Received: 14 February 2020 | Revised: 27 March 2020 | Accepted: 9 April 2020

DOI: 10.1002/ajmg.c.31789

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics

WILEY

Rare sex chromosome variation 48,XXYY: An integrative review

Amy A. Blumling | Kristy Martyn | Amy Talboy | Sharron Close

Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, Georgia

Correspondence
Amy A. Blumling, Nell Hodgson Woodruff School of Nursing, Emory University, 723 Highland Square Dr, Atlanta, Georgia, USA.
Email: ablumli@emory.edu

Funding information
Emory University Laney Graduate School Professional Development Support Funds; The Ryan Scovell Memorial XXYY Research Fund; The XXYY Project; Association for X and Y Chromosome Variations (AXYS)

Abstract

While the most common Sex Chromosome Aneuploidy (SCA) is 47,XXY, other variations, such as 48,XXYY, are less studied, perhaps due to its rarity. 48,XXYY occurs with an estimated prevalence of 1:18,000–40,000 male births. This SCA is associated with a variety of complex physical, psychological, and neuroanatomical findings. The purpose of this integrative review is to summarize the available evidence related to 48,XXYY and identify gaps in the literature. This study utilized integrative review and PRISMA-guided methodology to search six databases for information pertaining to 48,XXYY. There were no exclusion criteria related to design methodology, given the paucity of available research. Among 397 articles reviewed for potential inclusion, 30 articles remained after inclusion and exclusion criteria were applied. Seven of these articles concentrated solely on participants with 48,XXYY. Literature was summarized into categories of physical phenotype, psychosocial, behavioral, neurocognitive, and brain function. Clinical description of 48,XXYY has evolved over time to develop a deeper understanding of this complex disorder. Large gaps remain, especially a lack of experimental studies, clinical guidelines, and treatments. Additionally, few studies explore methodologies such as interviews or self-report surveys in this population. 48,XXYY presents with a wide spectrum of physical, psychological, and neurocognitive symptoms, and frequently requires complex interdisciplinary care. In order to better understand this disorder and to appropriately treat the individuals affected by it, future research should focus on experimental studies and research that utilizes a variety of methods, including participant interviews and patient-report surveys.

KEYWORDS

48,XXYY, integrative review, literature review, sex chromosome aneuploidy

1 | INTRODUCTION

One of the most rare and under-studied types of Sex Chromosome Aneuploidies (SCAs) is 48, XXYY (Orphanet Number—ORPHA: 10). With an estimated incidence of 1 in 18,000–40,000 male births (Coffee et al., 2009; Evans, Greenberg, Ramsay, & Hamerton, 1982; Kleczkowska, Fryns, & Van den Berghe, 1988; Nielsen & Wohlert, 1991; Robinson, Bender, Linden, & Salbenblatt, 1990), this SCA is associated with a wide spectrum of physical, neurocognitive, behavioral, and psychological issues. Due to complexity of phenotype, associated symptoms, and wide variation from person-to-person, 48,XXYY presents challenges in health care management. No tested clinical guidelines currently exist to inform health care providers about health surveillance, nor is there a body of evidence to support best practices for care. The purpose of this integrative review is to summarize known evidence about 48,XXYY, to identify gaps in knowledge,

and to suggest future research pathways that may lead to clinical interventions to address problems of individuals and families affected by 48,XXYY.

2 | CLINICAL DESCRIPTION

Sex Chromosome Aneuploidies (SCAs) are variations in the number of X and Y chromosomes in an individual. SCAs typically derive genetically from random nondisjunction events within gametes during cellular meiosis. When this occurs, either the spermatocytes, oocytes, or both, fail to completely separate in this stage of division (Evans et al., 1982; Kleczkowska et al., 1988; Muldal & Ockey, 1960; Nielsen & Wohlert, 1991; Sørensen, Nielsen, Jacobsen, & Rølle, 1978). SCAs are associated with varying degrees of physiologic and psychosocial symptoms resulting in a wide variety of individual phenotypes. Distinct SCA types may also present with an additional, unique spectrum of symptoms. The most common SCA is 47,XXY, also known as Klinefelter Syndrome. The incidence of 47,XXY is estimated to be 1 in every 450–600 male births (Bojesen, Juul, & Gravholt, 2003; Coffee et al., 2009; Evans et al., 1982; Herlihy, Halliday, Cock, & McLachlan, 2011; Nielsen & Wohlert, 1991). KS, or 47,XXY is not considered a rare disorder, and it is one of the most frequently studied SCAs. Other SCAs affect females as well as males, and include trisomies, tetrasomies, and pentasomies, with their incidence as shown in Table 1.

TABLE 1 List of sex chromosome aneuploidies and estimated incidence

Sex chromosome aneuploidy	Incidence
45,XO (Turner syndrome)	1:2,500 female births
47,XXY (Klinefelter's syndrome)	1:450 male births
47,XYY (Jacob's syndrome)	1:1,000 male births
47,XXX	1:1,000 female births
48,XXYY	1:18,000–1:40,000 male births
48,XXXY	1:50,000 male births
48,XXXX	Unknown (approx. 40 cases reported)
48,XYYY	Unknown (approx. 10 cases reported)
49,XXXXY	1:85,000–1:100,000 male births
49,XXXXX	Unknown (approx. 25 cases reported)
49,XXXYY	<1:1,000,000
49,XXYYY	<1:1,000,000
49,XYYYY	<1:1,000,000

Source: Bojesen et al. (2003), Coffee et al. (2009), Evans et al. (1982), Herlihy et al. (2011), Kleczkowska et al. (1988), Nielsen and Wohlert (1991), Robinson et al. (1990), Rovet, Netley, Bailey, Keenan, and Stewart (1995), Sorensen, Nielsen, Jacobsen, and Rolle (1978).

48,XXYY is one of the more rare SCAs, with an estimated incidence of 1 in every 18,000 male births (Coffee et al., 2009; Evans et al., 1982; Kleczkowska et al., 1988; Nielsen & Wohlert, 1991; Robinson et al., 1990). Males with the tetrasomy 48,XXYY typically have a more severe presentation involving physical, neurocognitive, and psychosocial characteristics (Hanley et al., 2015; N. Tartaglia, Ayari, Howell, D'Epagnier, & Zeitler, 2011; N. R. Tartaglia et al., 2017). While there is a wide spectrum of physical presentations in 48,XXYY, some of the most common physical findings in individuals are tall stature, hypertelorism with epicanthal folds, clinodactyly, pes planus, joint hyperextensibility, hypotonia, intention tremor, and radioulnar synostosis (N. Tartaglia et al., 2008; J. Visootsak & Graham, 2006). Additionally, individuals may present with a eunuchoid body habitus with wider hips than would be expected for males and narrow shoulders (Atik, Cogulu, & Ozkinay, 2016; N. Tartaglia et al., 2011; N. Tartaglia et al., 2008; J. Visootsak & Graham, 2006). Testicular pathology in this SCA leads to microorchidism, impaired fertility, and hypergonadotropic hypogonadism. The endocrinologic disruptions associated with hypergonadotropic hypogonadism may result in testosterone deficiency, which can lead to gynecomastia, reduced muscle mass, sparse body hair, and urological issues (Atik et al., 2016; Lote, Fuller, & Bain, 2013; N. Tartaglia, Borodyanskya, & Hall, 2009; N. Tartaglia et al., 2008). Physical health risks seen in individuals with 48,XXYY include increased risk for insulin resistance, reactive airway disease, generalized tremors or seizure disorders, deep vein thrombosis and peripheral vascular disorders, dental anomalies, and increased mortality from non-Hodgkin lymphoma cancer (N. Tartaglia et al., 2011; N. Tartaglia et al., 2008; J. Visootsak & Graham, 2006).

Many individuals with 48,XXYY initially present with delays in developmental milestones, including both speech and motor delays (J. Visootsak & Graham, 2006). Mild to moderate learning disabilities/disorders are also present in the majority of individuals with 48,XXYY (N. Tartaglia et al., 2008; J. Visootsak & Graham, 2006). An increased risk for several additional neurodevelopmental comorbidities, such as Attention Deficit/Hyperactive Disorder (ADHD) and Autism Spectrum Disorder (ASD), is also associated with 48,XXYY (N. Tartaglia et al., 2008; Nicole R. Tartaglia, Ayari, Hutaff-Lee, & Boada, 2012; N. R. Tartaglia et al., 2017; J. Visootsak, Rosner, Dykens, Tartaglia, & Graham, 2007). A recent study demonstrated that ASD is estimated to occur in 52% of individuals with 48,XXYY (N. R. Tartaglia et al., 2017).

The typical behavioral profile of 48,XXYY varies significantly by individual. However, individuals with 48,XXYY may display mood lability and ASD-like behaviors (N. Tartaglia et al., 2008; J. Visootsak et al., 2007). Individuals with 48,XXYY syndrome may experience a variable spectrum of psychosocial disturbances, mainly involving social interaction difficulties and mood disorders. The most common psychiatric disorders in this group include anxiety and depression (N. Tartaglia et al., 2011; N. Tartaglia et al., 2008). Due to complexity of these characteristics, interdisciplinary management is required.

The body of current literature about 48,XXYY focuses mainly on physical and psychological aspects of the disorder, in the context of the other known SCAs. The majority of studies involving 48,XXYY

have treated it as a variant of 47,XXY and have mainly conducted studies comparing the disorder to other SCAs. Clinical interventions and patient-centered needs are, to our knowledge, discussed less frequently. This integrative literature review aims to synthesize knowledge related solely to 48,XXYY, identify gaps in knowledge on 48,XXYY, and to discern future research needs.

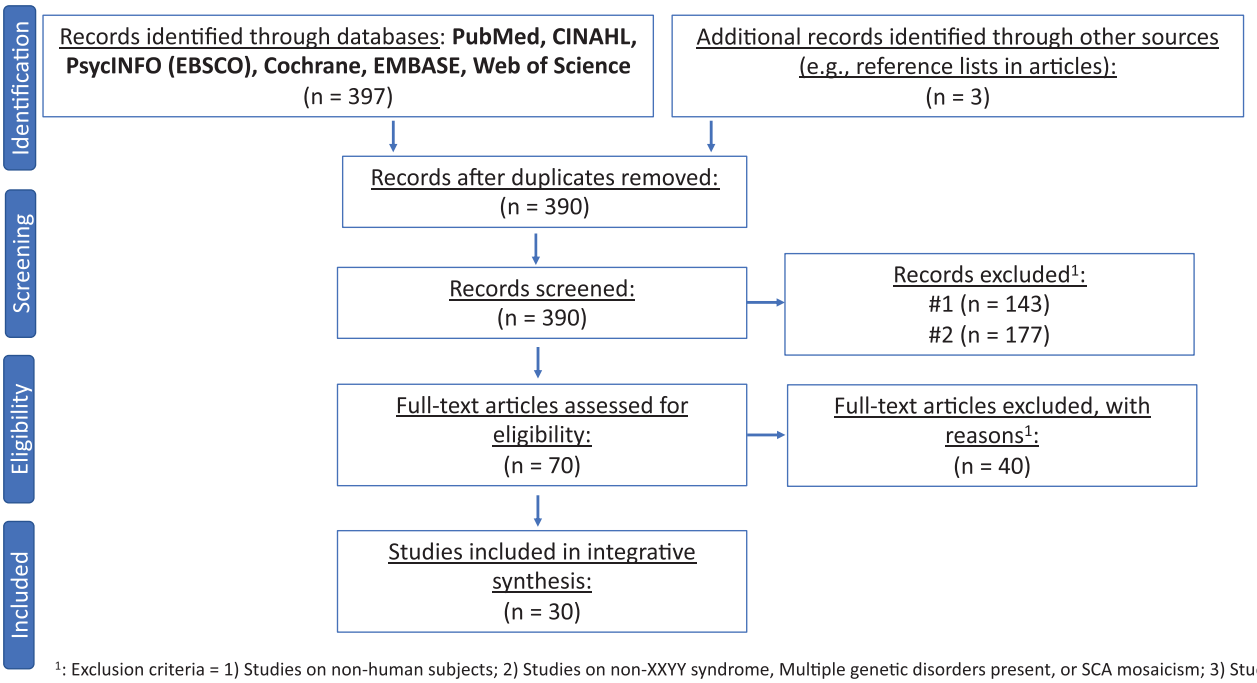
3 | METHODS

An in-depth literature review was performed using a combination of the Integrative Review methodology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009; Whittemore & Knafl, 2005). The Integrative Review methodology and analysis technique allow for a more diverse range of evidence types, such as non-experimental studies, to be utilized in reviews (Whittemore & Knafl, 2005). In addition, it provides guidelines for analyzing the appropriateness for review inclusion based on overarching review categories of interest and general goals (Whittemore & Knafl, 2005). This methodology, combined with the traditional PRISMA guidelines of study inclusion and exclusion processes, allow for a thorough, clear rationale related to study selection in reviews with a range of study types, as is seen in the SCA literature.

48,XXYY falls under the traditional Medical Subject Heading (MeSH) of "Sex Chromosome Aneuploidy," which also includes additional SCAs, such as 47,XXY. An initial search utilizing this traditional MeSH heading resulted in many articles on SCAs that were not specific to or did not include 48,XXYY as the aneuploidy of interest. Therefore, the search was performed again using the singular keyword phrase "XXYY". Six databases, including PubMed, CINAHL, PsycINFO (EBSCO), Cochrane, EMBASE, and Web of Science, were queried from 1960 to 2018.

4 | RESULTS

The search strategy for this review is shown in Figure 1. The initial search from the 6 databases resulted in 397 articles, with an additional 3 identified through other sources, for a total of 400 articles. After duplicates were removed, the remaining number of articles totaled 390. Of the 390 article titles and abstracts screened for inclusion or exclusion, 320 abstracts were excluded through two sets of revisions for the following exclusion criteria: (a) Studies on non-human subjects; (b) Studies on non-XXYY syndrome, Multiple genetic disorders present, or SCA mosaicism; (c) Studies on testing and diagnosis only; (d) Focus on only parents of XXYY children; (e) Non-English language; (f) Sample size ≤3 or "n" unlisted; (g) Unable to acquire full text after exhaustive search conducted by University Library loan services; (h) Duplicates not identified in the original review; (i) Book sections; (j) Limited focus of care/treatment/phenotype; and (k) Poster/Presentation abstracts. Inclusion criteria were broad and allowed for articles of varying study design in order to account for the limited information available on this topic.



[1]: Exclusion criteria = 1) Studies on non-human subjects; 2) Studies on non-XXYY syndrome, Multiple genetic disorders present, or SCA mosaicism; 3) Studies on testing and diagnosis only; 4) Focus on only parents of XXYY children; 5) Non-English language; 6) Sample size ≤3 or "n" unlisted; 7) Unable to acquire full text after exhaustive search conducted by Emory Inter-Library Loan librarians; 8) Duplicates not identified in the original review; 9) Book sections; 10) Limited focus of care/treatment/phenotype; and 11) Poster/Presentation abstracts

FIGURE 1 Adapted PRISMA diagram of article inclusion/exclusion process

Using the previously listed criteria, 70 abstracts remained and were then reviewed as full-text documents. Upon reviewing these studies, an additional 40 full-text articles were excluded according to exclusion criteria, and the result was 30 remaining full-text articles to be included in the final integrative review (Table 2). Data from the remaining 30 articles were extracted to examine the following elements of data analysis: categories of data types (e.g., physical, psychosocial, neurocognitive, etc.), contradictory or supporting evidence, and applicability to the overarching purpose of the integrative review (Liberati et al., 2009; Whittemore & Knafl, 2005). Nine articles were literature reviews of SCAs or SCA related symptoms, while the remaining 21 articles were primary or secondary data collection studies conducted with individuals who have SCAs. Of the 21 studies conducted with individuals with SCAs, all were the results of descriptive or observational primary or secondary data collections.

There were only 7 descriptive or observational studies, including the seminal case study describing the first individual with 48,XXYY, that focused solely on individuals with 48,XXYY; all others included multiple SCAs in the participant population, and 48,XXYY was not the primary focus (Table 2). There are currently no interventional studies in this population. These 7 studies with an exclusive 48,XXYY participant population were included in a final, detailed table summarizing the following characteristics: author, year, journal of publication, type of study, objectives, sample and subjects, interventions and measures, results, implications, and limitations (Table 3).

Descriptive reports and studies including 48, XXYY have been reported since the 1960s. Over the past 60 years, however, the body of literature about 48,XXYY has grown very slowly. This review includes 30 reports that describe the physical, psychological, and neurocognitive profile of individuals with 48,XXYY. Only seven of these studies utilized primary data collection techniques (e.g., observational, descriptive, case studies, etc.) and focused solely on 48,XXYY. As of yet, no experimental or randomized control studies exist that demonstrate high weights of evidence or generalizability for SCAs. The current literature on 48,XXYY can be organized into categories of Physical Phenotype, Psychosocial and Behavioral Aspects, and Neurocognitive and Brain Function.

4.1 | Physical phenotype

The original description of 48,XXYY was a case study of a 15 year old boy, published in 1960 by authors Muldal and Ockey. This seminal research was published almost 20 years after the first SCA, 47,XXY, or Klinefelter Syndrome, was described in 1943. The original case study of the boy with 48,XXYY was a detailed description of a "typical Klinefelter's syndrome" appearance, including gynecomastia, increased gonadotropin levels, decreased keto-steroids, and intellectual disability (Muldal & Ockey, 1960). In this brief description of the newly discovered SCA, the authors also described the paternal origin of the extra sex chromosomes, as well as the method of SCA development—nondisjunction of the chromosomes during meiosis (Muldal & Ockey, 1960). This case study focused on similarities of this disorder to 47,XXY and highlighted only a few physical findings with a mention of intellectual disability.

Over the following years, a variety of reviews and case studies were published detailing the most common physiologic findings associated with 48,XXYY, including small testes, azoospermia, gynecomastia, a eunuchoid body habitus, increased height, increased Follicular Stimulating Hormone (FSH), and testicular atrophy following puberty (Barr et al., 1964; Carr, Barr, & Plunkett, 1961). Early studies published shortly after the aneuploidy was first described in the 1960s, such as those authored by both Carr, et al. and Barr, et al. primarily emphasized the similarities of 48,XXYY to the first SCA discovered, 47,XXY. In 1963, Carr made the argument that 48,XXYY did not differ clinically from 47,XXY (Carr et al., 1961). A study by Barr et al. in 1964 focused on similarities between the two aneuploidies and presented 48,XXYY as a "variant" of 47,XXY, but with more severe intellectual disability (Barr et al., 1964). Barr et al. noted that occasionally, 48,XXYY also presented with some different physiologic findings as compared to 47,XXY, including vascular issues, dermatoglyphic alterations, and musculoskeletal aberrations (Barr et al., 1964). Ongoing endocrinological and urological findings described in this early literature of the 1960s and 1970s, specifically by Barr et al. and Sørensen et al., continued to highlight similar presentations between 48,XXYY and 47,XXY. In addition to azoospermia, small testes, and elevated FSH, researchers found similarities between 48,XXYY and 47,XXY testicular histological pathologies, such as hyalinized tubules (Barr et al., 1964; Sorensen et al., 1978). In addition to these findings, a 1974 study by Wright and Lauder described the similarities and differences of motor nerve conduction in individuals with SCAs. Median and ulnar nerve conduction velocity were similar between females with 47,XXX and males with 48,XXYY (Wright & Lauder, 1974). Overall, individuals with 48,XXYY had slower nerve conduction velocity and greater distal latency action potentials than control groups, individuals with 47,XXY, and individuals with 45,XO (Wright & Lauder, 1974).

During the 1980s and 1990s, there were fewer studies published about individuals with SCAs. Those that were published focused more on the psychological and behavioral functioning of individuals, rather than physical phenotype. Fryns et al. conducted a chart review looking at primarily psychological functioning of one of the largest longitudinal studies of SCA patients from the Leuven Cytogenetic Center in Belgium, titled "The Leuven Experience 1966-1987," with the original data published by Kleczkowska in 1988. In this description highlighting psychological functioning, however, Fryns also mentions for the first time observations of intention tremor, generalized tremors, fine coordination disturbances, and epilepsy in a small number of patients (Kleczkowska et al., 1988). Later studies reported varying types of tremors in the majority of individuals with 48,XXYY. In the few studies in the 1980s and 1990s that focused primarily on physical phenotype, there was often conflicting information. One descriptive study in 1991, by Borghgraef et al., postulated that the physical phenotype in 48,XXYY is unremarkable, in terms of its comparison to 47,XXY, and that the main difference between these two aneuploidies was related to intellect, psychosocial functioning, and behavioral issues, with 48,XXYY presenting more severely (Borghgraef et al., 1991). However,

TABLE 2 List of all studies included in integrative review

Authors; year	Title	Journal	Study type	Main focus and included SCA syndromes
1. Fish et al., 2017	"Influences of brain size, sex, and sex chromosome complement on the architecture of human cortical folding"	*Cerebral Cortex*	Descriptive/observational	-Gyrification, cerebral cortical folding, & sex chromosome dosage -SCAs: XXX, XYY, XXY, XXYY, XXXXY
2. Tartaglia et al., 2017	"Autism spectrum disorder in males with sex chromosome aneuploidy: XXY/Klinefelter syndrome, XYY, and XXYY"	*Journal of Developmental & Behavioral Pediatrics*	Descriptive/observational	-Autism spectrum disorder & SCAs -SCAs: XXY, XYY, and XXYY
3. Reardon et al., 2016	"An allometric analysis of sex and sex chromosome dosage effects on subcortical anatomy in humans"	*The Journal of Neuroscience*	Descriptive/observational	-Subcortical size/shape & SCAs -SCAs: XXX, XXY, XYY, XXYY, XXXXY)
[a]4. Hanley et al., 2015	"Brain and behavior in 48,XXYY"	*Neuroimage: Clinical*	Descriptive/observational	-Neuroanatomical phenotype of 48,XXYY -SCA: XXYY
5. Lin et al., 2015	"Mapping the stability of human brain asymmetry across five sex-chromosome aneuploidies"	*The Journal of Neuroscience*	Descriptive/observational	-Cortical thickness asymmetry & SCAs -SCAs: XXX, XXY, XYY, XXYY, XXXXY
6. Wade et al., 2014	"Effects of sex chromosome dosage on corpus callosum morphology in supernumerary sex chromosome aneuploidies"	*Biology of Sex Differences*	Descriptive/observational	-Corpus callosum morphometry & SCAs -SCAs:
7. Gropman & Samango-Sprouse, 2013	"Neurocognitive variance and neurological underpinnings of the X and Y chromosomal variations"	*American Journal of Medical Genetics Part C: Seminars in Medical Genetics*	Review of literature	-Variability in phenotype, clinical presentation, & physiology in SCAs -SCAs: XXY, XXYY, XXXY, XXXXY
8. Cordeiro, Tartaglia, Roeltgen, & Ross, 2012	"Social deficits in male children and adolescents with sex chromosome aneuploidy: A comparison of XXY, XYY, and XXYY syndromes"	*Research in Developmental Disabilities*	Descriptive/observational	-Social skills and deficits; variability among SCAs -SCAs: XXY, XYY, XXYY
9. Tartaglia et al., 2012	"Attention-deficit hyperactivity disorder symptoms in children and adolescents with sex chromosome aneuploidy: XXY, XXX, XYY, and XXYY"	*Journal of Developmental & Behavioral Pediatrics*	Descriptive/observational	-Attention-deficit hyperactivity disorder, impulsivity, associated symptoms, response to treatment & SCAs -SCAs: XXY, XYY, XXX, XXYY
10. Frühmesser & Kotzot, 2011	"Chromosomal variants in Klinefelter syndrome"	*Sexual Development*	Review of literature	-Phenotypes & comparisons of Klinefelter variants -SCAs: XXY, XXXY, XXYY, XXXXY, plus additional aberrations and rearrangements of X and Y chromosomes
11. Tartaglia et al., 2011	"48,XXYY, 48,XXXY and 49,XXXXY syndromes: Not just variants of Klinefelter syndrome"	*Acta Paediatrica*	Review of literature	-Clinical features, diagnosis, etiology, & distinction of SCAs -SCAs: XXYY, XXXY, XXXXY
12. Ottesen et al., 2010	"Increased number of sex chromosomes affects height in a nonlinear fashion: A study of 305 patients with sex chromosome aneuploidy"	*American Journal of Medical Genetics Part A*	Descriptive/observational	-Tall stature, SHOX gene expression, & SCAs -SCAs: XO, XXX, XXXX, XXXXX, XXY. XYY, XXXY, XXYY, XXXXY
13. Lenroot, Lee, & Giedd, 2009	"Effects of sex chromosome aneuploidies on brain development: Evidence from neuroimaging studies"	*Developmental Disabilities Research Reviews*	Review of literature	-Chromosome dosage, brain structure/function, & SCAs -SCAs: XXY, XYY, XXX, XXYY, XXXY, XXXXY, XXXXX

TABLE 2 (Continued)

Authors; year	Title	Journal	Study type	Main focus and included SCA syndromes
[a]14. Tartaglia et al., 2009	"Tremor in 48,XXYY"	*Movement Disorders*	Descriptive/observational	-Tremor, ataxia, dysarthria, nystagmus in 48,XXYY -SCA: XXYY
15. Visootsak & Graham, 2009	"Social function in multiple X and Y chromosome disorders: XXY, XYY, XXYY, XXXY"	*Developmental Disabilities Research Reviews*	Review of literature	-Impairment in social & verbal skills, expressive language deficits, language delays, and learning disabilities & SCAs -SCAs: XXY, XYY, XXYY, XXXY
[a]16. Tartaglia et al., 2008	"A new look at XXYY syndrome: Medical and psychological features"	*American Journal of Medical Genetics Part A*	Descriptive/observational	-Age stratification of: Diagnosis, phenotype, medical problems, medications, & psychological features of individuals with 48,XXYY -SCA: XXYY
17. Visootsak & Graham, 2006	"Klinefelter syndrome and other sex chromosomal aneuploidies"	*Orphanet Journal of Rare Diseases*	Review of literature	-Overview of SCAs, genetic testing, presenting age-related signs & symptoms, & treatment -SCAs: XXY, XXYY, XXXY, XXXXY
18. Swerdlow et al., 2005	"Cancer incidence and mortality in men with Klinefelter syndrome: A cohort study"	*Journal of the National Cancer Institute*	Descriptive/observational	-Mortality rates from lung, breast, prostate, and non-Hodgkin lymphoma cancers & SCAs -SCAs: XXY, XXXY, XXYY, XXXXY
19. Fryns, Kleczkowska, Kubień, & Van den Berghe, 1995	"XYY syndrome and other Y chromosome Polysomies. Mental status and psychosocial functioning"	*Genetic Counseling*	Descriptive/observational	-Intellectual disability, reason for karyotyping, & SCAs -SCAs: XYY, XXYY
20. Linden, Bender, & Robinson, 1995	"Sex chromosome tetrasomy and pentasomy"	*Pediatrics*	Review of literature	-Phenotype, clinical presentation, severity, and type of SCA -SCAs: XXXX, XXXXX, XXYY, XXXY, XXXXY, XXXYY, XYYYY, XYYY, XXYYY
[a]21. Borghgraef, Fryns, & Van Den Berghe, 1991	"The 48,XXYY syndrome. Follow-up data on clinical characteristics and psychological findings in 4 patients"	*Genetic Counseling*	Descriptive/observational	-Phenotypical findings and reason for chromosomal analysis in 48,XXYY -SCA: XXYY
22. Kleczkowska et al., 1988	"X-chromosome polysomy in the male. The Leuven Experience 1966–1987"	*Human Genetics*	Descriptive/observational	-Clinical phenotype, signs/symptoms, and age at diagnosis & SCAs -SCAs: XXY, XXYY, XXXXY
23. Dorus, 1980	"Variability in the Y chromosome and variability of human behavior"	*Archives of General Psychiatry*	Review of literature	-Variability in Y chromosome, relation to behavior, & SCAs -SCAs: XYY, XXYY
[a]24. Sørensen et al., 1978	"The 48,XXYY syndrome"	*Journal of Mental Deficiency Research*	Descriptive/observational	-Etiology and clinical findings in individuals with 48,XXYY -SCA: XXYY
25. Wright & Lauder, 1974	"Motor nerve conduction in 47,XXY and 48,XXYY males, and 47,XXX and 45,X females"	*Clinical Genetics*	Descriptive/observational	-Maximum motor nerve conduction in median and ulnar nerves of forearm & SCAs -SCAs: XO, XXX, XXY, XXYY

(Continues)

TABLE 2 (Continued)

Authors; year	Title	Journal	Study type	Main focus and included SCA syndromes
26. Casey, Street, Segall, & Blank, 1968	"Patients with sex chromatin abnormality in two state hospitals"	*Annals of Human Genetics*	Descriptive/observational	-Individuals with intellectual disability who have been institutionalized for aggressive or violent behavior & rates of SCAs -SCAs: XXY, XXXY
27. Hunter, 1968	"Klinefelter's syndrome and delinquency"	*British Journal of Criminology*	Descriptive/observational	-Individuals with intellectual disability who have been institutionalized for aggressive or violent behavior & rates of SCAs -SCAs: XXY, XXYY, XXXY
[a]28. Barr, Carr, Soltan, Wiens, & Plunkett, 1964	"The XXYY variant of Klinefelter's syndrome"	*Canadian Medical Association Journal*	Descriptive/observational	-Clinical phenotype of individuals with 48,XXYY; effect of multiple Y chromosomes -SCA: XXYY
29. Carr, 1963	"Chromosomal abnormalities and their relation to disease"	*Canadian Medical Journal Association*	Review of literature	-Descriptions of chromosomal aneuploidies, both autosomal and sex -SCAs: XO, XXY, XXYY, XXXY, XXXXY
[a]30. Muldal & Ockey, 1960	"The 'double male': A new chromosome constitution in Klinefelter's syndrome"	*The Lancet*	Descriptive/observational	-First reported case of 48,XXYY SCA: XXYY

[a]Study involves only individuals with 48,XXYY.

three years later, Linden et al. published a literature review on sex chromosome tetrasomies and pentasomies, and described 48,XXYY much differently than Borghgraef had previously. Linden et al. still depicted 48,XXYY as a "variant" of 47,XXY, with all of the symptoms previously reported, but also described varying severity of hypergonadotropic hypogonadism, as evidenced by decreased FSH and Luteinizing Hormone [LH]), unique facial characteristics, skeletal anomalies, and peripheral vascular disease found more commonly in the 48,XXYY population (Linden et al., 1995).

In the early 2000s, there was an increase in the amount of research conducted on SCAs, especially with 47,XXY, but also including the more rare variants, such as 48,XXYY. Between 2006 and 2013, an additional 11 studies or reviews are published that specifically address 48,XXYY as a unique syndrome, although it is often still compared to 47,XXY. Visootsak and Graham in 2006 published a literature review on the clinical signs, symptoms, and associated health issues of SCAs, the vast majority of which are comparable to those described by Linden et al. in 1995 (Linden et al., 1995; J. Visootsak & Graham, 2006). Over the 11 year period from 1995 to 2006, descriptions of the 48,XXYY physical phenotype continued to include the same commonly found symptoms: increased height, a eunuchoid body habitus with long limbs, sparse body hair, small testicles and penis, hypergonadotropic hypogonadism, gynecomastia, and reports of peripheral vascular disease, potentially related to leg ulcers and varicosities (J. Visootsak & Graham, 2006). As a result of these testicular disruptions, issues with reproduction are also commonly reported at these times and going forward (Linden et al., 1995; Liu et al., 2018; Roche et al., 2014).

Descriptions of physical phenotype published from the early 2000s and forward were consistent with what had been published previously. However, there are some important, more recent studies that have highlighted additional medical problems that are more prevalent in individuals with 48,XXYY. Tartaglia et al., and Frühmesser and Kotzot in the mid 2000s published descriptions of 48,XXYY showing increased risks for reactive airway disease, allergies, asthma, obstructive sleep apnea, and seizure disorders (Frühmesser & Kotzot, 2011; N. Tartaglia et al., 2011; N. Tartaglia et al., 2008). Some of the most recent descriptions of the physical phenotype have been expanded to include observations of specific postural and kinetic tremors that worsen over time, radioulnar synostosis, cleft palate, poor dentition, specific congenital heart defects, congenital hip dysplasia, pes planus and clubfoot, strabismus, scoliosis, and renal dysplasia (Frühmesser & Kotzot, 2011; N. Tartaglia et al., 2011; N. Tartaglia et al., 2009; N. Tartaglia et al., 2008). Some genetic insights are reported in later years that explain the physical symptoms frequently seen in SCAs, such as increased height. In 2010, Ottesen et al. describe the role of the SHOX gene on the sex chromosomes and the gene dosage effect that may contribute to increased height in individuals with SCAs (Ottesen et al., 2010). Finally, additional expansions of the phenotype from 2008 to the present, by Tartaglia, Gropman, and Swerdlow, reported additional risks for pulmonary embolism, deep vein thrombosis, hypothyroidism, recurrent otitis media, gastroesophageal reflux disease, constipation, Type 2 Diabetes Mellitus, and an increased

TABLE 3 Observational and descriptive studies of 48,XXYY exclusively

Authors; year	Article and Journal	Study type and objectives	Subjects	Interventions and measures	Results	Implications and limitations
1. Hanley et al., 2015	"Brain and behavior in 48,XXYY syndrome" *Neuroimage: Clinical*	Descriptive/observational; case control Objectives: Discern neuro-anatomical phenotype of the 48,XXYY using quantitative & qualitative analyses from MRI brain scans	*n* = 25 males with 48,XXYY *n* = 92 age and socio-economic matched typically developing 46,XY males Ages: 4–28 yrs	-Cognitive, behavioral, emotional, social functioning tests -MRI -Weschler abbreviated scales of intelligence -Social communication questionnaire -Social responsiveness scale -Child behavior checklist -Physical exam	-Subjects with 48,XXYY showed (compared to controls): --Lower IQ, verbal IQ, & performance IQ --Lower scores of social, emotional, & behavioral function --Smaller total brain tissue, gray & white matter volumes in frontal & temporal lobes --Larger gray & white matter in parietal lobe & lateral ventricular volume --Difference in skull shape, white matter lesions, prominent perivascular spaces, thin corpus callosum, colpocephal, periventricular cysts, & mega cisterna magna --Higher incidence colpocephaly (84%), white matter lesions (25%), & thin posterior body of corpus callosum (28%)	-Atypical brain development in 48,XXYY: Smaller & more abnormalities in white matter & ventricles -Visual–spatial skills are a cognitive strength in individuals with this condition, but verbal skills are weaker -Affective, behavioral, & social difficulties more common in 48,XXYY -Brain volume reduction appears mitigated by presence of additional Y chromosome -X chromosome influences overall brain volume more than total number of sex chromosomes Limitations: Lobar level of brain measurement, lack of data on parental origin of supernumerary chromosomes and levels of sex hormones
2. Tartaglia et al., 2009	"Tremor in 48,XXYY syndrome" *Movement Disorders*	Descriptive/observational; case series Objectives: Describe tremors in individuals with 48,XXYY; Detailed descriptions of subsample *n* = 3 participants	*n* = 10 males with 48,XXYY with tremor Ages: 3–26 years Mean age: 18.3 years	-Neurological exams with videotaping -Physical exam (PE) -Clinical rating scale for tremor -International cooperative ataxia rating scale -Medical history (Hx)	–100% demonstrated postural/kinetic tremors -Additional symptoms in some: Gait ataxia, dysarthria, nystagmus -Case 1:22 years with postural and kinetic tremor; Hx: Tremor at age 7; PE: Borderline IQ, ASD, mild dysmorphia, sleep apnea, seizures, esophageal spasms, nystagmus, dysarthria, hypogonadism -Case 2:13 years with postural & kinetic tremor; Hx: Tremor at age 4, comorbid cystic fibrosis diagnosis; PE: Saccadic ocular pursuit, postural tongue tremor, speech fluency modification -Case 3:17 yrs with postural & kinetic tremor; Hx: Tremor at age 10; PE: Saccadic ocular pursuit & widened stance	-Tremors common in 48,XXYY with varying severity -Common in adolescence -May differ from essential/primary tremor -Gene dosage may be associated with pathogenesis & severity -Pseudoautosomal regions on homologous supernumerary X & Y chromosomes may cause tremors -Tremors plus history of early developmental delays, learning disabilities, tall stature, or microorchidism should prompt analysis of possible SCA -Limitations: Small sample size; ascertainment bias

(Continues)

TABLE 3 (Continued)

Authors; year	Article and Journal	Study type and objectives	Subjects	Interventions and measures	Results	Implications and limitations
3. Tartaglia et al., 2008	"A new look at XXYY syndrome: Medical and psychological features" *American Journal of Medical Genetics: Part A*	Descriptive/observational; cross-sectional multi-center study Objectives: Describe the diagnosis, physical features, medical problems, medications, & psychological features of individuals with 48,XXYY; To stratify above descriptors by age groups	*n* = 95 males with 48,XXYY Ages: 1–55 years Mean age: 14.9 years	-Caregiver/parent reported questionnaires: Birth, medical, development, & psychiatric hx -Medical & educational records -PE -Developmental assessment: Mullen scales of early learning—AGS; Wechsler abbreviated scales of intelligence -Adaptive functioning measurement: Vineland-2 adaptive functioning interview; adaptive behavior assessment system—Second Ed -Brain MRI on subsample of *n* = 35	-Speech & language delays most common diagnostic indicator -Common Hx of: Feeding problems, clinodactyly, pes planus, poor dentition, apparent hypertelorism, upslanting palpebral fissures, epicanthal folds, hypotonia, micrognathia, tall stature, limited supination & pronation of forearm, intention tremor -Common parental reports: Sleep cycle disturbance, behavior worsening at 8–9 years, sugar cravings, nail biting, strong interests in computers & vehicles -Comorbidities: Allergies, asthma, congenital heart defects, radioulnar synostosis, inguinal hernia/cryptorchidism, seizures -Common adult medical problems: Hypogonadism, deep vein thrombosis (DVT), intention tremor, type 2 diabetes mellitus -Medications: 63.6% actively using TRT; 56% on other medications: Primarily psychopharmacologic medications for attention span, impulsivity, anxiety, mood instability -MRI: Nonspecific white matter abnormalities & enlarged ventricles -IQ: Range from impaired to average -Adaptive functioning impaired in areas of social skills, self-care, self-direction -Neurodevelopmental comorbidities: ADHD, ASD, mood disorders, tic disorders	-48,XXYY differs from 47,XXY in medical, neurodevelopmental, & behavioral characteristics -48,XXYY individuals: diagnoses are made earlier, characteristic facial features, physical & psychological issues -Need for TRT related to hypergonadotropic hypogonadism -Variability in MRI findings -Higher rate of mood disorders, developmental disorders, ADHD, ASD, psychiatric disorders, as compared to 47,XXY -Variation in severity possibly a result of gene dosage effects in pseudoautosomal regions of X & Y chromosomes that escape X-inactivation; may also be related to possible polymorphisms or alterations in DNA methylation/ epigenetic changes -Children with tremor, learning disabilities, or classic dysmorphic features should undergo karyotyping for SCA -Treatment: Screen for physical and psychosocial comorbidities, need for TRT, fertility options, additional therapies -Limitations: Cohort primarily Caucasian; ascertainment bias

TABLE 3 (Continued)

Authors; year	Article and Journal	Study type and objectives	Subjects	Interventions and measures	Results	Implications and limitations
4. Borghgraef et al., 1991	"The 48,XXYY syndrome. Follow-up data on clinical characteristics and psychological findings in 4 patients" *Genetic Counseling*	Descriptive/observational; case series Objectives: Describe physical & clinical findings in 4 patients with 48,XXYY & review their initial reason for chromosomal analysis; Comparison of current patients to previously reported cases	*n* = 4 males with 48,XXYY Ages: 4–25 years	-Medical Hx -Descriptions of psychiatric features -IQ scores -PE	-Case 1: Hx: Convulsions, omotor delay, behavioral problems; PE: Hyperlaxity of joints, obesity, slender extremities, mild dysmorphic features, hypotonia, severe speech delay, poor memory, concentration difficulties, decreased IQ, aggressive -Case 2: Hx: Motor delay, learning difficulties, behavior problems; PE: Long arms & legs, hypogonadism, small penis, hypoplastic scrotum, delayed bone age, speech deficit, poor memory & concentration, ataxia, shy/timid, volatile mood, low frustration tolerance -Case 3: Hx: Feeding issues after birth, epilepsy, speech delay, behavior problems, mild–moderate intellectual disability (ID), hx of institutionalization; PE: tall, small testes, no dysmorphic features, discrete spasticity of lower extremities, low IQ, violent behavior, lack of structure & self-control, autistic features, communication disorder -Case 4: Hx: Developmental delay, epilepsy, behavioral institutionalization, fugue states, hx of arson; PE: small testes, decreased IQ, behavioral problems, mood lability, sleep disorders, atypical personality disorder	-Indication for chromosomal analysis was presence of behavioral problems & personality disorders -Physical phenotype unremarkable in 4 patients; debate whether physical stigmata is present in 48,XXYY -Similarities among patients: ectomorphic, tall, soft testes, normal secondary sexual development -All patients presented for medical care related to severe behavioral problems -ID, learning disability, speech delay in all reported patients, but of varying degrees -Higher performance vs verbal IQ -48,XXYY males do not present distinct physical stigmata, but show similar psychosocial development issues & behavior problems -Majority have moderate ID & are susceptible to severe psychiatric problems plus highly reduced social integration -Limitations: Ascertainment bias; small sample size

(Continues)

TABLE 3 (Continued)

Authors; year	Article and Journal	Study type and objectives	Subjects	Interventions and measures	Results	Implications and limitations
5. Sørensen et al., 1978	"The 48,XXYY syndrome" *Journal of Mental Deficiency Research*	Descriptive/observational; case series Objectives: Present 6 cases of individuals with 48,XXYY & compare the clinical picture/phenotype with previous cases	*n* = 6 males with XXYY Ages: 10 months–47 years	-PE -Description of psychiatric features -Estimation of incidence rate -Genetic etiology	-Case 1:10 months; Hx of pneumonia; PE: failure to thrive, left kidney aplasia, right kidney dysplastic, slight developmental delay -Case 2:10 years; in psychiatric institution; Hx of developmental delay, learning disabilities, speech delay; PE: nervous, tics, low normal intelligence, concrete thinking, tendency to confabulation, clinodactyly -Case 3:17 years; Hx of cryptorchidism, ID, developmental delay; PE: tall, scanty pubic hair, small penis, low IQ -Case 4:29 years; Hx of ID, small testes; PE: delayed speech, low IQ, violent, abnormal EEG, tall, small testes & penis, scanty pubic hair, clinodactyly -Case 5:33 years; Hx of ID, developmental delays, respiratory infections; institutionalized for ID & larceny; PE: low IQ, tall, dental anomalies, hypogonadism -Case 6:47 years; Hx of ID; institutionalized for larceny; PE: low IQ, small penis & testes	-Incidence likely 1 in 50,000 -High prevalence in males with ID -More likely to display criminal or violent behavior -Etiology: successive or simultaneous nondisjunction during spermatogenesis and/or oogenesis -Common PE findings: hypogonadism, hyalinization of testicular tubuli, tall stature, clinodactyly, ID, psychiatric illnesses, behavior problems, gynecomastia, scanty pubic hair growth, minor skeletal aberrations, alterations in dermatoglyphics -Increased paternal age may be etiological factor -Extra heterochromatic material may impact cell division in the embryo, possibly leading to ID -Limitations: ascertainment bias; small sample size
6. Barr et al., 1964	"The XXYY variant of Klinefelter's syndrome" *Canadian Medical Association Journal*	Descriptive/observational; case series Objectives: Describe clinical features of 3 males with 48,XXYY; understand effects of additional Y chromosome	*n* = 3 males with 48,XXYY Ages: 20–47 years	-Medical hx -IQ -PE	-Case 1:20 years; Hx of talipes equinovarus, developmental delays, low IQ; PE: inguinal hernia, tall, gynecoid body shape & pubic hair, hypogonadism, hyalinzed tubules in testes, elevated FSH, hypothyroidism -Case 2:20 years, Hx of: developmental delays, delayed speech, low IQ; PE: tall, gynecoid pubic hair, sparse axillary & facial hair, high-pitched voice, small testes, elevated FSH, hypothyroidism	-Possible genetic etiology through nondisjunction of both X & Y chromosomes -Common findings: Moderate levels of ID, tall, elevated FSH, connective tissue hyalinization of testicular tubules, eunuchoid body habitus, vascular & cutaneous manifestations -48,XXYY subjects conform to Klinefelter's syndrome but with greater risk of ID

TABLE 3 (Continued)

Authors; year	Article and Journal	Study type and objectives	Subjects	Interventions and measures	Results	Implications and limitations
					-Case 3:47 years, PE: mild ID, narrow chest, tall, scoliosis, varicose veins, android pubic hair distribution, normal axillary & facial hair, small penis & testes, elevated FSH	-Y chromosome likely bears little genetic information -Limitations: Ascertainment bias; small sample size
7. Muldal & Ockey, 1960	"The 'double male': A new chromosome constitution in Klinefelter's syndrome" *The Lancet*	Descriptive/observational; case report; seminal article Objectives: Describe clinical findings of first male identified with 48,XXYY	*n* = 1 male with 48,XXYY Age: 15 years	-Medical hx -PE -Bone marrow biopsy	-"Klinefelter syndrome" appearance: -Normal male appearance, but with gynecomastia -High gonadotropin levels -Intellectual disability	-Genetic origin likely paternal & likely occurs via nondisjunction during meiosis -XXYY constitution is viable -Limitations: Small sample size; case report

mortality from non-Hodgkin lymphoma (Gropman & Samango-Sprouse, 2013; Swerdlow et al., 2005; N. Tartaglia et al., 2011; N. Tartaglia et al., 2008).

4.2 | Psychosocial and behavioral aspects

Psychosocial functioning in 48,XXYY has historically been reported with some degree of intellectual disability and psychosocial/executive functioning issues, as seen in the seminal case study described by Muldal and Ockey in 1960 (Muldal & Ockey, 1960). However, reports have varied widely over time in terms of how severe these issues are, largely due to methodological problems in early studies, such as ascertainment bias, small sample sizes, and pooling of multiple, different SCAs in statistical analyses. The first multi-participant studies of 48,XXYY, such as those conducted in the late 1960s to 1970s, recruited largely from hospitals or penal institutions for those with intellectual disabilities or individuals who had legal transgressions (Burnand, Hunter, & Hoggart, 1967; Casey et al., 1968; Hunter, 1968). Although there was debate on the exact cause and prevalence of the psychosocial problems experienced by individuals with 48,XXYY, early literature of the 1960s by Barr et al., Hunter, and Casey described the condition as one being associated with an increased frequency of behavioral problems in childhood, with the possibility for increased aggressive offenses, such as those against both inanimate objects and individuals (Casey et al., 1968; Hunter, 1968, 1969). The study by Barr et al. also hypothesized that the addition of an extra Y chromosome likely contributed little genetic information, and had only a small role in the abnormal development of individuals with 48,XXYY (Barr et al., 1964). Additional psychosocial findings in individuals with 48,XXYY, described by Sørensen et al. in 1978, included excessive shyness, a tendency towards confabulation of stories, preferring socialization with younger individuals, and occasionally violent or criminal acts (Sorensen et al., 1978). In his 1978 study, Sørensen et al. suggested that among individuals with intellectual disability, there may be a higher prevalence of 48,XXYY than is seen in unselected populations (Sorensen et al., 1978).

Because of the methodological issues of these early studies from the 60s and 70s, especially those related to recruitment from penal or mental institutions, reports in the 1980s and 1990s still promote 48,XXYY as a disorder associated with aggression, criminality, and moderate to severe intellectual disability. While Barr discredited the influence of an additional Y-chromosome on these psychological findings in the 1960s, other studies made the case for an association between variability in the Y chromosome (either in the form of supernumerary Y chromosomes, or variable length on the Y chromosome) and variability in human behavior. In 1980, Dorus reviewed data in which individuals with 47,XYY, 48,XXYY, or those with 46,XY plus variability in the length of the q arm of the Y chromosome were more likely to have aberrant behaviors, including increased aggression, criminality, and behavior/mood disorders (Dorus, 1980). Later observation by Frühmesser and Kotzot suggested that rearrangements of derivative Y chromosomes in a 47,XXY male was possibly associated with a

psychological phenotype similar to that seen in 48,XXYY males, including aggressive behavior, rapid alterations in mood, and immature social skills (Frühmesser & Kotzot, 2011).

Other psychosocial disorders and psychological problems reported from case studies of individuals with 48,XXYY showed consistent, severe behavioral issues, reduced ability to integrate socially, and violent and impulsive reactions (Borghgraef et al., 1991; Fryns et al., 1995; Kleczkowska et al., 1988; Linden et al., 1995; Sorensen et al., 1978). Psychotic reactions and psychotic episodes with loss of structure and self-control were also reported (Borghgraef et al., 1991; Fryns et al., 1995; Kleczkowska et al., 1988; Linden et al., 1995; Sorensen et al., 1978). However, these symptoms were reported from case studies with very small sample sizes or studies that sought individuals in mental or penal institutions, such as those studies by Sørensen et al. in 1978, and later studies in the 1980s and early 1990s by Borghgraef et al. (1991), Fryns et al. (1995), Kleczkowska et al. (1988), Linden et al. (1995), and Sorensen et al. (1978). However, as these early studies describing the psychosocial aspects of 48,XXYY were often affected by issues such as ascertainment bias and small sample sizes, they therefore presented potentially unreliable results.

Specific SCAs have been traditionally presented in the context of comparing one aneuploidy to another, as opposed to being studied and highlighted as their own individualized disorders with unique health concerns. This trend continued to occur throughout the 1990s and early 2000s. When defining affect and psychological health in 48,XXYY, Visootsak et al. in 2006 describe individuals with 48,XXYY as usually shy, but with a temperament that can become aggressive and impulsive, and experiencing higher rates of hyperactivity, aggression, conduct disorders, lower adaptive functioning, and depression, as compared to individuals with 47,XXY (J. Visootsak & Graham, 2006). Later studies, including some conducted by Tartaglia et al. and Visootsak et al., describe similar findings, but with more detailed descriptions and higher rates of maladaptive behaviors, internalizing and externalizing behaviors, Autism Spectrum Disorder (ASD) or ASD-like symptoms, and Attention-Deficit Hyperactivity Disorder (ADHD) as compared to 47,XXY (Nicole R. Tartaglia et al., 2012; N. R. Tartaglia et al., 2017; Visootsak & Graham, 2009). However, some of the most recent studies, such as those done by Tartaglia et al., find individuals with 48,XXYY have higher scores in the areas of daily living skills, socialization, and communication, as compared to other SCA tetrasomies and pentasomies (N. Tartaglia et al., 2011; N. Tartaglia et al., 2008; Nicole R. Tartaglia et al., 2012; N. R. Tartaglia et al., 2017).

Although 48,XXYY continues to be regarded as more severe in terms of cognitive impairment and psychosocial issues than 47,XXY, later evidence suggests that there is a wide spectrum of severity related to psychosocial issues. An updated review of the disorder in 2008 by Tartaglia et al. identifies similar maladaptive behaviors and psychosocial disorders as previously reported, but notes that only half of the individuals in the study were on psychopharmacologic medications, primarily related to attention span issues, anxiety, impulsivity, and mood instability (N. Tartaglia et al., 2008). Of this study population with Tartaglia et al., only one third of the individuals with 48,XXYY required hospitalization at some point for psychiatric reasons (N. Tartaglia et al., 2008). While individuals with 48,XXYY, and individuals with SCAs in general, appear to experience higher rates of certain psychosocial and neurocognitive disorders, such as Attention Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD), it is also evident, in the work by Tartaglia et al. and Cordeiro et al. in the late 2000s, that these psychosocial issues are not necessarily as prevalent or severe as previous literature reported (Cordeiro et al., 2012; N. Tartaglia et al., 2011; Nicole R. Tartaglia et al., 2012; N. R. Tartaglia et al., 2017). Additionally, Tartaglia et al. shows that psychiatric medications can be highly effective for many individuals with 48,XXYY with specific psychiatric symptoms, such as ADHD and mood disorders (N. Tartaglia et al., 2011).

Studies of 48,XXYY in the past 10–15 years have begun to identify detailed and distinct psychosocial findings that are unique to the 48,XXYY SCA, including positive and constructive affective or behavioral characteristics typically seen in these individuals. Cordeiro et al. observe in their 2012 study that there is preservation of skills in a social motivation subscale assessment, indicating a strong desire for and motivation by social interactions, but with deficits in social cognition, communication, and ASD-like mannerisms that make these interactions harder to achieve (Cordeiro et al., 2012). These unique differences in this population highlight the potential for interventions to mitigate ASD-like behaviors that individuals with 48,XXYY can potentially overcome, in light of their interest in connecting with others.

A final challenge in accurately describing the psychosocial and behavioral profile in 48,XXYY is the difficulty in determining whether certain symptoms or behaviors are related to the SCA itself and the presence of extra sex chromosomes, or a different, comorbid psychological or psychosocial disorder not caused by extra sex chromosome genetic material. As Tartaglia et al. note in their most recent 2017 publication, many of the decreased social skills noted in SCAs resemble or are manifestations of true ASD, and some individuals with SCAs are at an increased risk for having true diagnoses of ASD and ADHD (N. R. Tartaglia et al., 2017). However, it is important, but often extremely challenging, to differentiate neurodevelopmental disorders in SCAs, such as language disorders and anxiety, from psychosocial disorders or ASD (N. R. Tartaglia et al., 2017). In addition, men with 48,XXYY, like those with 47,XXY, may struggle with other social issues, such as lack of advanced education and unemployment. They are more frequently undereducated and underemployed, leading to not only socioeconomic difficulties, but also issues related to access to appropriate services, care, and educational or vocational opportunities (S. Close, Sadler, & Grey, 2016; Sharron Close, Talboy, & Fennoy, 2017; N. R. Tartaglia et al., 2017).

4.3 | Neurocognitive and brain function

Similar to the assessment and interpretation of physical and psychosocial functioning, neurocognitive descriptions of 48,XXYY have varied greatly throughout the literature. The neurocognitive aspects that

were described in early studies follow a similar pattern of highlighting primarily negative symptoms of this disorder, although these findings are impacted by the methodological vulnerabilities in this early research, such as small sample size and ascertainment bias. Research across the decades has transformed over time to describe a much more complex understanding of the neurocognitive functioning in 48,XXYY.

Early neurocognitive reports by Muldal and Ockey, Carr, and Barr et al. in the 1960s described 48,XXYY as causing almost universal intellectual disability, with average IQ in the moderately developmentally disabled range (Barr et al., 1964; Carr et al., 1961; Muldal & Ockey, 1960). Casey et al. and Hunter recruited from state hospitals for those with intellectual disability, and proposed the correlation that individuals with 48,XXYY who show intellectual disability often require hospitalization or institutionalization (Casey et al., 1968; Hunter, 1968). This correlation of a high risk of intellectual disability, criminal offenses, institutionalization, and 48,XXYY syndrome continued to be perpetuated in the literature by Sørensen et al., Dorus, and Kleczkowska throughout the 1970s and 1980s (Dorus, 1980; Kleczkowska et al., 1988; Sorensen et al., 1978). These early studies indicate that there is variability in the severity of intellectual disability, but that the majority of individuals are affected to some degree, with some studies listing 100% of individuals as having intellectual disability (Kleczkowska et al., 1988). However, the majority of participants from these studies or syntheses were again recruited from penal institutions and mental institutions specifically intended for those with intellectual disability, which introduces the possibility of misinterpretation of results due to sampling errors.

Literature in the 1990s related to intellectual and neurocognitive functioning in 48,XXYY begins to show some disagreement in the severity associated with the disorder. In terms of intelligence, Linden et al. and Borghgraef et al. report only mild intellectual disabilities in the 48,XXYY population (Borghgraef et al., 1991; Linden et al., 1995). Linden et al. also report neurocognitive features with varying presence and spectrum of severity, including motor and speech delays, with higher receptive skills vs. expressive skills (Linden et al., 1995). However, in 1995, Fryns et al. associates 48,XXYY with mild to moderate intellectual disability and high rates of neurocognitive issues, such as speech difficulty with dysarthia, dysphrasia, dyslexia, and delays in comprehension language (Fryns et al., 1995). Fryns et al. also hypothesize that the risk for intellectual disability (ID) and physical defects increases with the number of extra X-chromosomes, and only in second order with extra Y-chromosomes. The authors proposed that the presence of extra Y-chromosomes appeared to be more related to behavioral problems (Fryns et al., 1995). For example, individuals with 47,XYY, or a pure Y-chromosome polysomy only, were reported to have a different cognitive and behavioral profile than individuals with 48,XXYY. Fryns et al. reported that 28.3% of individuals with 47,XYY demonstrated ID with an idiopathic origin, with the majority displaying borderline normal intelligence to mild ID (Fryns et al., 1995). Of the individuals with 47,XYY who also had ID, 86% also displayed behavioral issues and difficulties in psychosocial functioning. Comparatively, in individuals with both X and Y chromosome polysomies, 80% demonstrated mild to moderate ID. Of the individuals with both X and Y chromosome polysomies who also had ID, 91.7% also displayed severe behavioral and psychiatric problems (Fryns et al., 1995).

Studies conducted in the 2000s describe some similar findings alongside some improved information related to intellectual functioning. Visootsak et al. report average full scale IQ in the 60–80 range, indicative of a range between mild intellectual disability to low-normal intelligence, but lower than that seen in 47,XXY (J. Visootsak & Graham, 2006). Visootsak et al. also find significantly lower verbal IQ as compared to performance IQ in this population (J. Visootsak & Graham, 2006). Reports of delayed speech were also included, and the authors note that individuals with 48,XXYY may be at risk for academic, behavioral, and social deficits (J. Visootsak & Graham, 2006). In 2008, Tartaglia et al. show that individuals with 48,XXYY struggle more with language based tasks, but they have strengths in visuoperceptual skills (N. Tartaglia et al., 2008). Additionally, adaptive functioning scores are also significantly decreased in this population, especially in areas related to communication, social skills, self-care, and self-direction (N. Tartaglia et al., 2008). These neurocognitive symptoms may increase the risk for academic and social deficits in these individuals. Neurocognitive reports by Tartaglia et al. also describe issues such as sensory processing/integration disorders, tic disorders, speech apraxia, and auditory processing disorders (N. Tartaglia et al., 2008).

The years including 2010 and beyond confirm much of the previous literature related to neurocognitive functioning in 48,XXYY, but they highlight the wide spectrum of variability seen in this population. Although Frühmesser and Kotzot still view 48,XXYY as a variant of 47,XXY, the authors mention that recent studies have reported learning disabilities and cognitive delays that are not nearly as severe as previously reported in the early literature (Frühmesser & Kotzot, 2011). In the past 10 years, Tartaglia et al. and Gropman and Samango-Sprouse have also noted that there appears to be a much larger spectrum of cognitive abilities in all SCAs, whereas in previous studies, virtually all were considered intellectually disabled (Gropman & Samango-Sprouse, 2013; N. Tartaglia et al., 2011). In 2013, Gropman and Samango-Sprouse emphasize the variability in cognitive functioning and strengths in visuoperceptual skills, as compared to language based tasks, but again acknowledged the continual history of ascertainment bias in this population (Gropman & Samango-Sprouse, 2013).

Finally, research on neurological anatomy in individuals with SCAs incorporated new evidence from neuroimaging studies beginning in the 2000s. Magnetic Resonance Imaging (MRI) studies had first been conducted on individuals with 47,XXY in the 1990s, and they slowly began to include the other SCAs in subsequent years. In 2009, the first literature review of neuroimaging studies of individuals with SCAs was published by Lenroot et al. to better understand how sex chromosome dosage may affect brain structure and activity. The majority of extant literature on neuroanatomy in SCAs since the 1990s focuses primarily on 47,XXY and also includes smaller samples of other SCAs, such as 47,XXX, 47,XYY, and 48,XXYY. Neuroimaging

case studies on 48,XXYY have shown nonspecific white matter abnormalities including white matter hyperintensities, frontoparietal cortical atrophy, enlarged ventricles, agenesis of the corpus callosum, corpus callosum lipoma, cortical dysplasia, and rarely, pituitary adenoma (Lenroot et al., 2009). Evidence from Wade et al. in 2014 supports these white matter variations in individuals with 48,XXYY, especially as related to differences in the morphometry of the corpus callosum (Wade et al., 2014). In addition, Wade et al. showed an overall increase in between-landmark distances in the corpus callosum of individuals with 48,XXYY, as compared to controls, theorizing that X and Y linked genes have differential effects on corpus callosum morphometry (Wade et al., 2014). Hanley et al. in 2015 demonstrated types of atypical brain development in individuals with 48,XXYY, including smaller total brain volume, abnormalities in both gray and white matter, such as white matter lesions, and abnormalities of the ventricular system (Hanley et al., 2015). These changes in brain structure may relate to the cognitive strengths in visual-spacial skills and relative weakness in verbal skills (Hanley et al., 2015). Additional studies report variations in anatomical brain regions and patterns, including subcortical size and shape that appear to be affected by X and Y chromosome dosage. In 2016, Reardon et al. discovered that pallidal volume of the basal ganglia is reduced in size in individuals with SCAs compared to controls, even when reductions of overall decreased total brain volume is taken into consideration (Reardon et al., 2016).

Despite these changes in certain areas of brain structure and the associated potential function, there appear to be areas of the brain that are not impacted by sex chromosome dosage and are similar between individuals with SCAs and controls. Both Lin et al. in 2015 and Fish et al. in 2017 have demonstrated that factors such as cortical asymmetry and cortical folding appear to be spared from significant changes in many individuals with SCAs (Fish et al., 2017; Lin et al., 2015). Both of these studies claim that X and Y chromosome dosage may exert focal changes and modifications in overall brain size in individuals with SCAs, but that global changes of early brain patterning, like cortical folding and asymmetry, are unaffected by sex chromosome dosage (Fish et al., 2017; Lin et al., 2015).

5 | DISCUSSION

Since the 1960s, there have only been 30 multi-participant case studies, observational studies, or syntheses published on the SCA 48,XXYY. The results from more than 50 years have expanded the description of the 48,XXYY phenotype, including physical, psychological, and neurocognitive aspects of the aneuploidy. These findings have led to the conclusion that 48,XXYY is a distinct disorder and not simply a variation of 47,XXY, or Klinefelter's Syndrome (N. Tartaglia et al., 2011). Research has shown unique physiological characteristics and neuroanatomical changes that are exclusive to this population.

The seminal case study of an individual with 48,XXYY by Muldal and Ockey in 1960 provided a brief description of a teenage boy with moderate intellectual disability, endocrine dysregulation, and some physical similarities to 47,XXY (Muldal & Ockey, 1960). This case study introduced 48,XXYY as a viable genetic aberration and suggested that other variations of sex chromosome aneuploidies may exist as well. This description evolved over time into more precise and intricate descriptions now seen in men with SCAs who exhibit wide ranges of physical, psychosocial, and neurocognitive function. Although there are common underlying genetic mechanisms for this disorder, such as nondisjunction meiotic errors in a gamete, or less frequently, postzygotic nondisjunction of an embryo, the spectrum and variability in both symptom and severity has been largely unexplained (Hager et al., 2012; Muldal & Ockey, 1960; N. Tartaglia et al., 2008).

The endocrinological, psychosocial, and neuroanatomical changes present in individuals with SCAs highlights the contribution of sex chromosomes to aspects of function and behavior. Although evidence demonstrates neuroanatomical changes in individuals with 48,XXYY, more research will be required to determine the exact mechanism of formation of these anomalies and how the anomalies are related to clinical presentation. Variability in every SCA presentation suggest that sex chromosome dosage and changes in X-inactivation likely have roles in why individuals with SCAs present with such wide variety and severity of symptoms. Findings such as these present a call to consider other neuroanatomical or genetic studies that might inform or explain the variability that we see in this population. Gropman and Samango-Sprouse specifically call for future research pathways related to gene dosage effects, skewed X-inactivation, or epigenetic modifiers that may play a part in the wide spectrum of severity seen in individuals with SCAs (Gropman & Samango-Sprouse, 2013).

Future neuroanatomical or genetic studies may contribute to deeper understandings about phenotypic and psychosocial deficits found to be common in this population. A small number of studies over the years have provided a glimpse of what the authors characterize as a typical phenotype presentation of 48,XXYY, with descriptions of characteristic symptoms. It is noted, however, that few symptoms are present 100% of the time and may not be characteristic of all cases. Symptoms of anxiety, depression, tremors, sleep issues, and food cravings are mentioned intermittently throughout the literature. In addition, individuals with SCAs often report fatigue, pain, role limitations, difficulty with treatment, and specific physical and neurocognitive vulnerabilities that affect their daily lives and overall quality of life. Complexity of clinical findings is variable from case to case and little research thus far has examined symptoms, health care challenges, and quality of life in these patients.

The most recent literature reviews that include 48,XXYY, published within the past 5–10 years, have integrated all of the previously known data on SCA tetrasomies and pentasomies, and they are now focused on suggestions for clinical management, care, and recommended future research pathways. Multidisciplinary health care for children with SCAs has been recommended by several clinical research groups, including Sharron Close et al. (2017), Gropman and Samango-Sprouse (2013), and N. Tartaglia et al. (2015). According to the clinical model of health care by Tartaglia et al., detailed management of children with SCA includes developmental-behavioral pediatrics, child psychology, pediatric neuropsychology, speech and

language therapy, physical therapy, occupational therapy, endocrinology, nursing, and educational services (N. Tartaglia et al., 2015). This complex model of care is recommended for all SCAs to be customized according to type of SCA and patient or family need. Since phenotypes are so variable, it is not possible to recommend a uniform targeted plan of care according to the type of SCA. Thus far, a model of care for adults with SCA has yet to be developed. In the United States, under the auspices of the Association for X & Y Chromosome Variations (AXYS), a Clinical and Research Consortium (ACRC) was formed to guide the development and implementation of multidisciplinary clinics.

To date, there is a lack of clinical guidelines for 48,XXYY with tested efficacies and treatment protocols for this population. Without a meaningful body of evidence to support the development of clinical guidelines, health care providers are unable to provide systematic effective care for all the SCAs, including 48,XXYY. Future research may address these issues by conducting studies utilizing experimental and randomized control trial designs. Future studies utilizing these methodological techniques would allow for stronger evidence-based practice recommendations for treatment and care in this population.

The vast majority of past literature on 48,XXYY is found in case reports and case series reported from clinicians and researchers. The body of literature associated with 48,XXYY currently has limited patient report surveys or participant interviews. Additionally, few studies utilize patient-centered qualitative methodologies to explore concerns from affected individuals. The absence of the patient and family voice in many of the publications renders it less likely to learn from the patient what they need and what their main concerns are. Future research should continue to explore how this condition affects individuals, families, and quality of life. Interventions are needed not only to address physical and psychosocial health concerns, but also to contribute to the establishment of new standards of care that are meaningful to patients.

5.1 | Limitations

This integrative literature review shows methodological limitations. With regards to methodology, the researchers excluded studies with less than four participants and any abstracts or conference proceedings. As 48,XXYY is a rare disorder, many of the study sample sizes are relatively small. Not including studies with a sample size of less than four may have resulted in studies with fewer participants being missed in the integrative review. However, limiting inclusion to only studies with at least four participants increases the likelihood of any generalizability among findings. In addition, the review did not include abstracts, presentations, or conference proceedings in the final review. This was done to allow the authors to perform a thorough assessment of each study. However, it may have resulted in certain information or topics being excluded that could potentially influence the overall body of knowledge related to 48,XXYY.

Finally, although literature reviews typically contain evaluations on levels of evidence (LOEs) for the inclusion of studies, this literature review did not appraise LOEs for study inclusion. Because the preponderance of studies on 48,XXYY are observational or descriptive, assessing levels of evidence is not appropriate, given the nature and aims of descriptive studies. The literature on 48,XXYY, and on the majority of SCAs, lacks experimental effectiveness, diagnostic, or prognostic studies that can be subject to LOE appraisal. Because of this, there is an inherently large gap in the literature related to interventional studies that support evidence-based practice for this population, an area that would benefit greatly from future research endeavors.

6 | CONCLUSIONS

48,XXYY is a rare genetic disorder affecting approximately 1 in 18,000 males. It presents with a wide variety of physical, psychosocial, and neurocognitive findings. Since the first description of the disorder in 1960, there has been a limited amount of research that has developed the understanding of this complex disorder. The majority of the literature is currently focused on physiologic and psychologic descriptions of the 48,XXYY phenotype. The wide spectrum of symptom variability is theorized to be related to sex chromosome dosage and skewed X-inactivation, but research is still needed to further understand these underlying genetic variations and their connection to clinical signs and symptoms in patients.

Current knowledge about 48,XXYY is based on primarily clinical opinion and low levels of evidence to support management of patient issues. Lack of evidence-based studies to support standards of care or efficacies of treatment for this population contributes to poor health outcomes in this population. The majority of literature, thus far, has lacked reports of patient-identified concerns and personal needs and preferences of those with 48,XXYY. There are also limited studies involving family members or caregivers. Future research addressing these issues through the use of qualitative and mixed-methodologies may provide better understanding on the quality of life and standardized care for individuals with 48,XXYY.

ACKNOWLEDGMENTS

This research was funded in part by the Association for X and Y Chromosome Variations (AXYS), The XXYY Project, The Ryan Scovell Memorial XXYY Research Fund, and Emory University Laney Graduate School Professional Development Support Funds.

ORCID

Amy A. Blumling https://orcid.org/0000-0002-6632-4150

REFERENCES

Atik, T., Cogulu, O., & Ozkinay, F. (2016). A rare sex chromosome aneuploidy: 48,XXYY syndrome. *Turk Pediatri Arsivi-Turkish Archives of Pediatrics*, *51*(2), 106–109. https://doi.org/10.5152/TurkPediatriArs.2016.1551

Barr, M. L., Carr, D. H., Soltan, H. C., Wiens, R. G., & Plunkett, E. R. (1964). The XXYY variant of Klinefelter's syndrome. *Canadian Medical Association Journal*, *90*, 575–580.

Bojesen, A., Juul, S., & Gravholt, C. H. (2003). Prenatal and postnatal prevalence of Klinefelter syndrome: A national registry study. *The Journal of Clinical Endocrinology and Metabolism*, *88*(2), 622–626. https://doi.org/10.1210/jc.2002-021491

Borghgraef, M., Fryns, J. P., & Van Den Berghe, H. (1991). The 48,XXYY syndrome. Follow-up data on clinical characteristics and psychological findings in 4 patients. *Genetic Counseling*, *2*(2), 103–108.

Burnand, G., Hunter, H., & Hoggart, K. (1967). Some psychological test characteristics of Klinefelter's syndrome. *The British Journal of Psychiatry*, *113*(503), 1091–1096.

Carr, D. H. (1963). Chromosomal abnormalities and their relation to disease. *Canadian Medical Association journal*, *88*(9), 456.

Carr, D. H., Barr, M. L., & Plunkett, E. R. (1961). A probable XXYY sex determining mechanism in a mentally defective male with Klinefelter's syndrome. *Canadian Medical Association Journal*, *84*, 873–878.

Casey, M. D., Street, D. R., Segall, L. J., & Blank, C. E. (1968). Patients with sex chromatin abnormality in two state hospitals. *Annals of Human Genetics*, *32*(1), 53–63. https://doi.org/10.1111/j.1469-1809.1968.tb00049.x

Close, S., Sadler, L., & Grey, M. (2016). In the dark: Challenges of caring for sons with Klinefelter syndrome. *Journal of Pediatric Nursing*, *31*(1), 11–20. https://doi.org/10.1016/j.pedn.2015.05.002

Close, S., Talboy, A., & Fennoy, I. (2017). Complexities of care in Klinefelter syndrome: An APRN perspective. *Pediatric Endocrinology Reviews: PER*, *14*(Suppl. 2), 462–471.

Coffee, B., Keith, K., Albizua, I., Malone, T., Mowrey, J., Sherman, S. L., & Warren, S. T. (2009). Incidence of fragile X syndrome by newborn screening for methylated FMR1 DNA. *The American Journal of Human Genetics*, *85*(4), 503–514.

Cordeiro, L., Tartaglia, N., Roeltgen, D., & Ross, J. (2012). Social deficits in male children and adolescents with sex chromosome aneuploidy: A comparison of XXY, XYY, and XXYY syndromes. *Research in Developmental Disabilities*, *33*(4), 1254–1263. https://doi.org/10.1016/j.ridd.2012.02.013

Dorus, E. (1980). Variability in the Y chromosome and variability of human behavior. *Archives of General Psychiatry*, *37*(5), 587–594.

Evans, J., Greenberg, C., Ramsay, S., & Hamerton, J. (1982). A cytogenetic survey of 14,069 newborn infants. IV. Further follow-up on the children with sex chromosome anomalies. *Birth Defects Original Article Series*, *18*(4), 169–184.

Fish, A. M., Cachia, A., Fischer, C., Mankiw, C., Reardon, P. K., Clasen, L. S., … Raznahan, A. (2017). Influences of brain size, sex, and sex chromosome complement on the architecture of human cortical folding. *Cerebral Cortex*, *27*(12), 5557–5567. https://doi.org/10.1093/cercor/bhw323

Frühmesser, A., & Kotzot, D. (2011). Chromosomal variants in klinefelter syndrome. *Sexual Development*, *5*(3), 109–123. https://doi.org/10.1159/000327324

Fryns, J. P., Kleczkowska, A., Kubień, E., & Van den Berghe, H. (1995). XYY syndrome and other Y chromosome polysomies. Mental status and psychosocial functioning. *Genetic Counseling*, *6*(3), 197–206.

Gropman, A., & Samango-Sprouse, C. A. (2013). Neurocognitive variance and neurological underpinnings of the X and Y chromosomal variations. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *163C*(1), 35–43. https://doi.org/10.1002/ajmg.c.31352

Hager, K., Jennings, K., Hosono, S., Howell, S., Gruen, J. R., Rivkees, S. A., … Rinder, H. M. (2012). Molecular diagnostic testing for Klinefelter syndrome and other male sex chromosome aneuploidies. *International Journal of Pediatric Endocrinology*, *2012*(1), 8. https://doi.org/10.1186/1687-9856-2012-8

Hanley, A. P., Blumenthal, J. D., Lee, N. R., Baker, E. H., Clasen, L. S., & Giedd, J. N. (2015). Brain and behavior in 48, XXYY syndrome. *Neuroimage-Clinical*, *8*, 133–139. https://doi.org/10.1016/j.nicl.2015.04.009

Herlihy, A. S., Halliday, J. L., Cock, M. L., & McLachlan, R. I. (2011). The prevalence and diagnosis rates of Klinefelter syndrome: An Australian comparison. *The Medical Journal of Australia*, *194*(1), 24–28.

Hunter, H. (1968). Kleinfelter's syndrome and delinquency. *British Journal of Criminology*, *8*(2), 203–207. https://doi.org/10.1093/oxfordjournals.bjc.a049127

Hunter, H. (1969). A controlled study of the psychopathology and physical measurements of Klinefelter's syndrome. *The British Journal of Psychiatry*, *115*(521), 443–448. https://doi.org/10.1192/bjp.115.521.443

Kleczkowska, A., Fryns, J. P., & Van den Berghe, H. (1988). X-chromosome polysomy in the male. The Leuven experience 1966-1987. *Human Genetics*, *80*(1), 16–22.

Lenroot, R. K., Lee, N. R., & Giedd, J. N. (2009). Effects of sex chromosome aneuploidies on brain development: Evidence from neuroimaging studies. *Developmental Disabilities Research Reviews*, *15*(4), 318–327. https://doi.org/10.1002/ddrr.86

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., … Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *The BMJ*, *339*, b2700. https://doi.org/10.1136/bmj.b2700

Lin, A., Clasen, L., Lee, N. R., Wallace, G. L., Lalonde, F., Blumenthal, J., … Raznahan, A. (2015). Mapping the stability of human brain asymmetry across five sex-chromosome aneuploidies. *The Journal of Neuroscience*, *35*(1), 140–145. https://doi.org/10.1523/JNEUROSCI.3489-14.2015

Linden, M. G., Bender, B. G., & Robinson, A. (1995). Sex chromosome tetrasomy and pentasomy. *Pediatrics*, *96*(4 Pt 1), 672–682.

Liu, D. F., Zhao, L. M., Hong, K., Mao, J. M., Yang, Y. Z., Zhang, Z., & Jiang, H. (2018). Fertility achieved through in vitro fertilization in a male patient with 48,XXYY syndrome. *Asian Journal of Andrology*, *20*(2), 208–209. https://doi.org/10.4103/aja.aja_44_17

Lote, H., Fuller, G. N., & Bain, P. G. (2013). 48, XXYY syndrome associated tremor. *Practical Neurology*, *13*(4), 249–253. https://doi.org/10.1136/practneurol-2012-000438

Muldal, S., & Ockey, C. H. (1960). The "double male": A new chromosome constitution in Klinefelter's syndrome. *The Lancet*, *276*(7148), 492–493. https://doi.org/10.1016/S0140-6736(60)91624-X

Nielsen, J., & Wohlert, M. (1991). Chromosome abnormalities found among 34,910 newborn children: Results from a 13-year incidence study in Arhus, Denmark. *Human Genetics*, *87*(1), 81–83.

Ottesen, A. M., Aksglaede, L., Garn, I., Tartaglia, N., Tassone, F., Gravholt, C. H., … Juul, A. (2010). Increased number of sex chromosomes affects height in a nonlinear fashion: A study of 305 patients with sex chromosome aneuploidy. *American Journal of Medical Genetics, Part A*, *152*(5), 1206–1212. https://doi.org/10.1002/ajmg.a.33334

Reardon, P. K., Clasen, L., Giedd, J. N., Blumenthal, J., Lerch, J. P., Chakravarty, M. M., & Raznahan, A. (2016). An allometric analysis of sex and sex chromosome dosage effects on subcortical anatomy in humans. *The Journal of Neuroscience*, *36*(8), 2438–2448. https://doi.org/10.1523/JNEUROSCI.3195-15.2016

Robinson, A., Bender, B., Linden, M., & Salbenblatt, J. (1990). Sex chromosome aneuploidy: The Denver prospective study. *Birth Defects Original Article Series*, *26*(4), 59–115.

Roche, C., Sonigo, C., Benmiloud-Tandjaoui, N., Boujenah, J., Benzacken, B., Poncelet, C., & Hugues, J. N. (2014). 48,XXYY men with azoospermia: How to manage infertility? *Gynecologie Obstetrique et Fertilite*, *42*(7–8), 528–532. https://doi.org/10.1016/j.gyobfe.2014.05.009

Rovet, J., Netley, C., Bailey, J., Keenan, M., & Stewart, D. (1995). Intelligence and achievement in children with extra X aneuploidy: a longitudinal perspective. *American journal of medical genetics*, *60*(5), 356–363.

Sorensen, K., Nielsen, J., Jacobsen, P., & Rolle, T. (1978). 48,XXYY syndrome. *Journal of Mental Deficiency Research*, *22*, 197–205.

Sørensen, K., Nielsen, J., Jacobsen, P., & Rølle, T. (1978). The 48,XXYY syndrome. *Journal of Mental Deficiency Research*, *22*(3), 197–205.

Swerdlow, A. J., Schoemaker, M. J., Higgins, C. D., Wright, A. F., Jacobs, P. A., & Group, U. C. C. (2005). Cancer incidence and mortality in men with Klinefelter syndrome: A cohort study. *Journal of the*

National Cancer Institute, *97*(16), 1204–1210. https://doi.org/10.1093/jnci/dji240

Tartaglia, N., Ayari, N., Howell, S., D'Epagnier, C., & Zeitler, P. (2011). 48,XXYY, 48,XXXY and 49,XXXXY syndromes: Not just variants of Klinefelter syndrome. *Acta Paediatrica, International Journal of Paediatrics*, *100*(6), 851–860. https://doi.org/10.1111/j.1651-2227.2011.02235.x

Tartaglia, N., Borodyanskya, M., & Hall, D. A. (2009). Tremor in 48,XXYY syndrome. *Movement Disorders*, *24*(13), 2001–2007. https://doi.org/10.1002/mds.22700

Tartaglia, N., Davis, S., Hench, A., Nimishakavi, S., Beauregard, R., Reynolds, A., … Hagerman, R. (2008). A new look at XXYY syndrome: Medical and psychological features. *American Journal of Medical Genetics, Part A*, *146*(12), 1509–1522. https://doi.org/10.1002/ajmg.a.32366

Tartaglia, N., Howell, S., Wilson, R., Janusz, J., Boada, R., Martin, S., … Zeitler, P. (2015). The eXtraordinarY kids clinic: An interdisciplinary model of care for children and adolescents with sex chromosome aneuploidy. *Journal of Multidisciplinary Healthcare*, *8*, 323–334. https://doi.org/10.2147/JMDH.S80242

Tartaglia, N. R., Ayari, N., Hutaff-Lee, C., & Boada, R. (2012). Attention-deficit hyperactivity disorder symptoms in children and adolescents with sex chromosome aneuploidy: XXY, XXX, XYY, and XXYY. *Journal of Developmental and Behavioral Pediatrics*, *33*(4), 309–318. https://doi.org/10.1097/DBP.0b013e31824501c8

Tartaglia, N. R., Wilson, R., Miller, J. S., Rafalko, J., Cordeiro, L., Davis, S., … Ross, J. (2017). Autism Spectrum disorder in males with sex chromosome aneuploidy: XXY/Klinefelter syndrome, XYY, and XXYY. *Journal of Developmental and Behavioral Pediatrics*, *38*(3), 197–207. https://doi.org/10.1097/DBP.0000000000000429

Visootsak, J., & Graham, J. M. (2006). Klinefelter syndrome and other sex chromosomal aneuploidies. *Orphanet Journal of Rare Diseases*, *1*, 42. https://doi.org/10.1186/1750-1172-1-42

Visootsak, J., & Graham, J. M. (2009). Social function in multiple X and Y chromosome disorders: XXY, XYY, XXYY, XXXY. *Developmental Disabilities Research Reviews*, *15*(4), 328–332. https://doi.org/10.1002/ddrr.76

Visootsak, J., Rosner, B., Dykens, E., Tartaglia, N., & Graham, J. M. (2007). Behavioral phenotype of sex chromosome aneuploidies: 48,XXYY, 48,XXXY, and 49,XXXXY. *American Journal of Medical Genetics Part A*, *143A*(11), 1198–1203. https://doi.org/10.1002/ajmg.a.31746

Wade, B. S., Joshi, S. H., Reuter, M., Blumenthal, J. D., Toga, A. W., Thompson, P. M., & Giedd, J. N. (2014). Effects of sex chromosome dosage on corpus callosum morphology in supernumerary sex chromosome aneuploidies. *Biology of Sex Differences*, *5*, 16. https://doi.org/10.1186/s13293-014-0016-4

Whittemore, R., & Knafl, K. (2005). The integrative review: Updated methodology. *Journal of Advanced Nursing*, *52*(5), 546–553.

Wright, M. O., & Lauder, I. J. (1974). Motor nerve conduction in 47, XXY and 48, XXYY males, and 47, XXX and 45, X females. *Clinical Genetics*, *6*(3), 205–215.

How to cite this article: Blumling AA, Martyn K, Talboy A, Close S. Rare sex chromosome variation 48,XXYY: An integrative review. *Am J Med Genet Part C*. 2020;184C: 386–403. https://doi.org/10.1002/ajmg.c.31789