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Beyond the Extra X and Y Chromosome: The Contribution of Familial Risk for Psychopathology to the Neurodevelopmental Phenotype of Children With Sex Chromosome Trisomy

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ABSTRACT

Individuals with an extra X or Y chromosome (sex chromosome trisomy or SCT) have an increased risk for symptoms of psychopathology and neurocognitive dysfunction. In this study, we evaluated the contribution of family history (FH) of neuropsychiatric or neurocognitive disorders to the phenotype of SCT. One hundred and six children with SCT and 102 nonclinical controls, all aged 1–7 years, and their primary caregiver (parent) participated. Rates of neuropsychiatric and neurocognitive disorders were collected for all first-degree family members of the children. Neurocognitive tests and parental questionnaires were used to evaluate children's neurobehavioral and neurocognitive phenotypes. Results showed no systematic differences in FH of neuropsychiatric and neurocognitive disorders between the SCT and control groups. No significant effect of a FH of psychiatric disorders was found on any of the child outcomes. FH of neurocognitive disorders had a single significant effect on child outcomes. Inattention problems in SCT were higher with a positive FH of neurocognitive disorders, showing dosage response effects. Familial factors may only minimally contribute to the overall phenotype of SCT on group level, although a positive FH of neurocognitive disorders may contribute to ADHD inattention symptoms in children with SCT, beyond the risk associated with the extra X or Y chromosome.

1 | Introduction

Sex chromosome trisomy (SCT) refers to a group of genetic conditions characterized by the presence of an additional sex chromosome (X or Y) beyond the typical XX or XY configuration. Estimated prevalence of SCT is about 1 in 650 live births (Bojesen et al. 2003). These conditions, Klinefelter syndrome (47, XXY), Triple X syndrome (47, XXX), and 47, XYY, have gained significant interest in the field of developmental psychology and genetics. Since SCT is associated with increased risk for psychopathology and neurocognitive dysfunction, it is relevant to understand the relative contribution of other genetic and contextual variance, such as familial risk. This research article aims to investigate the potential influence of familial risk for psychopathology on the neurodevelopmental phenotype associated with SCT.

Existing literature has consistently shown that individuals with SCT have an increased risk for neurobehavioral symptoms and risk for psychopathology, including autism spectrum

disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), anxiety, depression, as well as bipolar and psychotic disorders (Bojesen et al. 2006; van Rijn 2019). Additionally, SCT has been associated with a higher prevalence of learning, intellectual, and language disorders (Boada et al. 2009) and associated neurocognitive impairments (Leggett et al. 2010; van Rijn 2019; van Rijn et al. 2023). Neurobehavioral symptoms and cognitive vulnerabilities in SCT appear to be present already from an early age onwards, but may become more pronounced in later stages of development, and may also present as subdiagnostic symptoms or milder forms of psychopathology (Bonomi et al. 2017; Gravholt et al. 2018; van Rijn et al. 2023). These findings highlight the importance of studying SCT, as it has significant implications for individuals' mental health and overall well-being for which timely diagnosis is needed.

Over the past years, research has emphasized the variability of the phenotypic profile observed in individuals with SCT (Bonomi et al. 2017; Samango Sprouse et al. 2018). Despite a common chromosomal anomaly, individuals with SCT can exhibit a wide range of features, with varying severity, and may differ substantially in terms of physical, cognitive, and psychosocial outcomes. This heterogeneity suggests that multiple factors contribute to the expression of SCT-related traits, including genetic, epigenetic, hormonal, and environmental influences (Bonomi et al. 2017). Understanding the variability is important for advancing our knowledge of SCT, which is fundamental to improving healthcare through developing early and targeted diagnostic screening and (preventive) interventions.

To better understand factors contributing to the heterogenous neurodevelopmental profile of SCT, familial risk may be of interest. Familial risk refers to an increased susceptibility to psychopathology and neurocognitive disorders based on the presence of affected individuals within families. It includes both genetic heritability, which involves the transmission of genetic variations across generations, and shared contextual influences, which encompass environmental factors common to family members.

Although research on the contribution of familial risk in SCT is limited, familial risk has been extensively studied in the context of psychiatric disorders listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (A.P.A. 2013). Studies have consistently documented a heritability component to most of these disorders, with higher incidence rates observed among first-degree family members of individuals affected by them (Sullivan et al. 2012). For example, familial aggregation studies have demonstrated higher rates of mood disorders (Kendall et al. 2021), anxiety disorders (Hettema et al. 2001), bipolar disorder and schizophrenia (Lichtenstein et al. 2009; Smoller and Finn 2003), ADHD (Faraone and Larsson 2019), aggression (Beaver et al. 2008; Tuvblad and Baker 2011), and ASDs (Thapar and Rutter 2021) in relatives of affected individuals.

Similarly, investigations into learning, intellectual, and language disorders, explicitly reflecting neurocognitive developmental impact, have also identified a heritability component. Intellectual ability, defined as the general global capacity of intellectual functioning, associated with the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly, and learn from experience, is considered to be driven by genetics for a substantial part, with genetic loading increasing over the life span (Deary et al. 2022; Plomin and Von Stumm 2018). Twin studies, which compare the concordance rates between monozygotic and dizygotic twins, have consistently demonstrated a higher concordance rate for learning, intellectual, and language disorders among monozygotic twins, indicating a significant genetic influence, with family studies showing a higher prevalence of these disorders among close relatives of affected individuals, further supporting the role of familial factors (Bishop 2006; Erbeli et al. 2021; Pennington and Bishop 2009).

Given these findings, it is plausible and even likely that a positive family history (FH) of neuropsychiatric or neurocognitive disorders may contribute to the neurodevelopmental profile of SCT, in addition to the risk associated with the extra X or Y chromosome. It may represent one of many factors that potentially shape the phenotypic expression of SCT-related traits and help explain variability in neurobehavioral outcomes. Therefore, it is essential to explore the extent to which the neurobehavioral profile of SCT is influenced by familial factors in children with an extra X or Y chromosome.

The familial component of neurobehavioral and neurocognitive impairments in SCT has not been well investigated. Three earlier studies have investigated the impact of FH in SCT. All was focused on a FH of language-based learning disabilities and/or dyslexia in relation to speech/language/motor skills (Samango-Sprouse et al. 2014), reading (Brooks et al. 2023), and behavioral problems (Samango-Sprouse et al. 2013) in boys with 47, XXY. These studies suggest that familial risk for language/dyslexia may play a role in the phenotype of children with SCT and have contributed significantly to the idea that we should look for relevant background familial risk factors beyond the extra X or Y chromosome.

It is important to address such familial background factors and expand our knowledge by (1) focusing on the comparison of clinical groups with nonclinical groups, (2) investigating the broader context of familial risk including a range of psychiatric and neurocognitive disorders, and (3) focusing on a broader range of childhood outcomes in terms of neurobehavioral problems and overall intellectual functioning. As the impact of familial risk may depend on the type of psychiatric condition or intellectual impairment, it is important to be able to also investigate specific areas of impact. To provide in all this, the current study had two aims. First, to examine the rates of psychiatric classifications, as well as classifications of neurocognitive disorders (learning, intellectual, and language disorders), in first-degree relatives of children with SCT as compared to a general population sample. By comparing the rates of these disorders in relatives, we can gain insights into the potential contribution of familial factors to the reported increased prevalence observed in individuals with SCT. Second, this study aims to investigate whether the presence of symptoms of psychopathology and neurocognitive dysfunctions in children with SCT vary depending on the presence or absence of a FH of psychiatric or neurocognitive disorders in their first-degree relatives.

By exploring the role of familial factors in the neurobehavioral and neurocognitive phenotype of SCT, this research aims to enhance our understanding of the etiology and mechanisms underlying neurodevelopmental risk in SCT. If increased rates of familial risk for neuropsychiatric and/or neurocognitive disorders may in part explain the reported increased vulnerability for neurobehavioral and neurocognitive problems in children with SCT, it is important to incorporate this knowledge in optimizing psychoeducation, support, and treatment. If the familial risk does not significantly impact outcomes of children with SCT, this is important knowledge as it may suggest that the neurodevelopmental profile of children with SCT more likely primarily results from the extra X or Y chromosome or that other environmental factors may be involved. It is particularly relevant to study familial risk in early childhood, as knowledge of factors that play a role in the phenotype of SCT early in life may contribute to new developments in early support and intervention, with the potential to positively influence outcomes later in life.

2 | Material and Methods

2.1 | Ethics Statement

Signed informed consent was obtained from the parents of all participants, according to the declaration of Helsinki. This study was approved by the Ethical Committee of Leiden University Medical Center, the Netherlands, and the Colorado Multiple Institutional Review Board (COMIRB) in Colorado.

2.2 | Sample

This study was part of the TRIXY Early Childhood Study, Leiden University, the Netherlands. This longitudinal study comprises a baseline assessment and a follow-up evaluation after 1 year. Its primary objective is to identify potential neurodevelopmental risks in young children with an extra X or Y chromosome. The study included two groups: a group of 106 children with SCT and their primary caregiver (parent) and a group of 102 nonclinical control participants and their primary caregiver (parent). Age of the children ranged from 1 to 8 years, with a mean age of 3.7 (SD 1.9) years in the SCT group and 3.6 (SD 1.6) years in the control group. See Table 1 for all sample characteristics. The primary caregiver (parent) provided information about the family of the child, as well as the child's characteristics. In addition to parental reports, the study also included direct child assessments (neurocognitive tests). Parental education was measured using the Hollingshead scale (Hollingshead 1975).

Recruitment of the SCT group was done in the Netherlands, Belgium, and Colorado (USA), with the help of clinical genetics departments, pediatricians, and national support and advocacy groups. For the SCT group, ascertainment bias was assessed and three subgroups were identified: (a) "Active prospective follow-up" which included families who were actively followed after prenatal diagnosis, (b) "Information seeking parents" which included families who were actively looking for more information about SCT without having specific concerns about the behavior of their child, and (c) "Clinically referred cases" which included families seeking professional help based on specific concerns about their child's development. Control participants were recruited through public institutions in the Netherlands such as daycare centers and primary schools, as well as via the civil registry. Assessments were conducted at various testing sites, both national and international, including the TRIXY Center of Expertise at the Leiden University Treatment and Expertise Centre (LUBEC) in the Netherlands and the eXtraordinarY Kids Clinic in Developmental Pediatrics at Children's Hospital Colorado. Procedures and assessments were identical for the SCT group and control group.

Both the SCT and control groups adhered to certain exclusion criteria, which included a history of traumatic brain injury, severe hearing or visual impairment, neurological disorders, and colorblindness. Furthermore, as an inclusion criterion for both groups, the child and the primary caregiver (parent) were required to speak Dutch or English. All children involved in the study had normal or corrected-to-normal vision. In the control group, screening showed that none of the children scored in the clinical range on the Childhood Behavior Checklist (Achenbach and Rescorla 2000). In the SCT group, inclusion required the X/Y trisomy to be present in at least 80% of the cells, as confirmed by standard karyotyping.

TABLE 1 | Sample characteristics.

	SCT ($n=106$ families)	Control ($n=102$ families)	Group comparisons
Child age (years)	3.7 (SD 1.9)	3.6 (SD 1.6)	$p=0.68$ ($d=0.05$)
Number of fully biologically related siblings of child, per family	2.0 (SD 0.9)	2.0 (SD 0.8)	$p=0.80$ ($d=0.00$)
Average parental age (years)	39.4 (SD 4.9)	35.9 (SD 5.4)	$p<0.001$ ($d=0.73$)
Average parental education of both parents (Hollingshead)	5.9 (SD 0.9)	5.3 (SD 1.4)	$p=0.03$ ($d=0.52$)
Prenatal/postnatal diagnosis	71/35	n/a	
Prospective/information-seeking/help-seeking parents	54/32/20	n/a	
XXX/XXY/XYY	33/48/25	n/a	

Ethical considerations prevented genetic screening within the control group. However, given the prevalence of SCT, the risk of inadvertently including a child with SCT in the control group was deemed minimal and acceptable.

2.3 | Measures of Familial Risk

Two aspects of FH were considered: FH of neuropsychiatric disorders and FH of neurocognitive disorders, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric and Force 2013).

To collect data on FH, we used the FH method, wherein the information regarding the DSM classifications is gathered from family members (Ali et al. 2021). In this study, the primary caregiver (parent) provided information about FH of the child. We employed a structured checklist listing DSM classifications of psychiatric disorders Anxiety Disorders, Depressive Disorders, ASD, Schizophrenia/Psychotic/Bipolar Disorders, Attention-Deficit/Hyperactivity Disorder (ADHD), or Disruptive, Impulse-control, and Conduct Disorders) and DSM classifications of neurocognitive disorders (Intellectual Disability, Global Developmental Delay, Communication Disorders (speech/language), or Learning Disorders (including Specific Learning Disorders such as Dyslexia). The primary caregiver (parent) of the participating children was asked to report the presence or absence of DSM classifications in each first-degree family member of the child (mother/father/brothers/sisters), based on formal clinical evaluation ("Has family member "A" ever been diagnosed with condition "X""). Self-report measures of FH have been widely used and shown to be a practical and valid approach in research settings (Hardt and Franke 2007).

2.4 | Measures of Psychopathology Symptoms in Children

The Childhood Behavior Checklist (CBCL), a widely used parent-report questionnaire, was used to capture a broad range of behavioral and emotional problems in children. Due to the wide age range of our sample (1.5–7 years), we utilized two different versions of the CBCL: the version for children ages 1.5–5 years (Achenbach and Rescorla 2000) and the version for children ages 4–18 years (Achenbach 1991). These versions have different item sets and scoring procedures to accommodate the developmental differences between younger and older children. In this study, we used the subscales that were overlapping across the two age versions: anxiety, aggression, withdrawal, and attention problems. Because the two age versions differ in number of items per subscale, we calculated the average subscale score for each participant by dividing the raw score of the respective items by the total number of items in the subscale. This allowed us to obtain a summary measure of the average intensity of symptoms for each subscale. Primary caregivers (parents) of the children completed the CBCL questionnaire, rating the frequency and intensity of each behavior based on their observations. Each item is scored on a 3-point Likert scale, ranging from 0 (not true) to 2 (very true or often true).

In order to measure specific ADHD symptoms in terms of inattention as well as hyperactivity/impulsivity symptoms, the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) questionnaire was used (Swanson et al. 2012). The SWAN questionnaire is a widely used and validated rating scale designed to measure ADHD symptoms in children and adolescents. It provides a comprehensive evaluation of both inattention and hyperactivity/impulsivity domains. The SWAN questionnaire consists of a series of items that describe various behavioral manifestations associated with ADHD. Participants' primary caregivers (parents) were asked to rate the frequency of each behavior on a Likert scale, typically ranging from 1 (far below average) to 7 (far above average). The scale covers both positive and negative behaviors, allowing for a comprehensive assessment of ADHD symptoms within the context of normal behavior. The SWAN questionnaire provides a quantitative measure of ADHD symptomatology, enabling the comparison of symptom severity across individuals. It has demonstrated good reliability and validity in previous research studies, making it a reliable tool for assessing ADHD symptoms in both clinical and research settings.

In order to also capture various aspects of children's social and emotional functioning, the Ages and Stages Questionnaire: Social–Emotional (ASQ-SE) was used (Squires et al. 2015). The ASQ-SE is a standardized, parent-report questionnaire, that covers a range of social and emotional skills and behaviors. Primary caregivers (parents) of the children completed the ASQ-SE questionnaire, rating their child's behaviors and abilities based on their observations. Each item is scored on a 3-point Likert scale, with responses indicating whether a behavior is "often," "sometimes," or "rarely/never" observed in the child. The scores on the individual items are summed to obtain a total score, which provides an overall measure of the child's socio-emotional development. The ASQ-SE assesses various domains of socio-emotional development, including self-regulation, compliance, adaptive functioning, autonomy, affect, and social communication. It provides an indication of children's socio-emotional skills and behaviors in comparison to age-appropriate developmental milestones. The ASQ-SE has demonstrated good reliability and validity in assessing socio-emotional development in typically developing children.

In order to measure autism symptoms, the Social Responsiveness Scale (SRS-2) was filled in by primary caregivers (parents) in a subset of children aged 3 years and older. The SRS-2 is a widely used questionnaire-based measure that provides a quantitative assessment of social communication and interaction difficulties associated with ASDs (Constantino and Gruber 2012). The SRS-2 captures various domains of social behavior, including social awareness, social cognition, social communication, social motivation, and autistic mannerisms. Participants' caregivers or individuals familiar with the participants' behavior completed the SRS-3 questionnaire. Each item is rated on a 4-point Likert scale, ranging from 0 (not true) to 3 (almost always true). Higher scores indicate greater social communication and interaction difficulties associated with autism symptoms. The SRS-2 yields a total score as well as scores for five subscales: social awareness, social cognition, social communication, social motivation, and

autistic mannerisms. The total score and subscale scores provide an overall assessment of social responsiveness and help identify specific areas of social impairment characteristic of autism symptoms. The SRS-2 has demonstrated good reliability and validity in various populations, including individuals with ASDs (Constantino and Gruber 2012).

2.5 | Measures of Neurocognitive Functioning in Children

2.5.1 | Children 1–3 Years Old

The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) was used in our study to assess neurocognitive and language abilities in children aged 1–3 years. It is a widely recognized and standardized assessment tool specifically designed for evaluating developmental functioning in infants and young children aged 1–42 months (Bayley 2006). The Bayley-III encompasses various domains of development, including neurocognitive, language, motor, social–emotional, and adaptive skills. For our study, we focused on the neurocognitive and language domains as measures of overall intelligence (IQ) and verbal IQ, respectively.

The cognition score obtained from the Bayley-III reflects the child's performance in tasks assessing problem-solving, memory, attention, and perceptual processing abilities. This score provides an estimate of the child's neurocognitive development and serves as a measure of overall intelligence (IQ). Bayley (Bayley 2006) emphasized the strong correlation between the cognition score obtained from the Bayley-III and later intelligence test results in both typically developing children and those at risk for developmental delays. The language score from the Bayley-III has been widely utilized as a proxy or measure for verbal IQ, reflecting a child's language-related neurocognitive abilities.

The Bayley-III has demonstrated strong psychometric properties, including reliability and validity, in assessing developmental functioning in young children. In our study, the Bayley-III was administered by trained assessors following standardized procedures to ensure consistency and accuracy in scoring.

2.5.2 | Children 3–8 Years Old

Four subtests of the Wechsler Preschool and Primary Scales of Intelligence, 3rd edition (WPPSI-III) (Hurks et al. 2016; Sattler 2004) was used to assess neurocognitive and language abilities in children aged 3–8 years. The subtests were Block Design, Matrix Reasoning, Vocabulary, and Similarities. Total IQ estimates were calculated based on this shortform version of the WPPSI-III [41]. Verbal IQ was calculated based on Vocabulary and Similarities, which together form the Verbal Comprehension index score. These two subtests are widely used in the computation of Verbal IQ.

The WPPSI-III has demonstrated strong psychometric properties, including reliability and validity, in assessing developmental functioning in young children. In our study, the WPPSI-III was administered by trained assessors following standardized procedures to ensure consistency and accuracy in scoring.

2.6 | Statistical Analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 29. Percentages of children with and without a FH of any neuropsychiatric disorders or any neurocognitive disorders were compared using Chi-square analyses. Univariate GLM analysis was used to compare group characteristics stratified by group membership (SCT, control) and familial risk. Multivariate ANOVA was used to compare child outcomes in the SCT group stratified by familial risk. Threshold for significance was set at $p = 0.05$.

3 | Results

3.1 | Group Characteristics Familial Risk in SCT Versus Controls

First, we identified subgroups of children with and without FH of neuropsychiatric disorders or neurocognitive disorders, to evaluate sample sizes and group characteristics. In the SCT group, 37.7% ($n = 40$) of the children had a first-degree relative diagnosed with a neuropsychiatric disorder, and 19.8% ($n = 21$) of the children had a first-degree relative diagnosed with a neurocognitive disorder. In the control group, 24.5% ($n = 24$) of the children had a first-degree relative diagnosed with a neuropsychiatric disorder, and 17.6% ($n = 18$) of the children had a first-degree relative diagnosed with a neurocognitive disorder.

Univariate GLM analysis showed there was no significant interaction between research group (SCT, Control) and FH of psychiatric disorders on Child age ($p = 0.12$) or average parental education ($p = 0.57$). Also, there was no significant interaction between research group (SCT, Control) and FH of neurocognitive disorders on child age ($p = 0.20$) or average parental education ($p = 0.20$). In other words, the distributions of age and parental education were similar across subgroups stratified by FH in the SCT group and control group. Within the SCT group, a positive or negative FH of neuropsychiatric or neurocognitive disorders showed no significant differences in the distribution of timing of diagnosis, recruitment strategy, or specific karyotype. See Table 2.

3.2 | Aim 1: Comparison of Familial Risk in SCT Versus Controls

Chi-square analyses comparing the percentage of children with and without a FH of any neuropsychiatric or any neurocognitive disorders revealed no significant differences between the SCT and control groups. Analyses of specific categories of neuropsychiatric or neurocognitive disorders showed that a significantly larger percentage of children in the SCT group had a positive FH of anxiety disorder as compared to the control group, $\chi^2(1) = 10.6$, $p = 0.001$. Other specific categories did not show significant group differences. See Table 3.

TABLE 2 | Sample characteristics stratified by family history.

Family history of any neuropsychiatric disorders	SCT ($n=106$ families)		Control ($n=102$ families)		Statistics (group × family history)
	Yes ($n=40$)	No ($n=66$)	Yes ($n=25$)	No ($n=77$)	
Child age (years)	3.3 (SD 1.7)	3.9 (SD 2.0)	3.7 (SD 1.7)	3.5 (SD 1.6)	$p=0.12$
Average parental education (Hollingshead)	5.9 (SD 1.1)	5.9 (SD 0.8)	5.3 (SD 1.4)	5.4 (SD 1.4)	$p=0.57$
Prenatal/postnatal diagnosis	28/12	43/23			$p=0.67$
Prospective/information seeking/help seeking	18/15/7	36/17/13			$p=0.44$
XXX/XXY/XYY	16/14/10	17/34/15			$p=0.20$
Family history of any neurocognitive disorders	**SCT ($n=106$ families)**		**Control ($n=102$ families)**		**Statistics (group × family history)**
	Yes ($n=21$)	**No ($n=85$)**	**Yes ($n=18$)**	**No ($n=84$)**	
Child age	4.1 (SD 2.1)	3.6 (SD 1.9)	3.4 (SD 1.7)	3.6 (SD 1.6)	$p=0.20$
Average parental education (Hollingshead)	5.2 (SD 1.1)	6.1 (SD 0.7)	5.1 (SD 1.8)	5.4 (SD 1.3)	$p=0.20$
Prenatal/postnatal diagnosis	16/5	55/30			$p=0.44$
Prospective/information seeking/help-seeking	12/5/4	42/27/16			$p=0.76$
XXX/XXY/XYY	8/8/5	25/40/20			$p=0.70$

3.3 | Aim 2: Comparison of SCT Child Outcomes Stratified by Familial Risk

Multivariate ANOVA showed no significant overall main effect of familial risk for *neuropsychiatric disorders* on child outcomes (CBCL, ASQ, SWAN, VIQ, IQ), $F_{(9,78)}=1.6$, $p=0.12$. In contrast, multivariate ANOVA did show a significant overall main effect of familial risk for *neurocognitive disorders* on child outcomes (CBCL, ASQ, SWAN, VIQ, IQ), $F_{(9,78)}=2.0$, $p=0.05$, showing significant effects specifically on ADHD Inattention problems in children. Univariate ANOVA for specific domains of child outcomes (including SRS scores for a subset of children aged > 3 years) are presented in Tables 4 and 5.

Based on the significant effect of familial history of neurocognitive disorders on ADHD Inattention symptoms, subsequent explorative analyses were performed to test for "dosage" effects. ANOVA showed that the number of affected family members was associated with the degree of ADHD Inattention symptoms in children with SCT, $F_{(2,101)}=12.8$, $p<0.001$. Post hoc tests showed that the subgroup of SCT children with two or more affected family members ($n=6$) had significantly higher levels of ADHD Inattention symptoms as compared to SCT children with one affected family member ($n=14$, $p<0.001$) or SCT children with no affected family members ($n=82$, $p<0.001$). See Figure 1.

4 | Conclusion and Discussion

The heterogeneity in the neurobehavioral profile of individuals with SCT that has been reported in the literature suggests that multiple factors contribute to the expression of SCT-related traits. In our study, we specifically focused on exploring the potential role of familial risk on the neurobehavioral and neurocognitive phenotype of children with SCT. Familial risk refers to the increased likelihood of developing a disorder based on the presence of affected individuals within the family. Previous research has established the heritability component of psychiatric disorders and learning, intellectual, and language disorders, highlighting the contribution of familial factors to neurobehavioral and neurocognitive development (Plomin and Von Stumm 2018; Sullivan et al. 2012).

Given this background, we explored if familial risk, in addition to the presence of an extra X or Y chromosome, may shape the neurodevelopmental profile of children with SCT. To investigate this, we examined the prevalence of psychiatric and neurocognitive disorders in first-degree relatives of children with SCT. By comparing the rates of these disorders in relatives of children with SCT versus a general population sample, our first aim was to elucidate the potential contribution of familial factors to the increased prevalence observed in individuals with SCT. Our second aim was to assess whether the levels of neurobehavioral symptoms and problems in neurocognitive functioning in children with SCT varied depending on the presence or absence of a FH of psychiatric or neurocognitive disorders in their first-degree relatives.

With regard to our first aim, our study showed no systematic differences in rates of diagnoses of neuropsychiatric or neurocognitive disorders in first-degree relatives of children with SCT as compared to typically developing peers. This suggests that the reported increased vulnerability to psychopathology and neurocognitive deficits in individuals with SCT might not be attributed to familial factors. Although anxiety disorders were

TABLE 3 | Familial risk for neuropsychiatric and neurocognitive disorders in the SCT group versus control group.

	SCT ($n=106$ families)		Control ($n=102$ families)		
	Yes	**No**	**Yes**	**No**	**Group effects (chi square)**
FH of any neuropsychiatric disorders	37.7% ($n=40$)	62.3% ($n=66$)	24.5% ($n=25$)	75.5% ($n=77$)	$p=0.05$
FH of any neurocognitive disorders	19.8% ($n=21$)	80.2% ($n=85$)	17.6% ($n=18$)	82.4% ($n=84$)	$p=0.41$
Neuropsychiatric disorders					
FH of anxiety disorders	24.5% ($n=26$)	75.5% ($n=80$)	7.8% ($n=8$)	92.2% ($n=94$)	$p=0.001$*
FH of depressive disorders	82.1% ($n=19$)	17.9% ($n=87$)	90.2% ($n=10$)	9.8% ($n=92$)	$p=0.11$
FH of ASDs	3.8% ($n=4$)	96.2% ($n=102$)	3.9% ($n=4$)	96.1% ($n=98$)	$p=1.00$
FH of schizophrenia/psychotic/bipolar disorders	2.8% ($n=3$)	97.2% ($n=103$)	2.0% ($n=2$)	98.0% ($n=100$)	$p=0.52$
FH of attention-deficit/hyperactivity disorder (ADHD)	17.0% ($n=18$)	83.0% ($n=88$)	8.8% ($n=9$)	91.2% ($n=93$)	$p=0.10$
FH of disruptive, impulse-control, and conduct disorders	1.9% ($n=2$)	98.1% ($n=104$)	1.0% ($n=1$)	99.0% ($n=101$)	$p=1.00$
Neurocognitive disorders					
FH of intellectual disability or global developmental delay	3.8% ($n=4$)	96.2% ($n=102$)	2.9% ($n=3$)	97.1% ($n=99$)	$p=1.00$
FH of communication (speech/language) disorders	6.6% ($n=7$)	93.4% ($n=99$)	2.9% ($n=3$)	97.1% ($n=99$)	$p=0.33$
FH of specific learning disorders	16.0% ($n=17$)	84.0% ($n=89$)	14.7% ($n=15$)	85.3% ($n=87$)	$p=0.85$

*Significant at a threshold of $p=0.05$.

more prevalent in first-degree relatives of individuals with SCT as compared to nonclinical controls, indicating a potential role of familial risk, it is crucial to consider the unique challenges and stressors associated with having a child with SCT within the family, including the disclosure of a SCT diagnosis, which may also contribute to the observed higher rates of anxiety disorders in parents and siblings.

With regard to our second aim, considering outcomes of children with SCT against the background of familial risk, mixed effects were found. There was no significant effect of *family history of neuropsychiatric disorders* on any of the child outcomes. This suggests that the reported increased vulnerability for psychopathology and neurocognitive deficits in SCT cannot be attributed to familial risk for psychiatric conditions, either through genetic heritability or shared environmental factors. In contrast, our analysis did reveal a significant effect of *family history of neurocognitive disorders* on child outcomes. This effect was specific, as it was only observed for ADHD Inattention problems in SCT, which were higher with a positive FH of neurocognitive disorders. This finding highlights the importance of considering familial risk for neurocognitive disorders on the manifestation of ADHD symptoms in children with SCT. Explorative analysis showed that the number of affected family members was associated with the degree of ADHD Inattention symptoms in children with SCT; SCT children with two or more affected family members demonstrated significantly higher levels of ADHD Inattention symptoms compared to those with one affected family member or no affected family members. Although speculative, a "dosage" effect, where an increasing number of affected family members exacerbates the severity of ADHD Inattention symptoms in children with SCT, may point to heritability factors anchored in background genes, beyond the extra X or Y chromosome.

So does familial risk contribute to the neurobehavioral phenotype of children with SCT? Even though a significant impact was found for ADHD symptoms, none of the other domains of child outcomes, including socio-emotional problems, ASD, aggression, anxiety, withdrawal, and intellectual deficits, showed an impact of FH of neurocognitive disorders. Also, FH of neuropsychiatric disorders did not show any relation with the outcomes of children with SCT. If familial risk does not significantly impact the outcomes of children with SCT, this is important information, as it may suggest that the neurodevelopmental profile of children with SCT is primarily the result of the extra X

TABLE 4 | Child outcomes in SCT stratified by family history of psychopathology.

Child outcomes	SCT ($n=106$ children)		Statistics
	Positive FH of neuropsychiatric disorders ($n=40$)	Negative FH of neuropsychiatric disorders ($n=66$)	
Anxiety (CBCL raw score)	0.40 (SD 0.39)	0.29 (SD 0.29)	$p=0.10$ ($d=0.32$)
Withdrawal (CBCL raw score)	0.33 (SD 0.32)	0.31 (SD 0.30)	$p=0.76$ ($d=0.06$)
Attention (CBCL raw score)	0.59 (SD 0.45)	0.60 (SD 0.39)	$p=0.93$ *($d=0.02$)*
Aggression (CBCL raw score)	0.57 (SD 0.46)	0.45 (SD 0.32)	$p=0.11$ ($d=0.31$)
Autism symptoms (> 3 years) (SRS raw score)	60.8 (SD 29.3)	52.0 (SD 22.1)	$p=0.16$ ($d=0.34$)
Social problems (ASQ-SE raw score)	14.2 (SD 13.1)	10.6 (SD 7.4)	$p=0.08$ ($d=0.35$)
ADHD inattention (SWAN raw score)	2.2 (SD 2.5)	2.2 (SD 2.7)	$p=0.94$ ($d=0.00$)
ADHD hyperactivity (SWAN raw score)	1.9 (SD 2.7)	1.9 (SD 2.3)	$p=0.98$ ($d=0.00$)
IQ (bayley/WPPSI percentile score)	48.6 (SD 30.3)	41.3 (SD 31.1)	$p=0.27$ ($d=0.23$)
VIQ (bayley/WPPSI percentile score)	42.3 (SD 31.7)	41.5 (SD 31.1)	$p=0.91$ ($d=0.02$)

TABLE 5 | Child outcomes in SCT stratified by FH of neurocognitive disorders.

Child outcomes	SCT ($n=106$ children)		Statistics
	Positive FH of neurocognitive disorders ($n=21$)	Negative FH of neurocognitive disorders ($n=85$)	
Anxiety (CBCL raw score)	0.42 (SD 0.40)	0.31 (SD 0.32)	$p=0.18$ ($d=0.30$)
Withdrawal (CBCL raw score)	0.40 (SD 0.32)	0.30 (SD 0.30)	$p=0.17$ ($d=0.32$)
Attention (CBCL raw score)	0.71 (SD 0.47)	0.56 (SD 0.39)	$p=0.14$ ($d=0.34$)
Aggression (CBCL raw score)	0.61 (SD 0.49)	0.46 (SD 0.34)	$p=0.11$ ($d=0.36$)
Autism symptoms (> 3 years) (SRS raw score)	60.0 (SD 28.7)	54.0 (SD 24.3)	$p=0.42$ ($d=0.22$)
Social problems (ASQ-SE raw score)	14.2 (SD 12.4)	11.5 (SD 9.6)	$p=0.29$ ($d=0.24$)
ADHD inattention (SWAN raw score)	3.8 (SD 3.1)	1.8 (SD 2.3)	$p=0.002$* ($d=0.74$)
ADHD hyperactivity (SWAN raw score)	2.6 (SD 3.1)	1.7 (SD 2.2)	$p=0.12$ ($d=0.33$)
IQ (bayley/WPPSI percentile score)	40.8 (SD 33.4)	44.8 (SD 30.8)	$p=0.61$ ($d=0.12$)
VIQ (bayley/WPPSI percentile score)	41.4 (SD 34.9)	41.9 (SD 30.8)	$p=0.95$ ($d=0.01$)

*Significant at a threshold of $p=0.05$.

or Y chromosome, or that other environmental factors may play a role. This interpretation is also in line with the finding that overall rates of psychiatric and neurocognitive disorders were similar in first-degree relatives in the SCT group and nonclinical control group. Interestingly, there were no effects of FH of psychiatric or neurocognitive disorders on the level of anxiety in children with SCT; in other words, anxiety symptoms were increased in children with SCT irrespective of whether or not there were first-degree relatives diagnosed with anxiety disorder. This would fit with the idea that increased rates of anxiety in first-degree relatives of SCT may not necessarily represent familial heritable genetic risk, but possibly represent the product of environmental context such as having a child, brother, or sister with a genetic condition.

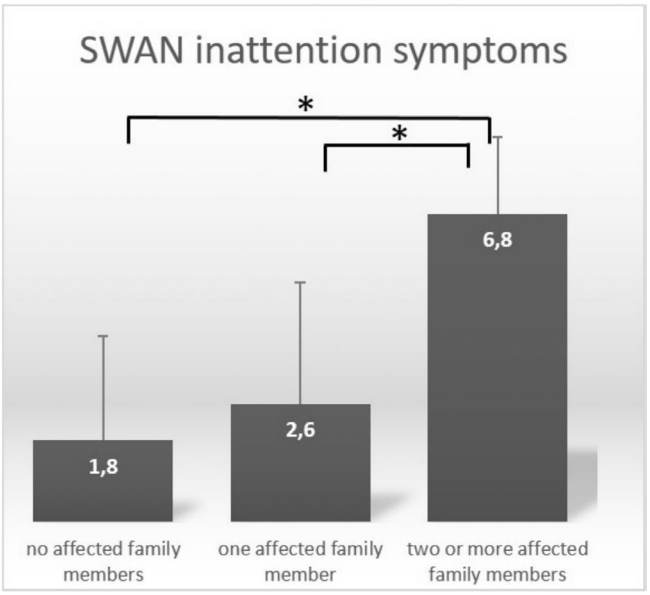

FIGURE 1 | Level of ADHD inattention symptoms in children with SCT stratified by FH of neurocognitive disorders (number of first-degree family members diagnosed with DSM-based neurocognitive disorders).

The findings from this study may have clinical implications for understanding the neurobehavioral and neurocognitive outcomes in children with SCT. While familial risk for psychiatric and neurocognitive disorders did not appear to significantly influence the overall neurodevelopmental phenotype of children with SCT, a notable exception was found in relation to ADHD symptoms, specifically ADHD Inattention problems, which were more pronounced in children with a FH of neurocognitive disorders. This suggests that, in some cases, familial risk—potentially through genetic factors—may exacerbate certain neurodevelopmental issues, such as attention deficits, in children with SCT. Clinically, this emphasizes the need for individualized assessments of children with SCT, considering both the chromosomal factors and any FH of neurocognitive disorders, especially when managing ADHD-related symptoms. Additionally, the lack of a broader familial risk effect across other neurobehavioral domains suggests that other genetic or environmental factors associated with SCT may play a more prominent role in these outcomes. This highlights the importance of adopting a multidisciplinary approach in clinical practice, considering a range of familial and environmental factors in the diagnosis and management of SCT. At the same time, the current findings may help to identify a neurobehavioral phenotype that is directly linked to having an extra X or Y chromosome, which may be relevant in psychoeducation for parents and individuals with these X and Y chromosome trisomies. It is important to acknowledge some limitations of our study. First, the assessment of familial history relied on self-reported diagnoses, which may be subject to recall bias or incomplete reporting. Future research should incorporate more comprehensive and validated measures to assess familial history. Second, our study focused on first-degree relatives of the child, and the potential contributions of more distant relatives or other familial factors were not explored. Further investigations should consider a broader range of familial relationships and factors to obtain a more comprehensive understanding of the influence of familial risk on SCT-related traits. Third, the children in the study were in early childhood (1–7 years). We cannot exclude that psychopathology resulting from familial risk may present later in development. Fourth, average parental age was significantly higher in the SCT group as compared to the control group. Although this is in line with standard genetic (prenatal) screening being more common with higher maternal age, parental age may be an important factor to consider. Finally, our study did not consider the timing of the onset of psychopathology in family members; future studies may consider to collect data on neuropsychiatric and neurocognitive disorders detected prior to the child's diagnosis. Also, bias in self-rating measures, especially due to recall or incomplete reporting, is a significant concern when assessing familial risk and psychopathology. To improve the validity of future studies, a multimethod approach is recommended, incorporating more objective clinician ratings. Structured diagnostic interviews, such as the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al. 1994), offer a systematic way to assess familial psychiatric histories. Additionally, a dimensional approach that quantifies the severity of symptoms (e.g., inattention, anxiety) rather than relying solely on categorical diagnoses (e.g., ADHD, anxiety disorder) could better capture the full spectrum of psychopathology. This approach would be more sensitive to familial effects and provide a clearer understanding of how familial risk factors contribute to more subtle neurodevelopmental outcomes in SCT. By combining clinician ratings with dimensional assessments, future research can improve the accuracy of familial risk evaluations and also better address the sub-diagnostic symptoms or more milder forms of ASD, anxiety, depression, and learning disabilities. An important avenue for further research will also be to study impact of genetic and environmental factors from a developmental perspective, taking into account that neuropsychiatric or neurocognitive vulnerabilities in SCT may present more pronounced at later stages of development, depending on brain maturation. This phenomenon has already been illustrated in several domains of cognitive development in SCT (Bouw et al. 2022; Kuiper et al. 2022). Also, more complex mental states such as anxiety, depression, or thought disorder typically emerge in late childhood or adolescence, as do more subtle forms of ADHD or EF impairments; it is important to extend the current study and evaluate impact of familial risk beyond the school-age years.

In conclusion, our overall findings highlight that FH for *psychiatric disorders* may not result in additional risk for neurodevelopmental problems in young children with SCT, above and beyond the risk associated with having an extra X or Y chromosome. While familial risk for *neurocognitive disorders* may contribute to some extent, in particular in relation to ADHD symptoms, these familial risk effect seems to be very specific. Overall, it is likely that other factors, such as the extra X or Y, other genetic variations or unique environmental influences, may play a more prominent role in driving the manifestation of the majority of neurobehavioral and intellectual vulnerabilities observed in young children with SCT. Understanding factors contributing to phenotypic variation in SCT is important for improving psychoeducation and developing more tailored and targeted diagnostic screening, interventions, and support strategies for individuals with SCT and their families, ultimately improving quality of life and mental health outcomes. Future research should continue to explore the underlying mechanisms

driving the neurodevelopmental outcomes in SCT, with a focus on identifying specific genetic and environmental factors that contribute to the heterogeneity observed in this population, also taking into account a life-time perspective as neurodevelopmental risk may present differently in (young) adulthood as compared to (early) childhood. SCT presents a unique opportunity to prospectively study these complex mechanisms that drive developmental risk. The current approach may fuel new studies in this direction.

Author Contributions

Sophie van Rijn: conceptualization and design, funding acquisition, methodology, project organization, data analysis, and writing and revising of original draft. **Kimberly Kuiper:** design, data collection, methodology, project organization, logistics, writing, reviewing and editing. **Hanna Swaab:** conceptualization and design, writing, reviewing and editing.

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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 study are available from the corresponding author upon reasonable request.

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