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Klinefelter syndrome: the effects of early hormonal intervention on competence and behavioral phenotype

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KLINFELETHER SYNDROME: THE EFFECTS OF EARLY HORMONAL INTERVENTION ON COMPETENCE AND BEHAVIORAL PHENOTYPE

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KLINEFELTER SYNDROME: THE EFFECTS OF EARLY HORMONAL INTERVENTION ON COMPETENCE AND BEHAVIORAL PHENOTYPE

LAUREN CHEN

ABSTRACT

Klinefelter syndrome (KS) (47,XXY) is the most common sex chromosomal anomaly in males with a prevalence of 1 in 650 males. This clinically relevant condition represents 3%–4% of the total patient population in male reproductive medicine practices. Klinefelter syndrome can manifest in different physical, cognitive, and behavioral phenotypes. The classical phenotypic descriptions are gynecomastia, hypotonia, tall stature, and hypogonadism. Currently there is no known treatment plan for adolescents who are diagnosed with this genetic condition. However, it has been hypothesized that early intervention through androgen replacement therapy can emulate a normal progression of puberty and improve the academic, social, and behavioral aspects of these adolescents.

Using standardized instruments, in the form of the Children Behavior Checklist (CBCL) and the Youth Self Report (YSR), we captured data on the patient’s competence and behavior, as well as the parents’ views on their child’s competence and behavior. These data were converted into percentile scores, T scores, and categorical data (normal, intermediate, and clinical). Difference of means was used to test for statistically significant differences between the scores of the KS patients and their parents on competence and behavioral aspects. T test for equality of means was run to determine if there was a significant difference between group scores. Pearson correlation tests were
done to see if there was an association between demographics of patients and competence/behavioral scores. We believed that there would be no statistically significant difference between how the parents score their child in the CBCL and how the child scores himself in the YSR in terms of demographics. We also believed that there would be no statistically significant difference or correlation between demographics and individual competence/behavioral scores.

A total of 39 groups of surveys were collected, together with demographic information on the maternal and paternal ages when the child was born, patient age, patient age when starting testosterone, patient age when starting anastrazole, and patient height and weight. We examined concordance frequencies in specific areas of the competence and behavioral questionnaires. Concordance was when the parent and the child agreed and evaluated the child as normal, intermediate, or clinical. Discordance was when the parents and the child disagreed; for example, the parent evaluated the child as “clinical,” but the child evaluated himself as “normal.”

This study, to our knowledge, is the first chart review study that involves a wide age range of males with KS. The study extends previous findings by providing data on how early hormonal intervention can improve the outlook of these patients’ lives. When taking aromatase inhibitors, the KS adolescents showed an overall reduction of aggression and rule-breaking behavior. When taking testosterone at an earlier age, the patient was less likely to have withdrawal depression. We also found the most discordance in total competence scores, suggesting that some parents may have unrealistic academic expectations for their child. Thus, when examining the data, we had
to be aware that there were varying views of success, which can shape how parents and child answer their respective surveys.

Our findings demonstrate the significance of early detection and treatment of Klinefelter syndrome, a disorder that is severely under-diagnosed throughout the world. The results also show that the desire of parents for their KS child to do well in school may affect their opinions on how their child is actually performing. Some limitations to this study include the decision to receive early hormonal intervention that was made exclusively between parents and their urologist. Furthermore, the socioeconomic status (SES) and educational characteristics of the families were not properly controlled, although the patient population was mostly likely similar because of the location of the clinic.

Future Klinefelter syndrome studies will need to focus on identifying the factors that contribute to the variability of behavioral symptoms. In turn, these studies will support the continuing development of evidence-based treatments for adolescents with Klinefelter syndrome.
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LIST OF ABBREVIATIONS

AR..............................................................Androgen receptor
ART..........................................................Assisted reproductive technology
ASEBA.......................................Achenbach System of Empirically Based Assessment
CAG..........................................................Cytosine-adenine-guanine
CBCL..........................................................Children Behavior Checklist
EMR..........................................................Electronic medical record
FSH..........................................................Follicular stimulating hormone
ICSI..........................................................Intracytoplasmic sperm injection
KS..........................................................Klinefelter syndrome
LH...........................................................Luteinizing hormone
PAR..........................................................Pseudoautosomal regions
PIQ..........................................................Performance IQ
SES..........................................................Socioeconomic status
TESE..........................................................Testicular sperm extraction
TRT..........................................................Testosterone replacement therapy
VIQ..........................................................Verbal IQ
YSR..........................................................Youth Self Report
INTRODUCTION

Klinefelter syndrome (KS) (47,XXY) is the most common sex chromosomal abnormality in males, with a prevalence of 1 in 650 males (Samango-Sprouse, 2015). KS is also clinically relevant in male reproductive medicine practices; the condition represents 3%–4% of the infertile patient population. Although there is considerable variation in physical phenotype among affected patients, the classical phenotypic descriptions are gynecomastia, hypotonia, tall stature, hypogonadism, and central obesity. In addition to these medical features, the presence of the extra X chromosome can lead to characteristic cognitive, social, and language deficits ranging from mild to severe (Boada et al., 2009). Early intervention through androgen replacement therapy, occupational therapy, physical therapy, and speech therapy has been associated with decreased obesity rates and improved academic and social aspects of adolescents with KS (Samango-Sprouse et al., 2013; Samango-Sprouse et al., 2015). Early detection of this genetic condition and constant management with early androgen therapy have been shown to improve overall health, academic progress, and social integration for many patients with KS.

History on Discovering Klinefelter Syndrome

The research on various phenotypic features of individuals with KS developed over three stages (Boada et al., 2009). Dr. Klinefelter first described the syndrome in 1942, and a discovery by Dr. Jacobs in 1959 identified the etiology of the condition to be
the presence of an extra X chromosome (Jacobs et al., 1959; Klinefelter et al., 1942). Later on, other investigators described increased rates of cognitive disabilities and other mental health problems in patients with the extra X chromosome. However the validity of these studies is controversial because the patient groups originated from mental health hospitals or long-term care facilities for developmentally challenged people (Bourgeois & Benezech, 1977; Eriksson, 1972; Johnston et al., 1974; Singh et al., 1974). Consequently, these cognitive studies were highly criticized as a result of potential bias, but they initiated the investigation of cognitive and genetic differences in XXY individuals.

In the next stage of research studies on males with KS, investigators tried to address the bias in prior studies. Newborns were screened for the 47, XXY genotype and were followed through adulthood. Many sites, such as Toronto, Denver, and Edinburgh, participated in this study; they pooled their findings and aggregated results at a global level (Netley, 1986; Ratcliffe et al., 1990; Robinson et al., 1990). These prospective studies shaped the current knowledge of KS in terms of developmental, physical, cognitive, and behavioral characteristics. One important finding was that patients with KS had a better cognitive outlook than stated in the earlier literature. These studies improved upon previous studies because they selected patients from birth, they were prospective, and they had a long-term follow-up. Many of the studies also tracked the KS male sibling(s) as a control group to avoid confounding variables from socioeconomic status (SES), parenting styles, and other environmental factors. However, the cohorts were relatively small—the Toronto study had 31 patients, Denver had 15 patients, and Edinburgh had 19 patients. Considering the prevalence of KS in the general population, a
more robust sample size was needed in future studies.

The third stage of studies began after the prospective studies and focused more on cognitive characteristics clinically presented in men with KS. This work included neuropsychological studies and studies that correlated cognitive outcomes to genetics (Boone et al., 2001; DeLisi et al., 1994; Ross et al., 2008; van Rijn et al., 2006; Zinn et al., 2005; Zitzmann et al., 2004). From these studies, researchers determined that not all males with KS are negatively affected cognitively, and that a large portion of the KS population was highly successful in academics and in future careers. However, these studies also determined that there was a subgroup of KS males that had neuropsychological impairment related to the extra X chromosome (Boada et al., 2009). Future studies were recommended to develop better treatment options, as well as identify the specific gene on the X chromosome that was responsible for the subgroup’s cognitive impairment.

Genetic Factors

There have been many theories as to how genetic factors are linked to the various types of phenotypes that appear in KS. These factors include the following: mosaicism, polymorphisms of specific genes on the X chromosome, parent-of-origin of the extra X chromosome due to imprinting differences or X chromosome isodisomy, and gene-dosage effects of X chromosome genes that escape X inactivation (Geschwind et al., 2000).

Mosaicism applies to individuals who have different populations of cells. In KS
this can appear as 46,XY/47,XXY; 47,XXY/48,XXXY; or other variations. The most common mosaicism in KS is 46,XY/47,XXY. Patients with this type of mosaicism seem to have better fertility rates than their non-mosaic counterparts (Seo et al., 2006; Steward et al., 1990). However, when comparing males with 46,XY/47,XXY mosaicism and non-mosaic KS males, researchers failed to find a significant difference in cognitive skills (Netley, 1986; Stewart et al., 1990). There have been reports that those who have tetrasomy and/or pentasomy mosaicism showed more cognitive deficits than those with 47,XXY due to the tetrasomic cell line. Therefore, it is generally accepted that mosaic patients with 46,XY have less KS characteristics than non-mosaic patients and that mosaicism with tetrasomy and/or pentasomy has more significant cognitive impairments.

Genetic polymorphism of specific genes on the X chromosome has been hypothesized as the reasoning behind phenotypic variability in KS males. In particular, the androgen receptor (AR) is of interest because of androgen deficiency that is present in KS males. The AR gene is polymorphic in the number of CAG (cytosine-adenine-guanine) repeats in the coding region, and the length of CAG repeats is inversely correlated to how responsive the receptor is to testosterone (Zitzmann, 2009). It has been hypothesized that KS males who have an AR receptor with less CAG repeats may have improved responses to circulating androgen and less severe KS phenotypic characteristics. Zitzmann found that men with KS and longer CAG repeats in the AR exhibited more significant physical features of KS (gynecomastia, tall stature), had social retardation, lacked professional employment, and were not as likely to be in a long-term relationship. This suggests that short CAG repeats in the AR are linked to less significant
physical features and improved social outcomes. Following Zitzmann’s work, two subsequent studies failed to find the link between CAG repeat length and cognitive skills (Ross et al., date; Stemkens et al., 2006). However, these studies were done on populations that differed in age and androgen exposure, and these two factors could affect receptor responsiveness in patients.

Parent-of-origin of the extra X chromosome has been studied to see if phenotypic variability may be related to an imprinted sex chromosome locus (Boada et al., 2009). Such imprinting may lead to differentially expressed maternal or paternal alleles resulting in the expression of X-linked recessive genes. For example, in girls with Turner syndrome (45,X) the parent-of-origin of the single X chromosome affects the phenotype. Turner girls who have maternally inherited X chromosome are more likely to be socially awkward and have autistic behavior than those who have paternally inherited X chromosome (Skuse et al., 1997). KS men with XXY have the extra X chromosome maternally inherited in 50%–60% of the cases (Hassled et al., 2007; Thomas & Hassold, 2003). Studies have generally agreed that the parent-of-origin of the extra X chromosome has no significant effect on cognition (Jacobs et al., 1988; Ratclifflè et al., 1991; Ross et al., 2008; Stemkens et al., 2006), motor skills (Ross et al., 2008), or other psychiatric issues (Boks et al., 2007). Also, if parent-of-origin did affect cognition, there would be a more bimodal distribution within the KS population to show maternal versus paternal origin rather than the well-known normal distribution developed by Bender in 1986.
**Figure 1:** Estimated Full-Scale IQ (FSIQ) distribution for children with 47,XXY compared to controls. There is a standard distribution of IQ scores, with a normal curve shifted to the left with the mean FSIQ at 91. Adapted from Bender, 1986a.

Overexpression of genes that escape X inactivation has also been hypothesized to affect physical features and varying cognitive phenotypes in KS (Geschwind et al., 2000; Linden et al. 1995; Rappold, 1993). 20% of X chromosome genes escape X inactivation, and a large portion of those genes are located in the pseudoautosomal regions (PAR) of the X and Y chromosomes (Cooke & Smith, 1986; Vogt et al., 1997; Willard et al., 1996). Most of the genes in the PAR regions are expressed and not inactivated. Therefore, in 47,XXY all three sex chromosomes have the genes expressed, and in KS males there were differences seen in PAR gene expression (Geschwind et al., 2000). Using microarray technology, Vawter et al. (2007) identified 129 differentially expressed genes, including 14 of which were X chromosome and 12 of which showed a significant relationship with verbal cognitive abilities.

**Physical Development Outcomes**

KS patients have variable physical phenotypes that may or may not manifest
during pubertal stages. Therefore, it may be hard to physically distinguish between these patients and other males with the traditional XY karyotype (Caldwell & Smith, 1972). Because there are no distinct physical features, there is a delay in diagnosis at birth and during infancy; affected toddlers have normal heights and weights. Even though a micropenis is sometimes seen in boys with KS, it is not considered a diagnostic trait of KS and is rarely enough of a reason to perform a karyotype. Small testicular size, however, is an indicative symptom of KS, though the difference in testes size does not become apparent until at least Stage II of the Tanner Scale (a system used to determine physical development in adolescents).

**Figure 2**: Tanner scale. This is a scale of physical development in children, adolescents and adults. It defines physical measurements of development based on external primary and secondary sex characteristics. Adapted from https://en.wikipedia.org/wiki/Tanner_scale.
The most consistent characteristic seen in prepubescent KS boys is a small delay in the ability to walk by the age of 2–4 months as a result of hypotonia (Paduch, 2012). This condition will elicit a cytogenetic evaluation, which will eventually lead to the diagnosis of KS. The lack of physical characteristics to diagnose toddlers and infants with KS has proved to make an early diagnosis difficult. Paduch (2012) suggests for pediatricians to look for subtle findings such as hypotonia, disproportional height, and delay in milestones compared with the KS patient’s male siblings.

Although it is hard to diagnose boys with KS pre-puberty, the typical physical traits become more apparent when the patients reach early adolescent years. Younger KS adolescents often have attention and behavioral problems, whereas older adolescents have issues with motor performance (Ross et al., 2008). Verri et al. (2010) found that with specific motor tasks, such as finger or foot tapping, boys with KS performed close to average levels; however, as the tasks became more complicated, the KS males failed to perform on the same level as the control group of XY males. These motor difficulties are not only of academic interest, but they also have psychosocial implications as well. KS males, who have less than average athletic ability combined with the typical disposition of excessive shyness and impulsivity, may have their social life and mental health negatively affected by their condition (Paduch, 2012). As a result of an early diagnosis, early intervention with androgen replacement therapy may not only improve physical performance, but also result in better social integration at school.

Males with KS have abnormal height; by the age of 7, over 50% of the boys will exceed the 97th percentile of height for their age group. The increase in height is most
significant between the ages of 5 and 8 and is due to elongated limbs (Ratcliffe, 1999; Schibler et al., 1974). Tall stature is a characteristic typical of young men with KS. The mechanism behind this is unclear, but it has been hypothesized that there is insufficient estrogen to close the epiphyseal plate in these boys. Although most KS men have hyperestrogenism, it is not certain when the onset of this increase in estrogen occurs. Also, most KS males are taller than expected prior to puberty, so it is unlikely that hormones play a dominant role in height for KS patients. According to Paduch’s review of patient growth charts (2012), the mean height appears to peak and plateau at age 17. However, weight changes in KS adolescents lag behind height changes, and a weight plateau is achieved 7 years after the height plateau (Paduch, 2012). Additionally, Paduch found that body mass index (BMI) is a less reliable measure of childhood obesity in KS because the increased height artificially lowers BMI. Instead, he suggests the Tanita InnerScan Body Composition Monitor Scale (Tanita Corporation of America, Arlington Heights, IL) to directly assess body fat percentage in KS patients.
Figure 3: Height and weight distribution of patients seen at Paduch’s practice. This cohort consists of 135 adolescents. Adapted from Paduch, 2012.

Sexual Development Outcomes

KS individuals typically initiate puberty at the same age as the general population, but they have delays in facial hair development and muscle development compared with their siblings. Penile growth is typically not affected, but the girth may be. In Paduch’s practice at Weill Cornell Medicine (New York, NY), KS patients (48,XXXY) have a
characteristic thickening of penile skin that causes the penile circumference to exceed the length. Scrotal development is normal, but as puberty progresses, testicular size is significantly decreased. In patients with KS, testicular volume dramatically decreases by Tanner stage IV, which predicts that the atrophy of testes occurs between Tanner stages II and III (Paduch et al., 2009). Decrease in testicular volume is also caused by damage to the germinal epithelium as well as peritubular fibrosis (Bolyakov & Paduch, 2011). It is interesting to note that the size of the epididymis does not change during pubertal development and remains the same as normal XY counterparts (Bolyakov & Paduch, 2011).

As previously stated, many KS adolescents enter puberty around the same age as the general population, but testosterone concentrations decline at late adolescence and early adulthood. Because of decreased androgen production, characteristics such as facial, body, and sexual hair do not develop, whereas features of eunuchoidism and gynecomastia can potentially develop. As a result, KS adolescents and KS men in their early twenties look much younger than their chronological age. The incidence rate of gynecomastia in KS ranges from 56% to 88% (Smyth & Bremner, 1998). Although testosterone levels are low, adolescents with KS start masturbation at a similar time to the general population. However, KS adolescents experience a significant delay in the age of first voluntary ejaculation. In healthy adolescents, the mean time difference from the age of first masturbation to the age of ejaculation is 2 months, but in KS adolescents, the delay is 9 months (Bolyakov & Paduch, 2012). This delay may occur because the S2-S4 region of the spinal cord, which is responsible for ejaculation, is sexually dimorphic and
is highly dependent on adequate levels of testosterone (Bolyakov & Paduch, 2012).

All KS patients are considered infertile, though there have been reports of pregnancy without assisted reproductive technology (ART). These cases are believed to have only occurred in mosaic KS men. With the introduction of new technology, such as intracytoplasmic sperm injection (ICSI), some KS fathers have an increased chance of fathering a child (Kaplan et al., 1963; Okada et al., 1999; Ron-El et al., 2000; Schiff et al., 2005). A study done by Schiff (2005) consisting of 42 KS men showed that the sperm retrieval rate was 72% for each testicular sperm extraction (TESE) attempt and that 69% of the patients achieved pregnancy using ICSI. Therefore, TESE and ICSI may be considered a good alternative for men with KS who want to reproduce. According to Paduch (2012), one should allow the patient to deliver semen samples by masturbation to initially check for sperm in the ejaculate before proceeding to surgical treatment options.

**Cognitive Outcomes**

Unlike other chromosomal aberration syndromes such trisomy 21, KS men generally are not in the intellectual disability range (Boada et al., 2009). Studies have found that the mean cognitive ability of patients with KS falls in the low-average to average range (Boada et al., 2009). Lower scores are believed to be due to deficits in the verbal aspect of cognitive ability rather than the nonverbal or spatial aspect (Boada et al., 2009).

Longitudinal studies that were conducted with KS children revealed differences in verbal IQ (VIQ) scores and performance IQ (PIQ) scores. The discrepancy between
verbal and performance scores was evident even at a young age (Pennington et al., 1982; Samango-Sprouse et al., 2001), and both verbal and nonverbal skills diminished over time (Bender et al., 1993). Furthermore, Boone (2001) found that as KS patients grew older, the VIQ score increased relative to PIQ, and that VIQ was no longer a deficit when the patient grew older. This may be a result of hormonal imbalances during puberty. Others have speculated that this may reflect a correlation between language processing ability and androgen treatment in adult patients (Boada et al., 2009). It may also be that PIQ decline in older KS patients is happening more rapidly than normal deterioration (Boada et al., 2009).

Outside confounding factors such as socioeconomic status (SES) can have an effect on the cognitive outcomes of patients with KS. Through correlation twin studies, it has been observed that differences in intelligence appear to vary with the SES of homes in which the children were raised in (Turkheimer et al., 2003). When parents with higher SES are told of their child’s diagnosis with KS, they proceed with the pregnancy despite this diagnosis (Boada et al., 2009). They are prepared when the child is born and are ready to increase the number of resources available for the child. Although most children with KS show developmental delays, a cohort of children received a mean IQ of 110, which is considered in the high average range, because their parents were part of the upper middle class and provided them with extra means (Samango-Sprouse, 2001).

Overall, there is significant variability when it comes to the cognitive outcome of children and adults with KS. Language and academic deficits appear to affect verbal skills, but these deficits seem more prominent in younger ages. Multiple outcome studies
have reported less of a discrepancy between VIQ and PIQ, and there are multiple working factors, such as SES, that determine what the ultimate cognitive function is for KS patients (Boada et al., 2009). Although some patients have above average or superior cognitive abilities, the proportion of men with KS who have these high levels of cognitive abilities are less than those in the general XY population.

**Language and Reading Competence**

In addition to general cognitive deficits, KS children and adults have specific difficulties with language and reading. These difficulties have been identified in 70%–80% of children (Boada et al., 2009), with delays in speech starting as early as 24 months of age (Robinson et al., 1990). Most of the difficulties stem from expressive language, but receptive language deficits were also noted. Moreover, KS patients have issues with phonemic discrimination, processing speeds, sentence verification tasks, and comprehension of language (Bender et al., 1993; Graham et al., 1988; Netley et al., 1982; Rovet et al., 1996; Walzer et al., 1990). Tasks with increased perceptual discrimination or short-term memory demands are activities that KS patients struggle with most. Auditory processing and verbal memory are the main cognitive deficits that are linked with these difficulties (Geschwind & Dykens, 2004). Furthermore, these language deficits are identified throughout adulthood with greater impairment to verbal memory, auditory memory, confrontation naming, and verbal fluency skills than in the control group (Bender et al., 1993; Boone et al., 2001; Gerschwind et al., 1998).

KS individuals also demonstrate deficits throughout their academic careers.
children represented a good proportion of patients who receive special education support, especially in language and spelling (Pennington et al., 1982; Robinson et al., 1986). Approximately 50%–75% of KS boys have shown a reading disability at some point in their development (Bender et al., 1986; Graham et al., 1988). Similar to language difficulties, overall academic difficulties in patients with KS continue throughout adulthood. About 70% of KS adults show evidence of reading disabilities (Boone et al., 2001; Geschwind et al., 2004).

As studies examined academic achievements in KS children, some authors have reported that the gap is not only limited to literacy; there is a group of KS patients who have an overall learning disability. Some KS children scored significantly lower compared to their sibling controls on math. By 18–20 years of age, KS children lagged more than five grade levels behind the control group in both reading and math (Rovet et al., 1996).

Although it is generally said that KS patients have a weakness in verbal and language skills, there is significant variance among KS males in language deficits similar to physical phenotypes. It has been reported that there is no difference between verbal and nonverbal reasoning skills, with both of these scores being in the low average to average range (Netley et al., 1986; Ross et al., 2008). It was also shown that KS patients were in the average range on literature and arithmetic skills. In addition, the academic performance of KS patients did not decline with age.

There have been inconsistencies within findings in the language domain. Although receptive language skills have been described as deficient in KS, Graham et al.
(1988) reported that their cohort scored within normal range on all receptive language skills except for one measuring syntactic comprehension. Bender (1993) reported no significant difference in ability to understand syntactical complexity, and Ross et al. (2008) did not find evidence of expressive or receptive vocabulary problems in their cohort of KS patients. Given the range of phenotypic severity in KS, the variability of conclusions across these studies is not surprising.

**Genetic and Hormonal Factors Affecting Cognition**

Although it is generally known that children with KS have learning deficits, there are still questions regarding the severity of these deficits. Additionally, the relationship between phenotypic variability and having an extra X chromosome or androgen deficiency is still unclear. Most verbal cognitive delays are present in sex chromosome trisomy diseases that are not typically associated with hormonal deficiency (47, XYY and 47, XXX), so it is likely that genetic factors play a bigger role in cognitive phenotype than hormonal factors, especially since cognitive deficits occur early in childhood prior to the onset of hormonal deficiencies. Furthermore, neuroanatomical differences in the temporal and front lobe volumes are present in KS children when compared with the control (Giedd et al., 2007). These findings support the argument of a genetic etiology. Although there have been studies done that suggest there may be a hormonal deficiency in KS neonates (Lahloud et al., 2004; Ross et al., 2005), another study by Aksglaede et al. (2007) reports that there is increased testosterone in KS children when compared with the control group. In order to clarify these conflicting results, better assays that accurately
measure testosterone levels will need to be utilized to determine if pre-pubertal androgen is at deficient or increased levels in KS children (Boada et al., 2009).

There is little argument that there are differences in androgen levels in KS males compared with the control group during young adulthood (Aksglaede et al., 2008; Winter, 1990). A time of their life where cognitive and neuropsychological differences are present. In normal children, androgen levels have been shown to be positively correlated with spatial abilities and negatively correlated with language abilities (Knickmeyer et al., 2005). Therefore, if cognitive skills in KS were related only to androgen deficiency, one would see decreased spatial abilities relative to language skills, which is not the case (Boada et al., 2009). However, early androgen levels do play a role in neurodevelopment (Friederici et al., 2008; Mercure et al., 2009; Swedloff et al., 1992), so more studies are needed to understand pre-pubertal androgen in KS children and its effect on cognition phenotype. Also, since neurodevelopment continues into early adulthood, there may be important effects of androgen deficiencies on the maturing brain of men with KS (Giedd et al., 2006; Lenroot & Giedd, 2006).

**Management Through Androgen Replacement Therapy**

The management of KS combines counseling, special education, and testosterone replacement therapy (TRT). Androgens can induce the development of male secondary characteristics, eliminate gynecomastia, and improve general behavior and work performance (Landin-Wilhelmsen et al., 1999; Ruvalcaba et al., 1989). TRT should begin at puberty and increase in dosage to maintain age-appropriate testosterone, estradiol,
follicle-stimulating hormone (FSH), and luteinizing hormone (LH) serum concentrations. TRT normalizes body proportions and male secondary characteristics; however, it does not treat infertility and small testes. The long-term benefits of TRT include reducing the risk of osteoporosis, autoimmune disease, and breast cancer (Mehta et al., 1993), promoting male phenotype development, increasing penile size, improving cognition, and decreasing gynecomastia and abdominal obesity (Wosnitzer et al., 2013).

In the past, testosterone was given intramuscularly, but this was proved to be inefficient because it required painful injections, visits to the pediatrician to administer the injection, and excessive levels of testosterone in the KS patient. These high levels contribute to the increase in blood concentration and the suppression of follicular stimulating hormone (FSH) and luteinizing hormone (LH) to undetectable levels. Consequently, topical testosterone is preferred because it achieves physiological levels of testosterone without suppressing FSH and LH. The topical testosterone has high compliance among the adolescent population (Mehta et al., 2014). TRT should be monitored at six weeks to determine how the patient is feeling, and the dosage should be adjusted every six months as determined by the progression of puberty.

KS is also associated with hyperestrogenism. This condition is most likely due to the increased adipose tissue present in KS patients as well as the increased activity of aromatase CYP19, an enzyme that converts testosterone to estrogen (Bolyakov & Paduch, 2012). Aromatase inhibitors such as anastrazole are helpful in adolescents with gynecomastia and central obesity that do not respond to topical testosterone. These aromatase inhibitors are used for one to two years, but not much longer because of the
risk of osteopenia. Overall, the early intervention of TRT results in improved academic, physical, psychological, and social development.

**Specific Aims/Objectives**

Androgen deficiency is a common characteristic in KS patients; however, there is minimal clinical data on the effects of testosterone therapy on psychological and cognitive features in KS males. Past studies have shown that early androgen treatment for patients diagnosed with Klinefelter syndrome, results in better self-esteem, attention, energy level, and general well-being (Gerschwind et al., 2004; Neilsen et al., 1987; Simpson et al., 2005).

This study aims to show that adolescents who are treated with testosterone and aromatase inhibitors during early-onset puberty will overcome the social, cognitive, and behavioral difficulties that are usually associated with this condition. In addition, we will compare this study to previous literature on KS behavioral phenotypes. Finally, we will assess the parent’s views on their child’s competence, internalizing, externalizing, and overall behavior score versus that of the child’s own self-reflection. For our study population, we will utilize the patient population of Dr. Darius A. Paduch at Weill Cornell Medicine (New York, NY).

The specific aims of the study are:

1. To determine if early hormonal intervention will alleviate the social, educational, and behavioral difficulties that Klinefelter syndrome boys usually encounter.
2. To characterize the behavioral phenotypes of Klinefelter syndrome adolescents seen at Weill Cornell Medicine and to compare these phenotypes to those described in the previous literature.

3. To assess how parental views on their child’s social life, schoolwork, and behavior differ from the child’s own self-reflection on these various aspects. Through this study we hope to eliminate the current stigma that the medical community has about KS. We hope to establish an understanding that with early hormonal intervention, boys diagnosed with this syndrome will be able to lead relatively normal lives as compared with the general population. We also hypothesize that parents put pressure on their child to perform to the best of his abilities and that there will be discordance between the parents’ view of their child and the child’s view of himself.
METHODS

Participants

Participants were recruited for research participation from the Urology Department at Weill Cornell Medicine, specifically the practice of Darius A. Paduch M.D., Ph.D. The study was approved by the Institutional Review Board (IRB) at Weill Cornell Medicine. The clinical evaluation was performed at Weill Cornell Medicine, and confirmatory karyotyping was carried out by the Male Infertility Laboratory at Weill Cornell Medicine.

Assessment Procedures

Patients received a physical examination during their regularly scheduled office visits. At this clinical office visit, maternal age and paternal age at the time of child’s birth was ascertained. The competence/behavioral questionnaire was done either online through a secure network or at an office visit. The questionnaires were distributed from January 2016 to March 2016. Medication regimen and age when beginning the medication were extracted from the patient’s electronic medical record (EMR).

Anthropometric Measurements

The clinical assessment included measurements of height in inches and weight in pounds. Pubertal development was assessed by an experienced urologist who specialized in seeing children with Klinefelter syndrome. Tanner stage was not measured, as most of the study subjects were past puberty and did not have a current Tanner stage documented. This information was extracted from each participant’s EMR.
**Parent Questionnaires**

The Child Behavior Checklist (CBCL) is a standardized measure of behavior problems and social competency in children ages 2 to 18 years and includes t scores for 10 problem behavior areas and 3 social competency areas (activities, social skills, and school). The behavior problem scales include internalizing behavior (anxiety depression, withdrawn depression, and somatic complaints), externalizing behavior (rule breaking and aggression), and total behavior domain scores. For the social competency areas, higher scores are considered good, whereas for the behavior problem scales, higher scores are considered bad.

For the social competency results, percentile nominal scores were converted into categorical data. Percentile scores above 7 were considered normal, percentile scores below 2 were considered clinical, and percentile scores between 2 and 7 were considered intermediate. The total competence T score was also converted into categorical data. T scores above 40 were considered normal, T scores below 37 were considered clinical, and T scores between 37 and 40 were considered intermediate. This categorical scale was predetermined on the standardized instrument’s scoring sheet.

For scoring the problem behavioral results, any percentile scores below 50 as a T score were converted to 49, and any percentile scores above 93 were converted to 94. This was done in order to standardize the scores that were considered below or above the scale provided by ASEBA (Achenbach System of Empirically Based Assessment). Nominal data were also converted into categorical data. For problem behavior areas, percentile scores above 98 were considered clinical, percentile scores below 93 were
considered normal, and percentile scores between 93 and 98 were considered intermediate. For total T scores that covered internalizing, externalizing, and total behavior domain scores, T scores below 60 were considered normal, T scores above 63 were considered clinical, and T scores between 60 and 63 were considered intermediate.

**Child Questionnaires**

The Youth Self Report (YSR) is a standardized measure in child psychology and was derived from the CBCL. The YSR was designed to evaluate the emotional and behavioral problems in adolescents. The measure assesses internalizing behavior (anxiety, depression, and somatic complaints) and externalizing behavior (rule breaking and aggression). There are also different subscale symptoms that measure eight empirically based syndromes. The measure assesses total competency using a scale that comprises competency in activities, social functioning, and school performance. For the competency areas, higher scores are considered good, whereas for the behavior problem scales, higher scores are considered bad.

For the social competency results, percentile nominal scores were converted into categorical data. Percentile scores above 7 were considered normal, percentile scores below 2 were considered clinical, and percentile scores between 2 and 7 were considered intermediate. The total competence T score was also converted into categorical data. T scores above 40 were considered normal, T scores below 37 were considered clinical, and T scores between 37 and 40 were considered intermediate.

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score were converted to 49, and any percentile scores above 93 were converted to 94. This was done in order to standardize the scores that were considered below or above the scale provided by ASEBA. Nominal data was also converted into categorical data. For problem behavior areas, percentile scores above 98 were considered clinical, percentile scores below 93 were considered normal, and percentile scores between 93 and 98 were considered intermediate. For total T scores that covered internalizing, externalizing, and total behavior domain scores, T scores below 60 were considered normal, T scores above 63 were considered clinical, and T scores between 60 and 63 were considered intermediate.

Genetic Testing

To confirm diagnosis, a peripheral blood karyotype was obtained, or previous medical records from doctors outside of Weill Cornell Medicine were evaluated. If a karyotype was obtained at Weill Cornell Medicine, a sample of blood was drawn. Cells from the blood are centrifuged, cultured, treated with reagents, and finally dropped on a microscope slide to dry. These slides are stained to induce a banding pattern and then photographed. A lab technician analyzed the image by using computer software that arranges the chromosomes in order of size.

Concordance

For concordance between parent and child frequencies, we decided to examine specific aspects of the competence and behavioral questionnaires. Results were
considered concordance if the parent and child both agreed and evaluated the child as either “normal,” “intermediate,” or “clinical.” Results were considered discordance if the parent and child disagreed and evaluated the child differently; for example, if the parent evaluated the child as “clinical,” but the child evaluated himself as “normal.”

We chose to focus our study more on anxiety depression, withdrawn depression, total competence, internalizing behavior, externalizing behavior, and total behavioral score. The total competence encompassed social skills, schoolwork, and the number of activities in which the child was involved. Internalizing behavioral scores included anxiety depression, withdrawn depression, and somatic problems. Externalizing behavioral scores included aggressive behavior and rule-breaking behavior. Finally, total behavioral score included internalizing behavioral aspects, externalizing behavioral aspects, and also social problems, thought problems, and attention problems.

**Statistics**

Raw scores were converted into percentile scores and t scores (mean of 50; SD of 10) are based on test-specific norms. Percentile scores and T scores were then converted into categorical data (clinical, intermediate, and normal). Difference of means was used to test for statistically significant differences between the scores of the KS patients and their parents on competence and behavioral aspects. Significant differences between group scores were determined using the t test for equality of means since normality was present. P values <0.05 were considered statistically significant. Pearson correlation tests were also run to see if there was an association between demographic variables and
competence/behavioral scores.

The first null hypothesis was that there was no statistically significant difference between how the parents score their child in the CBCL and how the child scores himself in the YSR in terms of demographics. The second null hypothesis was that there was no statistically significant difference or correlation between demographics and raw individual competence and behavioral scores.
RESULTS

Study Population

A total of 39 subjects were enrolled, resulting in 33 CBCLs and 31 YSRs collected. Some groups did not have one of the two questionnaires filled out, and this was indicated as “missing” when analyzing the data. Patient and parental demographic information is presented in Table 1. The mean maternal and paternal ages were 34.76±5.41 and 37.41±5.91 years old, respectively. The average age of patients who completed the questionnaire was 19.05±6.54 years old, with an age range of 6–40 years old. The average age of patients when they started taking anastrazole, more specifically Arimidex, was 16.66±5.72 years old. The average age for TRT initiation was 14.38±4.72 years old. The average height of patients was 69.82±5.86 inches, and the average weight was 155.13±43.17 pounds. Using the average height and average weight, there is a calculated value of 22.26 for BMI.

Table 1: Demographics of patient population.

<table>
<thead>
<tr>
<th></th>
<th>Age (years) N= 39</th>
<th>Age when starting Arimidex (years) N= 32</th>
<th>Age when starting Testosterone (years) N= 39</th>
<th>Height (inches) N= 39</th>
<th>Weight (pounds) N= 39</th>
<th>Paternal Age (years) N= 32</th>
<th>Maternal Age (years) N= 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>19.05</td>
<td>16.66</td>
<td>14.38</td>
<td>69.82</td>
<td>155.13</td>
<td>37.41</td>
<td>34.76</td>
</tr>
<tr>
<td>Std. Dev.</td>
<td>6.540</td>
<td>5.720</td>
<td>4.720</td>
<td>5.860</td>
<td>43.170</td>
<td>5.910</td>
<td>5.410</td>
</tr>
<tr>
<td>Minimum</td>
<td>6</td>
<td>10</td>
<td>4</td>
<td>45.00</td>
<td>45</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Maximum</td>
<td>40</td>
<td>36</td>
<td>32</td>
<td>76.77</td>
<td>270</td>
<td>51</td>
<td>44</td>
</tr>
</tbody>
</table>
**Adult Questionnaire Evaluation**

CBCL categorical competence results are shown in Figure 4. We excluded missing data from 6 questionnaires because 6 patients filled out the YSR while their respective parents did not fill out the CBCL. For activities, 81.8% of parents believed that their child was considered normal for his age group. For social skills, 78.8% of parents believed that their child was considered normal for his age group. For school, 36.3% of parents believed that their child was having trouble with schoolwork and was not doing well in school work. These results were in turn reflected in total competence. Only 48.5% of parents believed that their child was considered normal, and 51.5% believed that their child was considered intermediate or clinical in terms of competence. The areas of competence and behavior that were most clinical are: total competence, total behavior, and internalizing behavior.

**Figure 4:** CBCL categorical competence and behavioral results (N = 33).
**Child Questionnaire Evaluation**

YSR categorical competence results are presented in Figure 5. We excluded missing data from 8 questionnaires because 8 parents filled out the CBCL while the respective patient did not fill out the YSR. For activities, 87.1% of patients believed that they were normal and participated in enough activities for their age group. For social skills, 90.3% of patients believed that their social life was sufficient and normal for their age group. Although there was no separate T score for school, performance at school was included as part of the total competence score. For total competence, 80.6% of patients believed that they were considered normal.

**Figure 5:** YSR categorical competence and behavioral results (N = 31).
CBCL categorical behavioral problem results are displayed in Figure 4, while YSR categorical behavioral problem results are shown in Figure 5. For depression, 27.3% of parents believed that their child had some form of anxiety depression, and 15.2% of parents believed that their child had some form of withdrawal depression. While only 16.2% of patients felt that they had some form of anxiety depression, but 19.4% of patients felt that they had some form of withdrawal depression. For somatic problems, 81.8% of parents reported that their child was considered normal, and 96.8% of patients believed they were normal. For social problems, 24.2% of parents believed that their child had some form of social difficulties, while only 9.7% of patients believe they had social difficulties. 24.3% of parents believed that their child had thought problems and only 16.1% of patients believe that they had an issue. 27.3% of parents believed that their child had attention issues, while only 6.5% of patients believe that they had trouble with paying attention. For rule breaking, there were no parents who thought that their child was intermediate, but 6.1% of parents believed that their child was clinical. For aggressive behavior, 9.1% of parents believed that their child was clinical or intermediate. Lastly, only 3.2% of patients believed that they had any rule breaking problems or aggressive behavior. Internalizing issues included both depression scores and somatic problems, and 36.4% of parents believed that their child was suffering from internalizing problems, while only 25.8% of patients believe they were suffering from internalizing problems. As for externalizing issues, this category included rule breaking and aggressive behavior, and 24.3% of parents believed that their child was suffering from externalizing problems, while only 9.7% of patients believed they were suffering
from externalizing problems. For total behavioral categorical scores, only 60.6% of parents believed that their child was considered normal, while 80.7% of the patients believed they were normal.

**Concordance Frequency**

From the results in Table 2, the most concordance between parent and child was on externalizing behavior, with 80% of parents and patient agreeing with one another. Whereas the most discordance between parent and child was on internalizing behavior, with only 60% of parents and patient agreeing with one another.

**Table 2:** Concordance frequency table (N = 25).

<table>
<thead>
<tr>
<th></th>
<th>Frequency (n/total)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety Depression</td>
<td>18/25</td>
<td>72%</td>
</tr>
<tr>
<td>Withdrawn Depression</td>
<td>18/25</td>
<td>72%</td>
</tr>
<tr>
<td>Total Competence</td>
<td>19/25</td>
<td>76%</td>
</tr>
<tr>
<td><strong>Internalizing</strong></td>
<td><strong>15/25</strong></td>
<td><strong>60%</strong></td>
</tr>
<tr>
<td>Externalizing</td>
<td>20/25</td>
<td>80%</td>
</tr>
<tr>
<td>Total Score</td>
<td>17/25</td>
<td>68%</td>
</tr>
</tbody>
</table>

**Patient Demographics and Discordance**

As shown in Table 3, there was significance between anxiety depression and paternal age. With increasing paternal age, there was more discordance between the parents’ and child’s views on the child’s anxiety depression.
Table 3: Difference of means between patient demographics and discordance.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Demographic</th>
<th>Concordance (years)</th>
<th>Discordance (years)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Paternal age</td>
<td>36.41±5.185</td>
<td>42.43±5.94</td>
<td>0.021</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Externalizing</td>
<td>Age when starting Arimidex</td>
<td>14.47±1.727</td>
<td>12.25±1.5</td>
<td>0.032</td>
</tr>
<tr>
<td>Behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We also found significance between age when starting Arimidex and externalizing concordance, shown in Table 3. When starting Arimidex later, there was more concordance between the parents’ and child’s views on the child’s externalizing behavior. Externalizing behavior included aggressive behavior and rule-breaking behavior.

Correlation Between Demographics and CBCL/YSR Scores

We also ran Pearson correlation tests on demographics versus raw concordance scores for all domains of competence and behavioral scores. In Table 4, we found significance and a positive correlation between maternal age and adult social percentage as well as T score. With increasing maternal age, adult social percentage and T scores were higher, which indicated that the child’s social life was more fulfilling as reported by the parents.
Table 4: Pearson correlation tests between demographics and raw concordance scores

<table>
<thead>
<tr>
<th>Domain</th>
<th>Demographic</th>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBCL Social % Score</td>
<td>Maternal age</td>
<td>0.387</td>
<td>0.031</td>
</tr>
<tr>
<td>CBCL Social T Score</td>
<td>Maternal age</td>
<td>0.375</td>
<td>0.037</td>
</tr>
<tr>
<td>CBCL Withdrawn Depression T Score</td>
<td>Age when starting Testosterone</td>
<td>0.381</td>
<td>0.029</td>
</tr>
</tbody>
</table>

We also found significance and a positive correlation between the patient’s age when starting testosterone and adult withdrawn depression T score, shown in Table 4. With increasing patient age at the start of taking testosterone, adult withdrawn depression T score was higher. This implied that the child had some form of withdrawal depression as viewed by the parents.
DISCUSSION

The goal of this study was to collect clinical data that would help us analyze behavioral phenotypes in males with Klinefelter syndrome (KS) (47, XXY). We wanted to compare our data with earlier reports in the literature, and we were also interested in examining the parents’ view on their child’s upbringing and how it differed from the child’s own self-reflection. Our patient cohort encompassed mostly adolescents who were transitioning into college life or entering the work force. We wanted to be able to show that these patients, who started testosterone and aromatase inhibitors when they were in their early adolescent years, could successfully support themselves in the “real world” despite being diagnosed with Klinefelter syndrome. To our knowledge, this is the first chart review study that involves a wide age range of males with KS. The current study extends previous findings by providing data on how early hormonal intervention, with testosterone and aromatase inhibitors, improves the outlook of these patients’ lives in terms of overall competence and behavioral aspects. These findings support other studies by confirming a link between hormonal treatment and neurodevelopmental outcome in boys with KS (Mandoki et al., 1991; Patwardhan et al., 2002; Ross et al., 2005, 2009; Samango-Sprouse et al., 2012). This study not only correlates various demographic areas with different competence and behavioral aspects, but also expands on the psychological relationship between parents and child.

In our study, the majority of answers for the CBCL and YSR were normal. These results are similar to previous KS studies that utilized the same standardized instrument (Ross et al., 2012). Our study differs when looking at the CBCL total competence scores.
The total competence score evaluates social skills with peers and family members, success in school work, and the number of activities in which the child participates. Comparison of the percentile averages for CBCL/YSR activities and CBCL/YSR social skills showed that they were similar with scores of 81.8%/87.1% and 78.8%/90.3%, respectively. The only aspect that was not comparable between the two questionnaires was school work, as the YSR did not include a separate section to calculate the percentile and T score for this category. It is evident that many parents believed their son was struggling in classes because close to 40% of them considered their child to be either clinical or intermediate in this area. This score, in turn, shifted the CBCL total competence score so that the majority of parents believed that their child’s total competence was either clinical or intermediate.

These results may reflect how parents have unrealistic academic expectations for their child. Based on information from the EMRs, the patients in our study were achieving mainly A’s and B’s in their classes. These grades are considered above average by most educators. Whereas some parents may perceive a B as above average results, others may see it as only average or even below average. When evaluating this data, we must take into account how differing views of success can shape how the parents and child answer their respective questionnaires.

Previous studies have stated that many adolescents report feeling worse after stopping anastrazole, specifically Arimidex, in terms of their ability to concentrate and their overall energy level (Samango-Spouse et al., 2015; Wosnitzer et al., 2013). Our study confirms this observation because we found an overall reduction of aggression and
rule-breaking behavior in adolescents with KS who had early hormonal intervention. We also found that there was a significant difference between the patient’s age when he first started anastrazole, specifically Arimidex, and concordance between CBCL and YSR on externalizing behavior. When patients started Arimidex at a later age, the parents and child agreed more on the patient’s externalizing behavior. These results may simply reflect that the patient is older, more self-aware and can accurately evaluate his aggressive behavior or rule-breaking behavior. On the other hand, patients who are younger may simply not understand that this type of behavior is unacceptable or may not be aware that they are exhibiting aggressive/rule-breaking behavior. Further research is needed to make an evidence-based recommendation about optimal indications and duration of aromatase inhibitor therapy.

We also found that there was concordance between the age of the father when the child was born and anxiety depression scores. If the father was younger when the child was born, there was more agreement on the child’s anxiety depression. These results could be due to younger fathers being more energetic and willing to spend more time doing activities with his son. By spending more time with his child, the father may be able to detect whether his son exhibits signs of anxiety depression and may be able to accurately evaluate his son’s behavior. Alternatively, this could reflect that younger generations recognize anxiety and depression as a disease, and would encourage their child to get help, as opposed to hiding the condition.

Our study also confirms that early hormonal intervention was associated with improved behavioral outlook for patients with KS. Previous studies have shown that there
were no adverse outcomes related to TRT. The treatment was safe and effective in adolescents with KS and was not associated with suppression of serum LH or FSH (Mehta et al., 2014; Wosnitzer et al., 2013). In our study, there was a positive correlation between the age of the patient when he first began taking testosterone and the CBCL withdrawn depression score. Higher withdrawn depression scores signify that the child is more likely to be clinically depressed; therefore, our study showed that the later the patient started taking testosterone, the more likely he was to have a form of withdrawal depression. Future studies can elaborate on this aspect by having a randomized control trial with a larger, more varied cohort and a control group to truly see if taking testosterone at a later age will change the parents’ view on their child’s withdrawn depression.

In addition, we discovered a positive correlation between maternal age and CBCL social skill percentile and T score. This correlation implies that if the mother was older when the son was born, the parents perceived the adolescent as having a more fulfilling social life. These results may reflect that an older mother has a more established career, more time to spend with her child, and more resources to provide for her child because of a larger yearly income compared with a younger mother. This in turn may facilitate a more positive social environment for the child. On the other hand, these results could also simply show that older mothers can perceive and report their child’s social functioning differently from younger mothers.

There are limitations to this study that should also be taken into consideration. The decision to receive early hormonal replacement was made on an individual basis,
exclusively between parents and their urologist. Although the SES and educational characteristics of the families were similar because of the location of the clinic, there may be confounding factors that we were unable to account for, resulting in skewed data and more positive results. Important factors that were not consistently controlled in the current study include the amount of special education or tutoring that some KS children might have had, whether they had received hormonal treatment before coming to Weill Cornell Medicine, and their sensitivity to testosterone and anastrazole. Despite the strong associations between early hormonal treatment and positive behavioral, educational, and social outcomes in this study, causal relationships were unable to be drawn, particularly given the retrospective design of this study. As a result, these factors support the need for continued research into the impact of early treatment interventions in males with KS.
CONCLUSION

KS is the most frequent chromosomal abnormality in males, general practitioners should be aware of the various physical, cognitive, and behavioral phenotypes that are associated with this genetic disorder. Through early detection and appropriate management of low testosterone associated with KS, there is potential to have physical and behavioral benefits along with the improvement of general health, pubertal progression, academic progress, and social integration. Future KS studies will need to focus on identifying the underlying factors that contribute to the variability and severity of behavioral symptoms. These studies will help support the continuing development of evidence-based treatments for the KS population.

Our investigation on early hormonal intervention in KS males is important for several reasons. The findings demonstrate an improvement in neurologic progression in behavioral areas that are of importance and commonly associated in boys with KS. The work amplifies the significance of early detection and treatment in a disorder that is severely under-diagnosed throughout the world. The findings also show that the desire of parents for their child to do well in school may affect their opinions on how their child is actually performing. In addition, the results establish that in terms of school grades, the definition of success is relative, and reality may differ from what is actually reported. Finally, our study touches upon a correlation between parental age when having their child and various behavioral and competence scores. Future studies can more thoroughly investigate this factor by increasing patient cohort size as well as creating more homogeneity within the patient sample, such as socioeconomic background and parental
education. This will minimize confounding effects on developmental scores and maximize the ability to further understand the link between treatment, parental age, and neurodevelopmental outcome.

There has been consistent evidence from this study and others that indicate early diagnosis and management through hormonal intervention can mimic the normal progression of puberty for adolescents with KS and can be beneficial to the overall well-being of these children. There are still challenges with determining the endocrinological management of KS, such as understanding the ideal hormonal levels to facilitate optimal physical and neurobiological development. With improved knowledge of the molecular mechanisms that lead to hypogonadism, investigators will be able to plan and execute a randomized prospective clinical trial, which will develop ideal treatment regimens for males with KS in the future.
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Clinical Research Coordinator
June 2015–now
• Assists in developing clinical research studies, performs retrospective cohort analyses, assists with presentations and publication process, prepares consent forms and maintains HIPAA compliance for research studies through the IRB
• Works with various central administration offices to formulate budgets and submit federal grant applications

Stony Brook University Department of Sociology
Research Assistant
June 2011–January 2012
• Utilized video capturing devices and Excel spreadsheets to decipher and provide detailed analyses on sociological behavior in African cichlid fish
• Headed weekly meetings pertaining to progress of research project on dominance among cichlid fish

Stony Brook Hospital Department of Pediatrics
Head Clinical Research Assistant
June–December 2011
• Led the recruitment of test subjects and the administration of survey interviews for a home visitation program
• Collected literature searches, handled IRB submissions, analyzed articles, and systematized data entry
Texas Department of State Health Services  
*Laboratory Assistant*  
Austin, TX  
June–August 2010  
- Provided support to key staff members for special projects such as newborn screening and testing of bacillus on ice  
- Used the following skills: cell culture, crystallization, decantation, distillation, DNA extraction, filtration, flow cytometry, gel electrophoresis, intravital staining, PCR, serial dilution  

**RELATED EXPERIENCE**  
**MIDLAND International**  
*Project Manager*  
New York, NY  
December 2013–July 2014  
- Held seminars for health care providers on how to use the company’s electronic health records software, iClinic  
- Developed and executed a behavioral health module for the software to include Meaningful Use Stage 3 criteria  

Stony Brook University Department of Health Sciences  
*Teaching Assistant, Anatomy and Physiology/Medical Terminology*  
Stony Brook, NY  
June–August 2013  
- Facilitated classroom discussion sessions and hosted regular office hours for undergraduate students  
- Assisted faculty members with test and assignment grading  

**LEADERSHIP AND COMMUNITY SERVICE**  
**Stony Brook Alpha Sigma Alpha Sorority, Executive Board**  
September 2011–May 2014  
- Vice President of New Member Education, Vice President of PR and Recruitment  
- Helped donate 2,400 hours of service time to “Girls on the Run” and “S. June Smith Center” initiatives  
- Raised over $2,500 in the annual Polar Plunge of the Special Olympics  

**Stony Brook University Academic Judiciary Committee**  
September 2010–May 2014  
- One of four students selected to sit as a jury member on trials of students accused of academic dishonesty  
- Strived to maintain a healthy learning environment within the Stony Brook community  

**SKILLS**  
**Languages:** Fluent in English and Mandarin Chinese (lived in Hong Kong and Shanghai from 2002–2008)  
**Computer:** Proficient in Microsoft Access, Excel, PowerPoint, basic Python  
**Interests:** Traveling, cooking, flute, basketball, soccer  
