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Mental Health Diagnoses Associated with Sex Chromosome Anomalies

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Mental Health Diagnoses Associated with Sex Chromosome Anomalies

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Abstract

Mental Health Diagnoses Associated with Sex Chromosome Anomalies

By

Adaiah Priscillia Soibi-Harry

Background: Sex chromosome anomalies (SCA) are a group of congenital conditions that affect the number or structure of X and Y chromosomes. This study aims to characterize mental health diseases (MHD) commonly affecting SCA patients and compare the prevalence of MHD in individuals with SCA and matched referents.

Methods: Data from an ongoing study were used to identify eligible individuals enrolled in three Kaiser Permanente (KP) health plans between January 1, 1988, and January 31, 2017.[1] Participants with Klinefelter syndrome (KS), Turner syndrome (TS), or other SCA (TS and KS variants and mosaicisms) were identified using an electronic health record (EHR) screening algorithm, followed by a review of medical note excerpts and laboratory karyotype analysis results. Each SCA participant was matched with ten non-SCA males and ten non-SCA females on age (within five years), study site, race/ethnicity, and index date (enrollment date in the KP plan). Conditional Poisson regression models with a robust variance estimator, accounting for matched design, were used to compare the prevalence of each MHD across study groups. The results of each model were expressed as prevalence ratios (PR) and the corresponding 95% confidence intervals (CI).

Results: The analysis dataset included 261 participants with KS, 73 participants with TS, and 217 participants with Other SCA. MHDs were more prevalent in people with SCA across all categories. When KS patients were compared with male referents, the differences in prevalence were particularly pronounced for feeding and eating disorders (PR=12.5; 95% CI: 3.3-6.8), schizophrenia spectrum and other psychotic disorders (PR=4.3; 95% CI: 2.4-7.9), and suicidal ideation (PR=4.3; 95% CI 2.5-7.3). Among TS patients, the corresponding PR estimates relative to female referents were the highest for neuro-developmental disorders (4.5; 95% CI: 2.6-7.7) and disruptive, impulsive-control, and conduct disorders (2.4; 95% CI: 1.0-5.7). Personality disorders (PR=2.6; 95% CI 1.0-7.1) and neuro-developmental disorders (PR=3.4; 95% CI: 2.3-4.9) were notably higher in the other SCA group than among female referents.

Conclusion: People with SCA carry a greater MHD burden than the general population. Ensuring adequate access to and utilization of mental health services is an important healthcare priority in this group of patients.

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INTRODUCTION

Sex chromosome abnormalities (SCA) are a group of congenital disorders that affect the number or structure of X and Y chromosomes.[2] SCA occurs due to chromosomal nondisjunction during meiosis or early postzygotic developmental stages.[3] The prevalence of SCA varies from 1 in 400 to 1 in 2,500.[2,4–6] Abnormalities affecting the number of chromosomes can present as monosomies, where one chromosome is missing (45, X), or trisomies, where there is an extra chromosome (47, XXY; 47, XYY; and 47, XXX). Sex chromosome mosaicism, involving a combination of both normal and abnormal sex karyotypes, may also occur with the resulting phenotypic features, dependent on the percentage of the abnormal cell lines. The most common sex chromosome mosaicisms are 45, X/46, XX, and 45, X/46, XY.[7] Other SCA types, such as isochromosome Xq and Xp22 SHOX deletion, result from structural defects of a sex chromosome.

Diagnosis of SCA is challenging. Some conditions may be diagnosed incidentally during prenatal testing for other reasons, a few postnatally when they present with specific physical or developmental health problems or infertility as adults, but many people with SCA never get a diagnosis in their lifetime.[8,9] In the global north, prenatal diagnosis of SCA is well established with a cascade of testing events during pregnancy, beginning with a first-trimester risk assessment screening using maternal blood and a second-trimester fetal ultrasound scan. If the screening results are positive, a diagnostic workup is initiated, which may include invasive procedures such as chorionic villus sampling, amniocentesis (karyotyping), and, more recently, non-invasive tests using cell-free fetal DNA in maternal blood.[10,11] SCA is a heterogeneous group of disorders; therefore, their clinical presentation varies depending on the chromosomal abnormality involved and the presence or absence of mosaicism. We will describe the most common presentations.

Turner syndrome (TS), or congenital ovarian hypoplasia syndrome, is the most common SCA in females, affecting 1 in 2,000-2,500 live births.[12] It occurs when one set of genes from the short arm of one of the X chromosomes is completely or partially lost. The phenotype of TS is broad, with individuals with a 45, X karyotype having a more severe phenotype than those with mosaicism 45, X/46, XX or 45, X/46, XY.[13,14] These patients may present at birth with swollen arms and feet and webbed neck, short stature in childhood, issues with puberty in adolescence, and infertility in adulthood.[15,16] They are also at increased risk of congenital malformations, aortic dissection, osteoporosis, fractures, type 2 diabetes, ischemic heart disease, hypertension, stroke, and increased mortality.[5,17,18]

Klinefelter syndrome (KS) is the most common SCA in humans, occurring in 1 - 2.5 per 1,000 male live births.[4] KS occurs when meiotic nondisjunction of the X chromosome occurs, resulting in an extra X chromosome in a male offspring. About 90% of men with KS are 47, XXY, and 10% have mosaicisms (47, XXY/46, XY).[19,20] KS is the most common cause of hypogonadism in men and accounts for 4% of male infertility.[21,22] Only one in four men living with KS are diagnosed; most appear normal phenotypically.[23] KS presents as a tall man with narrow shoulders, broad hips, gynecomastia, small testes, azoospermia, reduced verbal intelligence, learning difficulties, and developmental delays.[24–28] Men with KS are also at increased risk for cardiovascular mortality,[20] metabolic syndrome,[29] osteoporosis,[30] and venous thromboembolism.[31]

Jacobs syndrome (JS) is a rare SCA occurring in 1 in 1,000 male live births.[32] JS arises from chromosomal nondisjunction during meiosis II in the father, resulting in an extra Y chromosome (47, XYY) or (46, XY/47, XYY) mosaicism in the offspring. The clinical presentation of JS varies, with most men not having any apparent phenotypic difference from their peers. Some clinical features associated with JS include macro-orchidism, tall stature,

macrocephaly, hypertelorism, increased risk for asthma, autism spectrum disorder, and seizures.[33] Men with JS also have an increased risk for behavioral problems, mild learning disabilities, and delayed speech and language development.[34]

Triple X syndrome or Trisomy X (TX) is the most common chromosomal abnormality in females, occurring in 1 in 1,000 females.[2,35] TX occurs due to nondisjunction during gametogenesis resulting in an extra X chromosome (47, XXX). The clinical presentation of girls with TX varies widely, with most appearing normal and having normal reproduction, and as a result, only about 10% of these women get a diagnosis.[2] The most common clinical presentation is genitourinary abnormalities, like unilateral kidney, renal dysplasia, ovarian malformations (Lin et al., 1993), and delayed language development.[36,37]

Previous studies have indicated that defects in sex chromosome genes may alter the basic differentiation process of neurons, encoding proteins, and synaptic transmissions in the brain.[6,38,39] Neuroimaging studies have also shown that the X and Y chromosomes affect brain circuits that regulate thoughts, emotions, attention, behavior, and impulses and subsequent positive adjustment and adaptation to daily life challenges.[40] Several studies have identified associations between psychiatric disorders and the sex chromosome genes in children and adolescents.[41–44] Recent population studies in Sweden and Denmark found that females with TS had a higher risk of childhood-onset autism spectrum disorders, schizophrenia, eating disorders, and behavioral and emotional disorders.[45] Sánchez and colleagues also found an increased risk of attention deficit hyperactivity disorder, bipolar disorder, and schizophrenia among young people with JS and TX and an increased risk of depression among males with KS and JS.[46]

The frequency of SCA diagnosis is expected to increase with recent improvements in prenatal detection of chromosomal and genetic anomalies using non-invasive screening tests.[47]

This creates a need to improve the understanding of mental health disorders (MHD) associated with SCA, as this will be essential for understanding etiological pathways, identification of specific targets for intervention, and more tailored mental health care for the affected population. MHD of SCA in childhood is well described in the literature, but relatively little is known about MHD in the life course and adulthood. Addressing this subject will require studying individuals with SCA within a wide age range and comparing them to a control population. With these considerations in mind, the current study aims to characterize MHD commonly affecting SCA patients and compare the prevalence of MHD in individuals with SCA and matched referents.

METHODS

Study Setting and Data Sources

The data for the current analysis were obtained from an ongoing study evaluating pathways to care in people with disorders of sex development (DSD).[1] "DSD Pathways" is an electronic health record (EHR) based retrospective/prospective cohort study of persons enrolled in three integrated healthcare systems: Kaiser Permanente Georgia (KPGA) that includes the area in and around Metro Atlanta, Kaiser Permanente Mid-Atlantic States (KPMS) that provides care to residents of Maryland, Virginia, and the District of Columbia, and Kaiser Permanente Southern California (KPSC) that covers Greater Los Angeles and surrounding counties. This study represents a cross-sectional analysis of the data pertaining to a subset of the DSD Pathways cohort restricted to SCA patients enrolled in one of the three participating KP sites between January 1, 1988, and January 31, 2017. Participants with confirmed SCA were identified using an EHR screening algorithm, supplemented by a review of medical note excerpts and linkages of records to laboratory karyotype analysis results. The cohort identification and validation followed the

following four steps: In Step 1, all KP EHRs were searched to identify records containing keywords and diagnostic codes related to any DSD condition. In Step 2, the records of all DSD cohort candidates were searched with a specific focus on diagnostic codes and keywords indicative of SCA. Step 3 of the algorithm involved a review of short text strings from clinical notes to confirm the presence of SCA and, whenever possible, categorize study participants according to specific SCA type. During Step 4. records of SCA candidates were linked to laboratory karyotype reports. Only participants with EHR-documented karyotypes (in laboratory reports or clinical notes) were eligible for inclusion in the present analysis. Based on the karyotype, each eligible participant was placed in one of the three diagnosis groups: KS, TS, and other SCA, which primarily included TS and KS variants and mosaicisms.

Each identified SCA participant was matched with ten non-SCA males and ten non-SCA females identified within the KP source populations. The matching was based on age (within five years), participating site, race/ethnicity, and index date (enrollment date in the KP plan). Cluster identity numbers were assigned for each matched group to allow for stratified analyses. SCA participants and their matched controls were then linked to mental health diagnostic codes. For the purpose of the present analysis, all relevant diagnostic codes were grouped according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) to create broader categories of mental health disorders. (American Psychiatric Association, 2013).

Statistical analysis

The primary independent variable of interest was SCA status (i.e., KS, TS, or other SCA) versus reference males or females. The dependent variables of interest included schizophrenia spectrum and other psychotic disorders, depressive disorders, anxiety disorders, feeding and eating disorders, bipolar and related disorders, disruptive, impulsive-control, and conduct disorders,

substance-related disorders, personality disorders, neurodevelopmental disorders, self-harm-definitive and possible, suicidal ideation, somatic symptom and related disorders, and other mental health disorders. The prevalence of mental health diagnoses among participants with each SCA type and male and female referents were calculated and presented as counts and percentages. Conditional Poisson regression with a robust variance estimator, accounting for the matched design, was used to compare the prevalence of each mental health disorder in SCA participants and their matched controls. The results of all models were expressed as prevalence ratios (PR) and the corresponding 95% confidence intervals (CI). All analyses used SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Ethical considerations

Emory University's institutional review board and the institutional review boards of the participating KP sites reviewed and approved the study activities. Informed consent was waived as the study was low-risk and involved de-identified EHR data, with access permission restricted to authorized personnel at each site.

RESULTS

The selection of participants in the SCA cohort is summarized in **Figure 1**. The initial broad search of the EHR identified 14,546 individuals. After reviewing text strings and karyotype analysis results, 551 individuals had confirmed SCA status, 261 with KS, 73 with TS, and 217 with other SCA (KS and TS variants or TS mosaicism). **Table 1** shows the baseline characteristics of all SCA participants. Across all SCA categories, more than 80% of participants were from the KPSC site. About 41% of the SCA participants identified as Hispanic, 30% as non-Hispanic White,

10% as non-Hispanic Black and 19% as Asian or Others. Most SCA participants (53%) were under the age of 18 at the time the SCA diagnosis was first documented in the EHR.

In participants with KS, the most prevalent MHDs were anxiety disorders (41.8%), neurodevelopmental disorders (34.5%), substance-related disorders (27.2%), depressive disorders (26.1%), and disruptive, impulsive-control, and conduct disorders (11.9%). Feeding and eating disorders (PR=12.5; 95% CI 3.3-46.8), schizophrenia spectrum and other psychotic disorders (PR=4.3; 95% CI 2.4-7.9), suicidal ideation (PR=4.3; 95% CI 2.5-7.3) and self-harm (PR=4.0; 95%CI 1.5-10.4) were significantly higher amongst KS participants compared to their male referents (**Table 2**).

As shown in **Table 3**, anxiety disorders (41.1%), neurodevelopmental disorders (38.4%), and depressive disorders (21.9%) were most prevalent in TS participants. When compared to female referents, the PR (95% CI) estimates were 4.5 (2.6-7.7) for neurodevelopmental disorders and 2.4 (1.0-5.7) for disruptive, impulsive-control, and conduct disorders. By contrast, the prevalence of anxiety disorders was similar in TS participants and female referents. (PR=1.3; 95% CI: 0.8-2.2)

In persons with other SCA, anxiety disorders (36.9%), depressive disorders (22.6%), and neurodevelopmental disorders (21.2%) were the most prevalent. (**Figure 2**). The most elevated prevalence ratios in this group were observed for somatic and related disorders compared to male referents (PR=2.8; 95% CI: 1.6-4.8) and for neurodevelopmental disorders compared to female referents (PR=3.4; 95% CI: 2.3-4.9) as well as for personality disorders compared to both reference groups with PR of 2.2 (95% CI 0.8-5.8) relative to reference males and 2.6 (95% CI: 1.0-7.1) relative to reference males. By contrast, the prevalence of substance-related disorders was lower

in participants with other SCA compared to both male and female referents with PR (95% CI) estimates of 0.3 (0.2-0.6) and 0.6 (0.3-1.0), respectively.

DISCUSSION AND CONCLUSIONS

This study provides population-based prevalence estimates of MHD associated with the most common SCA. Across all groups, persons with SCA experienced a high prevalence of depressive disorders, anxiety disorders, disruptive, impulsive-control, and conduct disorders, and neurodevelopmental disorders. However, when compared with their reference groups, only disruptive, impulsive-control, and conduct disorders and neurodevelopmental disorders remained consistently higher in all SCA groups. These findings are concordant with previously reported results from a large multi-center study by Falhammer et al., where they found that almost 50% of the SCA participants had at least one psychiatric diagnosis.[47]

Neuroanatomical studies show that extra X and Y chromosomes exert spatially overlapping effects on regional brain anatomy. Increased X or Y chromosomes are associated with the contraction of frontotemporal cortices, expansion of parieto-occipital cortices, and subsequent reductions in the relative sizes of several brain regions. This may theoretically explain the increased MHD prevalence reported in this population.[48–50]

Participants with KS seemed to be the most affected by MHD. They had a higher prevalence of eating disorders, schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, depressive disorders, anxiety disorders, disruptive, impulsive-control, and conduct disorders, substance-related disorders, personality disorders, neurodevelopmental disorders, self-harm, suicidal ideation and somatic symptoms and related disorders. This is

consistent with results observed by Rijn et al. and Skakkebaek et al.[44,51]. However, it contrasts with the findings of Mors et al., who did not find evidence for an increased risk of schizophrenia spectrum disorders in KS individuals.[52] Previous morphological and functional brain studies showed that KS individuals have reduced total brain and grey and white matter volumes compared to the general population.[48,53,54] Grey matter volume reduction in the hippocampus, para-hippocampal cortices, and amygdala may be associated with memory impairment, atypical temperament, passivity, and reduced sexual drive.[48,55,56] It is also hypothesized that genetic and hormonal factors may play a role in the high prevalence of MHD in KS individuals. KS is characterized by an extra X chromosome, leading to hormonal imbalances, notably lower testosterone levels. Testosterone plays a crucial role in brain development and function, and alterations in its levels can impact mood regulation and mental health.[57] The prevalence of disruptive, impulsive-control, and conduct disorders in KS participants was high when compared to their male referents, and this is in agreement with the findings of high levels of criminality in KS individuals by Stockholm et al.[58] Of note the elevated prevalence of eating disorders in persons with KS in this study was previously reported by Vries and colleagues although the proportion of affected individuals in our data was only 2% much lower than the 11% estimate in the Vries et al. study[59] This further corroborates recent studies showing that individuals with KS are prone to obesity and metabolic disease.[60–62] Of particular concern is the high prevalence of suicidal ideation and self-inflicted injuries found in our study as well as in the previous publications by Falhammer et al. and Singla.[47,63] Individuals with KS often face challenges related to body image, infertility, and difficulties in social interactions. These challenges can lead to feelings of isolation, low self-esteem, and depression, all of which are associated with an increased risk of suicidal ideation. A

recent study by Rijn and Swaab found that emotion regulation may be a potential target for treatment and intervention in individuals with KS.[64]

The prevalence of depressive disorders and anxiety disorders was also high among TS participants in this study. This is consistent with the findings of Avdic et al. and Sanchez et al.[45,46] Increased depression in TS may partly be related to hormone deficiency. Estrogen plays a complex role in the regulation of mood and emotional well-being. While estrogen has been associated with a potential protective effect against anxiety and depression in some contexts, its effects can vary depending on individual factors such as genetics, hormonal levels, and environmental influences. Premature ovarian failure is pathognomonic of TS and starts as early as 15 weeks after gestation.[65] Low estrogen and progesterone may influence various aspects of early neural development and predispose girls with TS to depression. Although the exact mechanism of estrogen's role in depression is not fully understood, the increased incidence of depression in women compared to men and the strong correlation between depression and periods of low estrogen (menopause, peripartum) draw attention to the possible role of this hormone in depression.[66,67] Depression and anxiety in TS may also be related to impaired social functioning as TS individuals are known to experience poor body image, low self-esteem, and self-perception of reduced social competence.[68,69] Differences in the anatomical and functional structure of the brain as a result of the aberrant X chromosome may also be implicated. Specifically, reduced volumes of the prefrontal cortices, superior temporal gyrus, amygdala, hippocampal formation, and temporal lobes have been shown in women with TS. It is suggested that amygdala hypermetabolism and cortisol release, as well as the defective modulation of limbic activity in the prefrontal cortex, may be linked to depression.[70–74] Our finding of increased prevalence of depressive disorders in TS participants, however, contradicted the results of the study by Wolstencroft et al.[70] The

disagreement between the two studies may be explained by their methodological differences. Unlike our study, which relied on the diagnoses documented in the EHR and included patients of all ages, the population in Wolstencroft et al. was restricted to children and adolescents 5-19 years of age, and the diagnoses in that study were ascertained based on questionnaires filled out by parents, teachers, and the participants.

We also found a higher prevalence of neurodevelopmental disorders in TS participants compared with their female referents. Neurodevelopmental disorders are conditions characterized by impairments in cognition, communication, behavior, and motor skills due to abnormal brain development. They include intellectual disability, communication disorders, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD). This finding agrees with similar findings from several previous studies.[47,72,73] However, it contradicts the results of the study by Lepage and colleagues, who did not observe differences in the prevalence of autistic or empathic traits between TS individuals and their referents.[71] It is important to point out, however, that unlike Lepage et al., our definition of neurodevelopmental disorders included many conditions. Moreover, the two studies differed with respect to their sample sizes – 16 TS patients and 16 referents in Lepage et al. 73 individuals with TS individuals compared to 730 referents in our study. Two previous studies showed that the prevalence of ADHD and ASD was 24% and 21%.[42,72] Several factors may contribute to the increased likelihood of ADHD and ASD, as well as other neurodevelopmental disorders in individuals with TS. As reviewed by Blanchett and Knickmeyer, mechanisms linking sex chromosome loss to altered neural development may involve imprinted gene expression failure, haploinsufficiency of gene expression, and uncovering of X-linked mutations.[73] It is proposed that the STS gene associated with hyperactivity and impulsivity is located within the Xp22.3 region implicated in the neurocognitive phenotype of TS. STS gene

polymorphism and mutation have been associated with an increased risk of ADHD.[74] Davenport et al. showed that the decreased gray matter volumes in the premotor, somatosensory, and parietal-occipital cortex in individuals with TS are already present at one year.[75] These structural deficits in the brain may be responsible for the cognitive and psychosocial outcomes of TS individuals.

We found an increased prevalence of MHDs in the other SCA group, which included TS and KS variants and TS mosaicism. Of note here is the high prevalence of anxiety disorders, depressive disorders, and neurodevelopmental disorders in these individuals. Kute et al. found that TS variants and mosaicisms were phenotypically different from TS individuals.[76] Based on these observations, we would expect that the prevalence of MHD in TS variants and mosaicisms would differ from that of individuals with classic KS and TS and be somewhat closer to that of the general population. Our results, however, agree with those of Vorsanova et al., who found a high prevalence of neurodevelopmental disorders in KS variants and mosaicisms.[77]

One of the main strengths of this study was the use of EHR from a large, well-defined population in the KP integrated health systems, which offered an adequate sampling frame and allowed the identification of relatively large numbers of people with a confirmed SCA diagnosis. As individuals living with SCA represent a hard-to-reach population, reliance on de-identified data from an integrated health record system allowed identifying eligible persons with SCA and referents without needing participant opt-in.

Perhaps the most important limitation of the present study is its cross-sectional design, which precluded longitudinal analyses capable of evaluating the timing of initial MHD diagnosis and changes in clinical presentation over an extended follow-up period. Another possible limitation of this study is the incomplete cohort ascertainment. Given that only approximately 25% of KS cases are diagnosed, persons identified in the EHR may represent those more

significantly impacted by their disorder or other related conditions. Consequently, there is a potential for selection bias, leading to an overrepresentation of individuals with SCA experiencing more significant mental health diagnoses. Further, the data for our study were not collected for research purposes. Thus, all information available for analysis was limited to the EHR and did not include patient-reported measures of mental health status.

In summary, despite the noted limitations, the present study provides convincing evidence that people with SCA carry a greater MHD burden than the general population. Ensuring adequate access to and utilization of mental health services represents a vital healthcare priority in this group of patients.

PUBLIC HEALTH IMPLICATIONS

The findings of the current study underscore a crucial aspect of public health: the mental health challenges faced by individuals with SCAs. These individuals experience various MHDs, highlighting the necessity of recognizing MHDs as part of the clinical presentation of SCAs.

Awareness of the mental health issues associated with SCAs is imperative. By increasing awareness, healthcare providers can become more vigilant in screening for MHDs among individuals with SCA. Early detection of mental health disorders can pave the way for timely intervention and treatment, potentially mitigating the impact of these conditions on individuals' lives. Moreover, ensuring adequate access to mental health services is paramount for individuals with SCAs. Public health efforts should prioritize initiatives aimed at improving access to mental health screening, counseling, therapy, and psychiatric care for affected individuals and their families. Education and support resources can also play a crucial role in enhancing understanding of the unique mental health needs and challenges faced by this population.

Individuals with SCA often encounter stigma and discrimination related to their genetic condition and mental health struggles. Public health efforts to reduce stigma and promote acceptance and inclusion through targeted education, advocacy, and policy initiatives are warranted. Further research into the underlying mechanisms and risk factors for MHDs in individuals with SCA is essential. Collaboration among public health agencies, advocacy organizations, and researchers can facilitate advancing knowledge and the development of evidence-based interventions to improve mental health outcomes. Integration of mental health screening and support services into healthcare systems serving individuals with SCA is crucial for ensuring comprehensive care. Multidisciplinary approaches incorporating genetics, endocrinology, psychiatry, psychology, and other relevant specialties can enhance the effectiveness of mental health interventions.

Lastly, public health policy and funding authorities should take into account the mental health needs of individuals with SCA. Advocacy efforts should focus on securing resources for research, education, screening, treatment, and support services to address the mental health disparities faced by this population effectively.

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FIGURES AND TABLES

Figure 1. Flow Diagram of SCA Study Participants

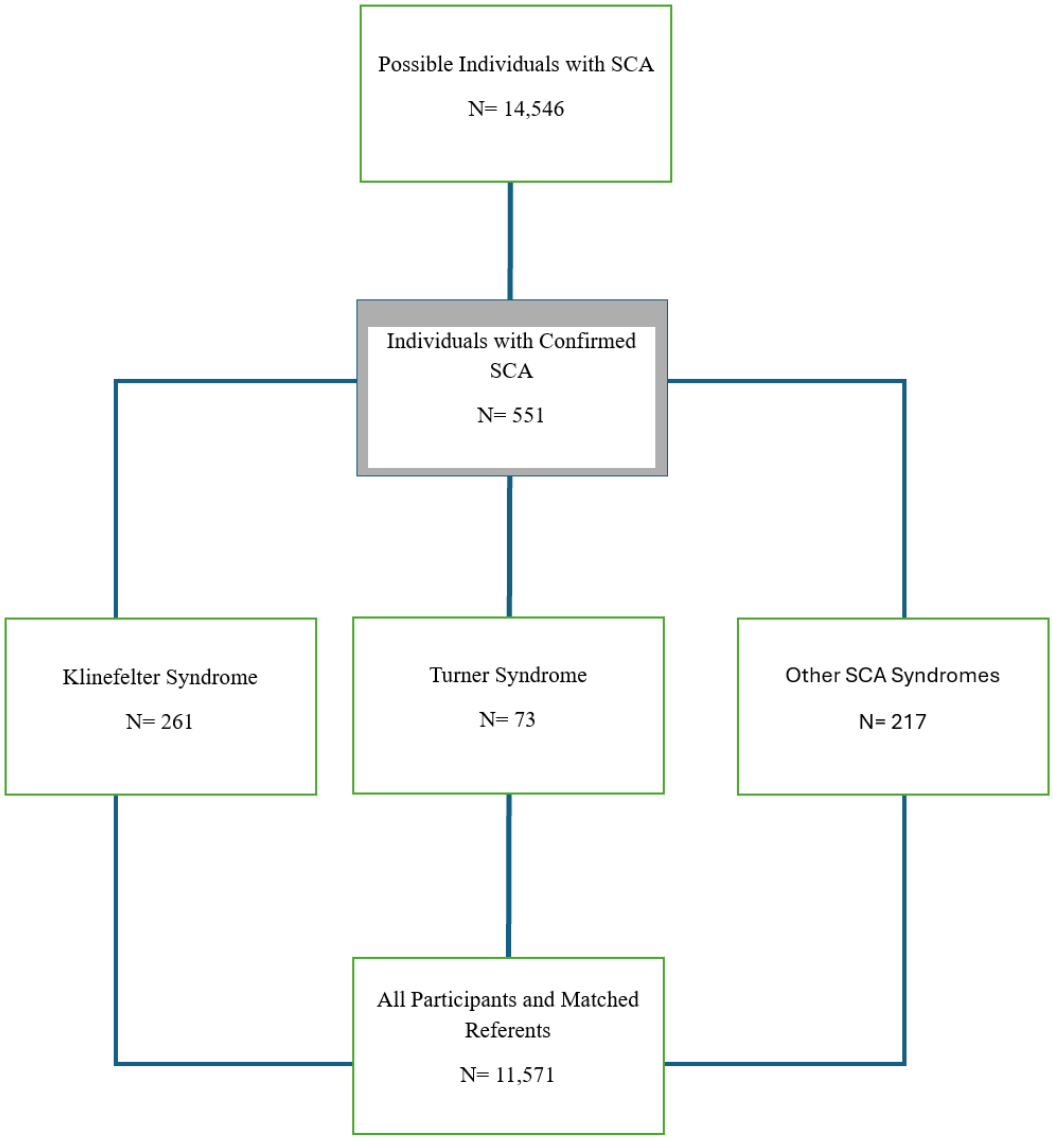


Table 1. Descriptive Characteristics of SCA Participants

Participant Characteristics	Turner Syndrome (n=73)		Klinefelter Syndrome (n=261)		Other SCA (n=217)	
	N	%	N	%	N	%
Site						
KPSC	65	89%	214	82%	191	88%
East Coast*	8	11%	47	18%	26	12%
Race/ethnicity						
Non-Hispanic White	23	32%	86	33%	57	26%
Non-Hispanic Black	11	15%	26	10%	20	9%
Hispanic	29	40%	101	39%	94	44%
Asian / Others*	10	13%	48	18%	46	21%
Era of index date$^{\sigma}$						
Prior to 2006	7	10%	30	11%	29	13%
2006 – 2011	34	46%	101	39%	100	46%
2012 – 2017	32	44%	130	50%	88	41%
Age at index date						
<18 years	57	78%	122	47%	115	53%
≥18 years	16	22%	139	53%	102	47%

*Combined categories to avoid reporting numbers <5.

$^{\sigma}$ Date of diagnosis of sex chromosome anomaly status in electronic health records. KPSC, Kaiser Permanente Southern California.

Table 2 Prevalence of Mental Health Diagnoses in KS Participants Compared to Male and Female Referents

Mental Health Diagnoses	KS Participants (n=261)	Male Referents (n=2610)	KS vs. Male Referents	Female Referents (n=2610)	KS vs Female Referents
	n (%)	n (%)	PR (95% CI)	n (%)	PR (95% CI)
Schizophrenia Spectrum and Other Psychotic Disorders	16 (6.1)	37 (1.4)	4.3 (2.4-7.9)	45 (1.7)	3.6 (2.0-6.4)
Bipolar and Related Disorders	18 (6.9)	77 (3.0)	2.3 (1.4-4.0)	106 (4.1)	1.7 (1.0-2.8)
Depressive Disorders	68 (26.1)	319 (12.2)	2.1 (1.6-2.9)	550 (21.1)	1.2 (0.9-1.7)
Anxiety Disorders	109 (41.8)	573 (22.0)	1.9 (1.5-2.5)	897 (34.4)	1.2 (0.9-1.7)
Feeding and Eating Disorders	6 (2.0)	4 (0.2)	12.5 (3.3-46.8)	28 (1.1)	1.8 (0.7-4.7)
Disruptive, Impulsive-Control, and Conduct Disorders	31 (11.9)	81 (3.1)	3.8 (2.5-5.9)	43 (1.6)	7.2 (4.5-11.7)
Substance-Related Disorders	71 (27.2)	389 (14.9)	1.8 (1.4-2.4)	226 (8.7)	3.1 (2.3-4.3)
Personality Disorders	12 (4.6)	34 (1.3)	3.5 (1.8-6.9)	24 (0.9)	5.0 (2.5-10.1)
Neurodevelopmental Disorders	90 (34.5)	295 (11.3)	3.1 (2.3-4.0)	197 (7.5)	4.6 (3.4-6.1)
Self-Harm	6 (2.3)	15 (0.6)	4.0 (1.5-10.4)	20 (0.8)	3.0 (1.2-7.5)
Suicidal Ideation	20 (7.7)	47 (1.8)	4.3 (2.5-7.3)	57 (2.2)	3.5 (2.1-5.9)
Somatic Symptoms and Related Disorders	21 (8.0)	77 (3.0)	2.7 (1.7-4.5)	156 (6.0)	1.3 (0.8-2.2)

Abbreviations: KS = Klinefelter syndrome, PR = prevalence ratio, CI=confidence interval

Table 3. Prevalence of Mental Health Diagnoses in TS Participants Compared to Male and Female Referents

Mental Health Diagnoses	TS Participants (n=73)	Male Referents (n=730)	TS vs. Male Referents	Female Referents (n=730)	TS vs. Female Referents
	n (%)	n (%)	PR (95% CI)	n (%)	PR (95% CI)
Depressive Disorders	16 (21.9)	68 (9.3)	2.4 (1.3-4.3)	131 (17.9)	1.2 (0.7-2.2)
Neurodevelopmental Disorders	28 (38.4)	148 (20.3)	1.9 (1.1-1.3)	62 (8.5)	4.5 (2.6-7.7)
Disruptive, Impulsive- Control, and Conduct Disorders	7 (9.6)	31 (4.2)	2.3 (1.0-5.3)	29 (4.0)	2.4 (1.0-5.7)
Anxiety Disorders	30 (41.1)	152 (20.8)	2.0 (1.2-3.3)	223 (30.5)	1.3 (0.8-2.2)

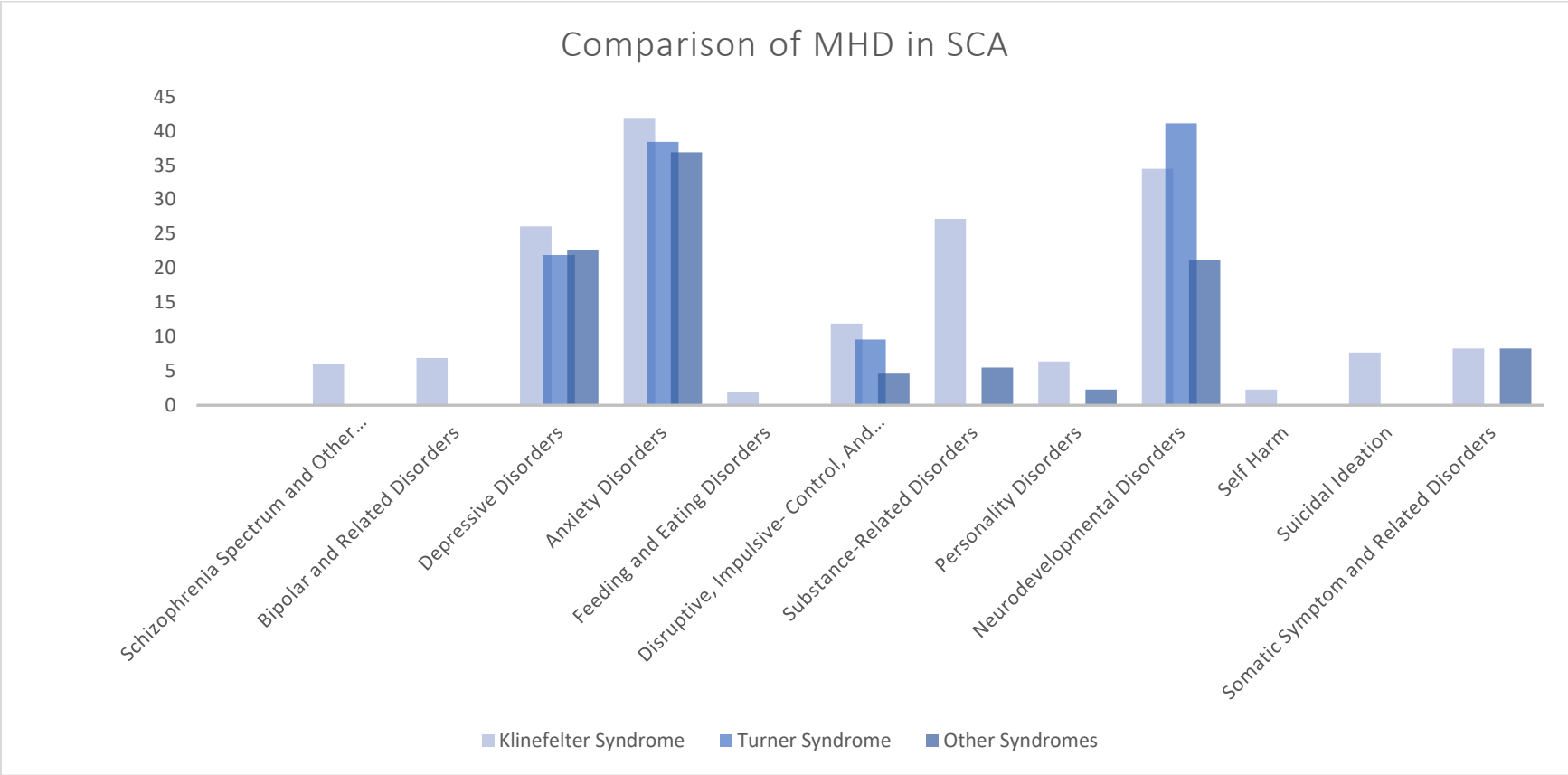
Abbreviations: TS = Turner syndrome, PR = prevalence ratio, CI=confidence interval

Table 4. Prevalence of Mental Health Diagnoses in Participants with Other SCA Compared to Male and Female Referents

Mental Health Diagnoses	Other SCA Participants (n=217)	Male Referents (n=2170)	Other SCA vs. Male Referents	Female Referents (n=2170)	Other SCA vs. Female Referents
	n (%)	n (%)	PR (95% CI)	n (%)	PR (95% CI)
Depressive Disorders	49 (22.6)	256 (11.8)	1.9 (1.4-2.7)	493 (22.7)	1.0 (0.7-1.4)
Anxiety Disorders	80 (36.9)	478 (22.0)	1.7 (1.2-2.2)	751 (34.6)	1.1 (0.8-1.4)
Disruptive, Impulsive- Control, and Conduct Disorders	10 (4.6)	54 (2.5)	1.9 (0.9-3.7)	44 (2.0)	2.3 (1.1-4.6)
Substance-Related Disorders	12 (5.5)	361 (16.6)	0.3 (0.2-0.6)	210 (9.7)	0.6 (0.3-1.0)
Personality Disorders	5 (2.3)	23 (1.1)	2.2 (0.8-5.8)	19 (0.9)	2.6 (1.0-7.1)
Neurodevelopmental Disorders	46 (21.2)	256 (11.8)	1.8 (1.3-2.6)	136 (6.3)	3.4 (2.3-4.9)
Somatic Symptoms and Related Disorders	18 (8.3)	64 (2.9)	2.8 (1.6- 4.8)	127 (5.9)	1.4 (0.8-2.4)

Abbreviations: SCA = sex chromosome anomalies, PR = prevalence ratio, CI=confidence interval

Figure 2. Comparison of Prevalence of MHD in SCA



Abbreviations: MHD = Mental heanth diagnosis, SCA = Sex chromosome anomally

REVIEW OF RELEVANT LITERATURE

Source	Purpose/Thesis	Type of Article	Level of Evidence	Major Findings
Goodman et al.	To assess the health status and patterns of care among people diagnosed with disorders of sex development	Research article	(III) Cohort study	"They demonstrated that by using standard codes, supplemented with analysis of digitized provider notes, it is possible to comprehensively identify patients with DSD among people enrolled in participating health plans."
Nielsen & Wohlert (1991)	To identify chromosome abnormalities found among 34910 newborn children	Research article	(III) Cohort study	"Klinefelter's syndrome was found in 1 per 576 boys, Turner's syndrome in 1 per 1893 girls. The total incidence of sex chromosome abnormalities was 1 per 426 children"
Skuse, Printzlau &Wolstencroft (2018)	Discussed five of the better-known sex aneuploidies: Turner syndrome (XO), Klinefelter syndrome (XXY), trisomy X (XXX), XYY, and XXYY	Review article	(VI) Review article	"In both typical and atypical sex chromosome karyotypes, there is random inactivation of all but one X chromosome. The mechanisms by which a phenotype results from sex chromosome aneuploidies are twofold: dosage imbalance arising from a small number of genes that escape inactivation, and their endocrinologic consequences."
Herlihy et al. (2011)	To determine the prevalence and diagnosis rates of Klinefelter syndrome (KS) in Victoria, Australia, and compare these to previous international findings	Research article	(V) Cross-sectional	"The birth prevalence of KS in Victoria is estimated to be 223 per 100,000 males (95% CI, 195-254), with about 50% of cases remaining undiagnosed."

Stochholm et al. (2006)	To study the prevalence, incidence, age at diagnosis, and mortality in Turner syndrome (TS) in Denmark	Research article	(V) Cross-sectional study	"A total of 349 women had a 45,X karyotype, 86 had a karyotype including an isochromosome Xq (isoXq), and 346 had another TS karyotype. Mortality was increased in TS with an SMR of 2.86 (95% confidence interval, 2.18-3.55). SMR was increased for coronary diseases, congenital malformations, endocrine diseases, and other causes. Age at diagnosis was mainly distributed in three periods: less than 1 yr of age (14.9%), during adolescence (10-17 yr) (33.2%), and during adulthood (38.5%), with a median age at diagnosis of 15.1 yr, decreasing during the study period ($P < 0.01$)"
Tartaglia, Huttaff-Lee & Boada (2012)	To compare attention-deficit hyperactivity disorder (ADHD) symptoms in 167 participants aged 6 to 20 years with 4 types of SCA	Research article	(V) Cross-sectional study	"In the total study group, 58% (96/167) met DSM-IV criteria for ADHD on parent-report questionnaires"
Wilson et al. (1989)	To identify chromosome mosaicism in 6,000 amniocenteses	Research article	(V) Crossectional study	"Multiple cell-multiple flask mosaicism was found in 0.20% of 6,000 amniocenteses, and multiple cell-single flask mosaicism was found in 0.92%."
Gunther et al. (2004)	To evaluate differences in phenotype and other clinical features between patients who have Turner syndrome diagnosed incidentally (on the basis of a prenatal karyotype performed for reasons unrelated to suspicion of Turner syndrome	Research article	(II) Randomised controlled trial	"Patients whose Turner syndrome was diagnosed incidentally had significantly fewer phenotypic features and cardiac defects, as well as a greater proportion of mosaic karyotypes, compared with patients whose Turner syndrome was diagnosed clinically."

Visootsak et al. (2013)	To describe the diagnosis experiences of parents of males with 47,XXY and 48,XXYY.	Research article	(V) Cross-sectional study	"The average time from initial parental concern to diagnosis of 47,XXY or 48,XXYY ranges from 2 to 5 years, with those presenting with developmental issues having a longer lag to diagnosis than those presenting with endocrinologic issues."
Cuckle & Maymon (2016).	Discussed the changing paradigm of perinatal screening for congenital disabilities	Review article	(VI) Review of prenatal screening methods	"Prenatal screening for cardiac abnormalities, fragile X syndrome and recessive genetic disorders are underutilized"
Gil et al. (2015)	To review clinical validation or implementation studies of maternal blood cell-free (cf) DNA analysis and define screening performance for fetal trisomies 21, 18, and 13 and sex chromosome aneuploidies.	Review article	(1) Systematic review and meta-analysis	"Screening for trisomy 21 by analysis of cfDNA in maternal blood is superior to all other traditional screening methods, with higher DR and lower FPR. The performance of screening for trisomies 18 and 13 and sex chromosome aneuploidies is considerably worse than that for trisomy 21"
Giacalone (2023)	To determine the prevalence and psychosocial correlates of depressive symptoms among adolescents and adults with Klinefelter syndrome.	Research article	(V) Crossectional study	"Individuals with Klinefelter syndrome may be at increased risk for depression."
Davenport (2010)	Discussed the approach to the patient with Turner syndrome	Review article	(VI) Review article	"Turner syndrome care requires screening for associated problems, early growth-promoting therapy, physiologic estrogen replacement therapy, and preventive care."
Koeberl, McGillivray &Sybert (1995)	We report our experience with 12 patients for whom prenatal diagnosis of 45, X/46, XX mosaicism was detected by amniocentesis for advanced maternal age or decreased	Research article	(IV) Case-control study	"The phenomenon of a milder phenotype for the prenatal group is similar to that observed for 45,X/46,XY diagnosed prenatally."

	maternal serum alpha-fetoprotein and compared them with 41 45, X/46, XX patients diagnosed postnatally			
Carr et al. (1986)	To assess the association between fetal cystic hygroma and Turner's syndrome	Research article	(V) Cross-sectional study	"Large nuchal cystic hygromas were observed in five second-trimester aborted fetuses at autopsy. Two female fetuses with generalized edema were karyotyped as 45,X. The association of generalized edema with large nuchal cystic hygromas was seen only in these two fetuses and represents strong phenotypic evidence of Turner's syndrome."
Lyon, Preece & Grant (1985)	To validate the growth curve for girls with Turner syndrome	Research article	(III) Cohort study	"The results indicate that the calculation of height standard deviation score from this chart allows a reasonable prediction of adult stature in any patient with Turner syndrome. In addition, the results indicate that while estrogen treatment causes an initial growth acceleration, it has no significant effect on adult height."
Apperly et al. (2018)	To determine the age and clinical features at the time of presentation and to identify potential delays in diagnosis of TS.	Research article	(III) Cohort study	"The majority of girls with TS were diagnosed only after the age of 5 years. Short stature triggered evaluation for most patients diagnosed in childhood and adolescence."
Sybert (1998)	To evaluate a large population of patients both cross-sectionally and longitudinally to determine the prevalence of cardiovascular malformations, the risk for dissection of the aorta, to determine whether there are	Research article	(III) Cohort study	"A total of 136 (56%) of 244 of Of these patients had cardiovascular abnormalities, 96 (71%) were structural, 40 (29%) were functional. Coarctation of the aorta and bicuspid aortic valve, alone or in combination, comprised 50% of the cardiac malformations. Aortic dissection occurred in three of the patients. All except 5 predisposing

	phenotype: karyotype correlations that can allow for specific recommendations, and to devise an appropriate screening protocol			risk factors of coarctation, bicuspid aortic valve, and HBP were present. No phenotype: karyotype correlations could be drawn with any certainty"
Frühmesser & Kotzot (2011)	To abstract the different phenotypes, which come about by the various karyotypes and to compare them to those with a 'normal' KS karyotype.	Review article	(I) Systematic review	"In Klinefelter patients, an almost linear increase in height and developmental delay was observed. Men with an additional isochromosome Xq show infertility and other minor features of 'normal' KS but not an increased height."
Gravholt et al. (2018)	To review recent developments in genetic, endocrine, and neurocognitive science, including the study of animal models	Review article	(VI) Systematic review	"Recent developments in genetics and genomics point to a fundamental change in our understanding of KS, with global epigenetic and RNA expression changes playing a central role in the phenotype."
Baziz et al. (2016)	To investigate genetic defects by karyotype analysis in Algerian infertile men using peripheral blood lymphocytes.	Research article	(VI) Case series	"Identified a homogenous Klinefelter syndrome patient with 47, XXY karyotype, a mosaic Klinefelter syndrome patient with 47, XXY/46, XY karyotype, and a 46, XX male. Fluorescence in situ hybridization showed that the sex-determining region Y was translocated to the short arm of the X chromosome in patients with 46, XX chromosomal constitution, and the presence of the SRY gene was confirmed by polymerase chain reaction and electrophoresis."
Van Assche et al. (1996)	We investigated cytogenetically 694 infertile men with abnormal sperm parameters. More patients are needed for this research to investigate the relationship, if	Review article	(1) Systematic review	'The number of cytogenetically investigated individuals in the different subgroups was too low to draw any conclusions. However, a statistically significant difference was found between the frequency of chromosome abnormalities in all three subgroups with two

	any, between the type of chromosome abnormality and its influence on the number, morphology and motility of spermatozoa.			abnormal sperm parameters and that in the control population"
Lanfranco et al. (2004)	To review the clinical features of Klinefelter syndrome	Review article	(VII) Review	"The frequency of sex chromosomal hyperploidy and autosomal aneuploidies is higher in spermatozoa from patients with Klinefelter's syndrome than in those from normal men."
Akcan et al. (2018)	To assess the age and presenting symptoms for diagnosis, clinical and laboratory findings, together with the presence of comorbidities	Research article	(III) Cohort study	"The most frequent clinical findings were neurocognitive disorders, speech impairment, social and behavioral problems and undescended testes."
Bojesen & Gravolt (2007)	To review Klinefelter syndrome presentation in clinical practice	Review article	(VII) Review	"Klinefelter syndrome is an underdiagnosed condition; only 25% of the expected number of patients are diagnosed, and of these only a minority are diagnosed before puberty."
Close et al. (2015)	To characterize associations among psychosocial well-being, physical phenotype, and sex hormones in a sample of youth with Klinefelter syndrome	Research article	(V) Cross-sectional study	"Pubertal boys presented with more KS traits compared with prepubertal boys (5.6 vs 4.2, P = .01). Boys diagnosed prenatally had a milder phenotype compared with those diagnosed postnatally. Gonadotropins were elevated without androgen deficiency in 45%. Psychosocial health scores indicated adverse quality of life (QOL) (67%), low selfesteem (38%), poor self-concept (26%), and risk for depression (16%) without a difference between pubertal groups."
Gropman & Samango-Sprouse (2013)	Discusses what is known about clinical variability in the XY syndromes collectively evaluated through careful multidisciplinary	Review article	(VII) Review	"Variability in clinical and cognitive functioning may reflect skewed X inactivation, mosaicism, or epigenetic factors that warrant further investigation"

	clinical evaluation including the clinical and neurobehavioral aspects of these conditions.			
Leggett et al. (2010)	To review systematically the neurodevelopmental characteristics of individuals with sex chromosome trisomies	Review article	(I) Systematic review	"Individuals with an additional X chromosome had mean IQs that were within normal limits but lower than the comparison groups, with verbal IQ most affected. Cognitive outcomes were poorest for females with XXX. Males with XYY had normal-range IQs, but all three groups (XXX, XXY, and XYY) had marked difficulties in speech and language, motor skills, and educational achievement."
Swerdlow et al. (2005)	To investigate mortality in men with Klinefelter syndrome	Research article	(III) Cohort study	"Overall, mortality was significantly raised [SMR, 1.5; 95% confidence interval (CI), 1.4–1.7] and from most major causes of death, including cardiovascular disease (SMR, 1.3; 95% CI, 1.1–1.5), nervous system disease (SMR, 2.8; 95% CI, 1.6–4.6), and respiratory disease (SMR, 2.3; 95% CI, 1.8–2.9)."
Tahani et al. (2018)	To assess different aspects of bone damage in untreated adult patients with Klinefelter Syndrome (KS) before and during testosterone replacement therapy	Research article	(III) Cohort study	"Fat measures were significantly higher in KS than control ($p < 0.01$). In contrast, mean lumbar spine, femoral neck and total hip bone mineral densitywere significantly reduced in KS compared to control ($p < 0.01$), while there was no difference in trabecular bone score."
Zöller et al. (2016)	To examine whether KS is associated with venous thromboembolism.	Research article	(III) Cohort study	"KS is associated with a high risk of VTE"
Stochholm, Juul & Gravholt (2010)	To access diagnosis and mortality in 47,XYY persons	Research article	(III) Cohort study	"The average prevalence was 14.2 47,XYY persons per 100,000. Their median age at diagnosis was 17.1 years. There was a significantly decreased lifespan from 77.9 years

				(controls) to 67.5 years (47,XYY persons). Total mortality was significantly increased compared to controls, with a hazard ratio of 3.6 (2.6-5.1).”
Bardsley et al. (2013)	To describe auxologic, physical, and behavioral features in a large cohort of males with 47,XYY (XYY), ages newborn to young adult.	Research article	(V) Cross-sectional study	“The XYY phenotype commonly includes tall stature, macrocephaly, macroorchidism, hypotonia, hypertelorism, and tremor. Physical phenotypic features were similar in boys diagnosed prenatally vs postnatally. Prenatal diagnosis was associated with higher cognitive function and less likelihood of an ASD diagnosis”
Ogutlu et al. (2019)	Discussed the psychiatric aspects of 47, XYY syndrome in a male adolescent patient diagnosed with attention deficit hyperactivity disorder, conduct disorder, mild intellectual disability, and Tourette syndrome	Research article	(VI) Case report	“This is the first demonstrative case of the presence of the XYY syndrome with Tourette syndrome, ADHD, CD and mild intellectual disability.”
Berglund et al. (2019)	To investigate change over time in incidence, prevalence and age at diagnosis among Turner syndrome, Klinefelter syndrome, Triple X syndrome (Triple X), and Double Y syndrome (Double Y) in Denmark.	Research article	(III) Cohort study	“The prevalence among newborns was as follows: TS: 59 per 100,000 females; KS: 57 per 100,000 males; Triple X: 11 per 100,000 females; and Double Y: 18 per 100,000 males. Compared with the expected number among newborns, all TS, 38% of KS, 13% of Triple X, and 18% of Double Y did eventually receive a diagnosis. The incidence of TS with other karyotypes than 45,X ($P < 0.0001$), KS ($P = 0.02$), and Double Y ($P = 0.03$) increased during the study period whereas the incidence of 45,X TS decreased ($P = 0.0006$). The incidence of Triple X was stable ($P = 0.22$). Conclusions The prevalence of TS is higher than

				previously identified, and the karyotypic composition of the TS population is changing. Non-diagnosis is extensive among KS, Triple X and Double Y, whereas all TS seem to become diagnosed. The diagnostic activity has increased among TS with other karyotypes than 45,X as well as among KS and Double Y."
Lin, Ndiforchu & Patell (1993)	To review genitourinary malformations in triple-X patients	Research article	(VI) Case report	"Cloacal exstrophy, unilateral renal agenesis, and Müllerian anomalies occurred in a live-born infant with a 47,XXX chromosome constitution. The patient extends the range of genitourinary anomalies reported in triple-X patients."
Otter et al. (2010)	To review the literature on Triple X syndrome	Review article	(VII) Review of literature	"Psychotic illness seems to be more prevalent in triple X adult women than in controls. Psychotic disorders respond well to psychotropic drugs. Triple X adults suffer more frequently from cyclothymic and labile personality traits."
Geerts, Steyaert & Fryns (2003)	To investigate the developmental profile of boys with karyotype 47,XYY and of possible problem areas during further development	Research article	(III) Cohort study	"They found that these patients are at considerably increased risk for delayed language--and/or motor development. From birth on, weight, height and head circumference are above average values. The majority attends kindergarten in the normal education circuit although in 50% of the cases psychosocial problems are documented. From primary school age on, there is an increased risk for child psychiatric disorders such as autism. Moreover, although normally intelligent, many of these boys are referred to special education programmes."
Warling et al. (2020)	Modeled relationships between general cognitive ability (estimated using full-scale IQ	Research article	(V) Cross-sectional study	"They found five regions where SCA significantly altered SA–FSIQ relationships, and five regions where SCA significantly altered CT–

	(FSIQ) from Wechsler scales) and regional estimates of surface area (SA) and cortical thickness (CT) (from structural MRI scans) in both aneuploid (28 XXX, 55 XXY, 22 XYY, 19 XXYY) and typically-developing euploid (79 XX, 85 XY) individuals.			FSIQ relationships. Most areas were characterized by positive anatomy-IQ relationships in health, but no or slightly negative anatomy-IQ relationships in SCA. Disrupted anatomical–cognitive relationships generalized from the full cohort to karyotypically defined subcohorts (i.e., XX-XXX; XY-XYY; XY-XXY), demonstrating continuity across multiple supernumerary SCA conditions."
Hong & Reiss (2014)	Review of cognitive and neurological aspects of sex chromosome aneuploidies	Review article	(VII) Review paper	"An apparent dose eff ect exists between number of sex chromosomes and performance in www.thelancet.com/neurology Vol 13 March 2014 314 Review cognitive subdomains of language and visuospatial ability, with monosomy putatively linked with non-verbal defi cits, and polysomy correlated with language-based impairments."
Delisi et al. (1994)	To review studies in which either complete karyotypes were determined for the whole sample or in which the presence of a Barr body in an individual was checked by full cytogenetic analysis	Review article	(I) Systematic review	"This review suggest that the sex chromosome aneuploidies, XXX and XXY, are increased in populations of patients with schizophrenia, whereas too few subjects have been surveyed to determine whether an association also exists with XYY"
Russell et al. (2006)	To assess the prevalence of ADHD in girls with TS and evaluate the contribution of imprinting on cognitive performance (IQ) and ADHD	Research article	(V) Cross-sectional	"There is an 18-fold increase in the prevalence of ADHD in girls with TS (24%) compared with girls in the general population (1.3%) (p < .01) and a 4.8 fold increase when compared with boys and girls in the general population (5%) (p < .05). In contrast to previous reports, our molecular studies in females with 45,X also

				showed no association between IQ scores and the parental origin of the intact X chromosome"
Tartaglia et al. (2008)	To assess the medical and psychological features in XXYY syndrome	Research article	(V) Cross-sectional study	"The mean age of diagnosis was 7.7 years. Developmental delays and behavioral problems were the most common primary indication for genetic testing (68.4%). Physical and facial features varied with age, although hypertelorism, clinodactyly, pes planus, and dental problems were common across all age groups. Tall stature was present in adolescents and adults, with a mean adult stature of 192.4 cm (SD 7.5; n = 22). Common medical problems included allergies and asthma (>50%), congenital heart defects (19.4%), radioulnar synostosis (17.2%), inguinal hernia and/or cryptorchidism (16.1%), and seizures (15%). Medical features in adulthood included hypogonadism (100%), DVT (18.2%), intention tremor (71%) and type II diabetes (18.2%). Brain MRI (n = 35) showed white matter abnormalities in 45.7% of patients and enlarged ventricles in 22.8%. Neurodevelopmental and psychological difficulties were a significant component of the behavioral phenotype, with developmental delays and learning disabilities universal but variable in severity. Twenty-six percent had full-scale IQs in the range of intellectual disability (MR), and adaptive functioning was significantly impacted with 68% with adaptive composite scores <70. Rates of neurodevelopmental disorders, including ADHD (72.2%), autism spectrum disorders (28.3%), mood disorders (46.8%), and

				tic disorders (18.9%), were elevated with 55.9% on psychopharmacologic medication overall."
Van Rijn et al. (2014)	To gain more insight into the social behavioral phenotype, and related autistic symptomatology, of children with an extra X chromosome in comparison to children with ASD.	Research article	(V) Cross-sectional study	"In the extra X group, levels of social dysfunction and autism symptoms were increased, being in between controls and ASD. In contrast to the ASD group, the extra X group showed increased social anxiety. The effects were similar for boys and girls with an extra X chromosome."
Björlin et al. (2021)	To examine the prevalence of neurodevelopmental and psychiatric disorders in females with Turner syndrome.	Research article	(III) Cohort study	"Females with Turner syndrome had a higher risk of neurodevelopmental or psychiatric disorder (OR 1.37, 95% CI 1.20-1.57), an eightfold increased risk of intellectual disability (OR 8.59, 95% CI 6.58-11.20), and a fourfold increased risk of autism spectrum disorder (OR 4.26, 95% CI 2.94-6.18) compared with the controls. In addition, females with Turner syndrome had twice the risk of a diagnosis of schizophrenia and related disorders (OR 1.98, 95% CI 1.36-2.88), eating disorders (OR 2.03, 95% CI 1.42-2.91), and behavioral and emotional disorders with onset in childhood (OR 2.01, 95% CI 1.35-2.99)."
Sánchez et al. (2023)	To evaluate population-based estimates of the prevalence and clinical detection rate of sex chromosome aneuploidies and the associated risks of psychiatric disorders in Denmark	Research article	(III) Cohort study	"The overall prevalence of sex chromosome aneuploidies was 1·5 per 1000 individuals. Each sex chromosome aneuploidy karyotype was associated with an increased risk of at least one index psychiatric disorder, with hazard ratios (HRs) of 2·20 (95% CI 1·42-3·39) for 47,XXY; 2·73 (1·25-6·00) for 47,XXX; 3·56 (1·01-12·53) for 45,X; and 4·30 (2·48-7·55) for 47,XYY. All karyotypes were associated with an increased risk of ADHD (HRs ranging from 1·99 [1·24-

				3·19] to 6·15 [1·63-23·19]), autism spectrum disorder (2·72 [1·72-4·32] to 8·45 [2·49-28·61]), and schizophrenia spectrum disorder (1·80 [1·15-2·80] to 4·60 [1·57-13·51]). Increased risk of major depressive disorder was found for individuals with 47,XXY (1·88 [1·07-3·33]) and 47,XYY (2·65 [1·12-5·90]), and of bipolar disorder for those with 47,XXX (4·32 [1·12-16·62]). The proportion of sex chromosome aneuploidy carriers who had been clinically diagnosed was 93% for 45,X, but lower for 47,XXY (22%), 47,XXX (15%), and 47,XYY (15%)"