

Sleep Disorders in Klinefelter Syndrome and Other Sex Chromosome Aneuploidies: A Narrative Review

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ABSTRACT

Background: Sex chromosome aneuploidies (SCAs) are among the most frequent types of chromosomal aneuploidies and include Klinefelter syndrome (47,XXY and higher-grade variants), 47,XYY syndrome, Turner syndrome (45,X), and trisomy X (47,XXX). These conditions share complex neurodevelopmental, endocrine, and metabolic features with important implications for reproductive and general health. Sleep plays a pivotal role in neurocognitive functioning, mood regulation, cardiometabolic homeostasis, and hypothalamic–pituitary–gonadal axis activity, yet sleep disorders remain poorly characterized and under-recognized in SCAs.

Methods: This narrative review synthesizes current evidence on sleep disturbances in SCAs, with particular emphasis on male phenotypes, while integrating evidence from female SCAs to highlight shared mechanisms and overlapping sleep phenotypes.

Results: Available data indicate an increased prevalence of insomnia, sleep fragmentation, excessive daytime sleepiness, circadian rhythm disturbances, and sleep-disordered breathing from childhood through adulthood. In Klinefelter syndrome, sleep alterations appear multifactorial, arising from the interaction between hypogonadism, obesity, psychiatric vulnerability, neurocognitive deficits, and possible circadian and melatonin dysregulation. Evidence in 47,XYY and higher-grade male SCAs, although limited, suggests a predominant contribution of neurodevelopmental and behavioral factors. Emerging findings also implicate oxidative stress as a potential mechanistic link between sleep disruption, metabolic dysregulation, and neurocognitive impairment.

Conclusions: Overall, the literature is fragmented and methodologically heterogeneous, underscoring the need for systematic sleep screening and integrated multidisciplinary management within andrological care pathways to improve long-term health and reproductive outcomes in individuals with SCAs.

1 | Introduction

Sex chromosome aneuploidies (SCAs) are among the most frequent types of chromosomal aneuploidies, with an estimated

prevalence of approximately 1 in 500 live births, and encompass heterogeneous clinical conditions such as Klinefelter syndrome (KS) (47,XXY and higher-grade variants), 47,XYY syndrome, Turner syndrome (TS) (45,X), and trisomy X (47,XXX). These

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; HPG, hypothalamic–pituitary–gonadal; KS, Klinefelter syndrome; OSA, obstructive sleep apnea; PSG, polysomnography; ROS, reactive oxygen species; SCAs, sex chromosome aneuploidies; TRT, testosterone replacement therapy; TS, Turner syndrome.

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conditions are characterized by a broad spectrum of somatic, neurocognitive, endocrine and metabolic manifestations, with a substantial impact on overall health and, in particular, on male reproductive health [1, 2].

In recent years, the close interrelationship among sleep, neurocognitive development, psychopathology, and hypothalamic–pituitary–gonadal (HPG) axis function has become increasingly evident. Sleep plays a crucial role in regulating executive functions, mood, and learning processes, and it also modulates hormonal secretion, including testosterone, as well as metabolic and cardiovascular parameters that are highly relevant for andrology [3, 4]. Conversely, hypogonadism, metabolic syndrome, and psychiatric disorders, all highly prevalent in SCAs, may amplify the risk of sleep disorders, creating vicious cycles that involve physical and mental well-being, school and work performance, quality of life, and sexual functioning [5, 6].

KS is the most extensively studied SCA in males, and even in childhood there is growing recognition of an increased burden of sleep problems, including difficulties in sleep initiation and maintenance, frequent nocturnal awakenings, sleep-disordered breathing, and circadian rhythm disturbances [7]. These alterations occur within a complex framework that includes vulnerability to psychopathology, attentional and emotional regulation difficulties, overweight/obesity, and hypogonadism, all of which may contribute to a specific “sleep phenotype” in KS [8]. At the same time, albeit based on more limited evidence, other male aneuploidies such as 47,XXY and higher-grade karyotypes (e.g., 48,XXYY, 48,XXXY) also appear to carry an increased risk of sleep disturbances, likely mediated by neurodevelopmental anomalies, psychiatric comorbidities, and somatic and metabolic factors [1, 9].

Despite the potential impact of sleep disorders on developmental trajectories and reproductive outcomes in males with SCAs, the current literature remains fragmented, with a predominance of observational studies on small samples, heterogeneous assessment methods, and limited distinction between developmental stages. Moreover, structured sleep screening protocols are largely absent from clinical pathways dedicated to SCAs in both pediatric and adult care, and data on the effects of therapeutic interventions (treatment of hypogonadism, ventilatory therapies, behavioral interventions) on sleep outcomes—and, consequently, on reproductive and sexual health—are scarce. Addressing these gaps is particularly relevant for an andrology-focused readership, as sleep disorders sit at the intersection of gonadal axis function, metabolic health, neurodevelopment, and quality of life, which are all key dimensions in the care of individuals with sex chromosome aneuploidies.

Against this background, the present review aims to critically synthesize the available evidence on sleep disturbances in sex chromosome aneuploidies. Given the clinical and andrological focus of this review and the relatively greater availability of data, particular emphasis is placed on male phenotypes (47,XXY, 47,YYY, and higher-grade variants). However, female SCAs (45,X and 47,XXX) are also discussed to provide a comparative framework, highlighting shared pathophysiological mechanisms and overlapping sleep phenotypes across SCAs. This integrated approach reflects the substantial commonalities among these

conditions, while acknowledging differences in hormonal and clinical profiles. In addition, the review will discuss unmet needs in the screening, diagnosis, and management of sleep disorders in this context and outline future research priorities aimed at improving general and reproductive health outcomes in individuals with SCAs.

2 | Biological and Neurocognitive Rationale

SCAs provide a unique human model to explore how sex chromosome dosage, gonadal dysfunction, and neurodevelopmental vulnerability converge to shape individual susceptibility to sleep disturbances. The combination of hypergonadotropic hypogonadism, metabolic comorbidities, and increased rates of neurocognitive and psychiatric difficulties in SCAs creates several biological pathways through which sleep architecture, circadian rhythms, and sleep-related breathing can be altered across the lifespan [10, 11]. To provide an integrated overview of the proposed relationships between SCAs, sleep disturbances, and associated comorbidities, we present a conceptual framework (Figure 1). This diagram illustrates how factors intrinsic to SCAs—including hypogonadism, neurodevelopmental and psychiatric vulnerabilities, and metabolic dysfunction—converge to increase susceptibility to various sleep disorders. Sleep disturbances, in turn, may act as mediators that amplify downstream consequences on neurocognitive, cardiometabolic, and reproductive outcomes. The figure distinguishes relationships supported by direct evidence in SCA populations from those extrapolated from related cohorts or hypothesized based on biological plausibility, highlighting current knowledge gaps and priorities for future research.

2.1 | Clinical Phenotypes of SCAs Relevant to Sleep Vulnerability

KS (47,XXY and higher-grade variants) is the most common male SCA and a leading cause of primary hypergonadotropic hypogonadism, typically associated with small testes, infertility, low testosterone levels, increased cardiometabolic risk, and a higher prevalence of language, learning, executive function, and social behavior/functioning difficulties, as well as mood and anxiety disorders. The 47,XXY karyotype is characterized by tall stature, variable testicular function, behavioral dysregulation, and elevated rates of neurodevelopmental and psychiatric diagnoses, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and anxiety, which themselves are closely linked to insomnia and circadian rhythm disturbance in the general population [8, 12, 13]. In females, TS (45,X) is marked by gonadal dysgenesis, estrogen deficiency, increased cardiometabolic burden, and specific neurocognitive and psychosocial vulnerabilities [14, 15], while 47,XXX is associated with variable cognitive deficits and increased rates of internalizing disorders [16]; both conditions share many of the same endocrine, metabolic, and neurodevelopmental risk factors observed in male SCAs, suggesting the presence of partially overlapping sleep vulnerability profiles across SCAs, although direct comparative studies are lacking.

Across these conditions, the clinical features described above—including gonadal dysfunction, metabolic comorbidities, and

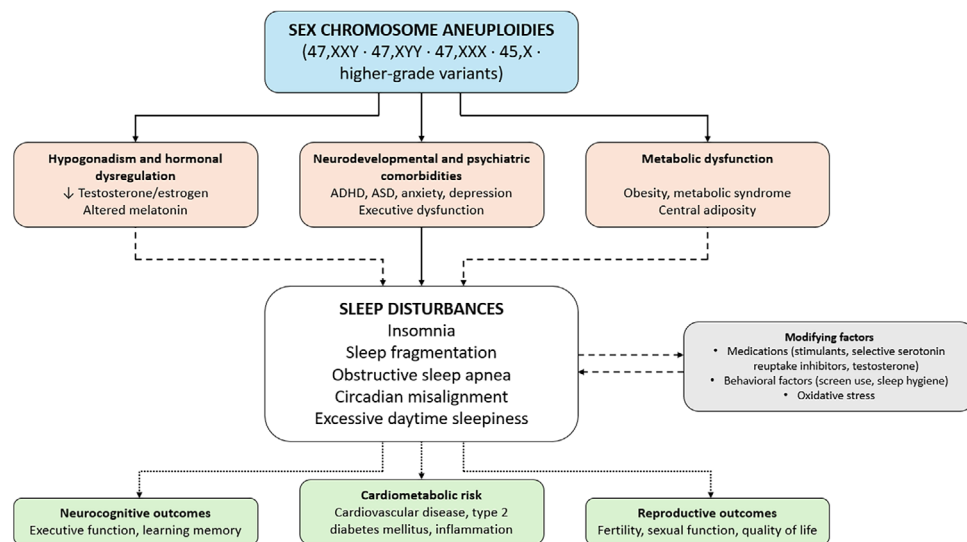


FIGURE 1 | Conceptual framework of sleep disturbances in SCAs: proposed mechanisms and levels of evidence. The diagram illustrates the proposed relationships between SCAs, contributing factors, sleep disturbances, and downstream outcomes. Line styles indicate level of evidence (solid lines: direct evidence from studies in SCA populations; dashed lines: evidence extrapolated from related populations (e.g., general hypogonadal, neurodevelopmental, or pediatric cohorts); dotted lines: hypothetical relationships requiring further investigation in SCAs). Sleep is positioned as both an outcome of SCA-related pathophysiology and a potential mediator influencing long-term neurocognitive, cardiometabolic, and reproductive health. Modifying factors (medications, behavioral factors, oxidative stress) may independently affect sleep or interact with primary pathways. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

neurodevelopmental vulnerabilities—represent established risk factors for sleep disturbances [1, 17, 18]. The following sections will examine the specific pathophysiological mechanisms through which these clinical features may contribute to sleep disruption in SCAs.

2.2 | Gonadal Axis, Testosterone, and Sleep

In males, testosterone secretion follows a circadian pattern, with nocturnal elevation and a decline in the late afternoon, and is tightly linked to consolidated, high-quality sleep [19]. Experimental and clinical data indicate that sleep restriction and sleep-disordered breathing can reduce total and free testosterone levels, while low testosterone is in turn associated with poorer sleep continuity, increased fatigue, and reduced sleep efficiency, suggesting a bidirectional relationship between androgen status and sleep regulation [20, 21]. Based on evidence from general hypogonadal populations, chronic hypergonadotropic hypogonadism in SCAs such as KS, often accompanied by central adiposity and metabolic syndrome, may predispose to fragmented sleep, excessive daytime sleepiness, and an elevated risk of obstructive sleep apnea (OSA) [13], although prospective studies specifically in KS are limited.

Testosterone replacement therapy in hypogonadal men can improve aspects of well-being and, in some cases, self-reported sleep, but supraphysiological or even standard replacement doses have been reported to aggravate or unmask OSA, underlining a complex dose-dependent effect of androgens on ventilatory control and upper airway stability. Moreover, in the general population, sex steroids influence thermoregulation, melatonin secretion, and clock gene expression; by extension, alterations in gonadal hormone levels in SCAs may contribute not only to

changes in sleep architecture and respiratory parameters but also to circadian rhythm misalignment and associated sleep–wake complaints [19–21].

2.3 | Neurodevelopment, Psychopathology, and Sleep in SCAs

The increased risk of neurodevelopmental disorders in individuals with SCAs directly contributes to sleep disturbances, including insomnia, difficulties in sleep initiation and maintenance, parasomnias, and circadian rhythm sleep–wake disorders. Language delay, learning disabilities, ADHD, and ASD, as well as higher rates of anxiety, depression, and other mood and psychotic disorders are highly prevalent in SCAs, with hazard ratios for psychiatric disorders ranging from 2.2 to 4.3 compared to the general population [22, 23]. In the general pediatric and neurodevelopmental literature, ADHD and ASD are associated with insomnia, sleep fragmentation, and circadian rhythm disruption, often due to underlying attentional dysregulation, hyperarousal, and altered sensory processing [24, 25]; given the high prevalence of these conditions in SCAs, similar mechanisms are likely operative in this population. Language and executive function deficits further impair the ability to self-regulate sleep routines and respond to environmental cues, increasing vulnerability to sleep initiation and maintenance problems [1]. Anxiety, emotional lability, and depressive symptoms specifically impact sleep patterns by increasing presleep arousal, rumination, and nocturnal awakenings, while also reducing sleep efficiency and quality. Hyperarousal and attentional dysregulation, common in ADHD and mood disorders, lead to increased difficulty falling asleep and maintaining sleep, as well as a higher risk of parasomnia. Emotional lability and anxiety exacerbate sleep fragmentation

and circadian misalignment, while depressive symptoms are linked to both insomnia and hypersomnia [25–27].

Deficits in executive functioning and adaptive skills—including impaired inhibitory control, working memory, cognitive flexibility, and planning—are well-documented specifically in 47,XXY, 47,XYY, and 47,XXX subjects. Based on evidence from neurodevelopmental populations and clinical experience, these deficits likely contribute to difficulties in maintaining regular sleep–wake schedules and adhering to sleep hygiene recommendations in individuals with SCAs. Clinical observations suggest that this population often struggle with organizing daily routines, initiating and completing tasks, and adapting to changes, which may impair their ability to establish consistent bedtimes, limit stimulating activities before sleep, and follow behavioral strategies that promote good sleep hygiene [1, 28, 29].

These executive and adaptive skill deficits interact with neurodevelopmental vulnerabilities and psychiatric comorbidities, which are highly prevalent in these populations. Attentional dysregulation and hyperarousal can lead to bedtime resistance, delayed sleep onset, and fragmented sleep, while anxiety and mood symptoms are associated with early-morning awakenings and non-restorative sleep [23, 25, 30]. These factors are further compounded by endocrine–metabolic abnormalities (e.g., hypogonadism, obesity, and metabolic syndrome), which increase the risk of sleep-disordered breathing and circadian rhythm disturbances. The combined effect of these pathways is that SCAs impact both subjective and objectively measured sleep from childhood through adulthood, as demonstrated in studies specifically conducted in 47,XXY and suggested by preliminary data in other SCAs. Objectively, actigraphy and polysomnography (PSG) reveal increased sleep fragmentation, longer night wakes, and reduced sleep efficiency, while subjectively, individuals report poorer sleep quality and greater sleep-related impairment. These sleep disturbances are persistent and multifactorial, reflecting the interplay of neurocognitive, psychiatric, and metabolic factors unique to SCAs [7, 18].

2.4 | Oxidative Stress and Sleep in SCAs

Emerging evidence suggests that oxidative stress is increased in SCAs, and may contribute to metabolic, cardiovascular, and neurocognitive complications by promoting cellular damage, inflammation, and impaired mitochondrial function. Hormonal deficiencies (testosterone or estrogen), metabolic disturbances, and gene dosage effects lead to elevated reactive oxygen species (ROS) and reduced antioxidant defenses, which drive insulin resistance, dyslipidemia, endothelial dysfunction, and neurocognitive impairment [8, 31, 32]. While the increased prevalence of metabolic syndrome, type 2 diabetes, cardiovascular disease, and cognitive deficits is well-documented across SCAs, the extent to which oxidative stress mechanisms causally contribute to these complications—versus serving as a correlate or consequence—remains to be established [33, 34].

Evidence from general and experimental populations indicates a bidirectional relationship between sleep disturbances and oxidative stress [35–37]. This relationship is hypothesized to be particularly relevant in SCAs given their baseline redox imbalance.

Sleep loss and fragmentation increase ROS production and impair redox homeostasis, while preexisting oxidative stress amplifies sleep pressure and disrupts sleep architecture [35–37]. Chronic sleep disruption further exacerbates oxidative damage, creating a feedback loop that worsens neurocognitive function, metabolic control, and cardiovascular risk. In SCAs, this cycle is potentiated by baseline redox imbalance, making these individuals particularly vulnerable to the adverse effects of poor sleep [7, 32, 38]. We hypothesize that pre-existing oxidative stress in SCAs potentiates the impact of chronic sleep disruption on brain function, metabolic control, and gonadal health by increasing neuronal vulnerability to ROS, impairing synaptic plasticity, and accelerating neurodegeneration and metabolic dysfunction. This may worsen executive dysfunction, mood disorders, and hypogonadism, and could contribute to earlier onset and greater severity of complications [1, 32, 35].

Although direct data linking oxidative stress, SCAs, and sleep parameters are still limited, integrating this dimension may help to explain why sleep disorders in SCAs can have disproportionate effects on neurocognitive outcomes and cardiometabolic risk, and it highlights a potential avenue for future mechanistic and interventional studies.

2.5 | Pharmacological and Behavioral Factors Affecting Sleep in SCAs

Beyond intrinsic biological vulnerabilities, pharmacological treatments and behavioral factors common in SCAs may independently contribute to sleep disturbances. Given the high prevalence of ADHD, anxiety, and depression in these populations, psychotropic medications are frequently prescribed and can significantly affect sleep parameters.

Stimulant medications (methylphenidate, amphetamines), widely used for ADHD management in SCAs, are associated with longer sleep latency, reduced sleep efficiency, shorter total sleep time, and increased insomnia risk (RR 1.6–3.8 compared to placebo), with effects most pronounced early in treatment and at higher dosing frequencies [39–41]. Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, commonly prescribed for anxiety and depression, can also induce or exacerbate insomnia, particularly in children and adolescents (OR 1.65 for treatment-emergent insomnia), while suppressing rapid-eye-movement sleep and occasionally triggering restless legs syndrome or bruxism [42–44]. Conversely, sedating antidepressants (e.g., trazodone, mirtazapine) and atypical antipsychotics may promote sleep but carry risks of daytime sedation and weight gain, the latter increasing susceptibility to OSA [45, 46].

Behavioral factors represent an additional, often underrecognized contributor to sleep disruption in SCAs. Digital media use, particularly interactive screen activities such as video gaming and social media, is strongly associated with delayed sleep onset, shorter sleep duration, and poorer sleep quality in adolescents and young adults. Proposed mechanisms include sleep displacement, blue light-induced melatonin suppression, and cognitive arousal from engaging content [47, 48]. Based on the executive function deficits documented in SCAs and evidence on screen use effects

from adolescent populations, individuals with SCAs may be particularly vulnerable to problematic screen use and poor sleep hygiene, potentially creating a feedback loop that exacerbates circadian misalignment and daytime dysfunction. This hypothesis warrants direct investigation in SCA cohorts. Clinicians managing sleep complaints in SCAs should therefore systematically assess current medications and screen/gaming habits, adjusting stimulant timing, considering alternative antidepressants with favorable sleep profiles, and implementing behavioral strategies to limit evening screen exposure.

3 | Male SCAs: Sleep Phenotype and Underlying Mechanisms

3.1 | 47,XXY

In children and adolescents, sleep disturbances are more prevalent in individuals with KS compared to age-matched controls, with the phenotype varying by age group. Validated sleep questionnaires reveal significantly higher rates of non-restorative sleep, disorders of initiating and maintaining sleep, disorders of arousal, and excessive somnolence, especially from school age onward. These findings support routine screening for sleep problems in pediatric KS, starting at age 6, using tools such as the Sleep Disturbance Scale for Children [7].

In adults with KS, objective actigraphy data show increased sleep disturbance, particularly longer night wakes, although other sleep parameters (latency, efficiency) may not differ significantly from controls. Subjective sleep complaints are also more common, but the correlation between subjective and objective sleep measures is lower in KS, suggesting altered sleep perception. In a study of adult men with KS, sleep disturbance was associated with age, educational level, and employment status, rather than KS status alone [38, 49].

A recent report in an adult with KS has highlighted that sleep problems in this condition may arise from multiple, interacting causes. The authors considered the possible contribution of OSA, treatment-induced central apneas related to testosterone supplementation, and disturbances of the sleep–wake circadian system accompanied by abnormal melatonin secretion [50]. Altered melatonin profiles and circadian rhythm sleep–wake disorders have in fact already been described in individuals with KS [51, 52]. Although some of these mechanisms may also play a role in younger patients with KS, others are likely to be less relevant in childhood. In particular, testosterone concentrations are generally within the normal range in boys with KS before puberty, and testosterone replacement therapy (TRT) during pediatric age is usually limited to specific situations, such as treatment of micropenis in early life or established hypergonadotropic hypogonadism in adolescence [53].

While TRT is the standard of care for hypogonadism in KS and is effective for improving physical, metabolic, and some neuropsychological outcomes [54], the impact on sleep is unclear due to a lack of randomized controlled trials specifically addressing sleep outcomes. Some reports suggest possible improvement in general wellbeing and reduction in fatigue with TRT, but these effects are not systematically linked to objective sleep measures

and require further prospective study [1]. Current clinical practice recommends TRT for hypogonadal symptoms in KS, typically initiated at puberty or upon diagnosis of androgen deficiency, using standard dosing regimens (e.g., topical, intramuscular, or transdermal preparations) titrated to maintain age-appropriate testosterone levels. However, the effects of TRT on sleep quality in KS patients remain inadequately studied, though limited evidence suggests potential benefits rather than harm. Limited evidence from a small follow-up study of 30 KS males treated with testosterone found that 77% benefited from treatment, with improvements including “less need for sleep” among other positive outcomes [55]. Patients with sleep complaints should undergo formal sleep evaluation, considering comorbid neuropsychiatric and psychosocial factors [38, 49]. While TRT may modestly worsen sleep-disordered breathing in those with existing OSA, this should be balanced against established benefits for masculinization, bone health, and metabolic parameters [56].

3.2 | 47,XXX and Other High-grade Male SCAs

Data on sleep disturbances in 47,XXX syndrome and higher-grade male SCAs remain sparse, with most evidence derived from small case series, cohort studies focused on neurodevelopment, or incidental findings in broader SCA evaluations. These conditions share with 47,XXY a heightened vulnerability to neurocognitive impairments, psychiatric comorbidities, and somatic features that predispose to sleep disruption, yet they exhibit distinct phenotypic profiles that may modulate sleep phenotypes differently [57–59].

The sleep phenotype in 47,XXX syndrome is likely shaped by a high prevalence of ADHD, ASD, anxiety, and depression, conditions that are associated with insomnia, sleep fragmentation, and circadian rhythm disruption in the general neurodevelopmental literature [30, 59]. Neurological features such as seizures and motor tics, which are more common in 47,XXX, may further contribute to sleep disturbance [59, 60]. Electroencephalogram studies in 47,XXX individuals have shown increased focal spikes and sharp waves during sleep, suggesting altered sleep microarchitecture, though gross sleep organization is typically preserved [60]. A patient with XXX trisomy, Rolandic spikes, and atypical evolution with continuous spikes and waves during slow sleep has also been reported [61]. Cognitive and behavioral phenotypes in 47,XXX, including impulsivity, externalizing behaviors, and language deficits, are associated with increased risk of sleep problems, and these issues often persist into adulthood [1, 62]. The overall morbidity profile of 47,XXX syndrome includes increased rates of psychiatric, neurologic, and endocrine disorders, which may further exacerbate sleep disturbances [33, 63]. Unlike classic KS, gonadal function in 47,XXX is typically preserved or only mildly affected, reducing the direct contribution of hypogonadism to OSA risk, though increased body mass index and hypotonia could still promote upper airway instability during sleep [59].

The sleep phenotype in higher-grade male SCAs is characterized by increased rates of insomnia, sleep fragmentation, and poor sleep quality, which are closely linked to neurodevelopmental, neuropsychiatric, and cognitive comorbidities [64–67]. In 48,XXYY, sleep disorders are frequently reported alongside

ADHD, anxiety, depression, and irritability, with parent-reported sleep problems and use of sleep medications being common in clinical cohorts [67]. Individuals with 48,XXXY and 49,XXXY exhibit more severe intellectual disability, expressive language deficits, and motor coordination problems, all of which contribute to sleep disruption and increased risk of behavioral sleep disorders [65, 68]. Anxiety-related symptoms and internalizing behaviors, which are prominent in 49,XXXY, further exacerbate sleep difficulties, and sleep problems tend to increase in severity with age [64]. There is a paucity of PSG data, but clinical and behavioral assessments consistently demonstrate that sleep disturbances are part of the broader neurobehavioral phenotype in these syndromes. The severity of sleep problems correlates with the number of supernumerary sex chromosomes, with more complex aneuploidies (e.g., 49,XXXY) showing greater impairment in adaptive functioning and sleep quality [9, 65], although systematic studies are needed to confirm this relationship.

Management of sleep disturbances in these populations requires a multidisciplinary approach, addressing underlying neuropsychiatric and medical comorbidities. There are no syndrome-specific guidelines for sleep disorder treatment, and interventions are extrapolated from general pediatric and neurodevelopmental populations [66, 67]. The relative preservation of gonadal function in 47,YYY contrasts with the hypogonadism of higher-grade variants, potentially shifting emphasis from endocrine-mediated sleep effects toward behavioral and neurological drivers [57, 58]. Although direct PSG studies are limited, self-reported sleep problems and poor sleep quality are more frequent in men with SCAs compared to population norms, and sleep complaints are a significant predictor of overall health status in this group [69]. Prospective, standardized assessments from early childhood are urgently needed to delineate sleep phenotypes, quantify prevalence, and explore links to long-term neurocognitive and reproductive outcomes in these understudied male SCAs.

4 | Sleep Disturbances in Female SCAs

Although earlier sections place greater emphasis on male SCAs, sleep disturbances in female SCAs such as TS (45,X) and trisomy X (47,XXX) show substantial overlap with those observed in male conditions. Examining these phenotypes within a unified framework provides important insights into the role of sex chromosome dosage, gonadal function, and neurodevelopment in shaping sleep regulation. Rather than representing contrasting entities, female and male SCAs appear to share multiple vulnerability pathways, including neurocognitive, psychiatric, and metabolic factors, although differences in hormonal milieu may modulate specific clinical expressions.

TS is characterized by partial or complete X-chromosome monosomy, leading to short stature, ovarian dysgenesis, estrogen deficiency, congenital cardiovascular anomalies, and increased cardiometabolic risk, alongside neurocognitive profiles featuring visuospatial strengths but verbal and executive function weaknesses. Obstructive sleep-disordered breathing is highly prevalent in pediatric patients with TS, with rates up to four times higher than in the general pediatric population. Risk factors include adenoid, tonsillar, and inferior turbinate hypertrophy,

low birthweight, failure to thrive, and increasing age. PSG is recommended for those with symptoms or risk factors, as untreated obstructive sleep-disordered breathing may exacerbate behavioral, neurocognitive, and growth problems in this population [70, 71]. Insomnia is also frequently reported, often in the context of anxiety, which is highly prevalent in TS. Insomnia symptoms include difficulty initiating or maintaining sleep and are commonly endorsed by both patients and caregivers, with anxiety being a major contributor [72]. Additionally, recurrent otitis media and palatal dysfunction in childhood can lead to disrupted sleep and frequent nighttime awakenings [73]. Rarely, other sleep disorders such as narcolepsy have been described in TS, but these are considered coincidental rather than causally related [74].

Trisomy X involves an extra X chromosome, manifesting with tall stature, hypotonia, developmental dyspraxia, language-based learning disabilities, difficulties in social behavior/functioning, and elevated rates of anxiety, depression, and ADHD. Triple-X may influence mental health and the overall well-being of the individuals across their whole life spans [75]. The most commonly associated sleep disorder in trisomy X is insomnia, which manifests as difficulty initiating or maintaining sleep and non-restorative sleep. This is primarily driven by the high prevalence of neuropsychiatric comorbidities in this population, all of which are well-established risk factors for insomnia and poor sleep quality [16, 30, 76–78]. Sleep complaints in 47,XXX often include increased daytime fatigue and sleep fragmentation, and these symptoms may be exacerbated by underlying cognitive and behavioral difficulties.

There is also an increased risk of sleep fragmentation and poor sleep quality secondary to neurodevelopmental delays, motor coordination problems, and, in some cases, seizure disorders, which are more common in 47,XXX than in the general population [1, 16, 77]. Currently, there is no evidence for a specific genetic risk for sleep-disordered breathing or other primary sleep disorders in trisomy X, and the overall burden of sleep disorders appears to be largely attributable to associated psychiatric and neurodevelopmental comorbidities rather than direct genetic effects, as seen in rare genetic syndromes [79].

Higher-grade female SCAs, such as tetrasomy 48,XXXX and pentasomy 49,XXXXX, are exceedingly rare conditions, characterized by profound intellectual disability, dysmorphic features, and severe neurodevelopmental delays. No systematic data on sleep disturbances exist in these populations, with available literature limited to anecdotal case reports that focus primarily on dysmorphology, growth failure, and congenital anomalies without addressing sleep parameters or PSG findings [68, 80–86]. Such scarcity underscores the challenges in extrapolating sleep phenotypes from lower-grade SCAs to these extreme karyotypes, where multifactorial neurodevelopmental burdens likely amplify sleep vulnerabilities indirectly.

5 | Future Directions, Limitations, and Clinical Implications

Current literature on sleep disturbances in SCAs is characterized by significant methodological heterogeneity and important

TABLE 1 | Summary of key studies on sleep disturbances in SCAs.

Study / Sleep assessment	SCA type / sample size	Age group / study design	Main findings	Limitations
Paparella et al. [7] / SDSC questionnaire	47,XXY / 30 KS vs. 30 controls	Children-adolescents (6–17 y) / Cross-sectional case-control	Higher rates of DIMS, DA, DOES, SHY in KS	Parent-reported; no PSG; single-center
Fjermestad et al. [38] / Actigraphy + PSQI	47,XXY / 27 KS vs. 27 controls	Adults (18–44 y) / Cross-sectional case-control	Longer night wakes; poor subjective-objective correlation	Small sample; no PSG; selection bias
Fjermestad et al. [49] / Actigraphy + questionnaires	47,XXY / 27 KS vs. 27 controls	Adults / Cross-sectional	Sleep disturbance associated with age, education, employment	Cross-sectional; limited generalizability
Rouen et al. [50] / PSG + melatonin profiling	47,XXY / 1	Adult / Case report	Multifactorial etiology: OSA, circadian dysregulation, TRT effects	Single case; not generalizable
Luboshitzky et al. [51] / Melatonin sampling	47,XXY / 10 KS	Adults / Case series	Decreased nocturnal melatonin secretion	Small sample; no control group in one study; dated methodology
Torniero et al. [60] / EEG during sleep	47,YYY / 4	Children-adolescents / Case series	Focal spikes/sharp waves during sleep	Very small sample; no standardized sleep measures
Bardsley et al. [59] / Clinical assessment	47,YYY / 90	Children-adolescents / Cohort (descriptive)	High rates of ADHD, anxiety; sleep not primary outcome	Sleep not systematically assessed
Visotsak et al. [65] / Parent questionnaires	48,XXYY, 48,XXXY, 49,XXXXY / 9, 6, 9	Mixed / Cross-sectional (behavioral)	Sleep problems reported; severity correlates with X number	Small samples; no objective measures
Lasutschinkow et al. [64] / CBCL	49,XXXXY / 31	Children (4–12 y) / Cross-sectional	Anxiety-related sleep difficulties	Parent-reported; no PSG/actigraphy
Pham et al. [70] / PSG	45,X (TS) / 172	Children / Retrospective cohort	OSA prevalence 4× higher than general population	Retrospective; referral bias
Fjermestad & Stokke [69] / Self-report	Mixed SCAs / 66 males	Adults / Cross-sectional survey	Sleep problems predict health status	Self-report only; heterogeneous sample

Abbreviations: CBCL, child behavior checklist; DA, disorders of arousal; DIMS, disorders of initiating and maintaining sleep; DOES, disorders of excessive somnolence; EEG, electroencephalogram; KS, Klinefelter syndrome; OSA, obstructive sleep apnea; PSG, polysomnography; PSQI, Pittsburgh sleep quality index; SDSC, sleep disturbance scale for children; SHY, sleep hyperhidrosis; TRT, testosterone replacement therapy; TS, Turner syndrome.

limitations. The majority of studies are cross-sectional, rely on small convenience samples, and use parent- or self-reported questionnaires rather than objective measures such as PSG or actigraphy (Table 1). Only a handful of studies have employed PSG, and these are limited to case reports or small case series. Randomized controlled trials evaluating the effects of interventions (e.g., TRT, continuous positive airway pressure, melatonin, behavioral therapy) on sleep outcomes are entirely absent. Furthermore, most research has focused on 47,XXY, with very limited data on 47,YYY, 47,XXX, and higher-grade aneuploidies. These gaps underscore the need for prospective, multicenter studies using standardized objective sleep assessments across all SCA subtypes and developmental stages.

Routine sleep screening is recommended in SCAs, and should be systematic and age-appropriate, leading to subsequent referral for PSG in the presence of certain red flags (Table 2). Integrated care teams involving endocrinologists, sleep specialists, and neuropsychiatrists should monitor for testosterone-induced OSA, obesity, and circadian misalignment [6, 87]. TRT, especially at supraphysiologic doses, can worsen or unmask OSA, and this risk should be balanced against the benefits for hypogonadism. Regular assessment for OSA symptoms and consideration of PSG before and after initiation or dose escalation of testosterone is prudent [6, 87]. Modifiable factors such as obesity, poor sleep hygiene, and circadian misalignment should be addressed through lifestyle interventions, behavioral therapy, and, when

TABLE 2 | Recommended sleep screening and management protocol in SCAs.

Age groups	Recommended screening tools	Key indications for polysomnography referral	Clinical considerations and interventions
Pediatrics (≥ 6 years)	Sleep Disturbance Scale for Children: validated for insomnia, arousals, somnolence	Habitual snoring, witnessed apneas, excessive daytime somnolence, treatment-refractory fatigue	Address obesity, poor sleep hygiene; monitor neurocognitive impact; multidisciplinary team (endocrinologist, neuropsychiatrist)
Adults	Epworth Sleepiness Scale + Pittsburgh Sleep Quality Index for sleepiness/quality; STOP-Bang for obstructive sleep apnea risk	Positive screening + red flags (snoring, apneas, fatigue); pre/post-testosterone therapy	Balance testosterone benefits vs. obstructive sleep apnea risk (monitor symptoms, polysomnography if needed); lifestyle/behavioral therapy for circadian issues
All ages	Electronic health record screeners; integrate with routine follow-up	High-risk features (obesity, adenotonsillar hypertrophy in Turner, hypogonadism)	Optimize modifiable factors (weight, hygiene); trial melatonin/ continuous positive airway pressure if indicated; track fertility/quality of life outcomes

Note: Questionnaires aid screening, but cannot replace polysomnography for definitive diagnosis, as per expert consensus. Future priorities: prospective actigraphy/polysomnography cohorts, biomarker trials (melatonin, oxidative stress), intervention studies. Integrated care enhances gonadal health and neurodevelopment.

indicated, pharmacologic or device-based treatments. Optimizing sleep health is essential for supporting gonadal function, fertility preservation, and overall quality of life in male SCA patients [6, 87].

Future research priorities include prospective cohort studies using objective sleep measures (e.g., actigraphy, PSG), biomarker studies (such as melatonin and oxidative stress markers), and intervention trials targeting sleep to improve neurocognitive and metabolic outcomes in SCA [88–91]. Standardized protocols for sleep screening and management should be developed and integrated into andrological care pathways to bridge current gaps. There is a need for longitudinal studies across diverse SCA subtypes, mechanistic research on sleep–endocrine interactions, and evaluation of multidisciplinary care models to determine best practices for improving long-term outcomes [88–90].

6 | Conclusions

Current evidence indicates that sleep disturbances are more prevalent in individuals with SCAs compared to the general population. In 47,XXY, studies using validated questionnaires have documented higher rates of insomnia, disorders of arousal, and excessive daytime somnolence from childhood onward, while actigraphy data in adults confirm increased sleep fragmentation and longer night wakes. Limited data in 47,XXY and higher-grade male SCAs suggest elevated rates of sleep problems, primarily linked to neurodevelopmental and psychiatric comorbidities. In TS, PSG-based studies demonstrate a four-fold increased prevalence of obstructive sleep-disordered breathing, whereas in 47,XXX, insomnia and sleep fragmentation appear driven by anxiety and neurodevelopmental factors. Across all SCAs, the interplay of hypogonadism, metabolic dysfunction, psychiatric vulnerability, and medication effects contributes to a multifactorial sleep phenotype. Despite these findings, the literature remains limited by small sample sizes, cross-sectional designs,

heterogeneous assessment methods, and underrepresentation of non-47,XXY karyotypes, and randomized controlled trials evaluating interventions on sleep outcomes are absent. Importantly, the convergence of sleep disturbances across both male and female SCAs supports the concept of shared underlying mechanisms related to sex chromosome dosage and neurodevelopmental vulnerability. Sleep disturbances in SCAs emerge as a critical, modifiable comorbidity that bridges neurodevelopment, endocrine function, and reproductive health, warranting integration into routine clinical practice. Targeted screening, timely PSG referral, and multidisciplinary interventions promise to mitigate these risks, enhancing cognitive, metabolic, and fertility outcomes. Advancing prospective research with objective sleep measures will solidify evidence-based protocols, transforming long-term care for this population.

Author Contributions

Roberto Paparella: conceptualization, methodology, writing – original draft. **Fabiola Panvino:** conceptualization, methodology, writing – original draft. **Ida Pucarelli:** writing – review & editing. **Luigi Tarani:** supervision – review & editing. All authors read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this review are included in this published paper.

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