Neurobehavioral and Psychosocial Issues in Klinefelter Syndrome

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Klinefelter Syndrome (KS) is a relatively common (1/500 to 1/1,000) genetic syndrome caused by an extra X chromosome in males, leading to an XXY karyotype. In most cases, the physical and neurobehavioral characteristics of KS are relatively mild, and KS is not usually associated with moderate or severe mental retardation. However, KS is often associated with significant language-based learning disabilities and executive dysfunction, making it a plausible genetic model for understanding the neurobiology of these areas of cognition that are so fundamental to learning in a classroom. Additionally, the psychosocial aspects of KS, which can have a significant impact on school performance and learning, have been explored only on an anecdotal level. We have conducted pilot studies in a small group of KS adolescents and adults to begin to identify the social, emotional, and adaptive behavior issues facing KS subjects and have identified several areas for further research. This includes characterization of mild maladaptive behaviors, as well as significant strengths in other areas. Further work is needed to determine how the social-emotional and cognitive features of the disorder interact or change over the lifetime of subjects and how the learning disabilities respond to hormonal or cognitive-based therapy.

Introduction

Extensive modern cognitive and behavioral evaluations of rare genetic syndromes have resulted in significant contributions to our understanding of the genetic contributions to specific aspects of cognition and behavior. Compared to even a decade ago, the amount of research has increased dramatically on the behavioral phenotypes of persons with genetic syndromes, including those with and without mental retardation (Bellugi, Wang, & Jernigan, 1994; Dykens & Hodapp, 2001). Although behavioral studies using mixed etiological groups are still dominant in the mental retardation field, more and more researchers from the behavioral and neurosciences are examining specific genetic etiologies regardless of IQ level, often with the aim of making connections between genes, brains, and behavior.

Several recent studies have increased attention to the neurobehavioral contributions from the sex chromosomes (e.g., Money, 1993; Skuse et al., 1997). Here we focus on Klinefelter Syndrome (KS), which has attracted our interest as a genetic model for language-based learning disabilities and altered cerebral dominance patterns (Geschwind, Boone, Miller, & Swerdloff, 2000). KS is caused by an extra X chromosome in males, which leads to a 46 XXY karyotype, instead of the typical 46 XY male karyotype (Amory, Anawalt, Paulsen, & Bremner, 2000). The contribution from paternal and maternal nondysjunction of the sex chromosomes is

approximately equal, in contrast to most other trisomy syndromes, where the cause is typically maternal nondysjunction (Harvey et al., 1991). In KS, the extra X chromosome causes endocrinological abnormalities characterized by low testosterone beginning in puberty. At this stage, KS males can be recognized by virtue of small testes and gynecomastia, as well as deficient production of sperm, all of which persist through adulthood. KS males are also at a higher than usual risk for breast cancer, restrictive lung defects, and lower bone mineral density, likely due to their altered hormonal balance (Amory et al., 2000; Mandoki, Sumner, Hoffman, & Riconda, 1991). Most KS subjects are also taller than average, although frank dysmorphology is absent, making the physical phenotype of most KS subjects unremarkable to the casual observer.

Our understanding of the neurobehavioral and psychosocial consequences of KS and the consequences of behavioral or pharmacologic intervention on these factors are limited (Amory et al., 2000; Geschwind et al., 2000; Nielsen et al., 1988). This is probably attributable to many factors, including the subtlety of the neurologic and behavioral phenotype in KS, which does not include mental retardation, frank dysmorphology, or prototypical aberrant behaviors, as is observed in some of the more extensively studied syndromes (Mandoki et al., 1991). Additionally, while KS is not rare (its prevalence is estimated to be 1/500 among males) (Nielson & Wohlert, 1990), many with KS are not aware of their genetic impairment. In fact, a recent epidemiologic study suggests that more than 75 percent of subjects with KS are not diagnosed (Bojesen, Juul, & Gravholt, 2003), and diagnosis is significantly delayed (i.e., not made in childhood) in the small proportion of subjects that are diagnosed. Therefore, most KS sub-

jects, their parents, and their teachers are not aware of the genetic anomaly that underlies their cognitive and behavioral problems.

Pioneering longitudinal studies by Ratcliffe, Robinson, and others (Bender, Linden, & Robinson, 1993; Ratcliffe, Butler, & Jones, 1990; Robinson, Lubs, Nielsen, & Sorenson, 1979; Robinson, Bender, & Linden, 1990; Robinson, Bender, Linden, & Salbenblatt, 1990; Stewart et al., 1982; Stewart, Netley, Bailey, & Parks, 1986) originally defined pervasive learning disabilities in children with KS. These learning disabilities occur in the background of what is essentially a normal IQ. These studies used standard psychoeducational batteries and provided strong validation of the concept that a significant proportion of KS subjects suffer from a language-based and/or attentional learning disability (Pennington, Bender, Puck, Salbenblatt, & Robinson, 1982; Rovet, Netley, Keenan, Bailey, & Stewart, 1996; Walzer, Bashir, & Silbert, 1990; Walzer, Graham, Bashir, & Silbert, 1982) that overlaps significantly with developmental dyslexia, as it involves core deficits in phonological processing and verbal memory (Bender, Puck, Salenblatt, & Robinson, 1986; Graham, Bashir, Stark, Silbert, & Walzer, 1988). Cross-sectional studies of adults with KS provide evidence that these focal deficits persist into adulthood (Boone, Swerdloff, Miller, Razani, & Lee, 2000; Porter, Gardner, DeFeudis, & Endler, 1988).

It is especially because of the specificity of the neurobehavioral deficits, as well as a paucity of studies probing the nature of the structural and cognitive basis for these problems, that study of this common syndrome provides an important opportunity for research into the genetic basis of language and attention. Furthermore, KS subjects often complain of serious social difficulties, but there is a lack of data on the psychosocial aspects of this condition. In this article, we review recent progress in understanding the neurobehavioral and psychosocial aspects of KS, emphasizing how strikingly little is known about this common genetic condition. Given the prevalence of KS and current estimates of significant verbal learning disabilities in boys, it is possible that between 2–4 percent of boys with developmental dyslexia could have KS, but with the vast majority being undiagnosed. Progress in this area will, no doubt, have an impact on our understanding of the contributions of sex chromosomes to cognition and behavior. These findings are of immediate importance to educators and clinicians.

NEUROBEHAVIOR

Deficits in the Language Domain

Longitudinal studies of psychoeducational performance have been performed in small numbers of KS subjects, as mentioned previously (e.g., Ratcliffe et al., 1990; Robinson, Bender, & Linden, 1990; Robinson, Bender, Linden, & Salbenblatt, 1990; Stewart et al., 1986). These studies have the strength that they involve prospective identification of subjects through genetic screening and, thus, do not have a significant ascertainment bias. From the results of these studies, it is clear that KS subjects are not mentally retarded

and display a wide range of IQs that average close to or slightly below average. Despite the fact that many KS subjects are near average or above average intelligence, they still demonstrate poor school performance and occupational success (Nielsen & Pelsen, 1997) and achievement below their other family members. Several studies have demonstrated that one of the major factors underlying this is a specific verbal learning disability (e.g., Bender et al., 1986; Geschwind et al., 2000; Graham et al., 1988; Mandoki et al., 1991; Money, 1993).

Evidence that language is a fundamental issue for these children and not secondary to other problems in school comes from studies by several investigators showing delay in achieving language developmental milestones in early childhood (Bender et al., 1986; Rovet et al., 1996; Stewart et al., 1986; Walzer et al., 1990). Later, at school age, this problem manifests as dyslexia, which is defined by poor reading in the setting of normal intelligence. KS males appear to have deficits in phonologic processing and deficits in verbal memory similar to those observed in children with dyslexia who have a normal chromosomal complement (Bender et al., 1986; Graham et al., 1988). Difficulties with arithmetic are also observed, but these are often secondary to the language-based difficulties. Deficient auditory processing and verbal memory are two of the key cognitive processes underlying these difficulties. Again, the evidence to date supports the notion that the underlying cognitive deficits are very similar to those observed in dyslexic children with a normal chromosomal complement (Bender et al., 1986; Geschwind et al., 1998; Graham et al., 1988).

These deficits in verbal learning cause children to fall behind in other subjects where the instruction is largely verbally based so that by the time KS subjects reach late adolescence, they can be several grade levels below their peers in many subject areas (Rovet et al., 1996). Work by Boone et al. (2001) and others (Porter et al., 1988) shows that deficits in reading and language persist into adulthood, although the picture in KS adults is more complex than in children.

Frontal-Executive Dysfunction

Frontal-executive functions appear to be significantly impaired in some KS adults and this impairment is not related to the degree of language dysfunction (Geschwind et al., 2000). A recent study in children with KS (Temple & Sanfilippo, 2003) confirms specific deficits in frontal-systems functioning, namely, problems with inhibitory skills. In this study, other cognitive domains comprising frontal-executive dysfunction (FED) (e.g., concept formation, problem solving, task switching, and speeded responding) were within the normal range. The specificity of these deficits needs to be confirmed in future studies, since a broader range of FED, especially when tasks were more verbally loaded, has been identified by Boone and colleagues (2000, 2001). It is likely that a cognitive domain as broad as FED may interact with other genetic and environmental factors to produce heterogeneity among KS patients—in this context, a unitary deficit would be surprising. Using specific cognitive tasks known to rely heavily on frontal-lobe function, Fales

et al. (2003) found deficits among adults with KS that were most consistent with dysfunction in verbal short-term memory. These findings support the concept that defects in frontal systems are caused by a language-based, left frontal-systems problem.

Heterogeneity of Cognitive Phenotype: KS as a Disorder of Cerebral Laterality

Not all adults with KS show the classic pattern of verbal deficits observed in children. In a study of 35 adults with KS, the majority of whom were identified through fertility or endocrinology clinics, KS men fell into three major groups (Boone et al., 2001). Not surprisingly, one of these groups is composed of those with performance IQ greater than verbal IQ, similar to the observations made in children and adolescents. However, a similar proportion of adults had verbal IQ equal to performance IQ, and a third and again similar proportion of adults showed verbal IQ greater than performance IQ (Boone et al., 2001). This last category of subjects had specific deficits in spatial cognition consistent with a right-hemisphere deficit, rather than the typical left-hemisphere deficit (Geschwind et al., 1998, 2000; Netley & Rovet, 1982).

How do these observations of nearly pervasive left-hemisphere dysfunction and anomalous dominance patterns observed in childhood fit with the observations of a potential subgroup of KS adults with predominantly right-hemisphere dysfunction? Because these right-hemisphere problems are not present in childhood, it is not known when and why they emerge in a subset of KS subjects. Boone hypothesized that the left-hemisphere-related cognitive problems observed in childhood may be replaced in this subset of adult patients with right-hemisphere deficits because of persistent hormonal deficiency that leads to a relative feminization of the brain (Boone et al., 2001). Another possibility is that KS predisposes an individual to anomalous cerebral dominance patterns in general, putting at risk any cognitive or behavioral processes that are usually strongly lateralized in the brain.

Studies by Geschwind et al. (1998, 2000) support the notion initially posited by Crow (1989) that the increase in nonright-handedness and other measures of left-hemisphere dysfunction, such as language difficulties, are due to a gene-dosage effect caused by the extra X chromosome. However, altered cerebral dominance patterns may also be due to differing patterns of X inactivation in one group of patients as compared to another. The influence of parent of origin or sex-specific chromosome inactivation on cognition has been recognized (e.g., Skuse et al., 1997), but nothing is known about its mechanisms or the role of X-chromosome inactivation in leading to variability in KS phenotypes. It may also be that, like others with dyslexia or specific language impairment, some KS subjects learn to use alternative strategies to overcome their language-based problems, but cannot overcome spatial or attentional problems with similar success. Nevertheless, the idea that KS subjects may have either left- or right-hemisphere-related dysfunction in adulthood warrants large-scale study of cognition in KS adults, along with assessment of X-chromosome inactivation patterns and the relationship of cognition with hormonal-replacement therapy. In addition, the contribution of somatic mosaicism within the brain may be a confounding factor that needs to be considered, but will be hard to control for antemortem.

NEUROBIOLOGY

The extent to which the underlying deficits in KS reflect genetic or hormonal causes remains open to debate, as suggested above. Geschwind and colleagues have posited that many of the features associated with anomalous dominance, such as verbal learning problems, result from a gene-dosage effect (Geschwind et al., 1998). The Androgen Insensitivity (AI) Syndrome provides an important comparison, since these subjects have the normal X-chromosome complement, but have female external secondary sex characteristics due to androgen-receptor dysfunction. These subjects are genetically male, but hormonally more female, since they do not respond to the masculinizing effects of testosterone. Subjects with AI have poor performance on tests of spatial cognition relative to nonaffected relatives, despite no differences in verbal or full-scale IQ (Imperato-McGinley et al., 1991). This is in contrast to KS subjects, who also have low androgen levels, but perform well on tests of spatial cognition, instead showing verbal deficits. The verbal and attentional learning deficits in KS children and adolescents are, therefore, more akin to what is observed in the more masculine hormonal phenotype, rather than hypogonadal males (Nielsen & Pelsen, 1997). This finding supports the notion that the KS language-related phenotype may be mostly due to genetic influences. Again, rigorous genotype-phenotype studies are needed to fully assess this hypothesis.

Neurology and Motor Function

Developmental dysphasia and fine motor and gross motor abnormalities are seen in adult and adolescent patients with KS (Geschwind et al., 2000; Robinson, Bender, & Linden, 1990; Robinson, Bender, Linden, & Salbenblatt, 1990). Similar findings have been reported in the learning disabled population with a normal chromosomal complement, who often show subtle motor delay. Bimanual coordination problems including mirror movements and motor overflow to the opposite limb were seen in one-third of adults with KS, suggesting that these problems persist; they are not simply a delay of maturation (Geschwind et al., 1998, 2000). Evidence from studies of handedness (measured as both hand preference and skill), measures of functional brain laterality, and neuropsychological testing suggest that altered brain dominance and left-hemisphere language specialization might play a role in the neurocognitive phenotype of KS subjects (Crow, 1989; Geschwind et al., 1998, 2000; Netley & Rovet, 1982, 1984; Ratcliffe & Tierny, 1982). Unfortunately, most KS subjects are not diagnosed until adulthood (if at all); as a result, how these data from relatively small populations can be extrapolated to the universe of males with KS is unknown. In spite of the studies discussed above, it is remarkable how little

is known about the developmental trajectory and prognosis related to specific cognitive domains in KS. Similarly, the neurologic features of these individuals have been described in only small samples (Geschwind et al., 2000). These studies are mostly limited to adults, and they clearly demonstrate many soft neurologic signs, including fine and gross motor problems (Geschwind et al., 1998, 2000). Still, how these and other motor complaints such as tremor are related to hormonal therapy or other factors is not known.

Neuroimaging and Anatomy

We are aware of only four published structural imaging studies in KS beyond case-report status. Warwick et al. (2003) found smaller whole brain volumes and increased ventricular volumes in XXY males than in controls. A recent study performed by Reiss and colleagues is based on a total of 10 subjects, half of whom received hormone-replacement therapy (Patwardhan, Eliez, Bender, Linden, & Reiss, 2000). This work revealed decreased left temporal lobe gray matter in five subjects who had not received replacement hormone, a finding that is consistent with the left-hemisphere language deficits observed in KS. However, the study was small and its interpretation has serious flaws (Kates & Singer, 2000). In a follow-up study, smaller amygdala volume was found in KS subjects (Patwardhan et al., 2002). Another case report in a KS patient with schizophrenia (Warwick, Lawrie, Beveridge, & Johnstone, 2003) showed reversal of the gross patterns of frontal and temporal lobe asymmetry. Although not discussed by Warwick and colleagues, the overall asymmetry index in KS subjects appeared to be reduced, relative to the male control subjects (Warwick et al., 2003, fig. 1). It is not known whether this reduction in the asymmetry coefficient is statistically significant, but the trend is striking. This finding of a more symmetric brain, or loss of typical asymmetries, would support the notion that the disruption of typical genetic mechanisms, biasing hemispheric asymmetry, is a factor in KS (see Geschwind et al., 2000).

Recent work by Itti and colleagues (2003) involved the use of SPECT to study resting cerebral perfusion in KS subjects in nine hormone-naïve right-handed KS subjects, compared with 22 controls. Peri-sylvian asymmetry biased toward the left was observed in the controls, but was absent in the KS subjects. Surprisingly, language-related regions such as the supramarginal gyrus, superior temporal gyrus, and angular gyrus showed significant rightward asymmetry. In some regions, the changes in perfusion could be correlated with performance on cognitive tasks, such as verbal memory (L hippocampus, R medial temporal gyrus, superior temporal gyrus, and insula), arithmetic (R angular gyrus), and verbal executive skills (L cerebellar hemisphere and R insula). This work demonstrates potential functional correlates of altered brain asymmetry that need to be followed up, using modern functional imaging with task specific activations. Overall, the structural and functional data available support the notion that typically asymmetric regions of the brain are disturbed. No modern neuropathological study of KS has been published, but such data would be invaluable to those trying to understand its neurobiological basis.

PSYCHOSOCIAL DEVELOPMENT INTO ADULTHOOD

Early etiology-based behavioral work in neurodevelopmental syndromes has emphasized striking cognitive-linguistic profiles rather than psychosocial development. For example, behavioral work on Williams Syndrome describes weaknesses in visual-spatial functioning, as well as remarkable strengths in certain aspects of linguistic functioning (e.g., Bellugi et al., 1994; Mervis, Morris, Bertrand, & Robinson, 1999). Only recently have researchers turned their attention to the maladaptive behaviors of these individuals, including their distinctive personalities and high rates of social disinhibition, anxiety, fears, and phobias (Dykens, 2003; Jones et al., 2001). For both Prader-Willi Syndrome and Williams Syndrome, then, researchers have just now begun to adopt a "whole-person" approach, one that appreciates other, less immediate or obvious aspects of behavioral functioning.

Behavioral research on males with KS follows this pattern, with little attention to the whole person, and a more intense focus on cognition, as described above. Thus, it is well established that many males with KS have average to low-average IQs with relatively intact nonverbal reasoning and characteristic deficits in language, reading, and executive functioning (e.g., Bender et al., 1986; Pennington et al., 1982). Recent data implicate difficulties encoding verbal information into working memory, as well as relative independence of difficulties with reading or language and executive functioning (Boone et al., 2000, 2001; Fales et al., 2003).

In contrast, much less is known about the social and emotional development of males with KS, including their social adjustment and mental-health status across the lifespan. In this regard, research on KS is similar to other genetic disorders that have a lopsided behavioral research history, with relatively well-developed understandings of language or cognition and less robust findings on the social, adaptive, personality, and emotional functioning of affected individuals.

Pilot Study of Personality and Emotional Issues in Males with KS

Some of the earliest published observations suggested that boys with KS are at risk for emotional maladjustment. These boys have been depicted as shy, reserved, withdrawn, dependent, and insecure Adults with KS were depicted as also showing increased passivity, as well as socially impulsive and inappropriate behavior (e.g., Mandoki et al., 1991; Stewart et al., 1986; Theilgaard, 1984). Early anecdotal reports suggested increased risks in adults of sociopathic personalities and serious psychopathologies (e.g., Nielsen, 1970). More rigorous, controlled studies, however, find little evidence for increased rates of major psychiatric problems in this population (Bender, Harmon, Linden, & Robinson, 1995; Bender, Linden, & Harmon, 2001; Nielsen & Pelsen, 1997). Although early misconceptions about these males have been laid to rest, the field still lacks a complete picture of the social and emotional functioning of males with KS, especially in adulthood.

We recently completed a pilot study of emotional and behavioral functioning in 15 adults with KS. KS subjects

ranged in age from 16 to 64 years, with a mean age of 38 ($SD = 15.56$); all had genetic confirmation of KS and were participants in a parallel study on cognition. Although these males were identified through a genetics clinic, they were not presenting at the clinic for medical or psychological management concerns. Except for two adolescents, all subjects reported being gainfully employed in the last six months. The majority of subjects had never been married (61 percent), with 8 percent being separated and 31 percent married at the time of the study.

Participants completed a standardized measure of personality and motivation—the Reiss Profile of Fundamental Goals (Reiss & Havercamp, 1998). The Reiss Profile assesses the degree to which respondents are motivated in 15 domains; a profile is generated that depicts motivational sensitivities across these domains (aversive sensations, citizenship, curiosity, family, food, honor, independence, order, physical exercise, power, rejection, sex, social contact, vengeance, social prestige). The Reiss Profile has well-established psychometric properties and is increasingly used in people with and without mental retardation.

In addition to the Reiss profiles, participants also completed a standardized measure of problem behaviors—Young Adult Self-Report (Achenbach, 1997)—which assesses internalizing symptoms (e.g., anxious/depressed; withdrawn) and externalizing problems (intrusive, aggressive, delinquent behavior) in adulthood. Subjects also responded to several cards from the Thematic Apperception Test (TAT), an open-ended task in which respondents are asked to tell a story about a series of ambiguous pictures. Stories were reviewed for salient themes, and this content analysis yielded 15 content codes that were reliably judged by raters who were unaware of the population under study.

On measures of personality and motivation, the group as a whole showed a common pattern of highs and lows across the 15 Reiss domains, $F(14, 154) = 3.73, p < 0.001$, suggesting that certain domains were either high or low motivators for the group. Figure 1 depicts the mean standardized scores for each domain. The results suggest areas that are both highly motivating and not particularly motivating for this sample. The group was not highly motivated by a need for social prestige, independence, or a desire to seek vengeance on others. They were also not particularly keen on avoiding physical pain.

Instead, the dominant motivating force for the sample was curiosity (see Figure 1). Thus, KS subjects gave the highest ratings in the curiosity factor to such items as: "I have a great deal of curiosity" (86 percent of sample); "I especially like games that make me think (e.g., bridge, chess)" (80 percent); "I love learning new skills" (75 percent); and "I enjoy learning about something in depth" (74 percent). Two other salient motivators were family issues, for example, "My family comes first" (80 percent) and "I enjoy taking care of my family" (69 percent); and also social contact with others, for example, "I enjoy meeting new people" (67 percent) and "I definitely like people" (60 percent). The group was also motivated by food, sex, honor, and physical exercise,
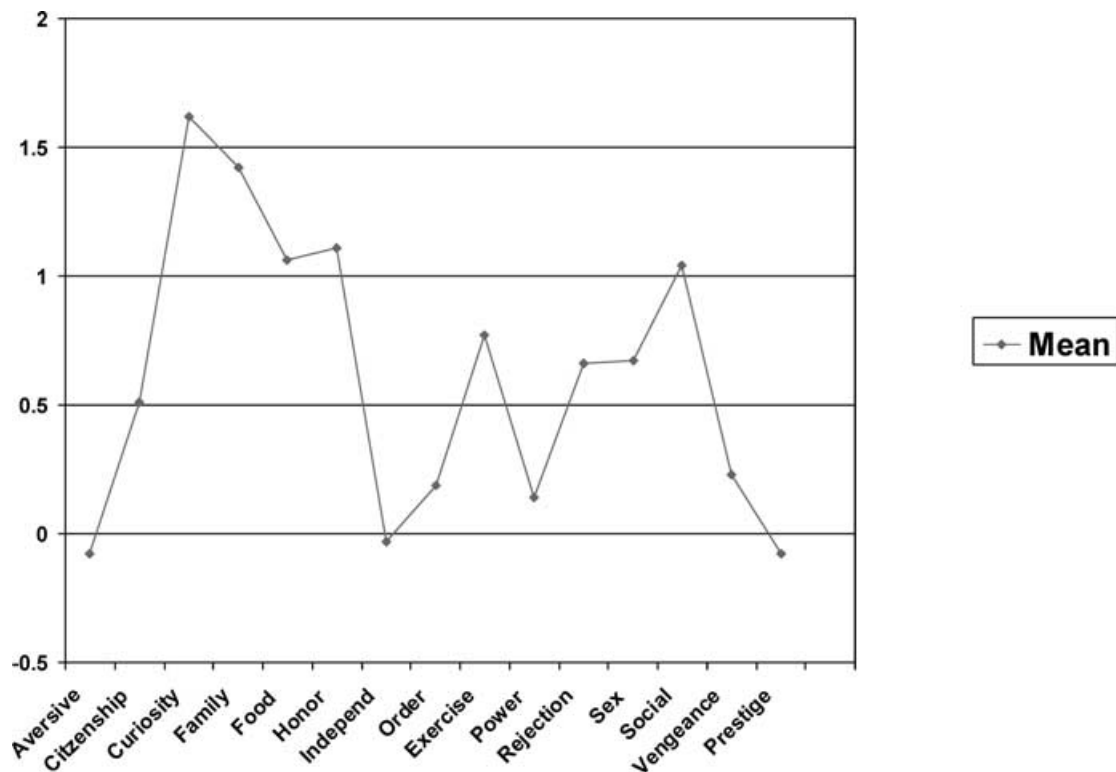

FIGURE 1   Mean standardized scores on the 15 factors of the Reiss Profiles of Fundamental Goals and Motivational Sensitivities in 15 males with KS.

although these motivators were less prominent than those mentioned above. None of these 15 domains showed significant age effects.

Internalizing and externalizing symptoms were assessed on the Self-Report Scale using average raw scores (averages were used as the number of items that comprised each domain were not equal). Internalizing symptoms ($M = 9.00$; $SD = 4.98$) were significantly higher than externalizing ones ($M = 3.69$; $SD = 2.38$); $F(1,14) = 19.18$, $p < 0.001$. Comparing internalizing to externalizing raw scores to cutoffs established by Achenbach (1997), just 14 percent of the sample had clinically elevated externalizing symptoms. In contrast, 43 percent showed clinically elevated scores on the internalizing domain. No significant age effects were found in externalizing or internalizing symptoms.

Although exploratory, the TAT stories revealed several frequent themes, seen in 50 percent or more of participants, that reflected the internalizing difficulties identified on the Self-Report Scale. These themes include: romantic conflict (71 percent of the sample), death or loss (71 percent), sadness or emotional upset (64 percent), family conflict (57 percent), empathy with others (50 percent), shirking responsibilities (50 percent), and exploitation/trauma (50 percent). Of these, the presence of family conflict in stories actually increased with age ($r = 0.66$, $p < 0.01$), with no other significant age effects.

REMAINING ISSUES

Psychosocial Adaptation and Motivation Throughout the Lifespan

The psychosocial data presented here both confirm previous findings and add new twists to previous understandings about emotional issues in males with KS. Consistent with previous reports, KS subjects in this sample were not highly motivated by a need for independence. Unlike previous findings, however, these results also suggested that these males had a more kind-spirited nature and were not particularly invested in social prestige as a motivating force in their lives. Instead, and somewhat discrepant with their lower IQs and learning disabilities, they reported being highly motivated by curiosity and learning new skills. In addition, although negotiating social relationships may be problematic for these males, they were nonetheless motivated to interact with others, and form meaningful relationships with friends, family, and romantic partners. Indeed, having close ties to family was a strong motivator for the group as a whole.

Consistent with previous reports of anxiety and depression in males with KS, approximately 45 percent of the sample had clinically elevated scores on the internalizing factor of the Young Adult Self-Report Scale. Internalizing symptoms were much more common and problematic than externalizing problems, and were reflected as well in participants' open-ended responses to the TAT. Dominant themes in these exploratory data included sadness and loss, conflicts with family and romantic partners, and being exploited by others. However, their stories also had themes that depicted empathy with others.

These preliminary findings show the promise of using both open-ended and standardized psychological assessments in males with KS. They also suggest important new avenues for research. First, research on the emotional functioning of males with KS could benefit from a life-span, developmental approach that extends into the older adult years. No consistent age effects were found in the small pilot sample described here—older and younger adults were similar in their internalizing symptoms and personality profiles, with a modest suggestion of increased family problems over time. After they pass through adolescence, the personality and emotional features of young adults with KS may be relatively stable, with no additional deleterious effects associated with XXY status that emerge later in adult development. Longitudinal studies with larger numbers of adults with KS are needed to test this idea rigorously.

Second, future work could benefit from a two-pronged approach that refines both maladaptive problems and strengths associated with KS. Although psychopathologies tend to be mild in males with KS, work is needed that identifies the extent to which internalizing symptoms form the backdrop of a mild, chronic dysthymic stance, or are related to more severe mood disorders and impairment. Further, research to date has focused on psychopathologies, yet our pilot findings suggest a host of more positive personality attributes in males with KS. These features include empathy with others, a noncompetitive, kind-spirited orientation, a valuing of family and relationships, and a curiosity to learn new things. Such positive attributes may contribute to higher levels of esteem, competence, and emotional adjustment in men with KS than have previously been appreciated.

A More Complete Integration of Research Findings

Studies are needed that relate social and emotional functioning to cognitive and neurological findings and that integrate these separate pieces of the KS puzzle into a more coherent picture of the "whole person." Although this whole-person approach was beyond the scope of this pilot study, future work might investigate whether reduced amygdala volumes or alterations in asymmetry or language regions in males with KS (Itti et al., 2003; Patwardhan et al., 2002) are associated with their personality profiles and propensities for internalizing problems. Studies could also be designed to determine whether males with more severe problems in executive function, encoding tasks, or language disabilities are at increased risk for internalizing disorders or maladaptive personality profiles. Further, they might investigate the specific compensatory strategies have served adults well in both vocational and personal arenas. Results from such studies have the potential for optimizing the mental well-being and successful life courses of males with KS.

A Final Note on Treatment in the Broader Context of LD

There is a great need for specific empirical data on the treatment of LD in subjects with KS. However, given the

significant overlap in the neurocognitive phenotype of KS and dyslexic children, as a practical matter it makes sense to apply the same intensive treatments known to work in children with idiopathic dyslexia to children with KS. Therapies concentrating on improving phonological-processing skills may be most valuable, as a deficit in this domain has been carefully documented in KS subjects, albeit in small numbers. In this regard, early intervention is critical, as poor reading can form the basis for failure to keep up in other disciplines. Whether the attentional or executive problems observed in some KS males respond to hormone-replacement therapy in adolescence, or the same pharmacologic treatments used in children with ADHD, is unknown. Anecdotal evidence suggests that most KS subjects feel more energetic and focused when on hormone replacement. Again, depending on the severity of the attentional dysfunction, carefully supervised therapeutic trials of stimulants may also be warranted. Finally, the possibility of KS should be considered by any educator (via pediatrician referral) who observes the combination of poor reading or attentional difficulties in a tall boy with clumsy fine motor skills. Early recognition may be beneficial, since hormone-replacement strategies can be initiated, preventing some of the medical sequelae and possibly improving the cognitive and behavioral outcome.

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