen in this population do seem to mediate the effect on verbal conceptual reasoning skills; however, these effects seem to be more prominent at younger ages. Longitudinal and adult outcome studies have reported less of a discrepancy between Verbal and Performance IQ. Finally, there are multiple factors that likely determine what the ultimate cognitive functioning is likely to be for individuals with KS. Some of these may be inherent in the way their extra X chromosome interacts with other background genes as well as environmental factors. Other factors, however, include SES, treatments and interventions, and educational variables. Future studies will benefit from attempting to understand the interaction among cognitive, linguistic, executive functioning, social and psychiatric strengths and weaknesses, as it is this interplay that will ultimately decide what the adaptive functioning of these patients is likely to be.

Language and Learning Disabilities in KS

Apart from general cognitive outcome, language and academic difficulties are the most widely studied cognitive domain in individuals with KS. There are now a number of studies in the literature that describe the language and reading difficulties, in particular, of children and adults with KS.

Language difficulties have been identified in 70–80% of children with KS starting at an early age. This finding has been relatively robust, being shown in prospectively ascertained samples [Leonard et al., 1979; Ratcliffe, 1982; Walzer et al., 1982; Bender et al., 1983a; Graham et al., 1988]. A study by Robinson et al. which looked at children identified with KS from a cohort of 40,000 births at a public hospital in Denver, CO, also noted that children with KS had delays in speech that were identifiable as early as 24 months of age [Robinson et al., 1979]. These studies were significant because they tested children prior to school age, and thus showed that speech and language problems preceded the academic achievement deficits that they would demonstrate at later ages. These early studies showed that difficulties with articulation, phonemic processing, and word retrieval, in addition to more general delayed expressive language skills, were common in children with KS.

Although most of the studies have identified expressive speech and language difficulties as primary, receptive language deficits have also been noted. Problems with phonemic discrimination, processing speed, and comprehension of grammatical and morphological aspects of language have been reported [Graham et al., 1988; Walzer et al., 1990; Bender et al., 1993]. Netley and Rovet also showed a significant difference between patients with KS and controls on a sentence verification task, where participants had to judge the veracity of sentences of varying linguistic complexity relative to a picture stimulus [Netley and Rovet, 1982b]. In their 2004 review of the literature, Geschwind and Dykens noted that auditory processing and verbal memory are core cognitive deficits that underlie many of the linguistic deficits seen in patients with KS [Geschwind and Dykens, 2004]. Thus, tasks with increased perceptual discrimination or short term memory demands are usually the ones where patients with KS struggle most.

Language difficulties in adolescence and adulthood have been identified in cohorts of patients followed longitudinally, or tested cross-sectionally at later ages. Bender et al. showed that adolescents with KS had significantly worse auditory memory, confrontation naming, and verbal fluency skills than matched controls [Bender et al., 1989, 1993]. In the Toronto longitudinal study [Rovet et al., 1995, 1996], children with KS were followed from age 6 to age 20. The study showed depressed verbal conceptual ability on IQ testing, with significant deficits in subtests measuring auditory memory, language comprehension, and expressive abilities. In this cohort, children with KS were deficient in comprehending and using syntactic information to judge the veracity of sentences [Netley and Rovet, 1982b]. Finally, studies conducted with unselected samples of adults have also shown impairment in verbal memory, verbal fluency, and confrontation naming (word retrieval) ability [Geschwind et al., 1998; Boone et al., 2001].

Another quite consistent finding reported in the literature on individuals with KS has been the extent to which these patients demonstrate deficits in academic achievement throughout their academic careers. Early studies that looked at the proportion of patients receiving special education support reported significantly elevated numbers of children with KS having academic difficulties in school, particularly in the literacy and spelling domains [Pennington et al., 1982; Robinson et al., 1986]. Approximately 50–75% of boys demonstrate a specific reading disability at some point in their development [Bender et al., 1986b; Graham et al., 1988].

As studies began to look more systematically at the academic achievement of children with KS, some have noted that the achievement gap is not constrained to the literacy domain. In the Toronto longitudinal study, the authors reported significantly lower achievement of children with KS compared to sibling controls on tests of word decoding, reading comprehension, spelling, written language skills, arithmetic, and math problem solving [Rovet et al., 1996]. Additionally, their performance on the standardized achievement tests declined relative to age and grade expectations, such that by the last time point (18–20 years of age), they were performing more than five grade levels behind the control group for reading and arithmetic skills. Thus, the academic deficits were not solely in the area of literacy, as some other studies have found, but also included problems in math calculation and problem solving, suggesting that at least a subgroup of children with KS demonstrate a more generalized learning disability profile.

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Similar to the oral language difficulties discussed earlier, academic difficulties of patients with KS can also persist into adulthood. In a study by Geschwind et al., ~ 70% of adult

participants showed evidence of reading disability [Geschwind et al., 1998]. Similar deficits in the literacy domain were reported by Boone et al. although in this study single word decoding was not as impaired, relatively speaking, as has been noted in the pediatric studies [Boone et al., 2001].

Although the preponderance of the evidence points to a specific cognitive profile in patients with KS, with verbal and language based skills being relative weaknesses, it is also important to note that there is significant variability among participants in these studies. For example, while the participants with KS in the Toronto longitudinal study showed a stable pattern of verbal conceptual skill weakness (VIQ) compared to nonverbal reasoning skills (PIQ) over time, other studies have reported different results. For example, a recent study by Ross et al. in 2008 that reported on the neurocognitive and academic achievement of 50 boys ranging in age from 4–18 years of age, there was no discrepancy between verbal and nonverbal reasoning skills, with both of these scores for the group being in the average to low average range [Ross et al., 2008]. Surprisingly, the academic achievement of the Ross et al. cohort was also in the average range on measures of single word decoding, spelling, and arithmetic. Furthermore, when the sample was broken down into younger (<10 years) and older patients (>10 years), academic performance did not seem to decline with age in any of the academic domains. A similar profile, where verbal conceptual skills were on par with nonverbal reasoning skills was seen in the testing of adolescent patients followed longitudinally in the Denver sample [Bender et al., 1993].

There are inconsistent findings in the language domain as well. Although receptive language skills have been reported as deficient in some studies, Graham et al. reported that children with KS scored within the normal range relative to age norms on all receptive language measures except for one measuring syntactic comprehension [Graham et al., 1988]. Bender et al. also noted no significant difference on the Token Test, which measures the ability to understand and process directions of increasing length and syntactical complexity [Bender et al., 1986a].

The recent study by Ross et al. also reports some inconsistent findings [Ross et al., 2008]. It is noteworthy that the sample size of this study is one of the largest reported to date in the pediatric age group. Although it has some limitations (e.g., lack of a control group, mixture of clinical and prenatal ascertainment), the larger N provides some extra reassurance that findings are not spurious. Contrary to previous studies, Ross et al. did not find evidence of expressive or receptive vocabulary problems in their cohort of patients. Furthermore, word retrieval skills on phonemic as well as semantic verbal fluency tasks were also normal. They did find that the patients with KS had difficulty with rapid naming skills (but only with colors and objects, and not when naming digits or letters), as well as on tasks measuring higher order language comprehension and formulation. Unfortunately, the latter tests do not measure syntactic or morphological competency as cleanly, thus precluding any conclusion about this particular cohort's skills in these more basic language skills.

Overall, the variability of results across studies is not that surprising. Apart from the likelihood that the disorder itself can have variable phenotypic expression, there are also several methodological factors in the way the syndrome has been studied that likely contribute to the variability in the literature. The latter include the small sample size of most of the studies, use of different types of control groups, the wide age range of the participants in many of the cohorts studied, the disparate batteries of tests that have been used to measure constructs of interest, and variability in the consistency with which possible mediating factors were controlled. In some studies, significant differences between children with KS and a control group were found, but the scores of the group with KS were not that discrepant from age norms. Statistical comparisons can often be misleading when sample sizes are

small; reporting of effect sizes would be useful in this regard, but few studies do so. In addition, it is important to note that there can be multiple reasons for a child's deficient performance on a particular task, especially for those tasks that are overdetermined.

Other important factors that have not been consistently controlled in previous studies, but that may mediate the neurocognitive outcome of patients with KS include the amount of special education or tutoring intervention children in the KS group received; whether or not they were naive to testosterone treatment; parental education and SES differences, and family history of speech, language or reading disability. The latter is particularly critical given the deficits being documented have genetic underpinnings in nonaneuploidy populations. Subgroups of individuals with KS may in fact be inheriting a genetic predisposition from allelic variations of genes on nonsex chromosomes that affect verbal and reading deficits, in addition to the effects of having an extra X chromosome. Understanding how background genetic influences add to, or interact, with sex-chromosome aneuploidy is important; yet, none of the studies to date have documented whether there are differences in outcome between patients with KS with and without a family history of speech, language, reading, or attentional disorders.

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Some of the studies in the literature have attempted to show that the cognitive profile in patients with KS with reading deficits is similar to that of children with dyslexia who do not have sex-chromosome aneuploidy [Bender et al., 1986a; Graham et al., 1988]. However, studies to date have not attempted to test cognitive models of reading and language deficits in KS. Various models now exist for language and reading disability in nonaneuploidy populations with specific combinations of endophenotypes accounting for, and predicting, language and reading outcome over time [Pennington, 2006; Pennington and Bishop, 2009]. Endophenotypes that have been found to be significant in such models include phonological representations/awareness, phonological memory, verbal, and nonverbal processing speed, as well as nonverbal IQ. Protective factors also need to be measured and analyzed; for example, it has also been recently reported that children with language disorder (who have no history of speech sound disorder) and whose rapid automatized naming is within normal limits are at less risk for developing dyslexia [Bishop et al., 2009]. Testing these types of models in KS would allow for a more robust understanding of whether the same underlying cognitive factors are indeed responsible for symptom level phenotypes. Finally, with advances in functional brain imaging, as well as genotyping and gene expression testing, the next wave of research in KS should integrate findings across various levels of analysis, allowing for a more complete story to unfold regarding the interplay among genetic, neurobiological, cognitive, and environmental etiological factors that contribute to the clinical phenotype.

Executive Function Studies

The term executive function (EF) refers to a general neuropsychological construct that encompasses a variety of higher order processes responsible for purposeful, goal-directed problem-solving [Gioia et al., 2002]. Important components of the executive system include self-awareness, initiation, inhibition, judgment, planning, organization, and decision making. The regulatory control of behavioral and emotional responding is often described within the EF domain, as is “working memory” or the ability to hold information in mind while completing a specific task. The relationship between the domains of attention and EF is complex, though the constructs undoubtedly overlap and are closely linked. In children and adults with KS, deficits in attention and EF are often reported anecdotally; however, actual

empirical studies are fairly sparse and hampered by a number of methodological problems (see Table 1).

Only one identified study systematically assessed attention and response inhibition using standardized neuropsychological tests in the KS population [Ross et al., 2008]. Impulsivity was not seen across the sample and interestingly, attention problems were only seen in children younger than 10 years of age. The authors posit that attention problems either resolve as children become older or children develop compensatory strategies that improve their performance. Others suggest that distractibility results from children having difficulty remaining on-task during work that is not understood and that attention problems may be secondary to verbal processing problems or learning disabilities rather than an independent comorbid attentional disorder [Rovet et al., 1996]. However, recent studies continue to report increased rates of ADHD and attentional problems in clinical samples of children with XXY [Tartaglia et al., 2006; Ross et al., 2008; Bruining et al., 2009], and further research about how the attention deficits may be related to broader executive function deficits or other cognitive factors is needed.

Only three studies were identified that investigated EF in children and adolescents with KS. Despite reports from parents and professionals of EF deficits, extant studies have generally documented intact skills on performance-based testing. Temple and Sanfilippo administered a comprehensive test battery to three boys with KS [Temple and Sanfilippo, 2003]. Although they documented deficits in inhibition, other EF skills, including concept formation, problem solving, task shifting, and planning, were all within the average range. Similarly, Ross et al. documented intact cognitive flexibility and fluency in their sample of 50 children aged 4–17 years [Ross et al., 2008]. In contrast to Temple and Sanfilippo's study, they did not find problems with inhibition. Bender and colleagues administered two EF tests, the Wisconsin Card Sorting Test and the Trail Making Test, to 14 adolescents with KS [Bender et al., 1993]. While performance on the Wisconsin Card Sorting Test, an untimed measure of concept formation, was average, low scores were obtained on the Trail Making Test, a timed test of working memory, attention, and cognitive flexibility. As strategic information processing was intact on the Wisconsin Card Sorting Test, the authors suggest that poor scores on the Trail Making Test may reflect slow processing speed rather than an independent EF deficit.

Similar to the pediatric literature, few studies have investigated EF in adults with KS. Boone and colleagues completed the largest study to date, which included 35 adult men with KS [Boone et al., 2001]. Compared to controls, men with KS demonstrated deficits on several EF tasks. The sample was divided into men with a VIQ < PIQ profile on IQ testing and men with a PIQ < VIQ profile. The group with the lower VIQ had more deficits on verbal EF tasks (including Verbal Fluency, Stroop Test, and Auditory Consonant Trigrams) while the group with the lower PIQ had more deficits on nonverbal EF tasks (including Wisconsin Card Sorting Test and Design Fluency).

The EF construct of working memory was investigated by Fales et al. in adult men with KS [Fales et al., 2003]. Deficits were found only on tasks of verbal working memory, whereas intact performance was seen on a nonverbal reasoning test. On the basis of these findings, the authors conclude that there is little support for the hypothesis of a global EF deficit in the KS population. Rather, they suggest that executive dysfunction is limited to the verbal domain and may result from childhood verbal deficits that continue into adulthood. A study by Bender et al. supports this contention, as they also failed to find deficits on a nonverbal measure of EF [Bender et al., 2001]. However, neither study explored executive skills in the context of other deficits, as the Boone et al. study did.

Given frequent anecdotal reports of EF problems in individuals with KS, the failure of most of these studies to find clear EF deficits may be surprising. However, the studies are characterized by a number of methodological limitations that need to be considered before drawing any firm conclusions. Of the three studies completed with children and adolescents, for example, two had small sample sizes [Bender et al., 1993; Temple and Sanfilippo, 2003], and the third was quite limited in the measures utilized, including only two tests of attention and EF skills [Ross et al., 2008].

To further understand the exact nature of EF difficulties in the population of individuals with KS, future studies will require larger sample sizes. This will allow subgroups of children to be established, including grouping children by IQ patterns, as done by Boone with an adult sample [Boone et al., 2001], or by the presence or absence of a language or reading disorder. Comparing performances between groups can help to elucidate patterns of EF skills seen in children with different cognitive profiles.

Future studies should also include both verbally mediated and nonverbally mediated EF tasks, as well as measures to simultaneously assess various aspects of attention (e.g., focused attention, sustained attention). Studies will need to include measures of other cognitive processes as well, including language skills, visual-perceptual skills, memory, and processing speed, to further understand how these cognitive processes contribute to any EF deficit. This will help to answer questions posed by previous researchers, such as whether attentional problems are a distinct deficit or secondary to language problems. In the Boone study sample, there was no correlation between deficits in language and EF skills, suggesting independent comorbidities [Geschwind et al., 2000]. Such findings will be important to explore in children with KS as well.

Research should also move toward a broader assessment of EF skills, including utilizing newer performance-based measures that evaluate EF in a developmentally appropriate manner. In recent years, there has also been criticism of an exclusive reliance on traditional, “paper-and-pencil” means of assessing EF skills, because the highly structured and controlled nature of the testing environment may not place enough demands on the executive system to accurately identify deficits [Bernstein and Waber, 1990]. Performance-based EF tests have also been criticized for having limited ecological validity, in that test performance does not always correlate with “real world” functioning [Gioia and Isquith, 2004]. As such, questionnaires have been developed that are completed by parents, teachers, and spouses to assess specific EF skills in the home and school environments. Use of such questionnaires in research with individuals with KS will help to gain not only a better understanding of the EF profile for individuals with KS, but also how these deficits manifest in everyday settings. In turn, this information can be used in combination with performance-based tests to develop appropriate treatments and therapies focused on EF difficulties.

Cerebral Dominance in KS

In typical brain development, there is asymmetry of language functioning between cerebral hemispheres, with language functioning localized to the perisylvian cortex of the left cerebral hemisphere in most right-handed individuals. In left-handed individuals or in those who are “nonright-handed,” these asymmetries can be reduced or reversed, leading to anomalous cerebral dominance. Thus, due to the language deficits in individuals with KS, there has been much interest in determining if increased rates of nonright-handedness and anomalous cerebral dominance may be more prevalent in KS and may explain the weaknesses in language skills. While there have been conflicting studies as to whether rates of nonright-handedness are increased in males with KS compared to the general population [Netley and Rovet, 1982a; Bender et al., 1983b; Geschwind et al., 1998; Ross et al., 2008],

many studies have reported findings from functional neuropsychological tasks and dichotic listening tasks that support higher rates of anomalous dominance [Garvey and Mutton, 1973; Netley and Rovet, 1984]. Also, neuroimaging studies have supported decreased left temporal lobe volumes [Patwardhan et al., 2000; Giedd et al., 2007], correlation of left temporal lobe volume with verbal cognitive measures [Itti et al., 2006], and loss of asymmetry on SPECT neuroimaging in right-handed males with XXY compared to controls [Itti et al., 2003]. The 2008 study by Ross et al. also identified significantly higher cognitive skills in both verbal and nonverbal tasks in right-handed children with XXY compared to the nonright-handed group [Ross et al., 2008]. Based on these results, there is great interest in the role of genetic and/or hormonal mechanisms on the degree of cerebral laterality in males with KS, and how this affects cognitive, learning, and psychosocial functioning.

> In recent years, there has also been criticism of an exclusive reliance on traditional, "paper-and-pencil" means of assessing EF skills, because the highly structured and controlled nature of the testing environment may not place enough demands on the executive system to accurately identify deficits…

Genetic and Hormonal Factors Affecting Cognition in KS

Although language and learning deficits are associated with KS, many unanswered questions remain regarding what aspects of the cognitive phenotype and phenotypic variability may be related to genetic effects of the extra X chromosome, the effect of androgen deficiency, or a combination of the two. As most aspects of the cognitive phenotype including speech/language delays, language-based learning disabilities, and strengths in nonverbal cognitive skills are similar to other sex chromosome trisomy conditions not typically associated with hormonal deficiency (47,XYY and 47,XXX), it is likely that genetic factors associated with the trisomy state play a more significant role in the cognitive phenotype than hormonal factors. Also, features of the cognitive phenotype often present in early childhood with speech/language delays and learning disabilities, prior to the onset of hormonal deficiency. While new studies support the idea that androgen deficiency may be present in the neonatal and prepubertal period in male children with XXY [Lahlou et al., 2004; Ross et al., 2005], another study suggested increased neonatal testosterone levels in KS relative to a large group of controls [Aksglaede et al., 2007]. Improved testosterone assays and additional studies will be needed to clarify if prepubertal androgen deficiency or androgen resistance is present in children with KS.

There is little dispute that measurable differences in androgen levels in males with KS emerge during adolescence and/or young adulthood when compared to control groups [Winter, 1990; Aksglaede et al., 2008], at which time the cognitive and neuropsychological differences are generally established. Neuroanatomical differences in temporal and frontal lobe volume are present in prepubertal children with KS compared to controls [Giedd et al., 2007], again generally supporting a genetic etiology. In typical children, prenatal and childhood levels of androgen have been shown to be positively correlated with spatial abilities and negatively correlated with language abilities [Knickmeyer et al., 2005], and thus if the cognitive phenotype in KS were related solely to early androgen deficiency, one would expect to find decreased spatial abilities relative to language skills. However, early androgen levels play a role in neurodevelopment and brain lateralization [Swerdloff et al., 1992; Friederici et al., 2008; Mercure et al., 2009], so further studies to understand prenatal and prepubertal androgen differences in males with KS and how they affect the cognitive phenotype of KS are important. Also, with increasing recognition that neurodevelopment continues through adolescence into young adulthood, there may also be important effects of androgen deficits on the maturing brain in adolescent and young adult males with KS [Giedd et al., 2006; Lenroot and Giedd, 2006]. In addition to organizational effects of androgen, the continuous effects of androgen on central nervous system (CNS) functioning also seem to

affect psychological functioning in adults with KS, although further studies are needed in this area.

Genetic Factors

Proposed genetic mechanisms to explain the phenotypic differences have included: (1) mosaicism, (2) polymorphisms of specific genes on the X-chromosome, (3) parent-of-origin of the extra X chromosome due to imprinting differences or X-chromosome isodisomy, and (4) gene dosage effects of X-chromosome genes that escape X-inactivation [Geschwind et al., 2000].

Mosaicism is the term used to describe a state in which there is more than one population of cells within an individual, and in KS this can include individuals with 46,XY/47,XXY, 47,XXY/48,XXXY, or other variations. The most common form of mosaicism in KS is 46,XY/47,XXY, and in general individuals with this genotype with a typical 46,XY cell line have been shown to have improved endocrine function and fertility rates compared to nonmosaic males [Stewart et al., 1990; Seo et al., 2006]. While studies in other aneuploidy groups such as Down syndrome (Trisomy 21) and females with sex chromosome aneuploidy (Turner syndrome and 47,XXX) have shown improved cognitive outcomes in individuals with mosaicism [Fishler et al., 1976; Bender et al., 1990], results of the prospective studies that directly compared males with 46,XY/47,XXY mosaicism to males with 47,XXY did not find significant differences in cognitive profiles [Netley, 1986; Stewart et al., 1990]. However, these studies included very small sample sizes of mosaic patients ranging in size from only 3–6 patients, and also did not report on the percentage of mosaicism in each case. There are not comparative studies between 47,XXY and individuals with mosaicism with a tetrasomy and/or pentasomy cell line (such 47,XXY/48,XXXY), however, case reports of individuals with these forms of mosaicism show increased cognitive deficits compared to typical males with 47,XXY due to the effect of the tetrasomy cell line. Thus, it is generally accepted that mosaic patients with a 46,XY cell line (46,XY/47,XXY) have fewer phenotypic features of KS than nonmosaic patients, and that mosaicism with tetrasomy or pentasomy cell lines (47,XXY/48,XXXY) have more significant cognitive impairments. Further studies are needed to determine how the degree of mosaicism affects cognitive and psychological functioning. The methodology of these studies in human subjects is complicated by the lower prevalence of 46,XY/47,XXY mosaicism compared to nonmosaic 47,XXY, and recognition that the degree of mosaicism measured in blood leukocytes may not be equivalent to what is present in brain or other tissues.

Genetic polymorphisms of specific genes on the X-chromosome have also been proposed to account for some of the phenotypic variability in males with KS, and the androgen-receptor (AR) gene on the X-chromosome has of particular interest due to the androgen deficiency associated with KS. The AR gene is polymorphic in the number of CAG (cytosine-adenine-guanine) trinucleotide repeats in the coding sequence of the gene, and the length of the CAG repeat inversely correlates with the responsiveness of the receptor to testosterone [Zitzmann, 2009]. It has been proposed that in males with KS, having an AR gene with a lower number of CAG repeats may be associated with an improved response to circulating androgen and less severe phenotypic features of KS. In a 2004 study of 77 males, age 18–65, newly diagnosed with KS, Zitzmann et al. found that in those with a longer AR CAG repeat length had more significant physical features of KS (taller adult height and higher rate of gynecomastia), as well as lower rates of professional employment and decreased likelihood of being in long-term relationships [Zitzmann et al., 2004]. These results suggested that a short AR CAG repeat length was associated with less significant physical features and improved social outcomes in males with XXY. Although this study was the first to identify a specific gene that may be related to the phenotypic features of XXY, direct assessment of cognitive or adaptive functioning of the subjects was not performed. Two subsequent studies

failed to find a significant association of AR CAG repeat length and cognitive measures. Ross et al. directly evaluated 50 children with XXY age 4–17 with a comprehensive battery of standardized cognitive, executive function, language, and motor assessments, and there were no significant differences between those with short and long AR CAG repeats except for in one subtest of spatial cognition, in which those with a long AR CAG repeat length had improved scores (opposite to predicted direction of effect found in the Zitzmann study) [Ross et al., 2008]. Another study that directly assessed IQ in 54 males with XXY age 2–56 also found no relationship to AR CAG repeat length [Stemkens et al., 2006]. Although these studies give conflicting results, they were completed on populations who differ greatly in age and androgen exposure (a subgroup of children in the Ross study were being actively treated with androgen therapy), which may have affected the results. For example, the differences in receptor responsiveness may be more significant in individuals who have not received exogenous testosterone treatment or who have lower levels of testosterone production before supplementation. Studies that evaluate these factors including age, androgen levels, and androgen treatment status will be important to determine if there is in fact any relationship between the AR CAG repeat length and the psychological phenotype of individuals with KS.

The relationship of the parent-of-origin of the extra X chromosome has also been studied to determine if phenotypic variability may be related to an imprinted sex chromosome locus leading to differential expression of maternal versus paternal alleles, or to X-chromosome isodisomy leading to expression of X-linked recessive genes. For example, a subset of girls with Turner syndrome have only one X chromosome (45,X), and studies in children with 45,X have shown that the parent-of-origin of the single X chromosome affects the phenotype. Females with Turner syndrome with a maternally inherited X chromosome are more likely to have social deficits and autistic behaviors than those with a paternally inherited X chromosome [Skuse et al., 1997]. In males with XXY, the additional X chromosome is maternally inherited in ~50–60% of cases [Thomas and Hassold, 2003; Hassold et al., 2007], and results of studies that have looked at the effect of parent-of-origin on the cognitive phenotype have generally supported that parent-of-origin of the extra X chromosome has no significant effect on cognitive phenotype [Jacobs et al., 1988a,b; Ratcliffe et al., 1991; Ross et al., 2008], motor skills [Ross et al., 2008], or other psychiatric disorders [Boks et al., 2007]. One study of 61 males age 2–56 with KS found that parental report of motor impairment or speech/language problems was significantly higher in the paternally inherited group, however direct assessment of cognitive skills in this study did not show statistically significant differences between groups [Stemkens et al., 2006]. Also, if parent-of-origin had a significant effect on cognition, one would expect a more bimodal distribution of cognitive skills within the population of individuals with KS due to the generally equivalent maternal versus paternal origin of the extra X chromosome, rather than the normal distribution shown in Figure 1.

Overexpression of genes that escape X-inactivation have also been proposed to be involved in the phenotype of KS since the severity of physical features and cognitive deficits increases with the number of additional X chromosomes [Rappold, 1993; Linden et al., 1995; Geschwind et al., 2000]. It is now known that up to 20% of X-chromosome genes escape X-inactivation, [Willard, 1996] and a large percentage of these genes are located in the pseudoautosomal regions (PAR) of the X&Y chromosomes which contain homologous genes [Cooke and Smith, 1986; Vogt et al., 1997]. Most of the genes in the PAR regions are not X-inactivated and remain active with their homologs on the second sex chromosome, guaranteeing an equal dosage of expressed sequences between the X and Y chromosomes. Thus, in 47,XXY these genes would be expressed from all three sex chromosomes compared to two chromosomes in 46,XY males. New techniques in expression microarrays have shown that measurable differences in pseudoautosomal gene expression can be seen in blood

samples of males with KS compared to controls [Geschwind et al, 1998]. A subsequent study directly evaluated cognitive and language skills in 11 patients with KS/XXY and six controls, and also ran microarray expression profiling on lymphoblast cell lines [Vawter et al., 2007]. This study identified 129 differentially expressed genes, 14 of which were on the X-chromosome and 12 of which showed significant correlation with verbal cognitive abilities. This study takes advantage of modern methodologies in genetics and has identified many important candidate genes for further study in 47,XXY. However, gene expression can be quite different between tissues and at different stages of development, and thus further understanding of the role of these genes in brain development and function will be needed to determine if they are associated with the cognitive findings in individuals with KS.

Androgen deficiency is a characteristic feature of KS, however few studies have directly examined the effects of testosterone therapy on psychological features in KS.

Hormonal Factors Influencing the Cognitive Phenotype

Androgen deficiency is a characteristic feature of KS, however, few studies have directly examined the effects of testosterone therapy on psychological features in KS.

In an uncontrolled, prospective study of 30 adults with KS, Neilsen et al. reported that testosterone therapy had a positive impact on self-esteem, attention, energy level, and general well-being [Nielsen et al., 1988]. In a recent cross-sectional study in 50 males with KS age 4–19, there were no differences in the neuropsychological results between androgen treated and untreated groups [Ross et al., 2008]. However, this study did not follow individuals prospectively to examine individual changes with treatment, the untreated group was much larger and included mainly prepubertal children, and the treatment group included three children who had received testosterone therapy for only 3 months in infancy. A study by Patwardhan et al. in 2000 describes neuroimaging and verbal fluency in 10 adults with KS who had been identified by newborn screening, and five of these men were currently or had been previously treated with testosterone, while the other five had not. In the untreated group, temporal lobe gray matter was decreased and verbal fluency scores were lower than in the treated group [Patwardhan et al., 2000]. These results are intriguing; however, the background data about doses and timing of previous treatment is unclear. Other reports and clinical experience in KS and other populations with androgen deficiency support Neilsen's findings of improved energy level and attention with testosterone treatment [Geschwind et al., 2000; Simpson et al., 2005], however prospective, controlled studies in the KS population have not been performed to determine which aspects of psychological functioning may change with androgen therapy. This question has been identified as a research priority for KS [Simpson et al., 2003], and prospective studies are currently underway.

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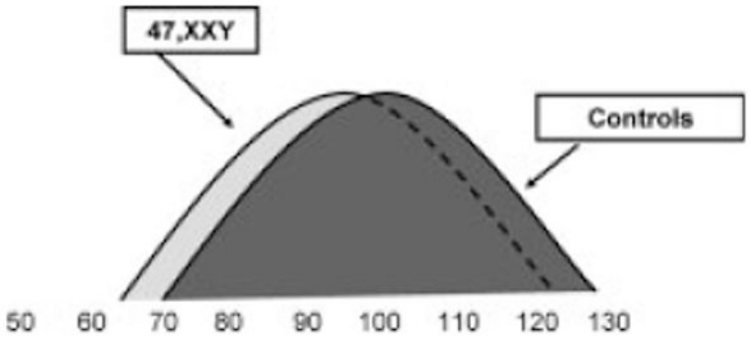

Fig. 1.

Estimated Full-Scale IQ (FSIQ) distribution for children with 47,XXY compared to controls. In 47,XXY, there is a standard distribution of IQ scores, with the normal curve shifted to the left with the mean FSIQ at 91. Adapted from Bender et al. 1986a.

Table 1

Summary of Executive Functioning Studies in Klinefelter Syndrome

Study	*n*	Age	Controls	EF Measures	Results
Temple and Sanfilippo, 2003	3	10	Yes	Wisconsin Card Sorting Test (WCST), Brixon Test, Trail Making Test, Hayling Sentence Completion Test, Stroop Test, Letter Cancellation Task, Verbal Fluency, Ruff Figural Fluency, Tower of London, Self-Ordered Pointing Task, Rey Figure	Impaired inhibition No deficits in concept formation, problem solving, task shifting, or planning
Ross et al., 2008	50	4–17	No	Conners' Continuous Performance Test, DKEFS Color Word Interference	Attention problems in younger children (<10), No deficits in inhibition, cognitive flexibility, or fluency
Fales et al., 2003	21	34 ± 3	Yes	N-back Task	Deficit in verbal working memory
				Transitive Inference Task	
				Matrix Task	
Bender et al., 1993	14	14–17	Yes	WCST	Reduced speed, Intact concept formation
				Trail Making Test	
Bender et al., 2001	11	26–36	Yes	WCST	Intact concept formation
Boone et al., 2001	35	16–61	Yes	Stroop Test	Mild deficits in verbal and nonverbal executive skills compared to controls; VIQ < PIQ group had more verbal EF deficits; PIQ < VIQ group had more nonverbal EF deficits
				Trail Making Test	
				Verbal Fluency	
				Auditory Consonant Trigrams	
				Word Sequencing	
				WCST	
				Design Fluency	
				Rey Tangled Lines	